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STUDIES TOWARDS THE SYNTHESIS OF MEDERMYCIN

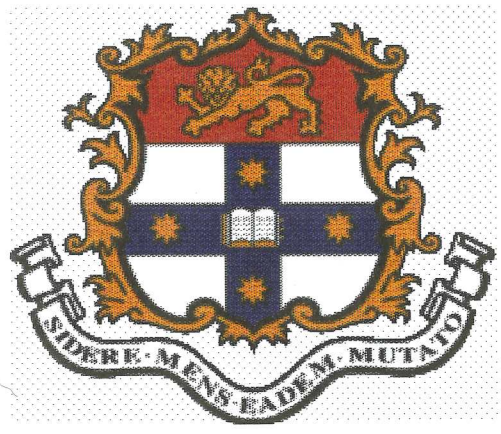
A thesis submitted in partial fulfilment of
the requirements for the degree of

Doctor of Philosophy

by

Timothy James Brenstrum

Department of Organic Chemistry
University of Sydney
September 1999



In every pearl
Lies a sandy grain
Of truth and doubt,
The catalysts
For our creativity.

Tim

PREFACE

This work was carried out in the Division of Organic Chemistry at the University of Sydney. All the results presented in this thesis are those of the author, except where due reference to the work of others has been made in the text.

Previous publications include:

"Synthesis of Deuterium Labelled Hexenols" M. A. Brimble, T. J. Brenstrum, C. J. Rush, G. J. Shaw, and D. C. W. Reid, *Journal of Labelled Compounds and Radiopharmaceuticals*, 1992, 629.

"Directed *Ortho* Metalations of Tertiary Benzamides Using Lactones as Electrophiles" M. A. Brimble, T. J. Brenstrum and R. J. Stevenson, *Tetrahedron*, 1994, **50**, 4897.

ABSTRACT

This thesis describes synthetic work directed towards the synthesis of the *C*-glycosyl pyranonaphthoquinone antibiotic medermycin **52**. The isolation, structure and biological activity of members of the pyranonaphthoquinone family of antibiotics is reviewed (section **1.1**), as well as previous approaches to the synthesis of pyranonaphthoquinones (section **1.2**) and methods for the formation of *C*-glycosides (section **1.3**).

The synthesis of medermycin **52** required the construction of an aryl β-*C*-glycosyl linkage. Initial work was therefore directed towards an investigation of the methods for the formation of aryl *C*-glycosides, in particular, of the *O*→*C*-glycoside rearrangement method. Model work using simple glycosyl donors, pyranose **216** and glycosyl fluoride **214**, in the Lewis acid catalyzed reaction with various naphthols, was unsucessful. Employing an alternative approach, *O*-glycosides **279**, **280**, and **281** were formed from pyranose **216** and naphthols **272**, **234** and **273** using Mitsunobu conditions, but attempts to rearrange these to the corresponding *C*-glycosides using a Lewis acid met with no success. Attention was turned to the more reactive 2-deoxy glycosyl donors, **266** and **238**, instead.

Successful *C*-glycosylation was realized using the glycosyl acetate **238** under trimethylsilyl triflate and silver perchlorate catalysis. Mixtures of *O*- and *C*-glycosides were obtained using dichloromethane as solvent. Optimally, however, when using acetonitrile as the solvent the desired β-*C*-glycosides, **240** and **293**, were obtained in yields of 97% and 82% respectively.

Naphthols **299** and **264**, envisaged as precursors for the synthesis of medermycin **52**, were next synthesized (along with their C-2 functionalized regioisomers **314** and **321**). Glycosylation was largely unsuccessful using the acetate protected glycosyl donor **238**, except in the case of 2-bromonaphthol **314** which gave *C*-glycoside **328**. On turning to the benzyl protected glycosyl donor **266**, a similar lack of reactivity was observed when using C-3 functionalized naphthols **299** and **264**. In this case, however, an unusual 1,6-hydride shift rearrangement occurred to give the bicyclic acetals **340** and **354**, as well as small amounts of the desired *C*-glycosides **329** and **263**. X-ray crystal structure analysis of the acetate **351** confirmed the unusal bicyclic acetal structure.

The enhanced reactivity of naphthol **247**, unfunctionalized at C-3, circumvented the rearrangement to give the *C*-glycoside **250**. The necessary introduction of an acetyl

group at C-3 could not easily be achieved. A less direct route, therefore, involved methylation to give **361**, oxidative demethylation to the quinone **357**, reductive monomethylation to naphthol **358**, regioselective bromination to give **364**, methylation to give **365**, introduction of an acetyl group *via* a Stille coupling to give ketone **359** and a second oxidative demethylation to give the key activated naphthoquinone **262**. The requirement for seven steps instead of three to reach this point dramatically reduced the directness of the synthesis, but meant that we were able to investigate the 2-trimethylsilyloxyfuran addition/oxidative rearrangement methodology, developed in this research group, as a means for installing the furopyran ring system.

Addition of 2-trimethylsilyloxyfuran to acetylnaphthoquinone **262** gave the diastereomeric adducts **261** as an inseparable mixture and oxidative rearrangement using ceric ammonium nitrate gave the unstable diastereomeric lactols **260**. Decomposition during the axial hydride reduction of **260** could be avoided by performing the reaction at -10 °C, affording the diastereomeric cyclic ethers **259**. Finally, removal of the methoxy and benzyloxy protecting groups, with concomitant epimerization at C-5, was achieved using boron tribromide to give the medermycin analogue **257** as a diastereomeric mixture.

ACKNOWLEDGEMENTS

At last it is done and I can take time to thank everyone who has supported me along the way....in sickness and in health, till chemistry do us part!! First of all, thanks to my supervisor, Prof. Margaret Brimble, for all the help along the way, the guidance, the encouragement and the prodding at the end. Your enthusiasm for chemistry is inspirational...

Thanks also to the University of Sydney, particularly the School of Chemistry for supporting me, financially and otherwise. Thanks also to the staff of the Department of Organic Chemistry, both academic and technical, who have helped me so much. Thanks to Prof. Damon Ridley for supervising me in Margaret's absence, and also to Assoc. Prof. Margaret Harding for being interested in my progress. Thanks to Dr. Ian Luck, Ming and Jaques on the nmr...Dr. Kelvin Picker, the HPLC whizz....Dr. Peter Turner for getting crystals to do their thing....the 5th floor boys; Carlo, Cliff and especially Bruce for those discussions about the latest vintage....

Thanks to the friends who have helped the labs to be fun, especially those I have formed special bonds with...Evan Oppen, Stu Robertson....fellow tennis players, canyoners and wine lovers when I was fresh on this soil...Mike Foulkes, Dr. Craig (Mav) Mitchell and Tony Turnbull...more than just fellow SOCOG'ers, buddies....not that I have been climbing or canyoning for a bit....thanks especially to Dr. Maureen (Mozza) Murphy for the companionship, the crazy dancing (and the proof-reading)...thanks Dr. Anthony (Ant) Ward for the regular coffee/pool routine...you left just at the right time.....and thanks Dr. Tesh, Jos, Dr. Hishani, and members past and present of the Brimble (international) empire...and thanks Tai for proof reading and just generally being a sweet guy...

On a personal level, thanks to the guys..Leigh, Luke, Rob, Sam,...life just wouldn't be the same...Luke, it was worth coming to Australia just to meet you and go to the parties...Sam, guess I'll be back in action now....Rob, its pretty good having a best friend for a brother..also thanks to Adam and Suz...to Jacinta for the antics..and Jess for your patience and love. Last of all thanks to my parents, Martin and Kathy, for putting up with my being broke and not coming back to visit much....

ABBREVIATIONS

2D	= two dimensional
Ac	= acetyl
aq.	= aqueous
ax	= axial
Bn	= benzyl
b.p.	= boiling point
Bu	= butyl
n-BuLi	= *n*-butyllithium
cat.	= catalyst
CAN	= ceric ammonium nitrate
CI	= chemical impact
cm^{-3}	= cubic centimetres
conc.	= concentrated
*m*CPBA	= *meta*-chloroperoxybenzoic acid
D	= deuterium
DEPT	= distortionless enhancement by polarisation transfer
DMAP	= dimethylaminopyridine
DMF	= *N*,*N*-dimethylformamide
DMSO	= dimethyl sulfoxide
eq	= equatorial
EI	= electron impact
equiv.	= equivalent
Et	= ethyl
FAB	= fast atom bombardment
h	= hour
HETCOR	= heteronuclear chemical shift correlation
HPLC	= high pressure liquid chromatography
HRMS	= high resolution mass spectrometry
Hz	= hertz
^{i}Pr	= *iso*propyl
IR	= infra-red
J	= nmr coupling constant (Hz)
LRMS	= low resolution mass spectrometry
LSIMS	= liquid secondary ion mass spectrometry
max	= maximum

Me	= methyl
min	= minute
mg	= milligram
M	= molar
mmol	= millimoles
mol	= moles
m.p.	= melting point
NBS	= *N*-bromosuccinimide
NMO	= 4-methylmorpholine *N*-oxide
nmr	= nuclear magnetic resonance
nOe	= nuclear Overhauser effect
Nu	= nucleophile
OAc	= acetate
Ph	= phenyl
Pr	= propyl
py	= pyridine
r.t.	= room temperature
s	= second
Tf	= triflate
TFA	= trifluoroacetic acid
TFAA	= trifluoroacetic anhydride
THF	= tetrahydrofuran
TLC	= thin layer chromatography
TMS	= tetramethylsilyl
TPAP	= *tetra-n*-propylammonium perruthenate

TABLE OF CONTENTS

		Page
Preface		i
Abstract		ii
Acknowledgements		iv
Abbreviations		v
CHAPTER 1: INTRODUCTION		
1.1	**The Pyranonaphthoquinone Antibiotics.**	1
1.1.1	Pyranonaphthoquinones lacking a γ-lactone moiety.	3
1.1.2	Pyranonaphthoquinones with a fused γ-lactone (or a carboxylic acid side-chain).	5
1.2	**Related Syntheses of Pyranonaphthoquinones.**	15
1.2.1	Syntheses involving the electrophilic substitution of 2-hydroxyallyl-1,4-naphthoquinones.	16
1.2.2	Syntheses involving the intramolecular addition of an alcohol to a double bond.	21
1.2.3	Oxidation of the "yellow pigment" precursor.	25
1.2.4	Oxidation of the Diels-Alder adduct formed from juglone **75** and 1-acetoxybutadiene.	26
1.2.5	Addition of dienes to activated 1,4-quinones.	27
1.2.6	Enantioselective synthesis of kalafungin **24**.	33
1.2.7	Enantioselective synthesis of medermycin **52**.	34
1.2.8	Summary.	37
1.3	**Methods for the Formation of Aryl *C*-Glycosides.**	38
1.3.2	Use of Metallated Aromatics.	39
1.3.3	Palladium Mediated Approaches to *C*-glycosides.	41
1.3.5	Friedel-Crafts couplings.	46

CHAPTER 2: DISCUSSION.

2.1 Aryl *C*-Glycosylation Studies. 56

2.1.1 Retrosynthesis and synthetic strategy. 56
2.1.2 Synthesis of coupling partners. 58
2.1.3 Investigation of aryl *C*-glycosylation methods. 61
2.1.4 Synthesis of 2-deoxyglycosyl donors. 68
2.1.5 Aryl *C*-glycosylation using 2-deoxyglycosyl donors. 70
2.1.6 Summary. 73

2.2 Aryl *C*-Glycosylation Using Naphthols 264 and 299. 74

2.2.1 Synthetic strategy for naphthols **264** and **299**. 74
2.2.2 Synthesis of 3-bromonaphthol **299**. 75
2.2.3 Synthesis of 3-acetylnaphthol **264**. 80
2.2.4 Alternative synthesis of bromonaphthalene **306**. 86
2.2.5 Aryl *C*-glycosylation using bromonaphthols **299** and **314**. 88
2.2.6 Aryl *C*-glycosylation using acetylnaphthols **264** and **321**. 99
2.2.7 Summary. 102

2.3 Synthesis of Acetylnaphthoquinone 262. 104

2.3.1 Revised retrosynthesis and synthetic strategy 104
2.3.2 Synthesis of naphthol **247**. 106
2.3.3 Synthesis of β-*C*-glycoside **250**. 108
2.3.4 Synthesis of glycosyl naphthol **358**. 109
2.3.5 Introduction of the acetyl group. 112
2.3.6 Synthesis of acetylnaphthoquinone **262**. 120

2.4 Synthesis of Medermycin Analogue 257. 121

2.4.1 Synthesis of furonaphthofurans **261**. 121
2.4.2 Synthesis of furonaphthopyrans **260**. 124
2.4.3 Reduction of lactols **260** to cyclic ethers **259**. 127
2.4.4 Deprotection and epimerization of cyclic ethers **259** to give medermycin analogue **257**. 129

2.5 Conclusions and Future Work. 132

CHAPTER 3: EXPERIMENTAL

3.1 General Details. 134

3.2 Aryl *C*-Glycosylation Studies. 137

3.2.1 Synthesis of coupling partners. 137
3.2.2 Investigation of aryl *C*-glycosylation methods. 140
3.2.3 Synthesis of 2-deoxyglycosyl donors. 144
3.2.4 Aryl *C*-glycosylation using 2-deoxyglycosyl donors. 149

3.3 Aryl *C*-glycosylation Using Naphthols 264 and 299. 153

3.3.1 Synthesis of 3-bromonaphthol **299**. 153
3.3.2 Synthesis of 3-acetylnaphthol **264**. 159
3.3.3 Alternative synthesis of bromonaphthalene **306**. 164
3.3.4 Aryl *C*-glycosylation using bromonaphthols **299** and **314**. 167
3.3.5 Aryl *C*-glycosylation using acetylnaphthols **264** and **321**. 174

3.4 Synthesis of *C*-Glycosylacetylnaphthoquinone 262. 178

3.5 Synthesis of Medermycin Analogue 257. 191

Appendix. 197

References. 206

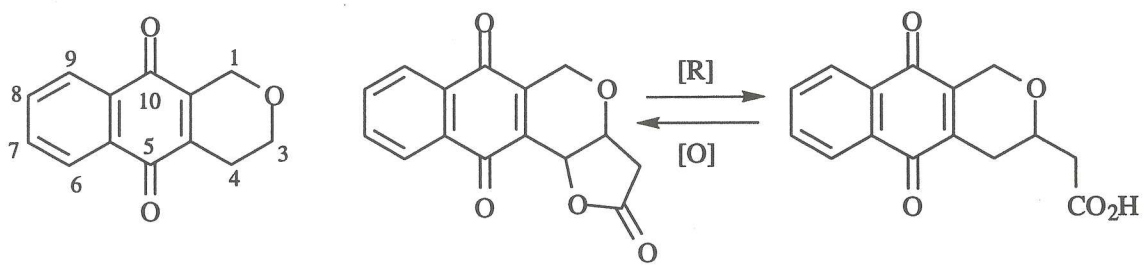
CHAPTER ONE

INTRODUCTION

1.1 The Pyranonaphthoquinone Antibiotics

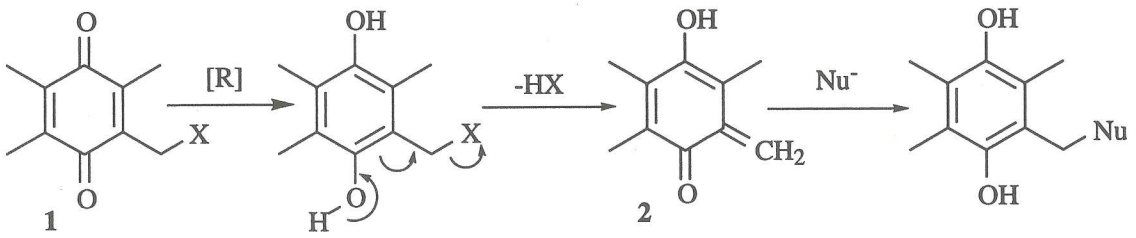
The naphthoquinones are the largest sub-group of naturally occurring quinones. The pyranonaphthoquinone antibiotics are an important member of this family. A common structural element is the naphtho[2,3-*c*]pyranquinone ring system for which the numbering is outlined (figure 1). While many of these dihydronaphthopyrans are 5,10-quinones the corresponding 6,9-quinones are not uncommon. Many pyranonaphthoquinones also contain an additional γ-lactone moiety fused to the pyran ring, or a carboxylic acid side-chain which results from ring opening of the γ-lactone.

Figure 1



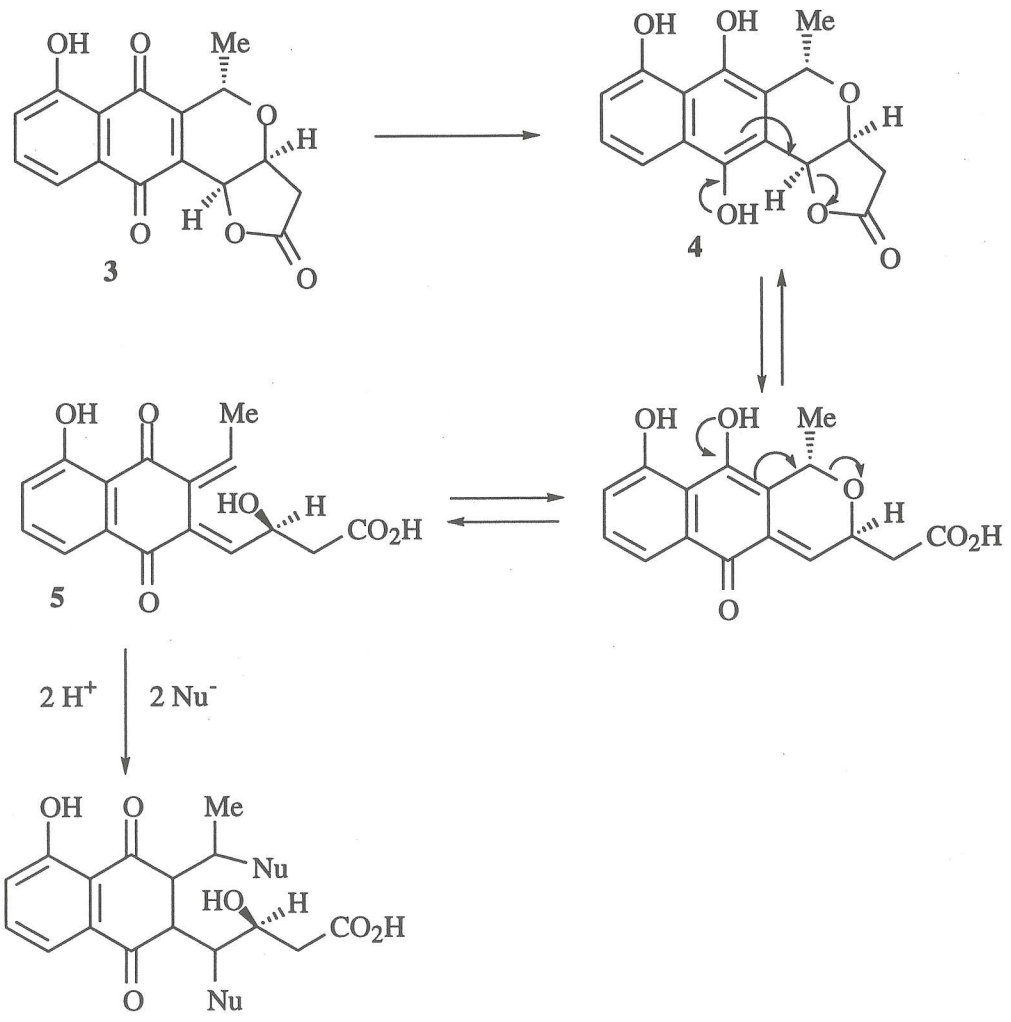
A large number of the pyranonaphthoquinone antibiotics exhibit biological activity, including activity against gram positive bacteria, viruses, pathogenic fungi and yeasts. In addition, many show cytoxicity towards cancer cells. Sartorelli, Lin and co-workers[1] found that simple quinones such as **1** show marked antineoplastic activity and proposed that quinone methides such as **2** are the key alkylating agents *in vivo* (scheme 1). Since reduction is the first step it was postulated that this approach could allow therapeutic attack to be effectively directed against the more anaerobic cells of solid tumours.

Scheme 1



In 1977 Moore[2] extended this idea, pointing to quinones containing the fused pyrano-γ-lactone moiety as compounds ideally suited to act as dialkylating agents by the bioreductive mechanism. Using nanaomycin D **3** as an example, reduction generates the hydroquinone **4**, then ring opening of the γ-lactone is initiated by the free hydroxyl group on the naphthalene ring. A second such opening of the pyran ring affords the bis-quinone methide **5** which is set up for dialkylation with suitable nucleophiles (scheme 2). As a consequence of their activity, as well as their potential as bioreductive alkylating agents, Moore suggested a program directed towards the synthesis of compounds bearing a ring system similar to **3**.

Scheme 2



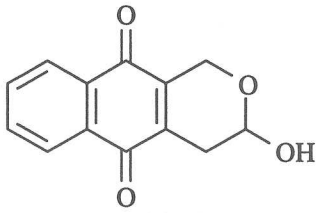
1.1.1 Pyranonaphthoquinones Lacking a γ-Lactone Moiety.

(i) Monomeric examples.

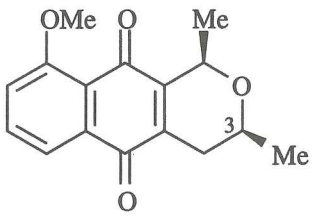
Pyranonaphthoquinones which do not have the additional γ-lactone moiety are typically isolated from fungal or plant sources and some are aphid pigments. A range of such compounds are shown below (figure 2). The most simple of these is psychorubin **6** which was isolated[3] from *Psychotria rubra* and exhibits significant cytotoxicity against KB tumour cells. Eleutherin **7** was isolated,[4] along with its C-3 epimer isoeleutherin, from the rhizomes of *Eleutherine bulbosa* and has been used as a coronary vasodilating agent in the treatment of heart diseases such as angina pectora.[5,6]

Species of the fungal genus *Fusarium* produce naphthazaroid (5,10-dihydroxynaphthoquinone) pigments such as fusarubin **8** and marticin **9**. Such compounds have received special attention because of their antibiotic, insecticidal and phytotoxic properties.[7] In addition fusarubin **8** has been shown to have antitumour properties[8] and to inhibit cell division.[9] Extraction of the bark of various *Ventilago* species has provided a range of ventiloquinones[10] such as ventiloquinone E **10**. Thysanone **11** was isolated[11] from *Thyanophora penicilloides* after screening of fungal extracts. It was found to inhibit the human rhinovirus 3C-protease enzyme and therefore has potential as a chemotherapeutic agent for the common cold.

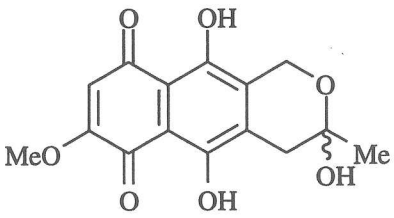
Figure 2



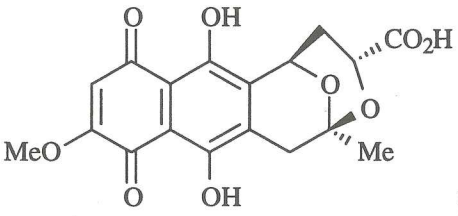
psychorubin **6**



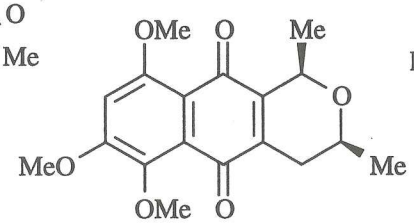
eleutherin **7**



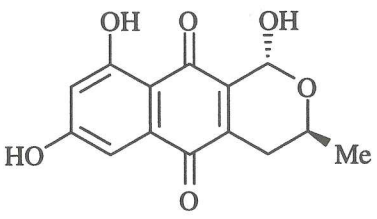
fusarubin **8**



marticin **9**



ventiloquinone E **10**

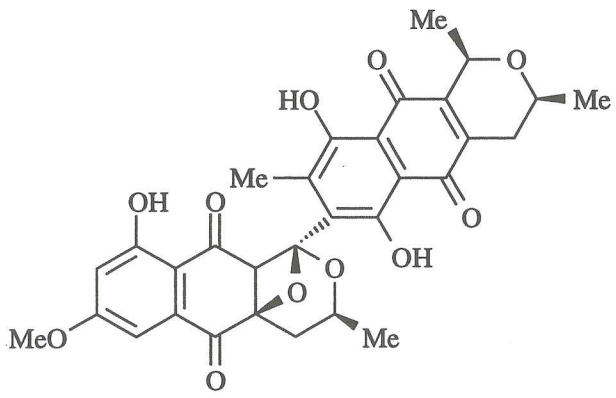


thysanone **11**

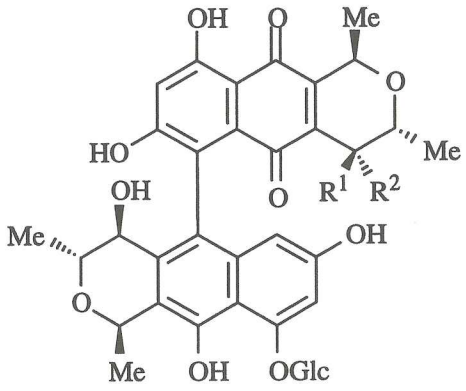
(ii) Dimeric examples.

The dimeric ventiloquinone **12** was isolated[12] (along with monomeric ventiloquinones) from *Ventilago goughii*. A similar class of compounds including protoaphin-*fb* **13**, protoaphin-*sl* **14** and deoxyprotoaphin **15**, have been isolated[13-15] from aphid pigments. Reductive cleavage[16] of each of these gave glucoside B **16** as well the quinone fragments quinone A **17**, quinone A' **18** and deoxyquinone A **19** respectively (figure 3).

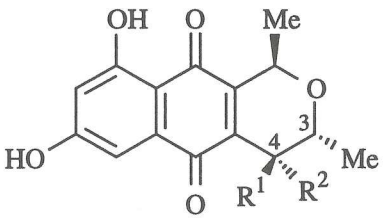
Figure 3



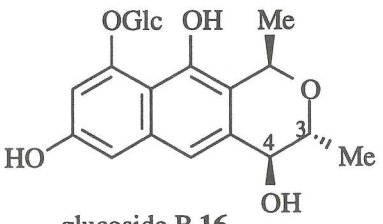
12



protoaphin-*fb* **13** : R^1=OH, R^2=H
protoaphin-*sl* **14** : R^1=H, R^2=OH
deoxyprotoaphin **15** : R^1=H, R^2=H
(Glc = glucose)



quinone A **17** : R^1=OH, R^2=H
quinone A' **18** : R^1=H, R^2=OH
deoxyquinone A **19** : R^1=H, R^2=H

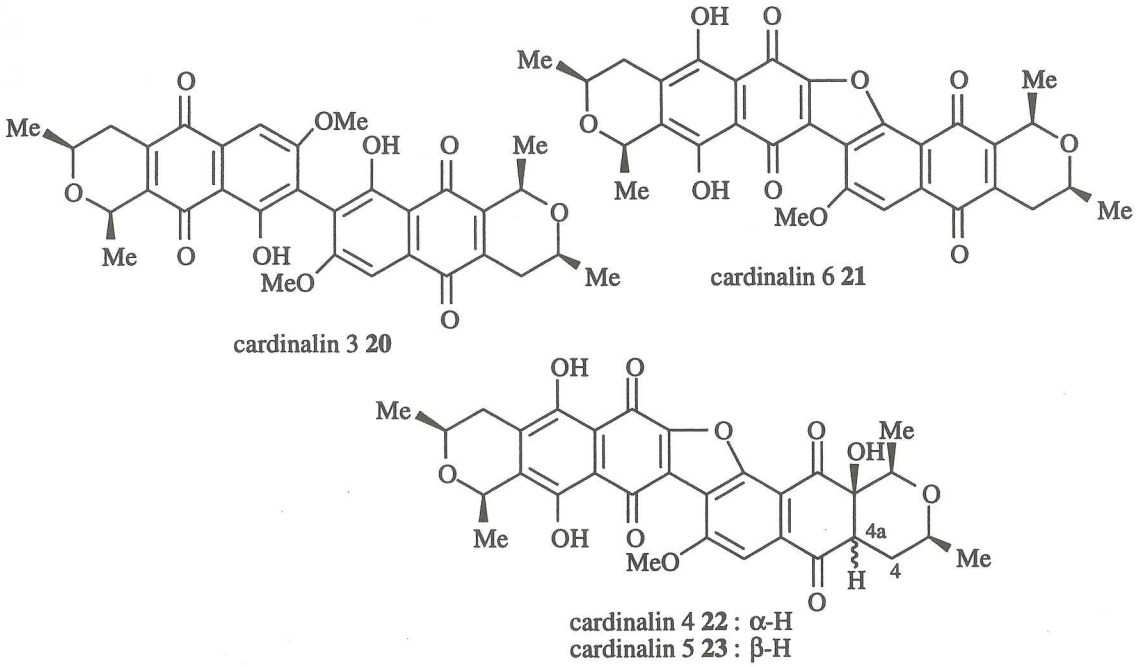


glucoside B **16**
(Glc = glucose)

The cardinalins are a new series of dimeric quinones that were isolated[17] from the New Zealand toadstool *Dermocybe cardinalis*. They are the first class of pyranonaphthoquinones to be discovered in higher order fungi. Two examples are the symmetrical dimer cardinalin 3 **20** containing a bis-naphthoquinone skeleton, and cardinalin 6 **21** which contains a naphthazarin moiety linked *via* a benzofuranoid bridge to naphthoquinone unit (figure 4). Some cardinalins have shown cytotoxic activity against

P-388 murine leukaemia, typically those containing a tetrahydropyranyl ring such as cardinalins 4 **22** and 5 **23**.

Figure 4



1.1.2 Pyranonaphthoquinones With a Fused γ-Lactone (or Carboxylic Acid Side-chain).

(i) Simple monomeric examples.

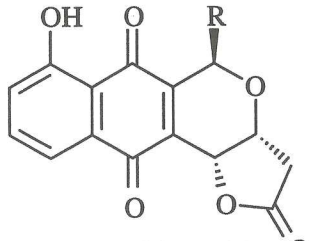
In contrast to the pyranonaphthoquinones mentioned above (figures 2, 3, 4), members of the family with an additional fused γ-lactone ring or carboxylic acid side-chain are predominantly isolated from bacteria and in most cases from the genus *Streptomyces* (figure 5). Kalafungin **24** was isolated[18] from *S. tanashiensis* and shown to be inhibitory against a variety of pathogenic fungi, yeasts and protozoa as well as both gram-positive and gram-negative bacteria.[19] It was also found to be cytotoxic to mouse leukaemia cells[20] and to inhibit platelet aggregation.[21] Dihydrokalafungin **25** was initially formed after genetic manipulation of wild type strains which produced tetrahydrokalafungin **26**[22] (where the C4a-C10a bond is saturated) but was subsequently found occurring naturally in *Nocardia* species.[23] Dihydrokalafungin **25** displayed activity against gram-positive bacteria, dermaphytes and fungi.

The nanaomycins were isolated[24-28] from *S. rosa* var. notoensis, a soil borne bacterium. Nanaomycin D **3** is the enantiomer of kalafungin **24** and likewise nanaomycin A **27** is the enantiomer of dihydrokalafungin **25**. Their antibacterial activity was shown

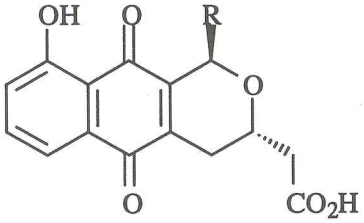
to be linked to the ability to produce superoxide radicals at the cell membrane.[29-31] Nanaomycins B **28** and E **29** are the C4a-C10a dihydroderivatives of nanomycin A **27**, the first arising from *anti*-addition of water, the second from epoxidation. Nanaomycin C **30** is the amide of **27**. Five new nanaomycins were produced by a strain of *S. Rosa* var. *notoensis* isolated[32] from soil in Japan. The β-series are the methyl esters of nanomycins A **27** and E **29**, while the α-series are variants of nanaomycins A **27**, B **28** and E **29** with side-chain alcohols instead of carboxylic acids. They were moderately active against mycoplasmas and fungi, but all displayed weaker activity than nanaomycin A **27**.

The frenolicins were obtained from various *Streptomyces* species and are similar in structure to kalafungin **24** but bear a propyl instead of methyl group at C-1. Frenolicin **31**, bearing a C4a-C10a epoxide moiety, was isolated[33] from *S. fradiae* and found to exhibit only weak antibacterial activity.[34] Hydrogenation and reoxidation of **31** afforded deoxyfrenolicin **33**, which was also isolated[35] along with frenolicin B **32** from *S. roseofulvus*. Both **32** and **33** showed activity against fungi and mycoplasmas,[35] with **33** also being used as an anticoccidial agent[36] in poultry and swine, and strongly inhibiting platelet aggregation.[37]

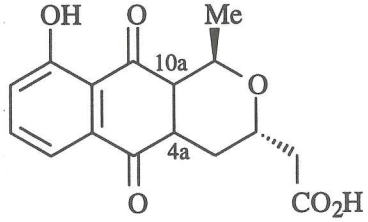
Figure 5



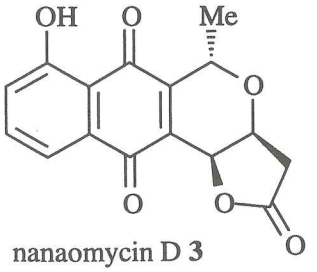
kalafungin **24** : R=Me
frenolicin B **32** : R=*n*-Pr



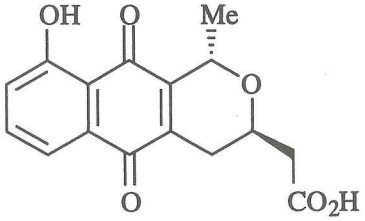
dihydrokalafungin **25** : R=Me
deoxyfrenolicin **33** : R=*n*-Pr



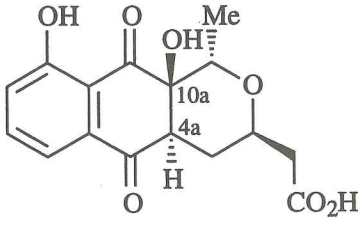
tetrahydrokalafungin **26**



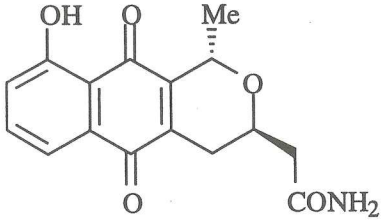
nanaomycin D **3**



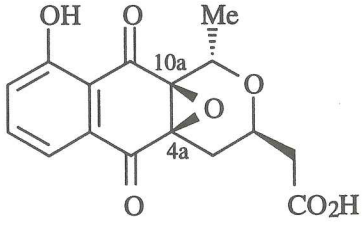
nanaomycin A **27**



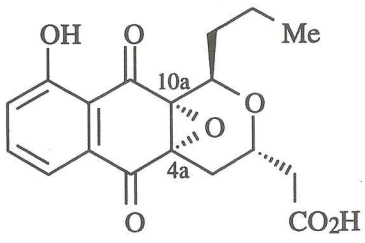
nanaomycin B **28**



nanaomycin C **30**



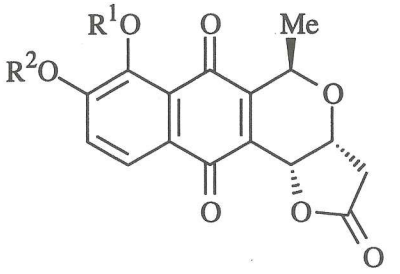
nanomycin E **29**



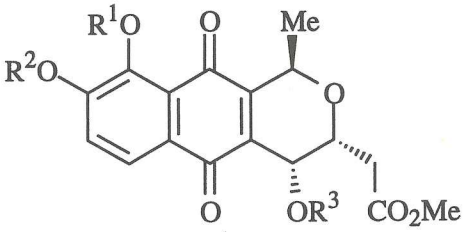
frenolicin **31**

The arizonins **34-39** possess a 7,8-dioxygenated nucleus (figure 6). They were isolated[38] from the fermentation broth of *Actinoplanes arizonaensis* and vary from one another in the degree and position of *O*-methylation, and whether the aliphatic portion of the molecule is present as a γ-lactone or an acyclic methyl ester. The arizonins were found to exhibit antimicrobial activity[39] against pathogenic strains of gram-positive bacteria, with arizonins A1 **34** and B1 **35** showing the most potent activity.

Figure 6



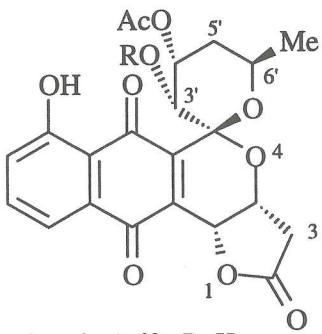
arizonin A1 **34** : R^1=Me, R^2=H
arizonin B1 **35** : R^1=H, R^2=Me
arizonin C1 **36** : R^1=R^2=Me



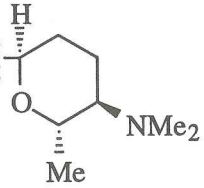
arizonin A2 **37** : R^1=Me, R^2=R^3=H
arizonin B2 **38** : R^1=H, R^2=Me, R^3=H
arizonin C3 **39** : R^1=R^2=R^3=Me

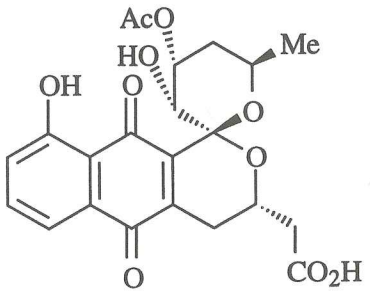
The griseusins A **40** and B **41** were isolated[40] from *Streptomyces griseus* and found to contain the unique 1,7-dioxaspiro[5.5]undecane ring system (figure 7). Griseusin A **40** has a γ-lactone ring while griseusin B **41** has a carboxylic acid side-chain. An interesting variant, 3'-*O*-α-D-forosaminyl-(+)-griseusin A **42**,[41] contains an additional aminopyran ring. The griseusins were found to be moderately active[40,41] against gram-positive bacteria *in vitro*.

Figure 7



griseusin A **40** : R=H
3'-*O*-α-D-forosaminyl-(+)griseusin A **42** : R =



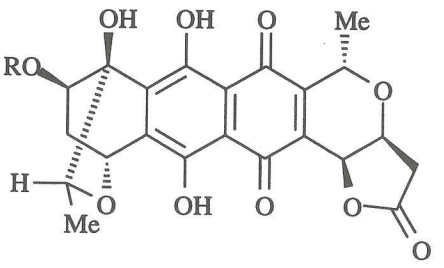


griseusin B **41**

(ii) Carbohydrate modified pyranonaphthoquinones.

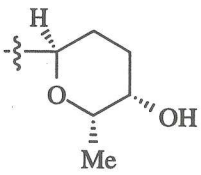
The antibiotic granaticin **43** and related compounds have been isolated[42-46] from several species of *Streptomyces* and are distinguished by the attachment of two oxygen containing heterocycles at each side of a naphthazarin nucleus (figure 8). The unusual 2-oxabicyclo[2.2.2]oct-5-ene ring system is also present in the more simple quinone sarubicin **44**.[47-49] Dihydrogranaticin **45** is simply the open chain form of granaticin **43**. Granaticin B **46** gives granaticin **43** and L-rhodinose[46] on acid hydrolysis and dihydrogranaticin B **47** is the ring opened form of **46**. Granaticinic acid **48** differs from dihydrogranaticin **47** in having a C-10 hydroxyl group and rapidly lactonizing to form granaticin **43**. Granaticin **43** is highly active against gram-positive bacteria and protozoa, exhibits activity against P-388 lymphocytic leukaemia in mice and shows cytotoxicity towards KB cells.[44] It has been reported to inhibit RNA, DNA and protein synthesis[50] and to exert strong activity against Ehrlich carcinoma cells.[51] Most of the granaticin derivatives show strong antibacterial activity[52] as well as inhibiting RNA synthesis.[50] Grananticin B **46** also shows inhibition of transplanted tumours in rodents.[53]

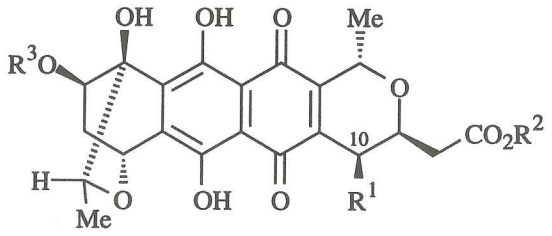
Figure 8



granaticin **43** : R = H

granaticin B **46** : R =

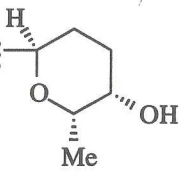


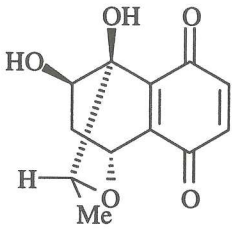


dihydrogranaticin **45** : $R^1 = R^2 = R^3 = H$

dihydrogranaticin B **47** : $R^1 = R^2 = H$, $R^3 =$

granaticinic acid **48** : $R^1 = OH$, $R^2 = R^3 = H$

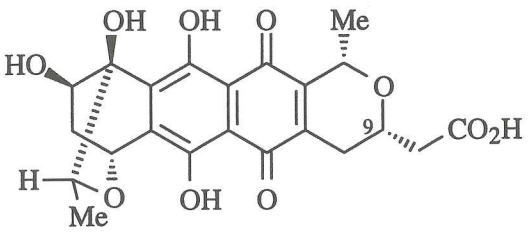




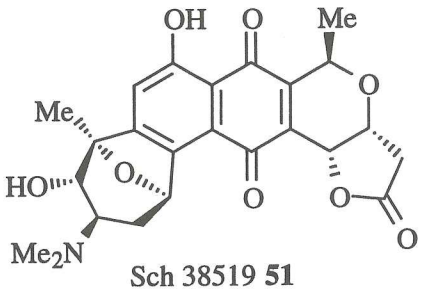
sarubicin A **44**

Dihydrogranatirhodin **49** was produced[54] by a genetically altered *Streptomyces violaceoruber* organism (figure 9). It is the C-9 epimer of dihydrogranaticin **45** having the same configuration at this carbon as actinorhodin **50** (see figure 12). Sch 38519 **51** is a unique isochromanquinone antibiotic isolated[55] from a *Thermonospora* species. Biological testing showed that **51** inhibits the aggregation of human platelets and is also active against both gram-positive and gram-negative bacteria.[55,56]

Figure 9



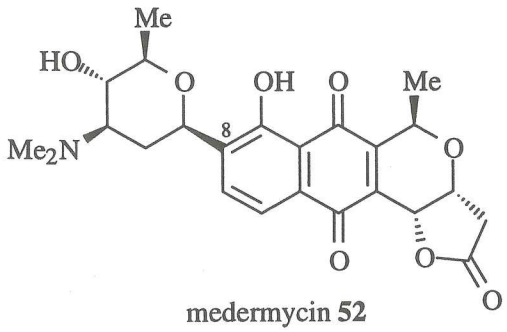
dihydrogranatirhodin B **49**



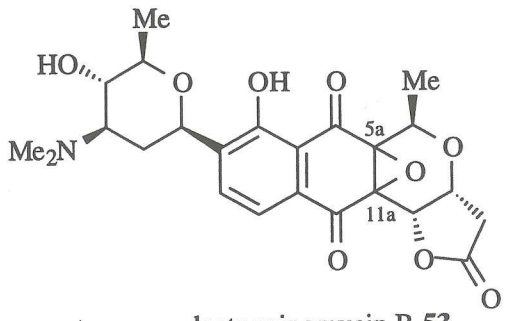
Sch 38519 **51**

Medermycin **52** was isolated[57] as a monohydrochloride salt from a strain of *S. tanashiensis* and the structure shown[58,59] to contain the same skeleton as kalafungin **24** with an amino sugar moiety on the naphthoquinone nucleus at C-8 (figure 10). There was some confusion when Tanaka *et al.* reported the isolation[60] and structure[61] of lactoquinomycin (also as a hydrochloride salt), and suggested that medermycin **52** could be an isomer of lactoquinomycin on the basis of apparent differences in their physicochemical properties and biological activities. This was resolved, however, when the synthesis of **52** by Tatsuta *et al.*[62] allowed comparison of the synthetic and natural samples, showing all three to be identical.

Figure 10



medermycin **52**

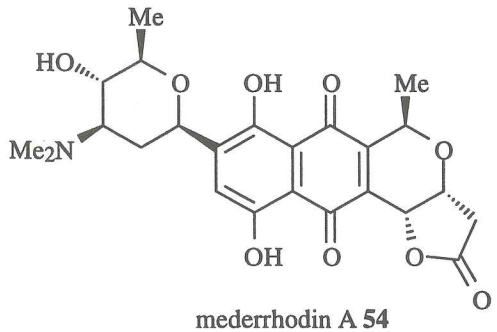


lactoquinomycin B **53**

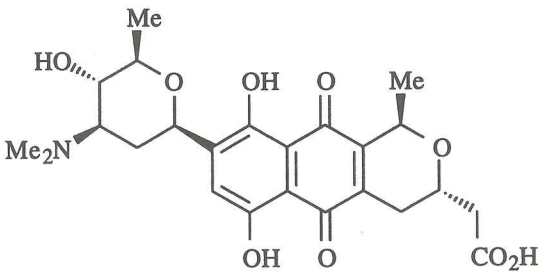
Medermycin **52** is highly active against gram-positive organisms[60] although gram-negative bacteria and fungi showed little or no response.[57] Medermycin **52** was effective against neoplastic cells *in vitro*, antibiotic cell lines of L5178Y lymphoblastoma and Ehrlich carcinoma in mice.[60] It also showed inhibition of human leukaemia K 562 cells as well as platelet aggregation.[37] The inhibition of the biosynthesis of DNA, RNA and protein in cells by medermycin **52** is thought to be due to superoxide radical generation as for the naphthazarins.[63,64] Lactoquinomycin B **53** was isolated[65] from *S. tanashiensis* IM8442T and shown to contain an epoxide moiety between C-5a and C-11a, whose stereochemistry is yet to be determined. **53** inhibited gram-positive bacteria but was not active against fungi. It showed cytotoxicity against a range of human and murine tumour lines, and was more effective against adriamycin and bleomycin resistant cell sublines than against the parental cell line.[65]

The development of molecular cloning has allowed the isolation of biosynthetic genes.[66,67] Transfer of gene sequences coding for actinorhodin **50** biosynthesis into the medermycin **52** producer *S. tanashiensis* resulted in production[54,58] of the hybrid antibiotics mederrhodins A **54** and B **55** (figure 11). Mederrhodin A **54** showed lower activity than medermycin **52** against gram-positive bacteria and platelet aggregation,[37] but exhibited a similar level of activity against gram-negative bacteria. Mederrhodin B **55** was inactive against all bacteria tested.[54]

Figure 11



mederrhodin A **54**

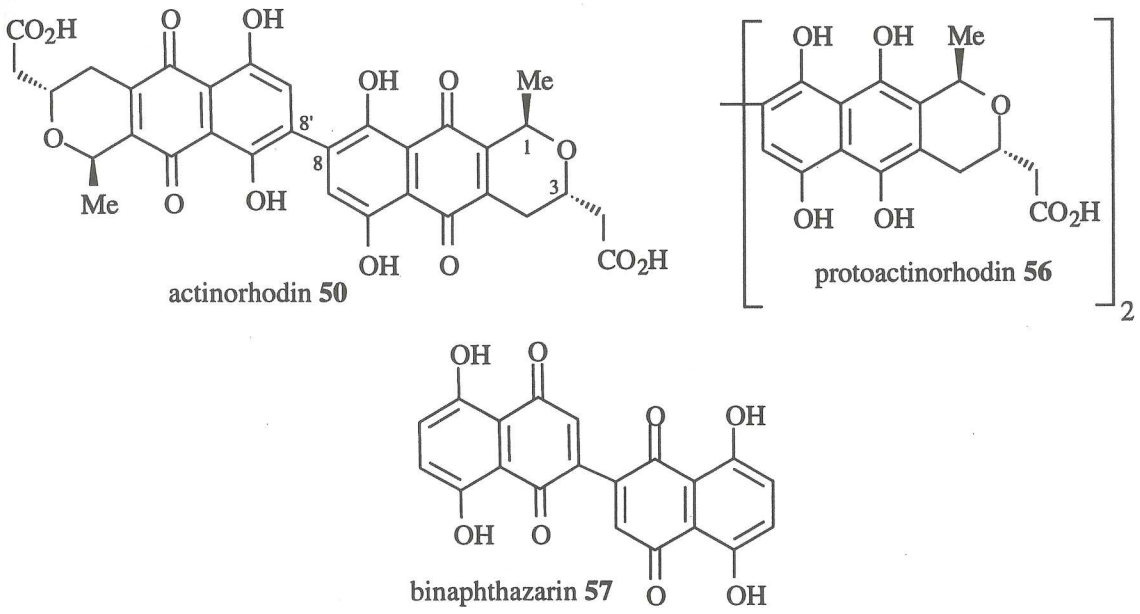


mederrhodin B **55**

(iii) Dimeric pyranonaphthoquinones.

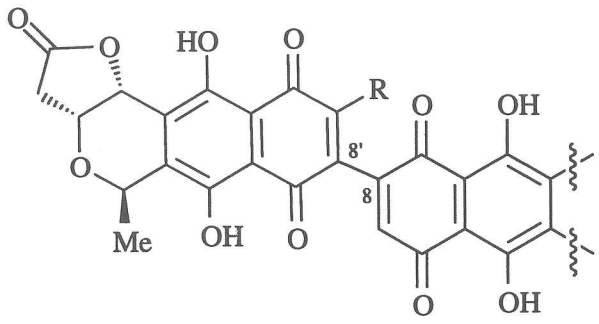
Actinorhodin **50** is a red pigment isolated[68-70] from the actinomyces species *Streptomyces coelicolor*, but is present in the mycelium in hydroquinone form as the almost colourless protoactinorhodin **56** (figure 12). Actinorhodin **50** is dimeric in structure with a C8-C8' linkage. The dominant tautomeric form[71-73] has the quinone and quinol rings reversed as in binaphthazarin **57**[74] with the pyran ring fused to the quinol. The major tautomer of granaticin **43** is also in this form.

Figure 12

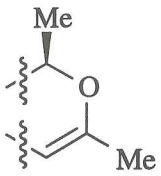


Other actinorhodin congeners isolated[75] from *S. coelicolor* were α-**58**, β-**59**, γ-**60**, δ-**61**, ε-**62** and ε-*iso*-**63** (figure 13). α-Actinorhodin **58** shows one half corresponding to **59** and the other bearing an unsaturated moiety. γ-Actinorhodin **60** is the di-lactone of **50** and is symmetrical, while β-actinorhodin **59** differs only by the presence an *iso*-propyl group at C-7 on one of the subunits. The halves of δ-actinorhodin **61** are connected not only by a direct carbon-carbon bond, but also by a lactone forming another 6-membered ring in the centre of the molecule. The unsymmetrical dimer ε-actinorhodin **62** is comprised of a lactone half and an acid half. The carboxylic acid half of ε-*iso*-actinorhodin **63** is connected at C-7 rather than C-8, and it is thought that the mistakenly dimerised product reflects an early precursor in actinorhodin biosynthesis. Little has been noted about the biological activity of the actinorhodins except that actinorhodin **50** itself exhibits activity[68] against *S. aureus*.

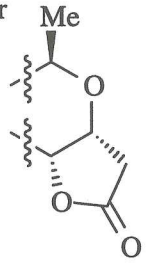
Figure 13



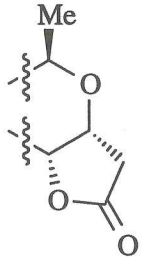
α-actinorhodin **58**
R = H



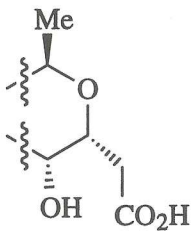
β-actinorhodin **59**
R = *i*-Pr

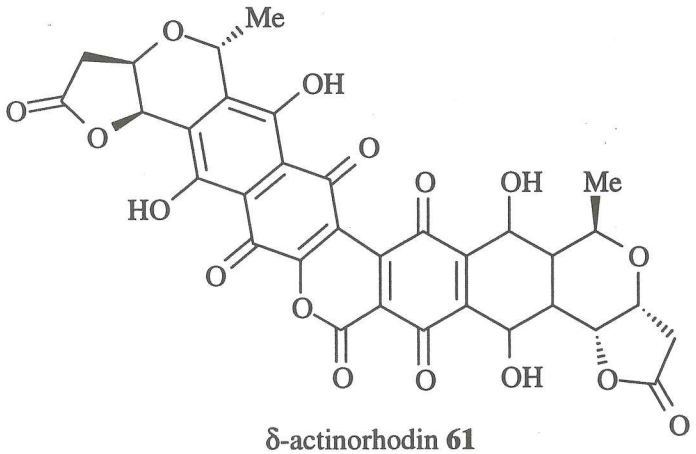


γ-actinorhodin **60**
R = H

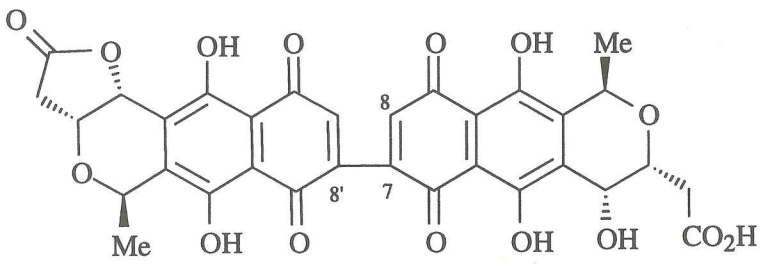


ε-actinorhodin **62**
R = H





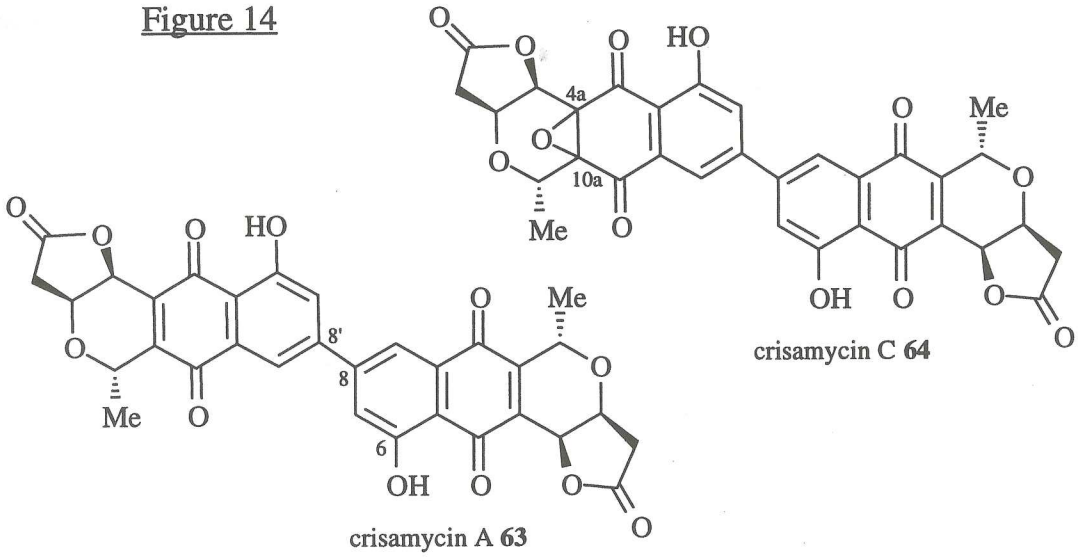
δ-actinorhodin **61**



ε-*iso*-actinorhodin **63**

Crisamycins A **63** and C **64** were isolated[76] from an antibiotic complex produced by the microorganism *Micromonaspora purpureochromogenes* subspecies halotolerans (figure 14). They are C-8/C-8' linked dimers and have an unusual substitution pattern amongst the pyranonaphthoquinones, both bearing a hydroxyl group at C-6. Crisamycin A **63** exhibits *in vitro* activity[77] against gram-positive bacteria, B16 murine melanoma cells and viruses, but shows little or no activity towards gram negative bacteria or fungi. Crisamycin C **64** was shown to be more potent than crisamycin A **63** but shared the same spectrum of activity.[78] The antibiotic complex from which they were isolated has been reported to have both antibacterial and antitumour properties.[79]

Figure 14

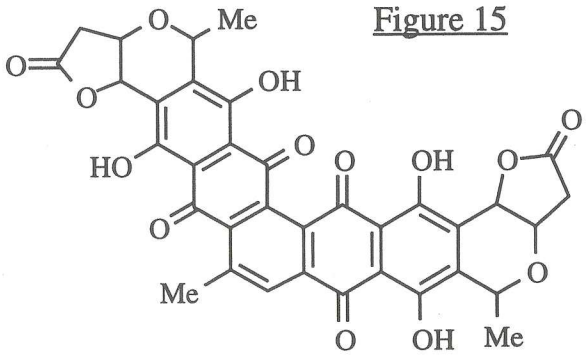


crisamycin C **64**

crisamycin A **63**

Phenocyclinone **65** is a red pigment isolated[80] from *S. coelicolor*. It consists of a naphthazarin pyran-γ-lactone tetracyclic ring system fused on either side of a methyl benzene moiety, although the absolute stereochemistry is undefined (figure 15).

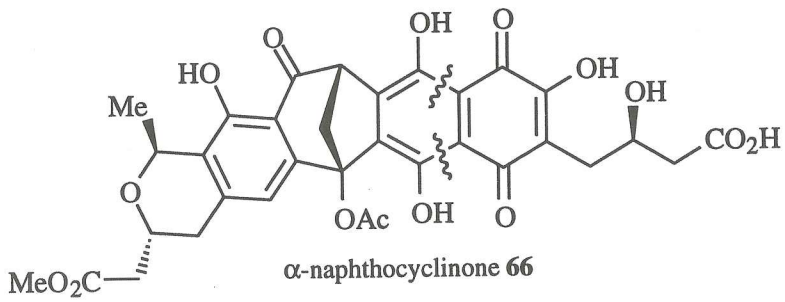
Figure 15



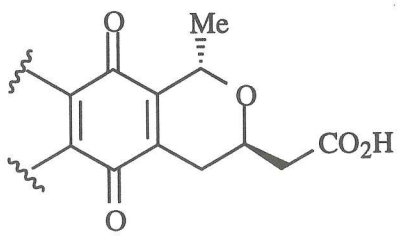
phenocyclinone **65**

The naphthocyclinones are a series of closely related pigments which were isolated[81,82] from cultures of *S. Arenae* (figure 16). They are unsymmetrical dimers in which one of the benzoisochromane units has been modified into an aryl ketone moiety. The naphthazarin chromophore is connected to this aryl ketone *via* two carbon-carbon bonds to give a bicyclo[3.2.1]octadienone system. A few representative members of this family are α-**66**, β-**67** and γ-naphthocyclinone **68**, although there are many other variations[83] on this theme. β-**67** and γ-naphthocyclinone **68** were found to be inhibitory against gram-positive bacteria,[82] whereas α-naphthocyclinone **66** was inactive, suggesting that the pyran ring plays an important role. Derivatives of these and other naphthocyclinones were also tested,[83] with several analogues displaying marked activity against bacteria.

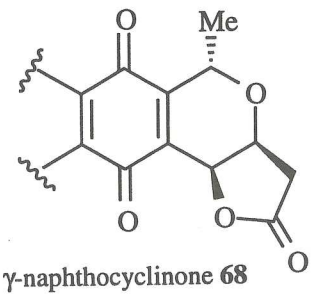
Figure 16



α-naphthocyclinone **66**



β-naphthocyclinone **67**

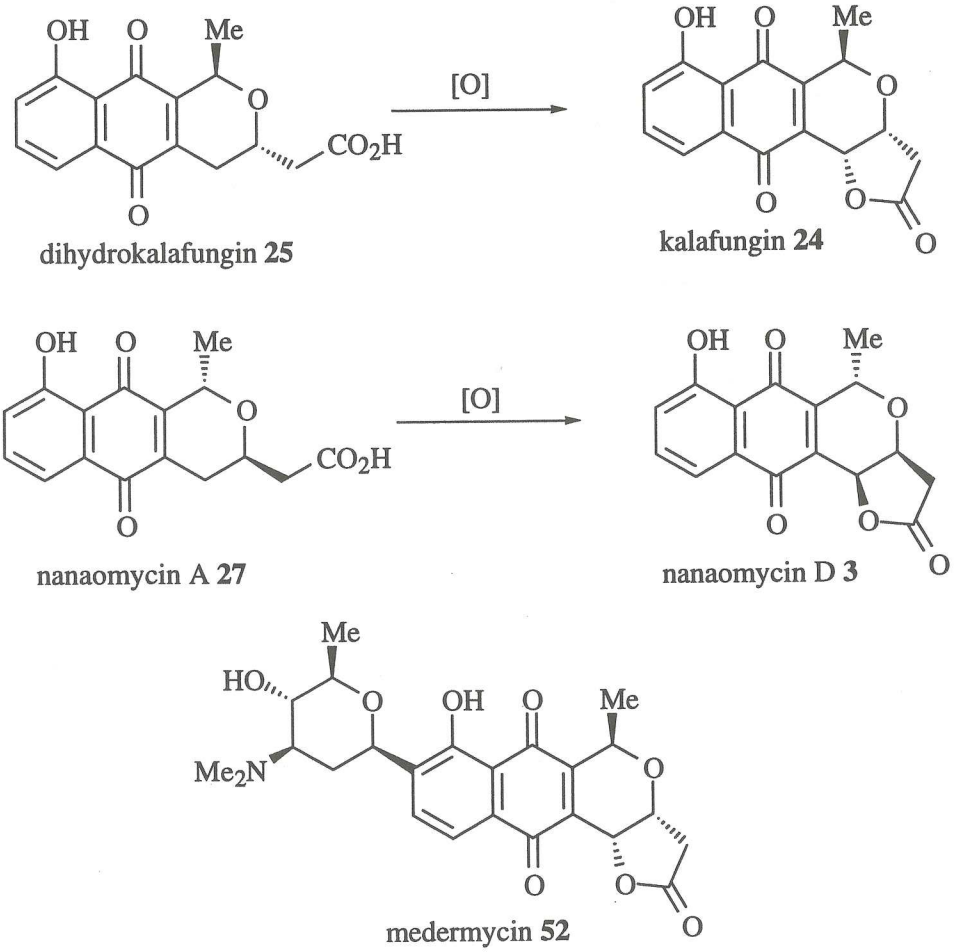


γ-naphthocyclinone **68**

1.2 Related Syntheses of Pyranonaphthoquinones

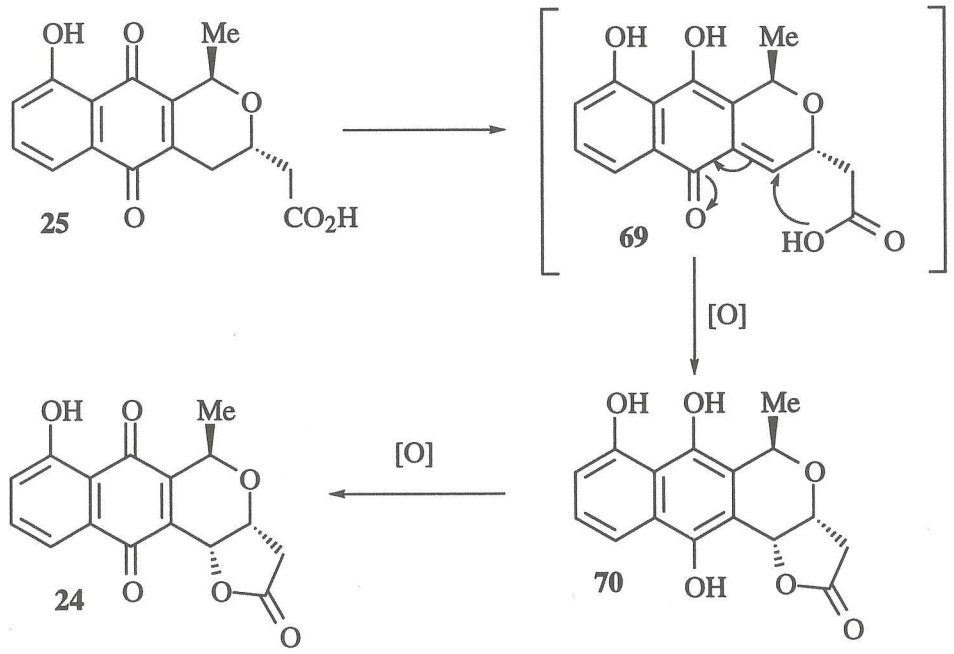
There have been a range of different approaches to synthesizing pyranonaphthoquinone antibiotics especially with regard to construction of the pyran and γ-lactone rings. This section will examine previous strategies for the synthesis of kalafungin **24**, the pyranonaphthoquinone moiety of medermycin **52**, and the only total synthesis of medermycin **52**. Since nanaomycin A **27** can be readily oxidized to nanaomycin D **3** by stirring in methanol,[27] any racemic synthesis of nanaomycin A **27** and its enantiomer dihydrokalafungin **25** [denoted (±)-**27**] constitutes a racemic synthesis of kalafungin **24** and nanaomycin D **3** [denoted (±)-**24**]. Thus the synthesis of nanaomycins A **27** and D **3** falls within the scope of this discussion (figure 17).

Figure 17



A mechanism for the oxidative cyclization of **25** to **24** has been outlined[84] involving a quinone methide intermediate **69**. Intramolecular conjugate addition of the carboxylic acid onto the enone gives the quinol lactone **70** which can be readily oxidized to give the quinone **24** (scheme 3).

Scheme 3

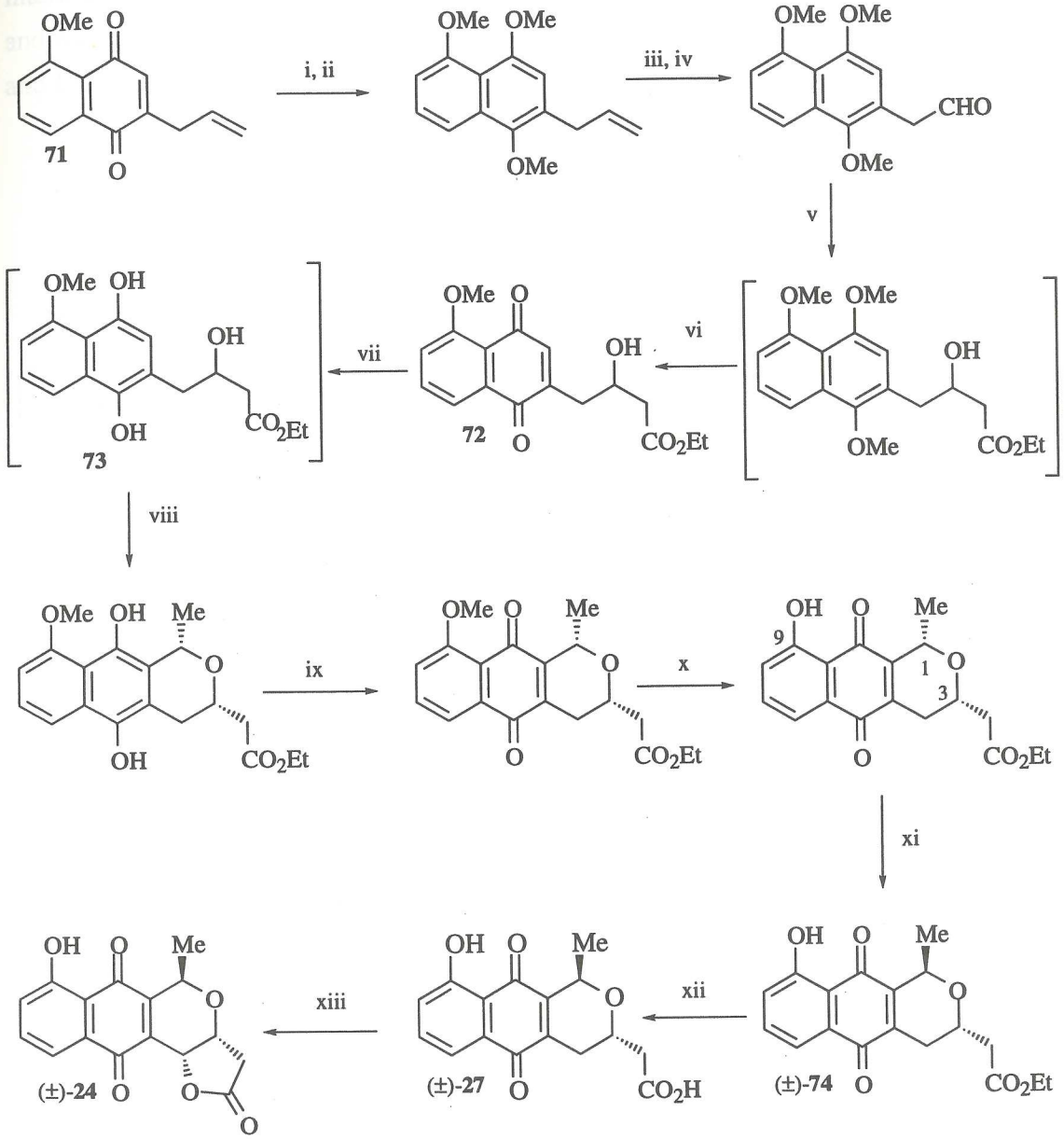


1.2.1 Syntheses Involving the Electrophilic Substitution of 2-Hydroxyallyl-1,4-naphthoquinones.

(i) Li and Ellison.

In 1978 Li and Ellison[84] reported the first racemic synthesis of kalafungin **24** as well as nanaomycins A **27** and D **3**. Their approach originates from Schmid's method[85] for the synthesis of eleutherin **7** (for structure see figure 2). An early intermediate in the synthesis was allylnaphthoquinone **71** from which the key intermediate **72** was produced in 6 steps (scheme 4). Cyclization to the dihydropyran was effected by reduction of the quinone **72** with zinc powder and hydrochloric acid, and treatment of the hydroquinone **73** with acetaldehyde in the presence of hydrochloric acid. The cyclization gave compounds with the incorrect *cis* stereochemistry, but epimerization at C-1 was effected with concentrated sulfuric acid to give a 2:1 ratio of the *trans* and *cis* isomers, from which the pure *trans* isomer (±)-**74** was isolated by fractional recrystallization. Acidic hydrolysis of the ethyl ester gave racemic nanaomycin A (±)-**27** which upon aerial oxidation in methanol afforded the racemic kalafungin (±)-**24**.

Scheme 4

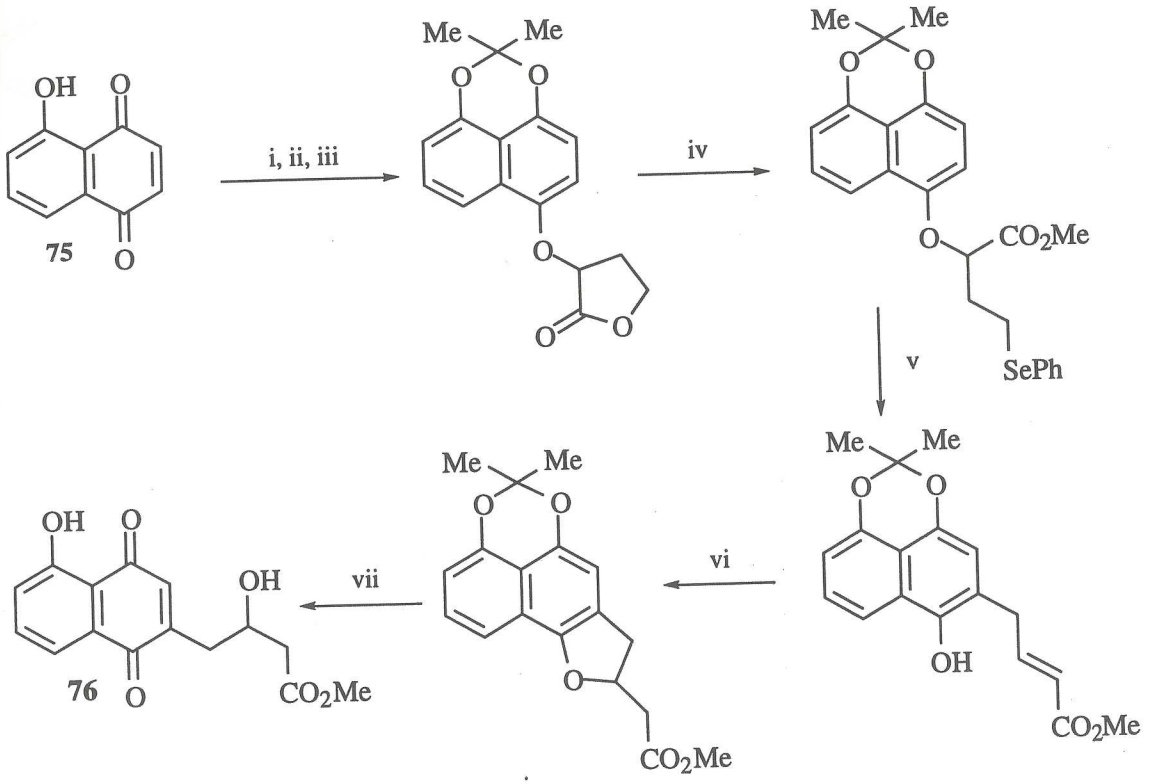


Reagents and conditions: (i) $Na_2S_2O_4$, Et_2O (ii) aq. KOH, Me_2SO_4, 2 h (iii) OsO_4, $KClO_4$, THF, 6 h (iv) $NaIO_4$, ^tBuOH, H_2O, 2 h (v) TBDMSOC(OEt)=CH_2, $TiCl_4$, CH_2Cl_2, -78 °C, 8 h (vi) $Ce(NH_3)_2(NO_3)_6$, MeCN, H_2O, 5 min. (vii) Zn-HCl, THF, 10 min. (viii) CH_3CHO, HCl, 60 °C, 4 h (ix) Ag_2O, Et_2O, 5 min. (x) $AlCl_3$, CH_2Cl_2, 1 h (xi) conc. H_2SO_4, 30 min. (xii) conc. HCl, 8 h (xiii) MeOH, air.

(ii) Yoshii et al.

Another group to employ this type of approach were Yoshii *et al.*[86] The key intermediate **76** was prepared from juglone **75** using a Claisen rearrangement (scheme 5) and was then transformed into racemic nanaomycin A (±)-**27** using the methodology of Li and Ellison[84] (see scheme 4).

Scheme 5

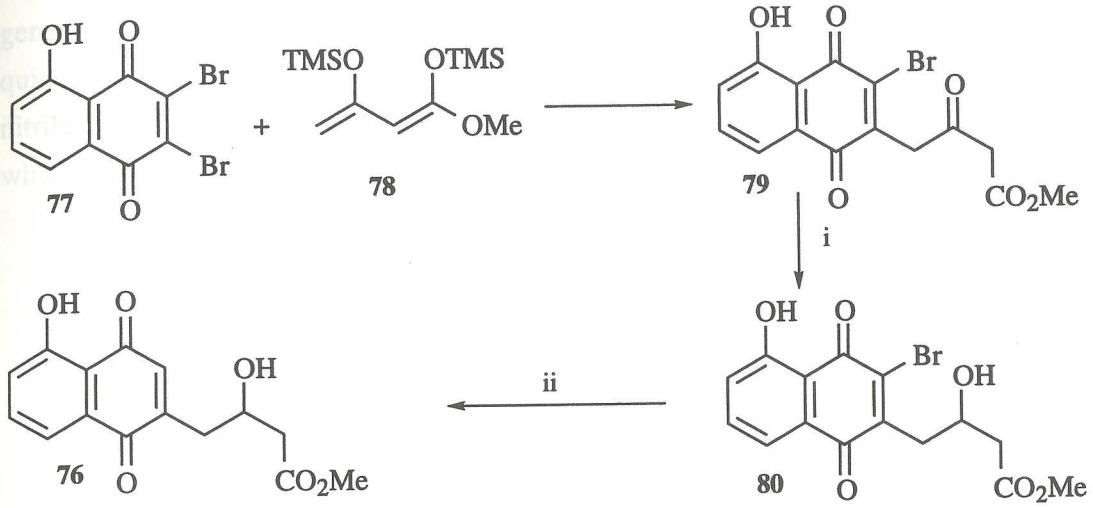


Reagents and conditions: (i) $Na_2S_2O_4$, EtOAc-H_2O (ii) $Me_2C(OMe)_2$, Me_2CO, $BF_3.OEt_2$ (iii) α-bromo-γ-butyrolactone, DMF, CsF, 120 °C or KF-celite, MeCN, 60 °C (iv) PhSeNa, DMF, then CH_2N_2 (v) H_2O_2, THF, r.t., then 90 °C (vi) MeOH, Na_2CO_3 (vii) AgO, HNO_3.

(iii) Cameron et al.

Cameron *et al.*[87] have reported another approach to intermediate **76** involving the uncatalyzed conjugate addition of activated butadiene **78** to quinone **77**, a reaction which competes with conventional Diels-Alder cycloaddition (scheme 6). The ketoester **79** was then reduced with sodium borohydride and the resulting hydroxyester **80** dehalogenated with stannous chloride and methanolic hydrogen chloride to give **76**.

Scheme 6

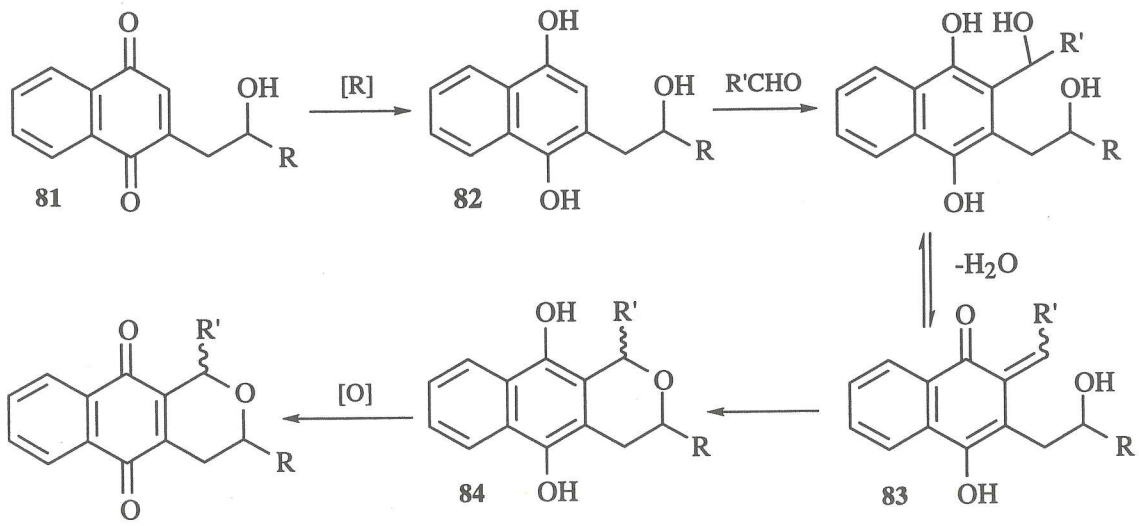


Reagents and conditions: (i) $NaBH_4$, THF, -78 °C (ii) $SnCl_2$, HCl-MeOH.

(iv) Liebeskind and South.

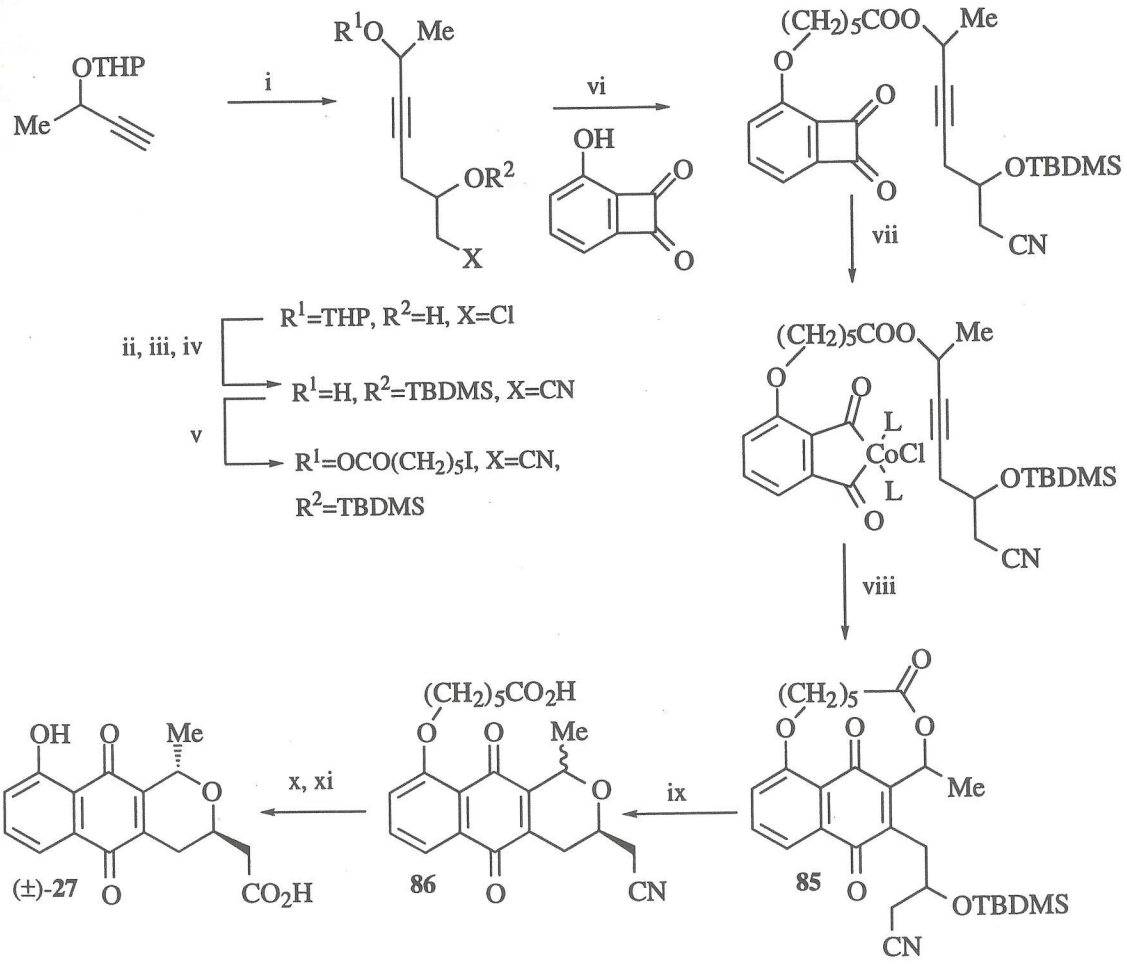
Liebeskind and South[88] suggested a mechanism for the dihydropyran ring cyclization (scheme 7) whereby reduction of quinone **81** to the hydroquinone **82** followed by condensation with an aldehyde and dehydration would give *ortho*-quinone methide **83**. Intramolecular 6-*endo*-trig ring closure would then afford the dihydropyran **84**.

Scheme 7



This rationale was then used to develop a synthesis of racemic nanaomycin A (±)-**27** (scheme 8).[88] The intramolecular addition of an alkyne to a phthaloyl-cobalt complex generated the naphthoquinone **85**. Reduction then gave the dihydropyran **86** *via* an *ortho*-quinone methide intermediate. Removal of the hexanoyl group and hydrolysis of the nitrile completed the synthesis, affording a 3:1 mixture of the *trans* and *cis* epimers, from which racemic nanaomycin A (±)-**27** could be crystallized.

Scheme 8



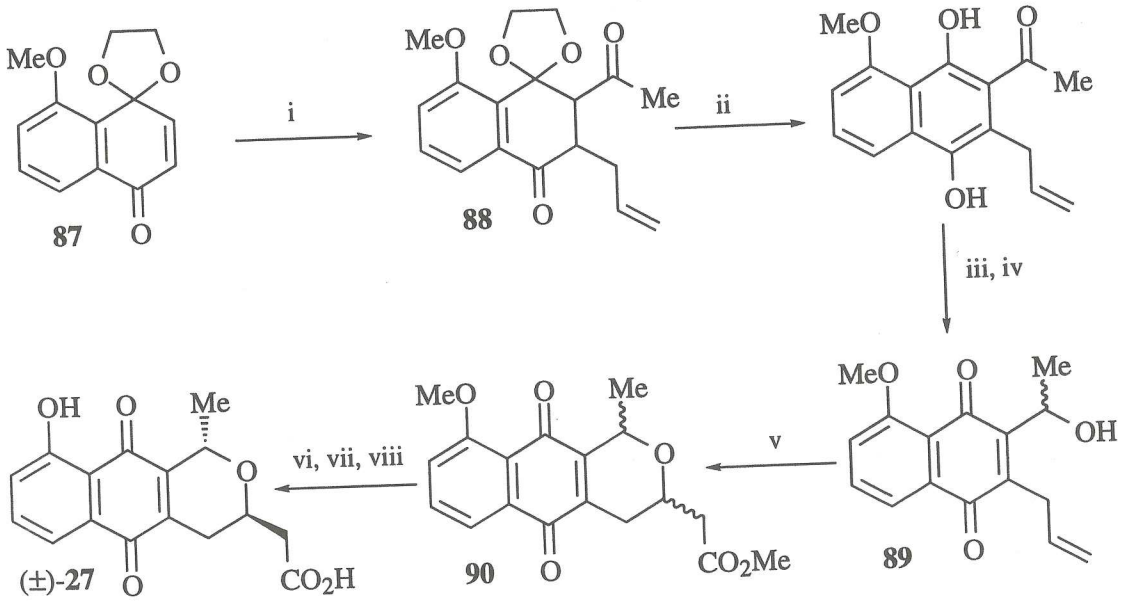
Reagents and conditions: (i) *epi*-chlorohydrin, $BF_3.OEt_2$, THF, -78 °C (ii) NaCN (iii) TBDMSCl (iv) PPTS (v) 6-iodohexanoylchloride (vi) DBU, MeCN (vii) $ClCo(PPh_3)_3$ (viii) $AgBF_4$, MeCN (ix) Zn, HCl-Et_2O, Ag_2O (x) $AlCl_3$ (xi) H_2SO_4.

1.2.2 Syntheses Involving the Intramolecular Addition of an Alcohol to an Alkene.

(i) Semmelhack et al.

A different type of approach to those mentioned previously involves the intramolecular addition of an alcohol to a double bond to form the dihydropyran ring. Semmelhack *et al.*[89,90] used this method for the synthesis of racemic nanaomycin A (±)-**27** (scheme 9). Conjugate addition of the acylate-nickel anion to the quinone ketal **87** and trapping of the resulting enolate with an allyl halide afforded the key intermediate **88**. Hydrolysis of the ketal, reduction of the ketone and oxidation gave the naphthoquinone **89**. An intramolecular alkoxycarbonylation reaction then gave the dihydropyran **90** as a mixture of *cis* and *trans* isomers. This was converted to racemic nanaomycin A (±)-**27** by demethylation with aluminium trichloride, equilibration to the *trans* isomer in sulfuric acid and hydrolysis of the methyl ester with dilute aqueous base.

Scheme 9

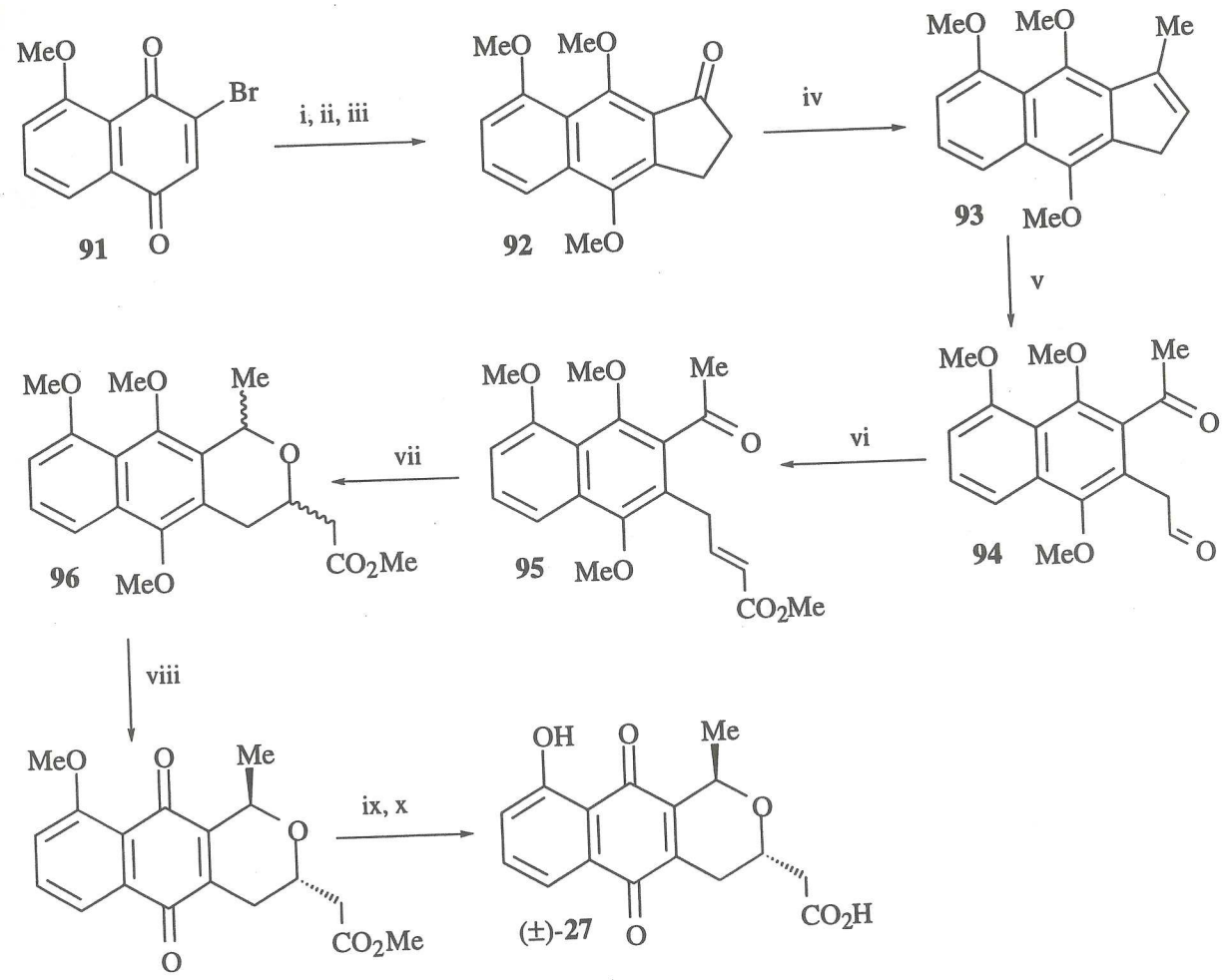


Reagents and conditions: (i) MeLi, $Ni(CO)_4$, Et_2O, -50 °C then HMPA, $CH_2{=}CHCH_2I$ (ii) 6m HCl, dioxane (iii) $NaBH_4$, THF (iv) DDQ, MeOH, 0 °C (v) $PdCl_2(MeCN)_2$, $CuCl_2$, CO, MeOH, 25 °C (vi) $AlCl_3$, CH_2Cl_2, 0 °C (vii) conc. H_2SO_4 (viii) KOH, EtOH.

(ii) Yoshii et al.

Yoshii *et al.*[91] also explored this type of approach (scheme 10). The benzindanone **92** was formed in 3 steps from the bromonaphthoquinone **91**. Reaction of **92** with a Grignard reagent and reduction of the carbinol gave the benzindene **93** which was oxidized with osmium tetroxide and sodium *meta*-periodate. The resultant keto-aldehyde **94** was immediately treated with a Wittig-Horner reagent to give the conjugated ester **95**. Reductive cyclization then gave a mixture of the *cis* and *trans* naphthopyrans **96** (2:3) which were separated by chromatography. The *trans* isomer of **96** was further elaborated by oxidation with CAN, followed by cleavage of the methyl ether with aluminium trichloride and hydrolysis of the methyl ester using acid to give racemic nanaomycin A (±)-**27**.

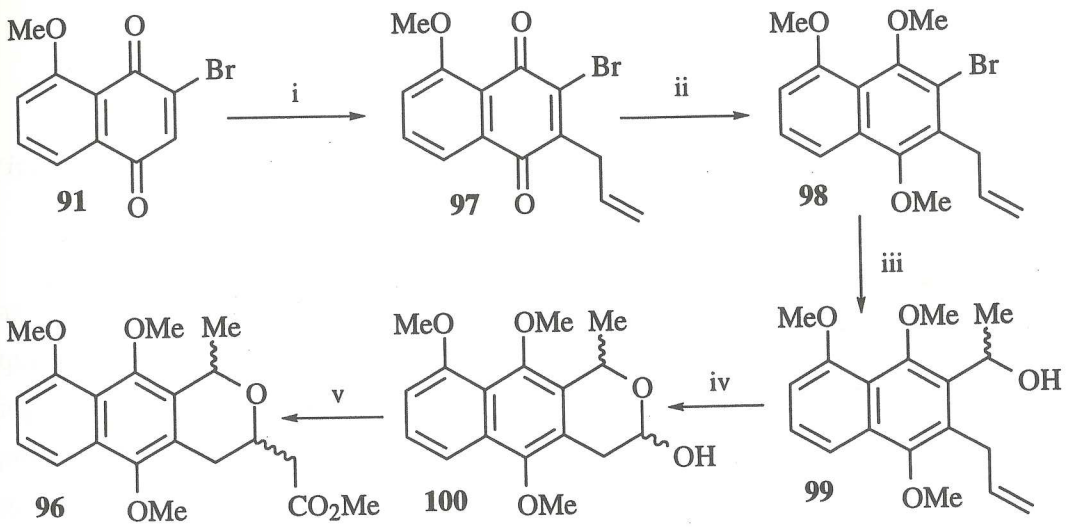
Scheme 10



Reagents and conditions: (i) $MeO_2CCH_2CO_2H$, $K_2S_2O_8$, Ag_2O (ii) $Na_2S_2O_4$, Me_2SO_4, KOH (iii) ^nBuLi, THF, -78 °C (iv) MeMgI, Et_2O, HCl (v) OsO_4, $NaIO_4$ (vi) $Ph_3P(O)CH_2CO_2Me$, NaH (vii) $NaBH_4$ (viii) CAN (ix) $AlCl_3$ (x) conc. HCl.

During the course of the above work a more direct route to nanaomycin A **27** was reported (scheme 11).[91] This involved formaton of the allyl derivative **97**, reductive methylation, and condensation of acetaldehyde with the anion of **98** to give the naphthyl carbinol **99**. Cleavage of the olefinic bond with osmium tetroxide gave the lactol **100** as a mixture of diastereomers. Horner-Wittig methodology then afforded the *cis* and *trans* naphthopyrans **96** as before.

Scheme 11

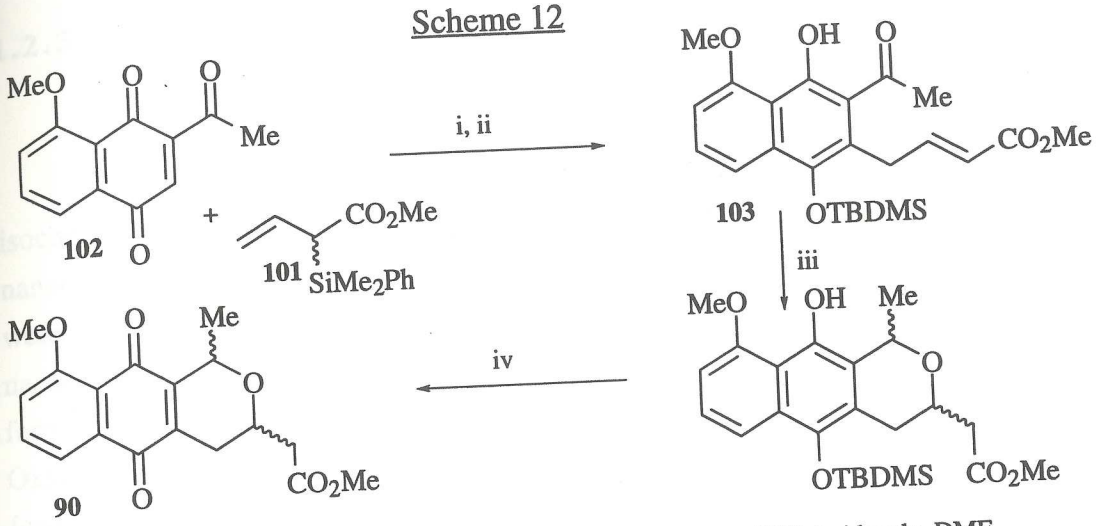


Reagents and conditions: (i) CH_2=$CHCO_2H$, $K_2S_2O_8$, Ag_2O (ii) $Na_2S_2O_4$, Me_2SO_4, KOH (iii) ^{n}BuLi, THF, -78 °C, MeCHO (iv) OsO_4, $NaIO_4$ (v) Ph_3P=$CHCO_2Me$, NaH.

(iii) Uno et al.

Uno[92] produced a very elegant example of this approach (scheme 12) based on his work towards the synthesis of eleutherin **7**. Lewis acid mediated addition of the silylated butenoate **101** to the quinone **102** and protection of the resultant alcohol to avoid cyclization gave the adduct **103**. Reductive cyclization and oxidative demethylation then gave dihydropyran **90** which was elaborated (see scheme 9) to give racemic nanaomycin A (±)-**27**.

Scheme 12

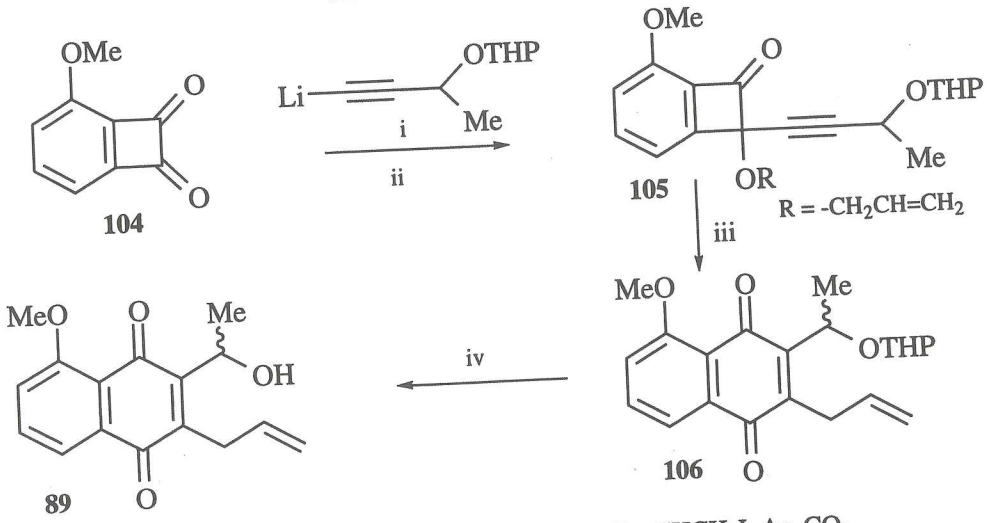


Reagents and conditions: (i) $SnCl_4$, CH_2Cl_2, -78 °C (ii) TBDMSCl, imidazole, DMF (iii) $NaBH_4$, MeOH (iv) CAN, MeCN.

(iv) Moore and Decker.

Moore and Decker[93] produced a synthesis of nanaomycins A **27** and D **3** as well as kalafungin **24** based on the thermal ring expansion of 4-alkynylcyclobutenones to quinones (scheme 13). The dione **104** developed by Liebeskind (see scheme 8) was regioselectively alkynylated forming the alkynyl ether **105**. Thermolysis in refluxing *para*-xylene gave the naphthoquinone **106** which upon cleavage of the protecting group gave the key allyl alcohol **89**. Conversion of **89** to racemic nanomycin A (±)-**27** was then carried out according to the procedure of Semmelhack *et al.* [89,90] (see scheme 9).

Scheme 13

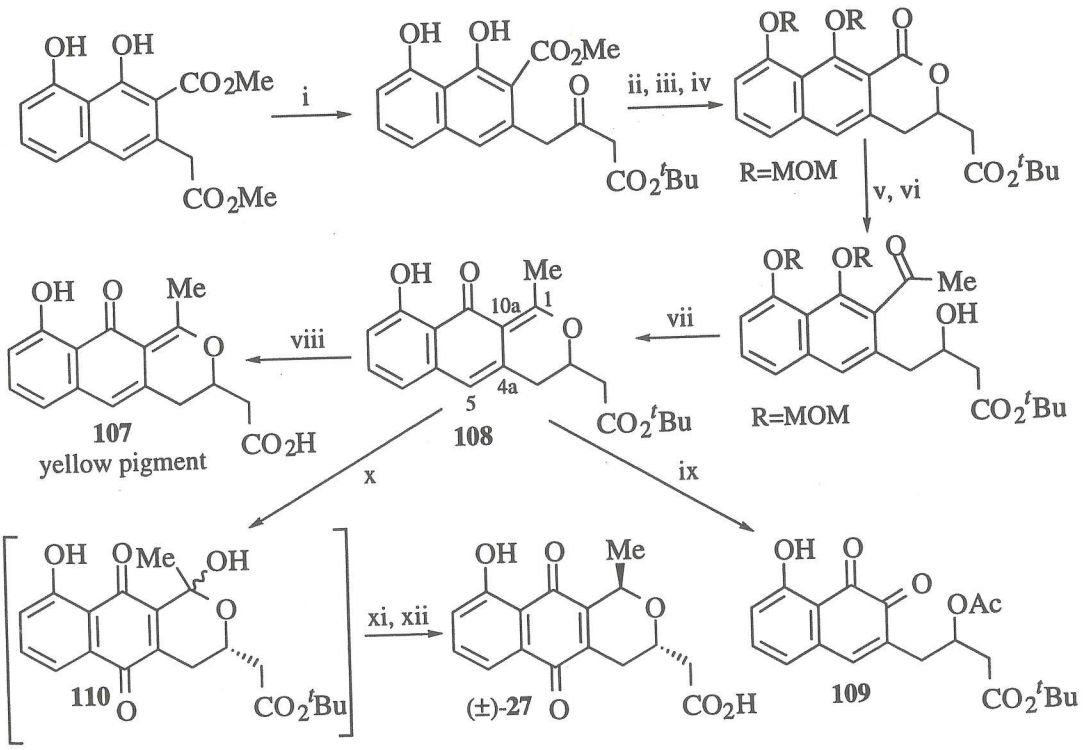


Reagents and conditions: (i) THF, -78 °C (ii) CH_2=$CHCH_2I$, Ag_2CO_3 (iii) *p*-xylene, 138 °C (iv) AcOH, THF, H_2O.

1.2.3 Oxidation of the "Yellow Pigment" Precursor.

Yellow pigment **107** was isolated as an intermediate in the biosynthesis of isochromanequinone antibiotics such as kalafungin **24**, actinorhodin **50**, and possibly the nanaomycins.[94] Yamaguchi *et al.*[95] developed a synthesis of yellow pigment **107** and were able to biomimetically convert its *tert*-butyl protected precursor **108** to racemic nanaomycin A (±)-**27** (scheme 14). Treatment of **108** with *m*-CPBA resulted in formation of the unstable *ortho*-quinone **109** (through cleavage of the 1-10a bond). Oxidation with 1,2-dioxirane, however, gave the *para*-quinone **110** (presumably *via* formation of an epoxide at the 4a-5 position). Lactol **110** was reduced to the *cis* pyran by Kraus's methodology[96] and was then equilibrated to the *trans* isomer and the *tert*-butyl ester cleaved using concentrated sulfuric acid to give to racemic nanaomycin A (±)-**27**.

Scheme 14

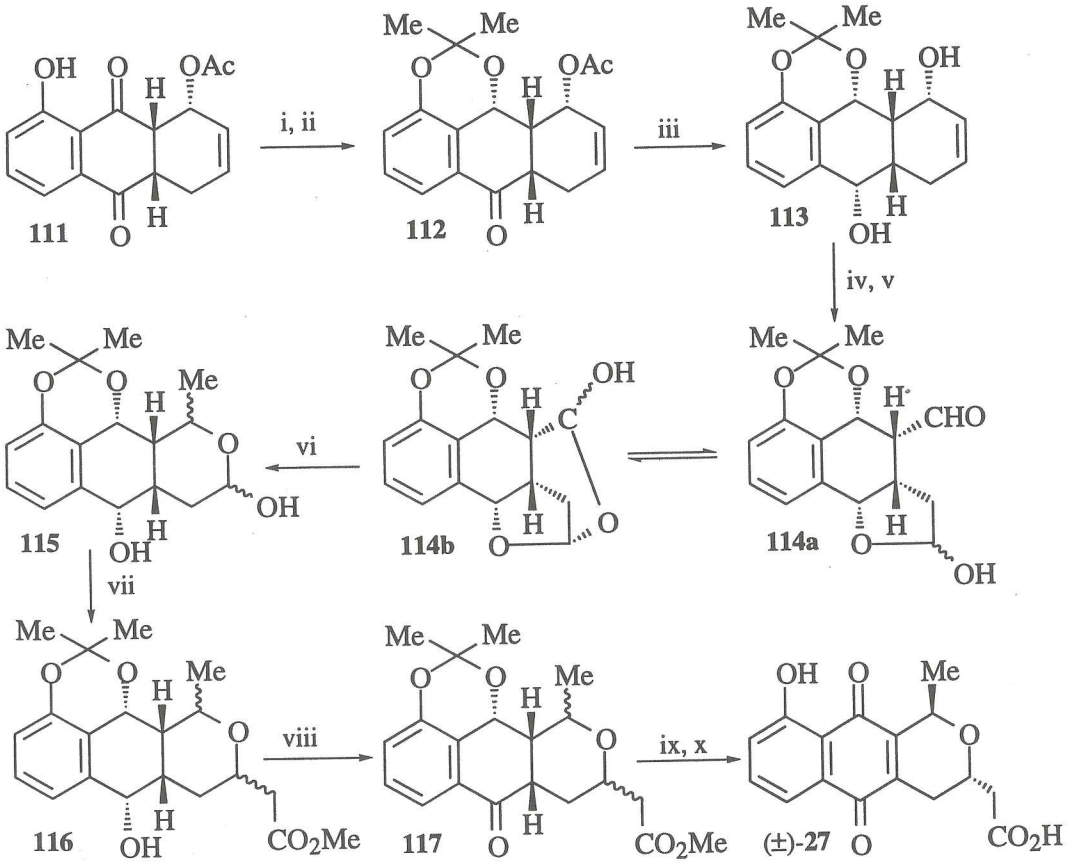


Reagents and conditions: (i) LDA, AcO^{t}Bu, THF, -78 °C (ii) $NaBH_4$, EtOH, -45 °C (iii) Et_3N, CH_2Cl_2, 0 °C (iv) MOMCl, ^{i}PrNEt$_2$, CH_2Cl_2 (v) LDA, $AcOCMe_2CH{=}CH_2$, THF, -78 °C (vi) $Pd(OAc)_2$, Ph_3P, Et_3N, HCO_2H, THF, reflux, 30 min. (vii) HCl, MeOH, 0 °C (viii) CF_3CO_2H, CH_2Cl_2, 5 h (ix) MCPBA, CH_2Cl_2, -25 °C (x) 3,3-dimethyldioxirane, C_6H_6, 18-crown-6, 2 h (xi) Et_3SiH, CF_3CO_2H, CH_2Cl_2, -78 °C (xii) conc. H_2SO_4, C_6H_6, 30 min.

1.2.4 Oxidation of the Diels-Alder Adduct Formed from Juglone 75 and 1-Acetoxybutadiene.

Ichihara *et al.*[97] used methodology developed for the synthesis of racemic frenolicin A (±)-**31** to synthesize racemic nanomycin A (±)-**27** (scheme 15). The versatile intermediate **111** was formed by the Diels-Alder reaction of juglone **75** and 1-acetoxybutadiene. Regioselective reduction of **111** yielded a ketoalcohol which was protected as an acetonide **112**. Further reduction gave the diol **113** which upon oxidative cleavage and treatment with base afforded an equilibrium mixture of **114a** and **114b**. The appropriate choice of reagent for the reverse Grignard addition then determined whether the frenolicin or nanaomycin ring system would be formed. Treatment of the lactol **115** with Wittig-Horner reagent gave the cyclized methyl ester **116** which was oxidized to the ketone **117**. Finally DDQ oxidation (in the presence of *para*-toluenesulfonic acid) afforded the quinone and hydrolysis of the methyl ester with base gave racemic nanomycin A (±)-**27**.

Scheme 15



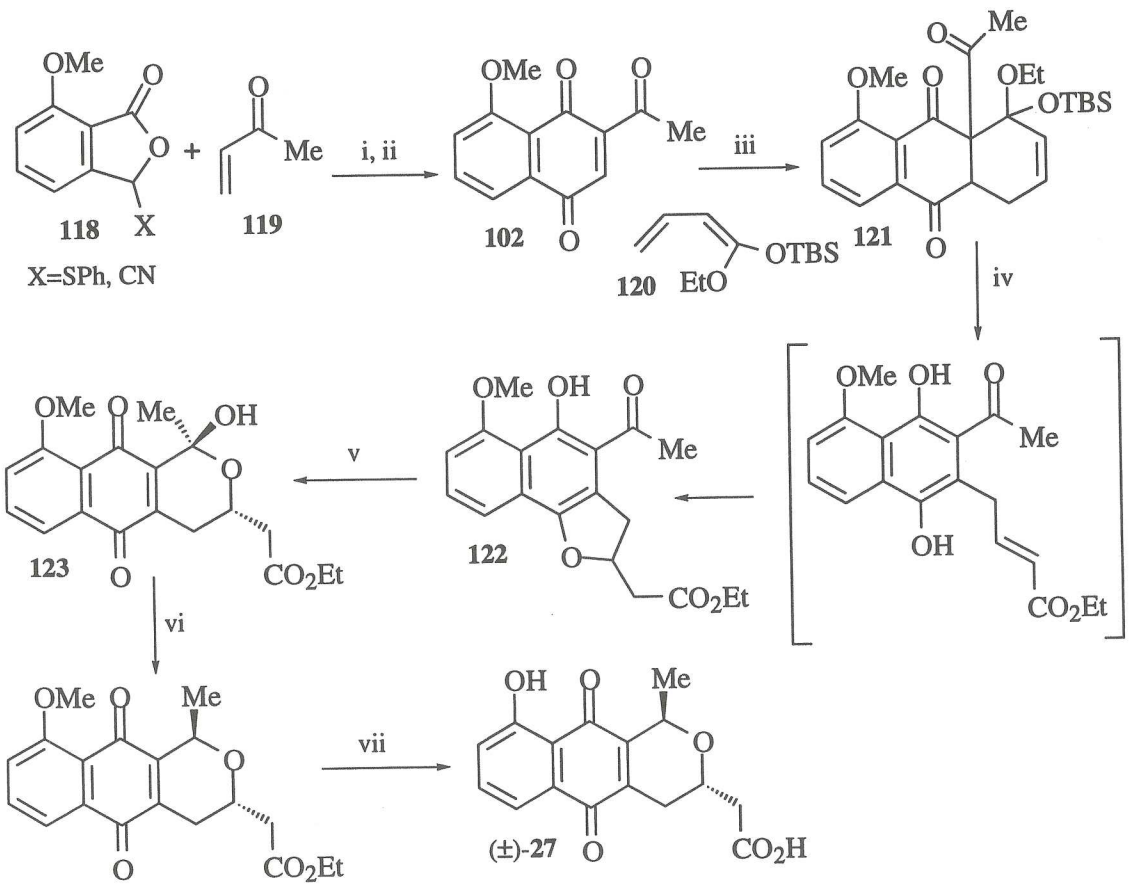
Reagents and conditions: (i) $NaBH_4$, THF, 5 °C (ii) Me_2CO, $Me_2C(OMe)_2$, $BF_3.OEt_2$ (iii) $LiAlH_4$, Et_2O (iv) OsO_4, $NaIO_4$, ^tBuOH-H_2O (v) $MeCO_2Na$, DABCO (vi) MeMgBr, Et_2O (vii) $[MeCO_2CH_2P(Me)Et_2]^+Br^-$, ^nBuLi, DMSO (viii) PCC, CH_2Cl_2 (ix) DDQ, TsOH, MeOH (x) KOH, EtOH.

1.2.5 Addition of a Diene to a 2-Acetyl-1,4-naphthoquinone or 2-Acetyl-1,4-benzoquinone.

(i) The addition of silyloxydiene 120 to the 2-acetyl-1,4-naphthoquinone 102.

Kraus *et al.*[96] developed a synthesis involving both phthalide annulation chemistry[98] and Diels-Alder methodology (scheme 16). Michael addition of the anion of phthalide **118** to enone **119** followed by base induced cyclization and oxidation gave the acetylnaphthoquinone **102**. Addition of the diene **120** gave the Diels-Alder adduct **121** which then fragmented and cyclized in the presence of base to give the adduct **122**. Oxidation afforded the lactol **123** which was reduced using trifluoroacetic acid and triethylsilane and then demethylated to generate racemic nanaomycin A (±)-**27**.

Scheme 16

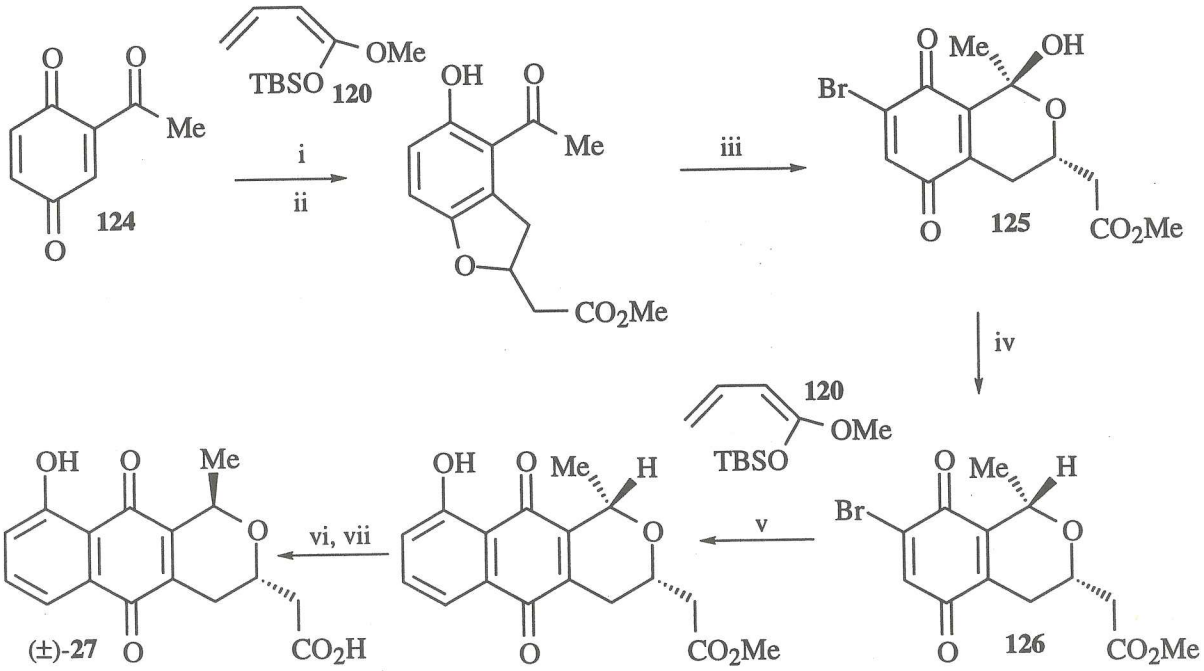


Reagents and conditions: (i) ^{t}BuOK (ii) CAN (iii) CH_2Cl_2 (iv) Bu_4NF (v) CAN (vi) Et_3SiH, CF_3CO_2H (vii) BBr_3.

*(ii) The addition of silyloxydiene **120** to 2-acetyl-1,4-benzoquinone **124**.*

Additional work by Kraus *et al.*[99] led to a more facile synthesis of variously functionalized pyranonaphthoquinones including racemic nanaomycin A (±)-**27** (scheme 17). The addition of diene **120** to the activated quinone **124** and subsequent base induced retro-Claisen reaction of the Diels-Alder adduct proceeded in an analogous fashion to that seen for the previous synthesis. Oxidative rearrangement and regioselective bromination afforded the lactol **125** and reduction gave the cyclic ether **126**. The second Diels-Alder addition of diene **120** to bromoquinone **126** proceeded regioselectively, with epimerization and deprotection of the acid side-chain affording racemic nanaomycin A (±)-**27**.

Scheme 17

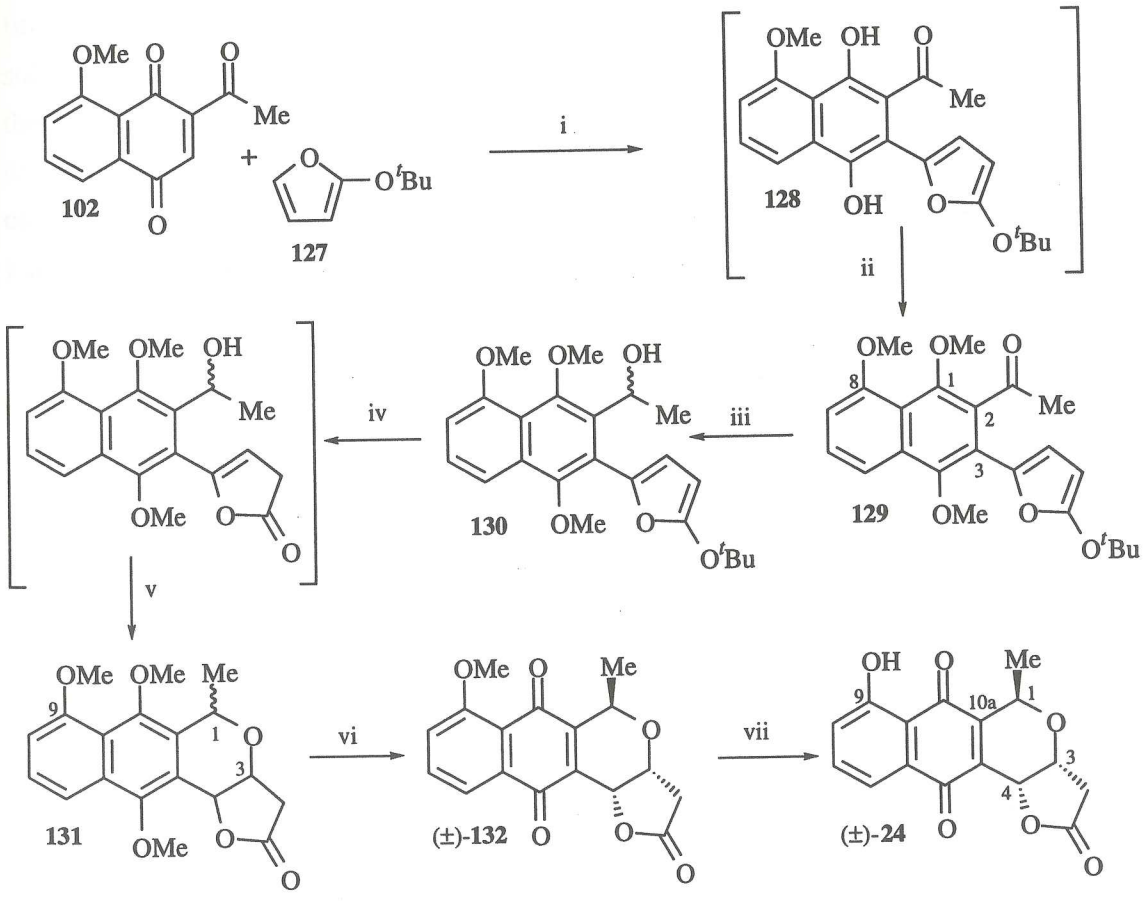


Reagents and conditions: (i) **120** (ii) Bu_4NF (iii) Br_2, $TiCl_4$ (iv) Et_3SiH, CF_3CO_2H (v) **120**, Et_3N (vi) conc. H_2SO_4 (vii) conc. HCl.

*(iii) The addition of tert-butoxyfuran **127** to the 2-acetyl-1,4-naphthoquinone **102**.*

In 1983 Kraus *et al.*[100] reported a synthesis of racemic kalafungin (±)-**24** wherein the furonaphthopyran skeleton was constructed using *tert*-butoxyfuran **127** as a butenolide anion equivalent (scheme 18). Conjugate addition of **127** to the 2-acetyl-1,4-naphthoquinone **102** gave the Michael adduct **128** which was reductively methylated *in situ* to afford **129**. Hydride reduction to the alcohol **130** followed by a deprotection-cyclization sequence gave the cyclized product **131** as an epimeric mixture at C-1. Oxidation then gave exclusively the *trans* isomer (±)-9-*O*-methylkalafungin **132** and demethylation furnished racemic kalafungin (±)-**24**.

Scheme 18



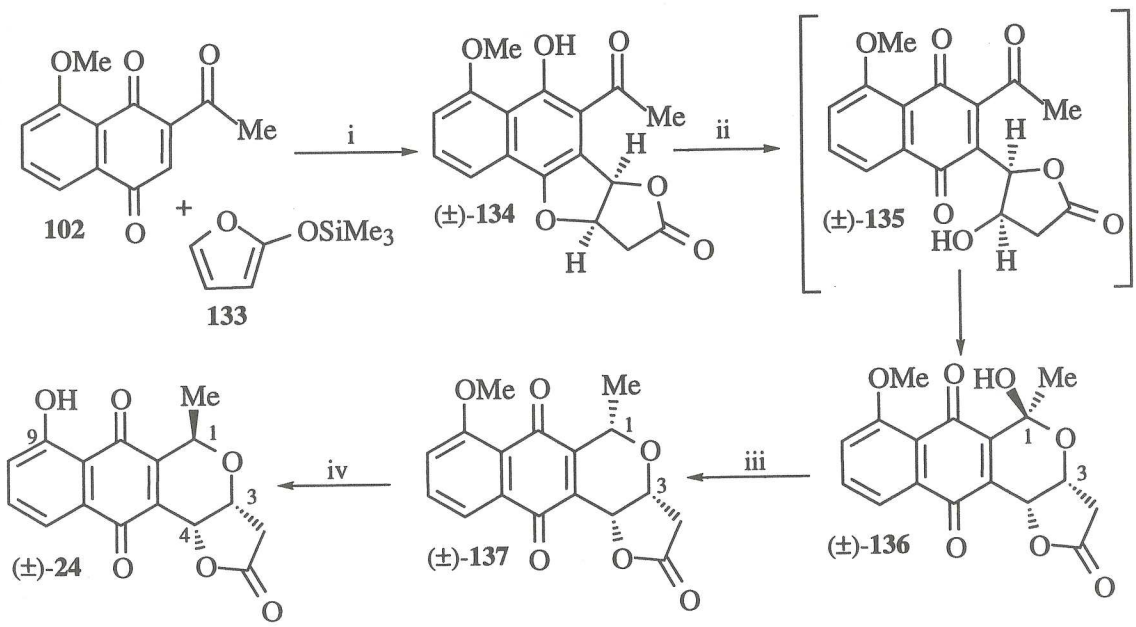
Reagents and conditions: (i) PhMe, 25 °C, 24 h (ii) K_2CO_3, Me_2SO_4 (iii) $LiAlH_4$, -10 °C (iv) CF_3CO_2H, CH_2Cl_2 (v) DBN (vi) AgO, HNO_3 (vii) BCl_3, CH_2Cl_2, -78 °C.

*(iv) The addition of 2-trimethylsilyloxyfuran **133** to the acetylnaphthoquinone **102**.*

Brimble *et al.*[101] subsequently developed a synthesis of racemic kalafungin (±)-**24** which utilized 2-trimethylsilyloxyfuran **133** as a butenolide anion equivalent (scheme 19). Although Kraus *et al.*[100] had explored the 1,4-addition of butenolide anion equivalents to quinones, the potential of this reaction for generating the furofuran ring system had not been realized due to the robust nature of the *tert*-butoxy protecting group. In contrast, use of the more labile silyloxyfuran promoted ring closure *via* an intermediate butenolide to generate the heterocycle (±)-**134**, which contains the unusual *cis*-6b,9a-dihydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one ring system.

Conjugate addition of 2-trimethylsilyloxyfuran **133** to the activated naphthoquinone **102** afforded the Michael adduct (±)-**134** as a racemic mixture. Treatment with either CAN or silver(II) oxide/nitric acid effected rearrangement to the furonaphthopyran (±)-**136** *via* oxidation to the quinone intermediate (±)-**135** and subsequent cyclization. Using the method of Kraus *et al.*[96] the hemiketal (±)-**136** was then reduced to give (±)-*epi*-9-*O*-methylkalafungin **137**, with a *cis* relationship between the alkyl groups at C-1 and C-3. Treatment with excess boron tribromide effected epimerization at C-1, as well as deprotection of the methyl ether, to afford racemic kalafungin (±)-**24**.[102]

Scheme 19

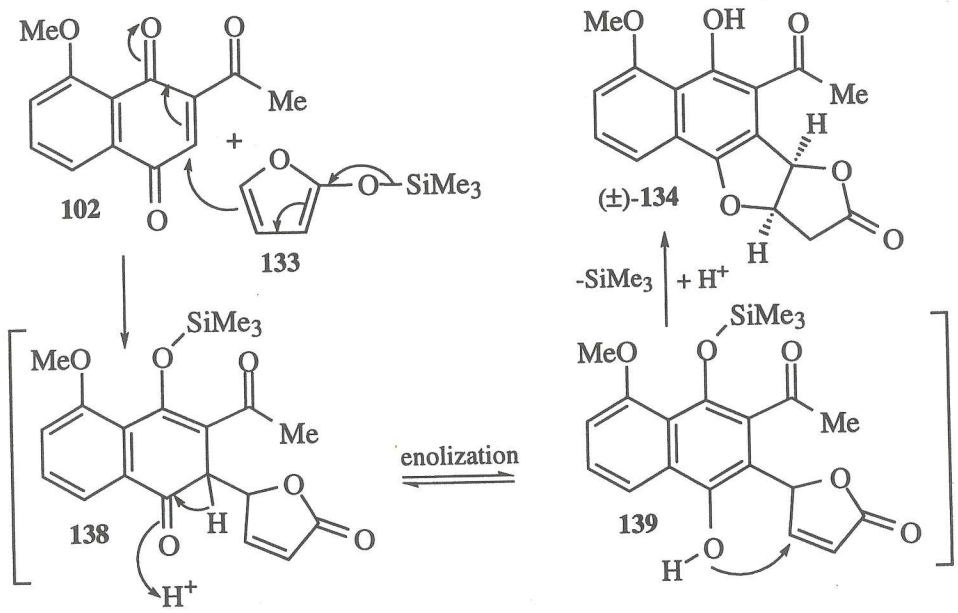


Reagents and conditions: (i) **133**, MeCN (ii) AgO, HNO_3 or CAN, MeCN (iii) Et_3SiH, CF_3CO_2H, CH_2Cl_2 (iv) BBr_3, CH_2Cl_2.

*Mechanism of the 2-trimethylsilyloxyfuran **133** addition.*

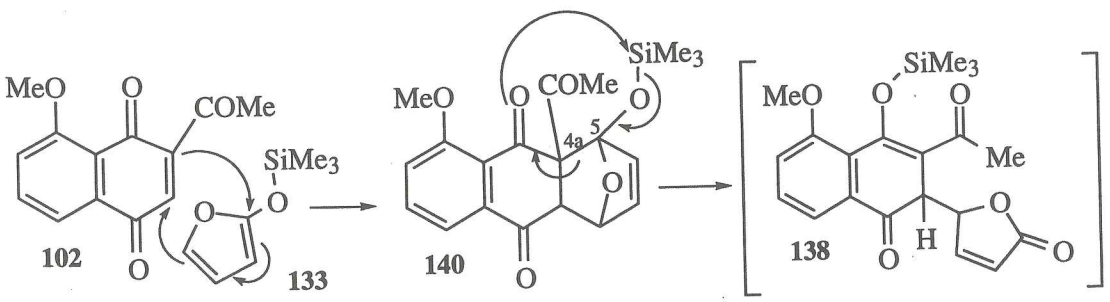
According to the proposed mechanism,[101,103-105] after the initial 1,4-addition addition of 2-trimethylsilyloxyfuran **133** to the activated quinone **102**, tautomerism of the Michael adduct **138** affords the enol **139** which then undergoes ring closure *via* a second Michael addition to give the furonaphthofuran adduct (±)-**134** (scheme 20).

Scheme 20



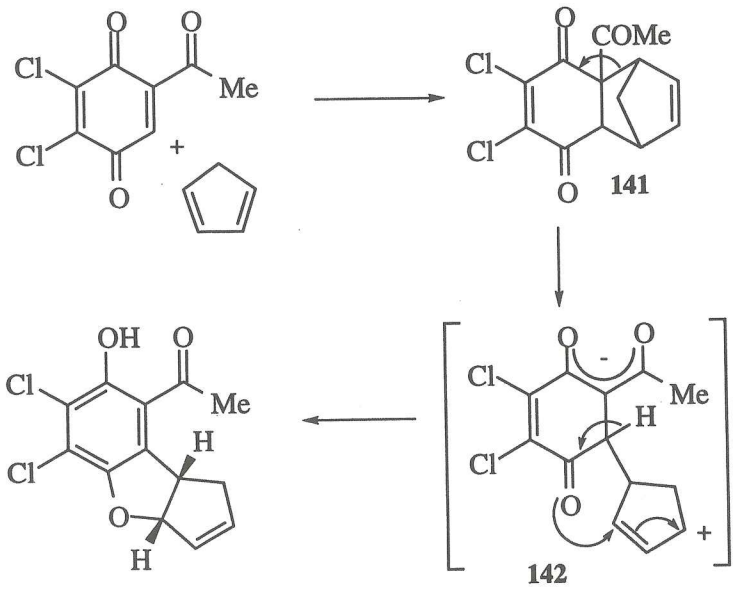
Another possible mechanism involves a Diels-Alder pathway (scheme 21). The [4+2] cyclo-addition of diene **133** to naphthoquinone **102** would generate the adduct **140**. Cleavage of the "4a-5" carbon-carbon bond would give **138** which could enolize and then cyclize to afford the furonaphthofuran ring system in the same fashion as the Michael approach.

Scheme 21



Support for this alternative mechanism can be found in the reported fragmentation and rearrangement of the Diels-Alder adducts of activated quinones under acidic conditions.[106-108] Adducts such as **141** are noted for their propensity to undergo selective cleavage of one of the two newly formed carbon-carbon bonds, and according to such a mechanism acetyl substituents favour the required bond fission by resonance stabilization of ionic intermediates such as **142** (scheme 22).

Scheme 22



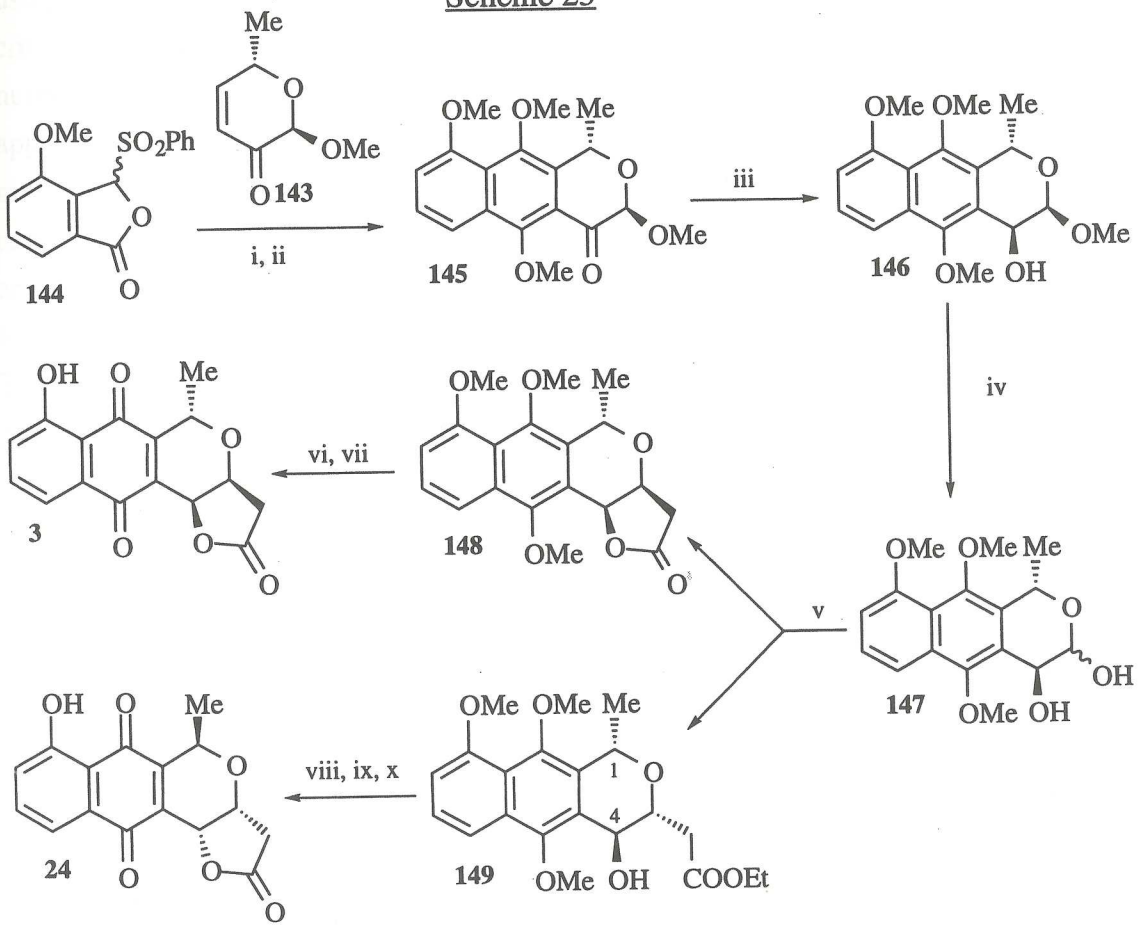
Thus the precise mechanism for the addition remains unclear. It may be that some reactions proceed *via* a direct Michael addition while others proceed *via* a Diels-Alder fragmentation pathway.

1.2.6 Enantioselective Synthesis of Kalafungin 24

In 1985 Tatsuta *et al.*[29] reported the first enantioselective total syntheses of kalafungin **24** and nanaomycin D **3**. Instead of using duplicate parallel sequences to produce the two enantiomers, both optical antipodes were produced from the common intermediate **147**, providing what is termed an "enantiodivergent" synthesis.[109]

The annulation step is similar to that employed by Kraus *et al.*[96] (see scheme 16), but uses the L-rhamnose derived enone **143** which has a greater degree of inherent stereochemistry. Condensation with the anion of phthalide **144** and methylation of the hydroquinone gave the ketone **145**. Stereoselective reduction with sodium borohydride gave the *S*-alcohol **146** which was hydrolysed to give the key intermediate **147** (scheme 23).

Scheme 23



Reagents and conditions: (i) BuLi, ^{t}BuOH, THF, -78 °C (ii) Me_2SO_4, K_2CO_3, Me_2CO (iii) $NaBH_4$, MeOH (iv) HCl, AcOH, 80 °C (v) $Ph_3P{=}CHCO_2Et$, PhMe (vi) CAN, CH_3CN, H_2O (vii) $AlCl_3$ (viii) CAN, MeCN, H_2O (ix) $AlCl_3$ (x) H_2SO_4, reflux, PhMe.

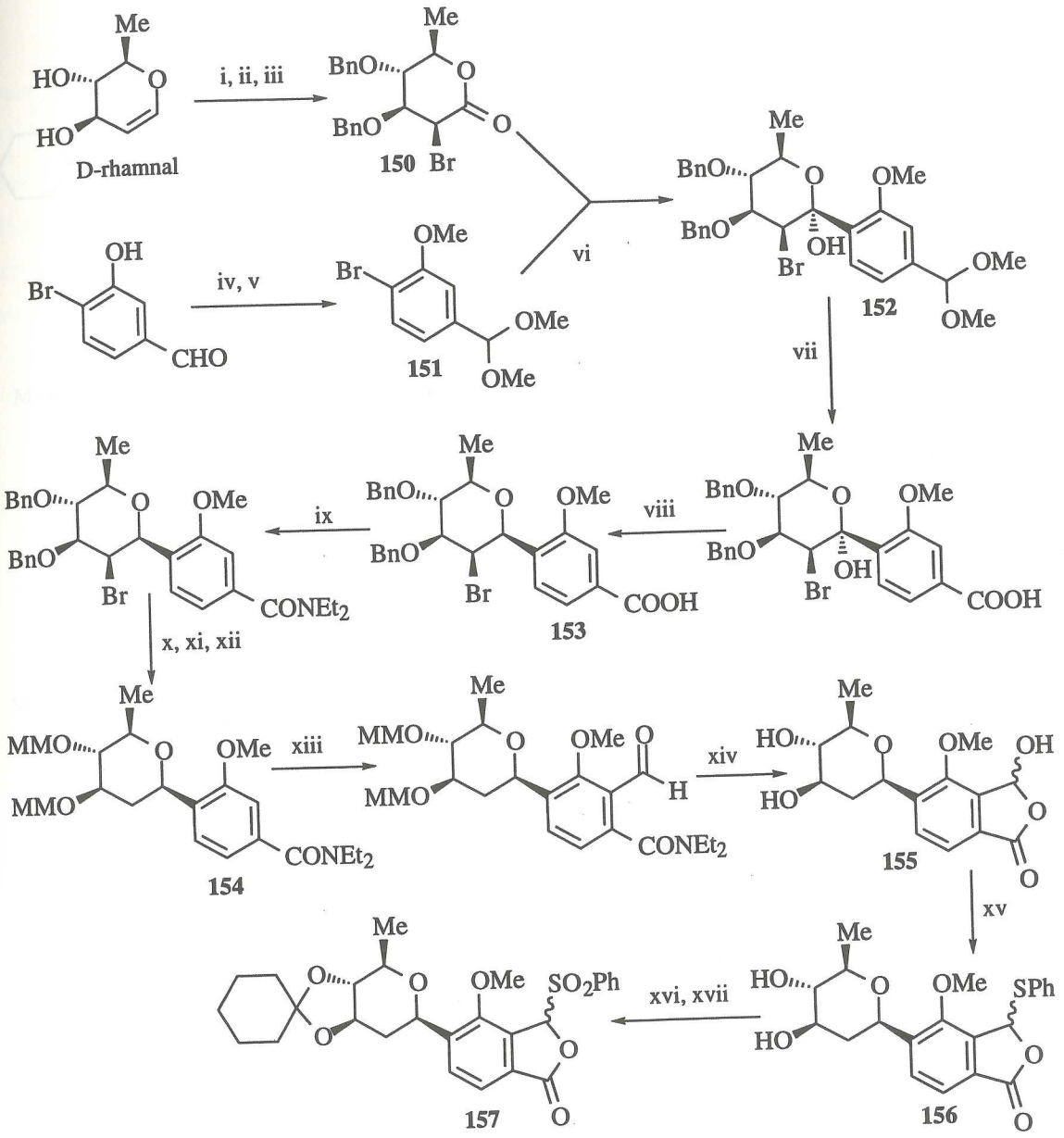
The hemiacetal **147** was submitted to a Wittig reaction to give two products. Lactone **148** results from intramolecular Michael cyclization of the intermediate α,β-unsaturated ester and concomitant lactonization of the 3,4-*cis* hydroxy ester. The 3,4-*trans* hydroxy ester **149** results from Michael cyclization without lactonization. Lactone **148** was then treated with ceric ammonium nitrate to give a quinone which was then demethylated using aluminium trichloride to give nanaomycin D **3**. In the same fashion the ester **149** was oxidized to the quinone and demethylated. Epimerization of the C-1 and C-4 positions was then achieved with sulfuric acid, lactonization being completed by refluxing in toluene to give kalafungin **24**.

1.2.7 Enantioselective Synthesis of Medermycin 52.

In 1990 Tatsuta *et al.*[62,110] reported the first total synthesis of medermycin **52** using the methodology described for the synthesis of kalafungin **24** (scheme 24).[29] The critical *C*-glycosidation reaction was conducted at the beginning of the synthesis. While a number of methods were explored to this end,[111] all were inferior to his ultimate approach. Thus the D-rhamnal derived lactone **150** was coupled with lithiated **151** to give the α-hydroxy compound **152**. Hydrolysis of the acetal, oxidation to an acid and reduction of the lactol then gave the β-*C*-glycoside **153**. Conversion of the acid to an amide, radical debromination and protecting group manipulation gave *C*-glycoside **154**. Regioselective formylation and hydrolysis of the amide then gave the hemiacetal **155**. Treatment with thiophenol gave sulfide **156**. Oxidation to the sulfone and *O*-protection gave the key phthalide **157**.

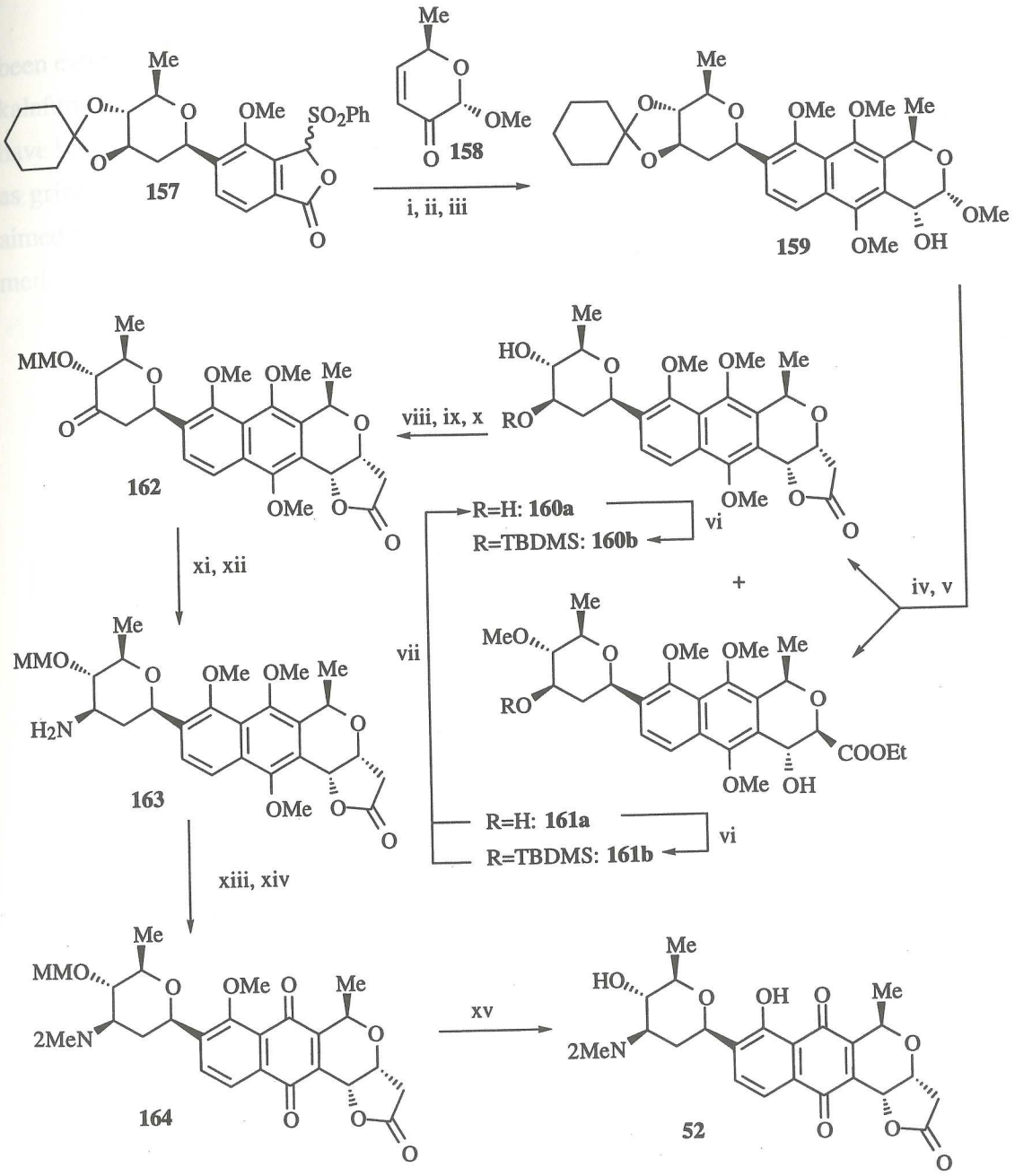
The annulation reaction was accomplished according to the previous synthesis,[29] but using the D-rhamnose derived enone **158** bearing stereochemistry suitable for medermycin **52** (scheme 25). The Wittig reaction with the key intermediate **159** gave a mixture of lactone **160a** and ester **160a** through Michael cyclization of the Wittig product with or without lactonization. Protection of the less hindered 3'-position allowed separation of the two products, and the undesired **161b** could be recycled through retro-Michael and Michael cyclizations at C-3 to a mixture of **160a** and **161a** (an "enantioconvergent" approach[112]). Protection, deprotection and oxidation steps followed to afford the ketone **162**. Installation of the amino group was now required. Ketone **162** was converted to an epimeric mixture of amines **163** and **163'** *via* an oxime. *N,N*-Dimethylation and oxidative demethylation of **163** gave the quinone **164**. Deprotection with aluminium trichloride completed the synthesis of medermycin **52**. Notably, introduction of the amine and the dimethylation/oxidative demethylation step each proceeded in only 37% yield.

Scheme 24



Reagents and conditions: (i) BnBr, NaH, DMF (ii) NBS, H_2O, MeCN (iii) PCC, MS-3Å, CH_2Cl_2 (iv) Me_2SO_4, K_2CO_3, Me_2CO (v) $CH(OMe)_3$, IR 120B, MeOH (vi) ^nBuLi, THF, -78 °C (vii) H_2NSO_3, $NaClO_2$, Me_2CO (viii) Et_3SiH, CF_3CO_2H, CH_2Cl_2 (ix) 1,1'-bis(benzotriazolyl)oxalate, Py, MeCN, Et_2NH (x) Bu_3SnH, AIBN, PhMe (xi) H_2, $Pd(OH)_2/C$, MeOH (xii) MM-Cl, $^iPr_2NEt$, $CHCl_3$ (xiii) ^tBuLi, TMEDA, DMF, THF (xiv) dioxane, HCl, 75 °C (xv) PhSH, TsOH, 130 °C (xvi) *m*CPBA, CH_2Cl_2 (xvii) 1,1-dimethoxycyclohexane, CSA, DMF, 40 °C, 25 mmHg.

Scheme 25

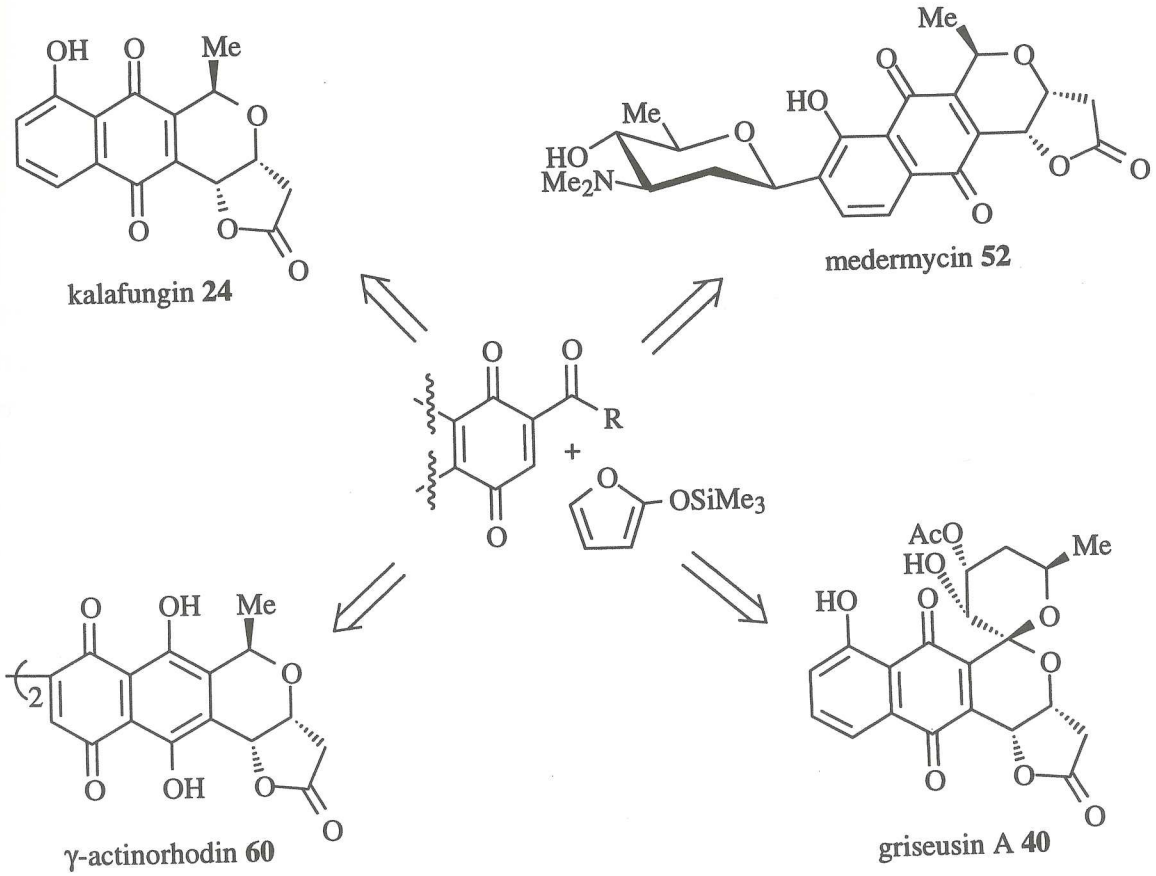


Reagents and conditions: (i) ^{t}BuLi, ^{t}BuOH, THF, -78 °C (ii) $NaBH_4$, MeOH (iii) Me_2SO_4, K_2CO_3, Me_2CO (iv) HCl, AcOH, 80 °C (v) $Ph_3P{=}CHCO_2Et$, PhMe (vi) TBDMS-Cl, imidazole, DMF (vii) TsOH, PhH (viii) MM-Cl, $^{i}Pr_2NEt$ (ix) Bu_4NF, THF (x) PCC, MS-3Å, CH_2Cl_2 (xi) $NH_2OH.Cl$, Py (xii) Raney Ni, H_2 (xiii) $NaBH_3CN$, HCHO, AcOH (xiv) CAN, MeCN, H_2O (xv) $AlCl_3$, CH_2Cl_2.

1.2.8 Summary.

The 2-trimethylsilyloxyfuran addition/oxidative rearrangement methodology has been extended to the synthesis of a range of pyranonaphthoquinone antibiotics including kalafungin **24**,[101,102] the arizonins[113,114] and the frenolicins.[115] Recently, investigations have been directed towards the synthesis of more complex pyranonaphthoquinones such as griseusin A **40**[116,117] and γ-actinorhodin **60**[118-120] (figure 18). In the present work, we aimed to use this methodology to develop a more efficient approach to the synthesis of medermycin **52**.

Figure 18



Since the first major obstacle in such a synthesis was the construction of the β-*C*-glycoside linkage, various strategies for the synthesis of *C*-glycosides are presented in the next section.

1.3 Synthesis of Aryl *C*-glycosides.

The aryl-*C*-glycosides are a naturally occurring class of compounds which have attracted considerable attention due to their activity as antibiotics. The isolation, structure elucidation and biological evaluation of these antibiotics has been reviewed.[121] Their activity is attributed to the formation of stable complexes with DNA. The absence of an oxygen atom between the carbohydrate and the aryl moieties of aryl-*C*-glycosides provides stability, whereas *O*-glycosides are much more suceptible to acidic and enzymatic hydrolysis (figure 19).

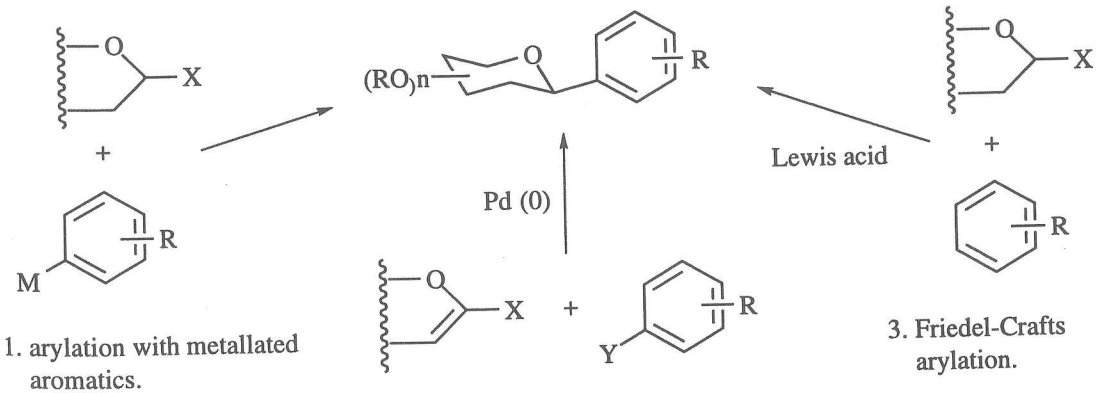
Figure 19



C-glycoside *O*-glycoside

There have been many syntheses of aryl-*C*-glycosides reported, as well as a number of reviews on the subject.[122,123] Strategies for the synthesis of aryl-*C*-glycosides can be divided into three broad categories (figure 20). The first is the arylation of appropriate sugar derivatives using metallated aromatic compounds. The second approach is the palladium mediated arylation of glycals. The third type of strategy involves Friedel-Crafts chemistry, with Lewis acid activation of a glycosyl donor and subsequent capture of the generated oxonium species by an aromatic compound.

Figure 20



1. arylation with metallated aromatics.

2. palladium(0) mediated arylation.

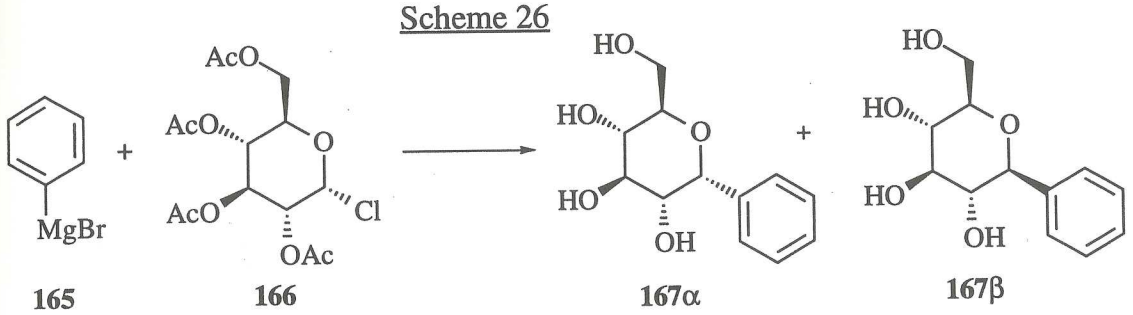
3. Friedel-Crafts arylation.

1.3.1 Arylation with metallated aromatics.

(i) Glycosyl halides.

Metallated aromatic compounds, usually Grignard reagents or lithiated species, can be coupled with glycosyl halides. Generally this type of approach has resulted in reactions with poor yields and low stereospecificity. An example is the Grignard reaction between acetochloroglucose **166** and phenylmagnesium bromide **165** which resulted in the formation of *C*-glycoside **167** as a mixture of anomers (α:β, 1:3.3) in 65% yield (scheme 26).[124] The removal of the acyl protecting groups by side-reaction with the Grignard reagent was a serious drawback to this approach, although yields and stereoselectivity were worse when using alkyl protecting groups.

Scheme 26



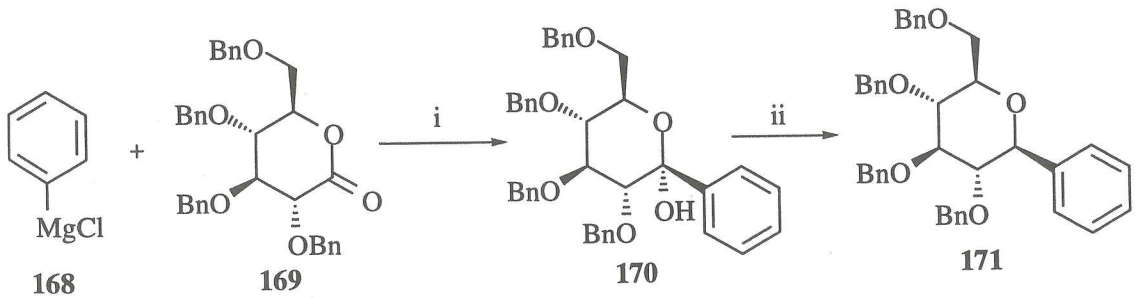
165 **166** **167α** **167β**

Reagents and conditions: THF, -78 °C to 0 °C.

(ii) Sugar lactones.

A more successful variation uses a sugar lactone as the glycosyl donor. Since a lactol is produced, reduction is then necessary to give the required *C*-glycoside. Kraus and Molina[125] pioneered this approach, coupling phenylmagnesium chloride **168** and lactone **169** to give the lactol **170** (scheme 27). Axial hydride reduction then gave the desired β-*C*-glycoside **171**.

Scheme 27

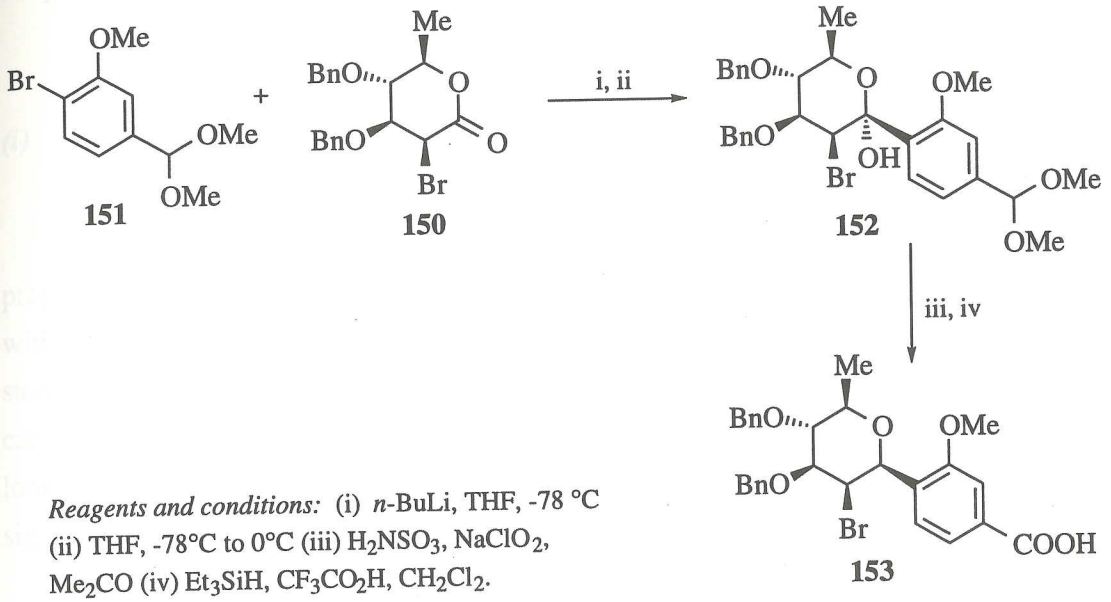


168 **169** **170** **171**

Reagents and conditions: (i) THF, -78 °C to 0 °C (ii) Et_3SiH, $BF_3.OEt_2$, CH_2Cl_2.

In the total synthesis of medermycin **52** by Tatsuta *et al.*[62] (section **1.2.7**) the key glycosylation step utilized this methodology (scheme 28). The aryl bromide **151** was lithiated and then reacted with the sugar lactone **150**, affording the lactol **152**. After deprotection of the side-chain, selective hydride reduction successfully afforded the β-*C*-glycoside **153**.

Scheme 28

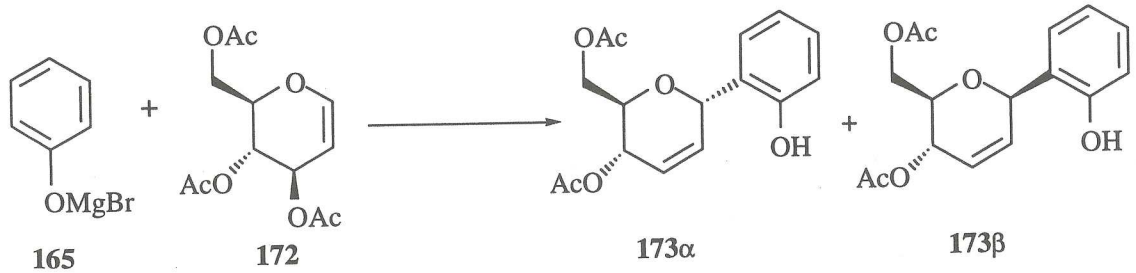


Reagents and conditions: (i) *n*-BuLi, THF, -78 °C (ii) THF, -78°C to 0°C (iii) H_2NSO_3, $NaClO_2$, Me_2CO (iv) Et_3SiH, CF_3CO_2H, CH_2Cl_2.

(iii) Bromomagnesium phenolates.

Bromomagnesium phenolates have also been used as aryl nucleophiles, with glycosylation occuring *ortho* to the hydroxy group. An example by Casiraghi, Cornia *et al.*[126] is the reaction of the glucal **172** with the bromomagnesium phenolate **165** under ultrasonication to afford a mixture of the *C*-glycosides **173** (α:β, 29:1) in 63% yield (scheme 29). In general, α-*C*-glycosides were obtained from pyranose sugars while furanose sugars gave β-*C*-glycosides.[127]

Scheme 29



Reagents and conditions: Ultrasound, CH_2Cl_2.

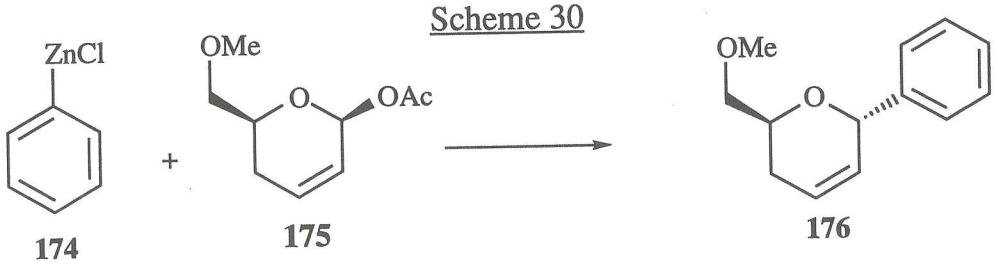
1.3.2 Palladium mediated approaches to *C*-glycosides.

The extensive development of palladium chemistry in recent times has resulted in the application of this mild and powerful method for carbon-carbon bond formation to the field of *C*-glycoside synthesis. A brief overview of the types of palladium mediated coupling reaction available is presented in this section.

(i) π-Allyl complexes.

Dunkerton *et al.*[128] were the first to apply the chemistry of π-allylic systems to the preparation of simple *C*-glycosides. The palladium(0) mediated reaction of glycal **175** with phenylzinc chloride **174** gives α-allyl-*C*-glycoside **176**, with inverted stereochemistry at the anomeric position (Scheme 30). This method requires only a catalytic amount of palladium and works well in terms of yield and stereoselectivity as long as there is no substituent at position 4 in the glycal, in which case the yields drop significantly.

Scheme 30

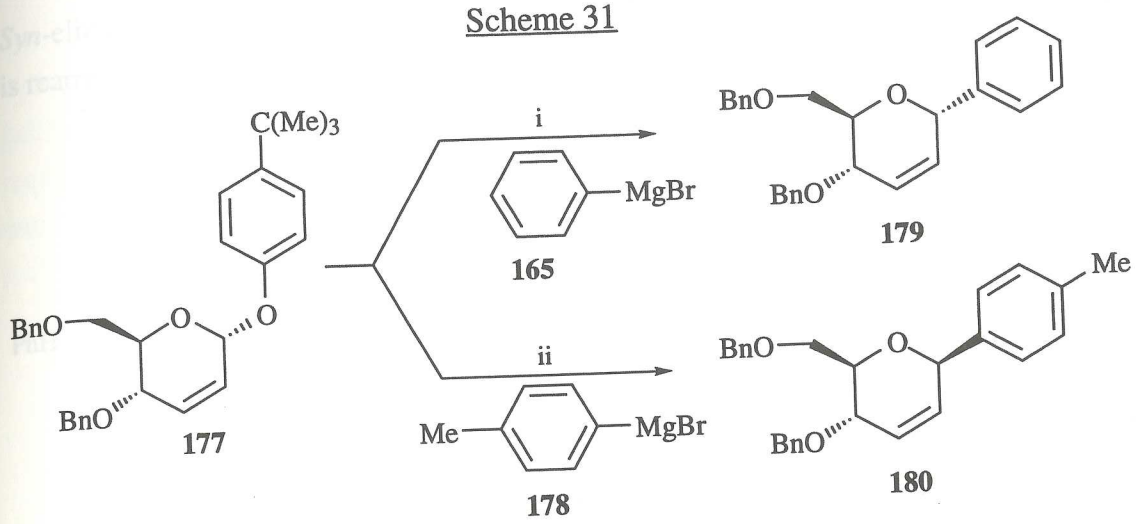


174 **175** **176**

Reagents and conditions: $Pd(PPh_3)_4$, THF.

Recent work by Sinou *et al.*[129] allowed manipulation of the product stereochemistry by variation of the catalyst (Scheme 31). Reaction of α-*O*-glycoside **177** with phenylmagnesium bromide **165** under palladium(0) catalysis afforded α-*C*-glycoside **179** in 95% yield, whereas the nickel-mediated reaction of **177** with arylmagnesium bromide **178** afforded β-*C*-glycoside **180** in 85% yield. Importantly, this new approach allowed the presence of a substituent at the 4 position in the glycal.

Scheme 31

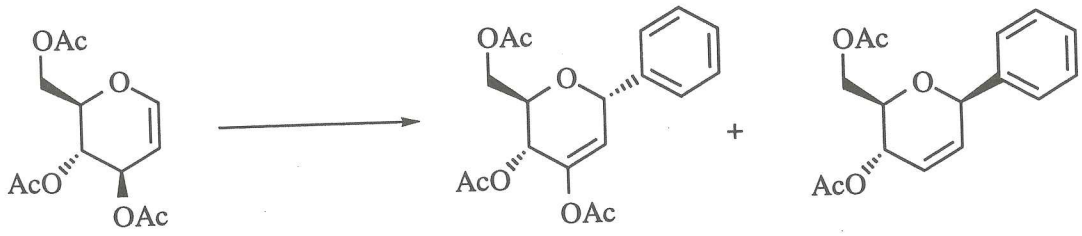


Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, THF (ii) $NiCl_2(dppe)$, THF.

(ii) Glycals and unactivated aromatic rings.

The palladium mediated arylation of glycals is referred to as Heck-type coupling.[130] Early work using unactivated aromatic rings and glycals was carried out by Czernicki *et al.*[131] Elevated temperatures and several equivalents of either the glycal or the aryl compound were required. An example is the reaction of glucal **172** and benzene in the presence of palladium(II) acetate to give the α-*C*-glycoside **181** as well as a small amount of the β-*C*-glycoside **173** (scheme 32).

Scheme 32



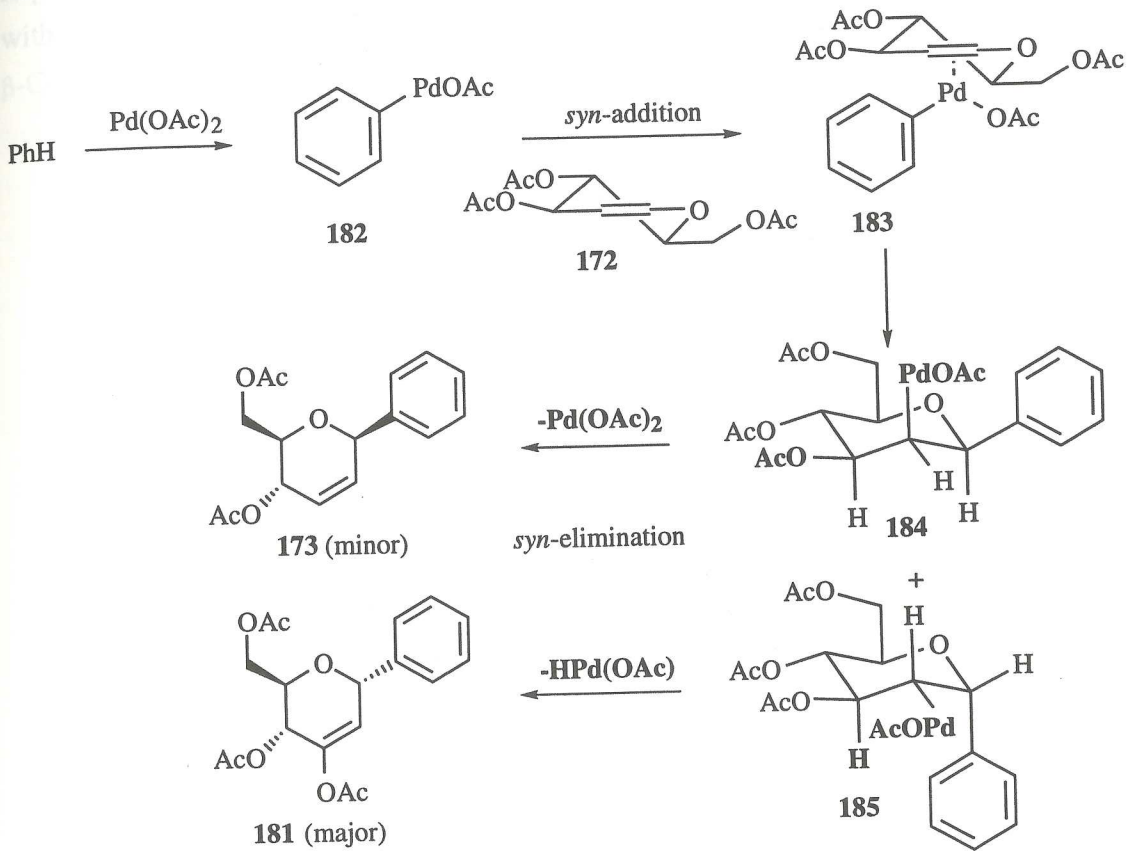
172 **181** (54%) **173** (10%)

Reagents and conditions: C_6H_6, $Pd(OAc)_2$, AcOH.

A mechanism for the Heck-type coupling[132,133] has been proposed, which helps to explain the reaction outcome (scheme 33). An aryl species such as benzene is inserted into a palladium species to give an activated palladium species **182**. This then complexes with a glycal **172** to give a π-complex **183**. *Syn*-addition of the aryl-palladium species to both the top and the bottom faces of the glycal double bond gives the adducts **184** and **185**.

Syn-elimination then affords the *C*-glycosides **173** and **181**. Generally the double bond is rearranged in the product when using glycals which lack an anomeric substituent.

Scheme 33



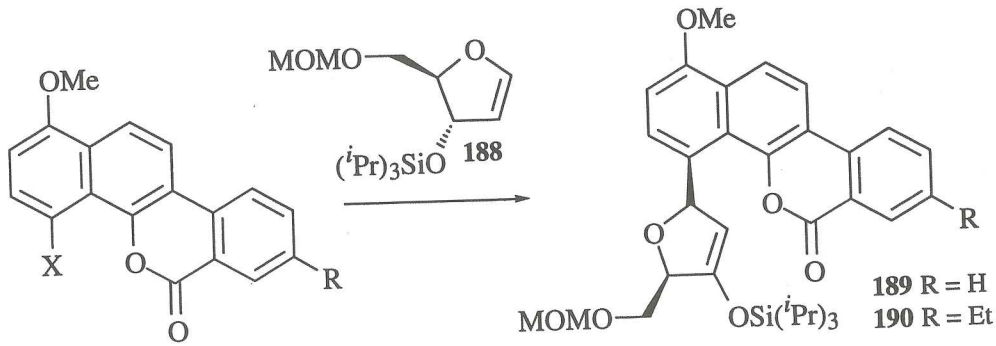
(iii) Glycals and activated aromatics.

Due to the low yields obtained using unactivated aromatics, the use of substituted aryl compounds was explored. The introduction of tin or mercury substituents in the aromatic moiety has two major advantages. Firstly, the reactive aryl palladium species is formed more easily by transmetalation so the reaction requires milder conditions than those described above. Secondly, the metal atom directs the site of glycosylation in the aryl nucleophile.

Daves *et al.*[134] used such methodology in the synthesis of the anthracycline *C*-glycosides **189** and **190** (scheme 34) which have the same ring system as the antibiotics ravidomycin, the gilvocarcins and the chrysomycins A and B. Initially, aryl stannanes such as **186** were used since the mercury derivatives of this type were very insoluble. The coupling of **186** with the furanose glycal **188** required a stoichiometric amount of palladium acetate, affording the β-*C*-glycoside **189** in 66% yield.

Aryl iodides were found to be superior to stannanes because instead of undergoing transmetalation with a palladium(II) species, oxidative addition of palladium(0) occurs. This means that only a catalytic quantity of palladium catalyst is required since palladium(0) is regenerated in the reaction. Aryl iodide **187** was coupled with the furanose glycal **188**, using a catalytic amount of palladium acetate, to afford the β-C-glycoside **190** in 85% yield.[135]

Scheme 34

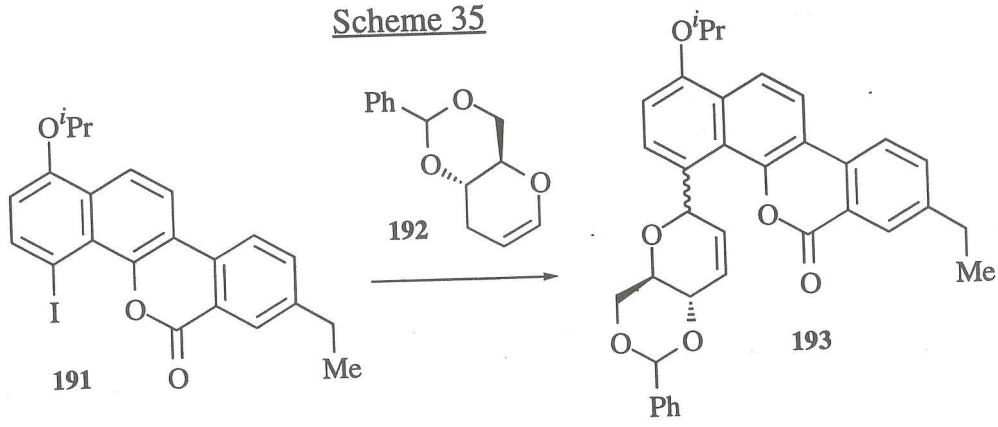


186 X = $SnBu_3$, R = H
187 X = I, R = Et
189 R = H
190 R = Et

Reagents and conditions: $Pd(OAc)_2$, MeCN.

Whereas furanose glycals tend to give β-C-glycosides, pyranose glycals favour the formation of α-products. For example, the reaction of aryl iodide **191** with the pyranoid glycal **192** in the presence of a catalytic amount of palladium acetate afforded the *C*-glycosides **193** (α:β, 9:1) in 61% yield (scheme 35).[132]

Scheme 35



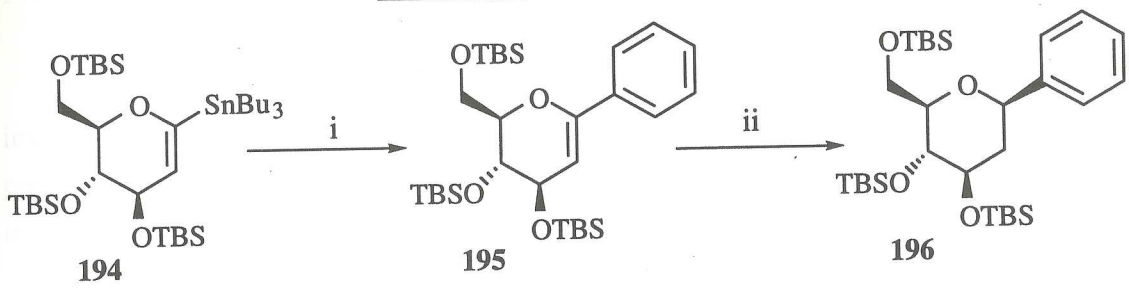
Reagents and conditions: $Pd(OAc)_2$, MeCN.

(iv) Organopalladium cross-coupling reactions.

Whereas Heck-type couplings involve the palladium mediated arylation of unsubstituted glycals, organo-palladium cross-coupling reactions use substituted glycals. This is important for two reasons. Firstly, functionalization of the glycal converts the coupling step into a reductive elimination instead of a *syn*-elimination, so the position of the double bond does not change. Secondly, since there are functional groups on both coupling partners, this approach is the mildest and most efficient of the methods for palladium mediated *C*-glycosidation.

The coupling of anomeric stannanes with aryl halides is referred to as a Stille-type coupling.[136] The polarity of the glycal is reversed at the anomeric centre by forming a vinyl anion, which is then trapped by an organometallic electrophile. For example, Friesen *et al.*[137] coupled stannane **194** with bromobenzene to give the *C*-glycoside **195**, which was then selectively reduced from the axial direction to afford **196** (Scheme 36).

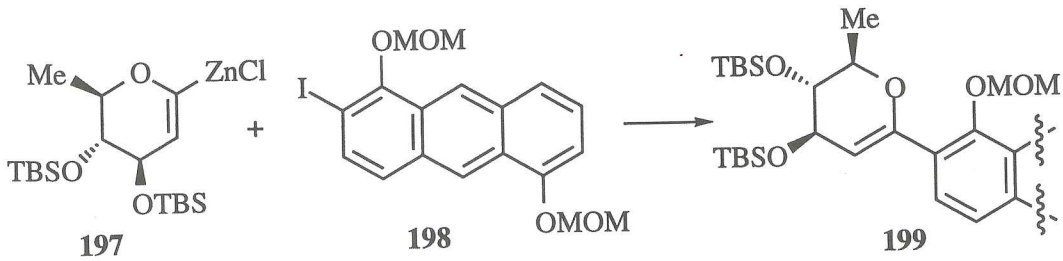
Scheme 36



Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, PhBr, THF (ii) $NaBH_3CN$, HCl, EtOH.

In the synthesis of vineomycinone B_2, Tius *et al.*[138] found that the organozinc reagent **197** worked best in the palladium catalyzed coupling with aryl iodide **198** to afford the desired *C*-glycoside **199** in 78% yield (scheme 37).

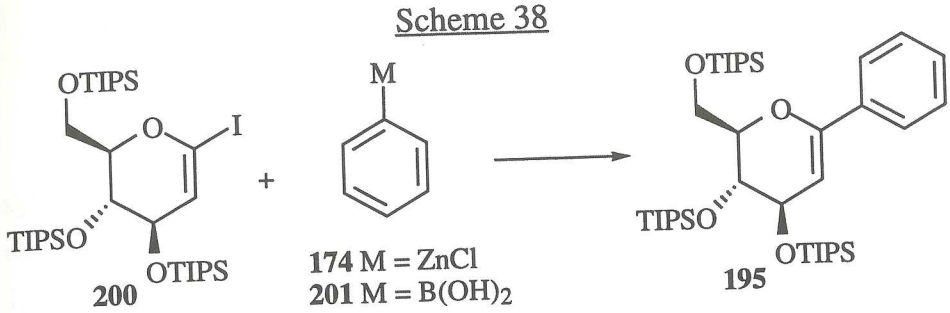
Scheme 37



Reagents and conditions: $Pd(PPh_3)_2Cl_2$, DIBAL, THF.

In the course of their studies, Friesen *et al.*[139,140] encountered problems with the Stille approach and decided to reverse the sense of the coupling, successfully reacting arylzinc and arylboron compounds **174** and **201** with glycal iodide **200** under palladium mediation to give the *C*-glycoside **195** (Scheme 38). This type of reaction is known as a Suzuki-type coupling.

Scheme 38

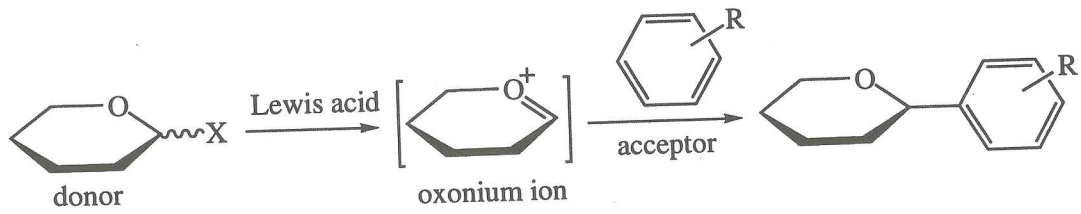


Reagents and conditions: $Pd(PPh_3)_2Cl_2$, THF.

1.3.3 Friedel-Crafts *C*-glycosylation.

The Friedel-Crafts approach is the classic method for aryl *C*-glycoside synthesis, involving the reaction of an activated glycosyl donor with an aromatic acceptor in the presence of a Lewis acid. The Lewis acid acts to promote oxonium ion formation, thereby increasing the electrophilicity at the anomeric center (scheme 39).

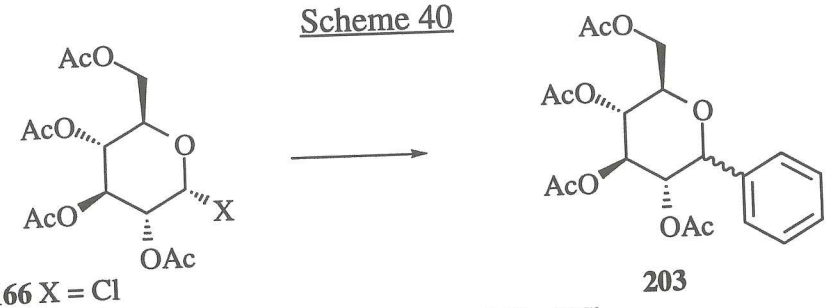
Scheme 39



(i) Using unactivated aromatic rings.

The first example of a *C*-glycosylation was carried out in 1945 by Hurd and Bonner[141] using the Friedel-Crafts approach. Acetochloroglucose **166** was reacted with benzene in the presence of aluminium trichloride to give the *C*-glycoside **203** although side-reaction between the acetate protecting groups and the Lewis acid resulted in poor yields. A similar result was obtained for the anomeric acetate **202** (scheme 40).

Scheme 40



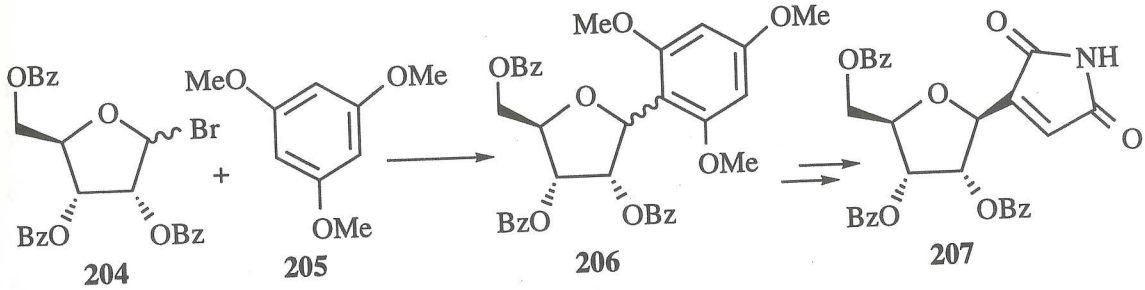
166 X = Cl
202 X = OAc

203

Reagents and conditions: C_6H_6, $AlCl_3$.

Much of the early interest in *C*-glycosylation was in the area of *C*-nucleoside synthesis, providing many examples of couplings between the ribofuranosyl series and easily degradable aromatic moieties. An example is the reaction of the bromide **204** with 1,3,5-trimethoxybenzene **205** under activation by zinc oxide, to give the *C*-glycoside **206** (scheme 41).[142] Subsequent elaboration afforded showdomycin **207**.

Scheme 41

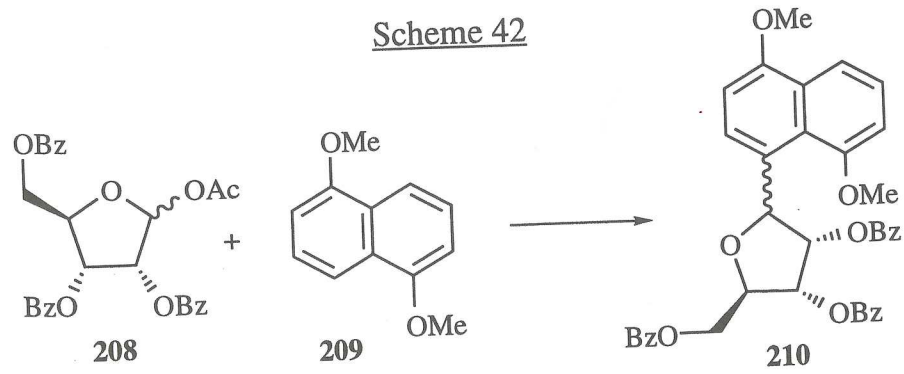


204 **205** **206** **207**

Reagents and conditions: ZnO, C_6H_6.

A more recent example reported by Hamamichi *et al.*[143] is the reaction of acetate **208** with the naphthalene **209** under tin(IV) chloride activation to give the *C*-glycosides **210** (α:β, 1:5) in 61% yield (scheme 42). This methodology was also used by Daves *et al.*[144,145] in the preparation of anthracene *C*-glycoside antibiotics.

Scheme 42

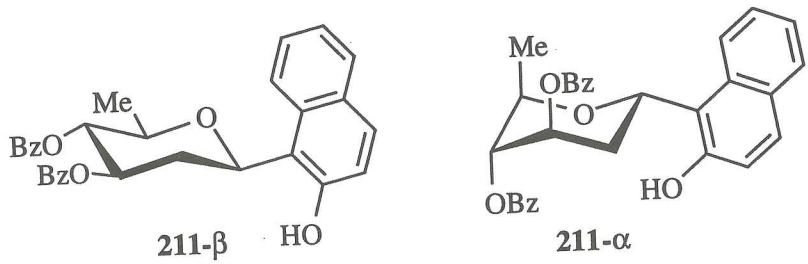


208 **209** **210**

Reagents and conditions: $SnCl_4$, C_6H_6.

Whereas furanoses tend to give mixtures of anomers in Friedel-Crafts glycosylation reactions, pyranoses give predominantly the β-anomer. This is because there is a much larger difference in stability between anomers in the pyranose series. The extent to which the anomeric aryl substituent favours the equatorial position is remarkable. Compound **211**-α adopts a $^1C_4$ conformation, even by forcing substituents at C-3, C-4 and C-5 into axial positions (figure 21). Because of this difference in stability, if there is a path for equilibration, the more stable isomer **211**-β will be enriched.[123]

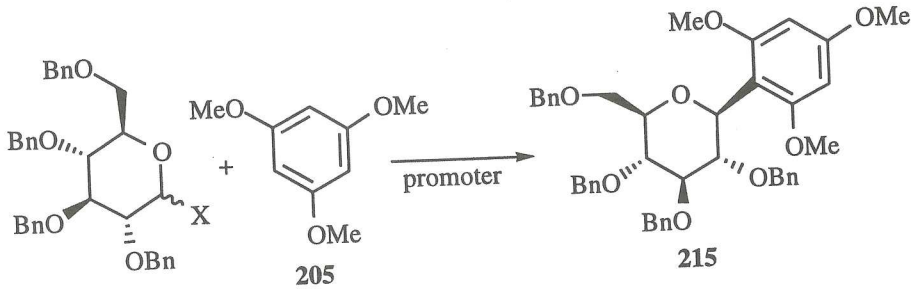
Figure 21



211-β **211**-α

Although acetate groups are most often used to activate the anomeric position, many others have been used successfully. For example, trichloroacetimidate **212** reacted with 1,3,5-trimethoxybenzene **205** in the presence of boron trifluoride diethyl etherate to give the β-*C*-glycoside **215** in 76% yield.[146] Likewise, the thiopyridyl donor **213** was activated with silver(I) triflate[147] and the fluoride donor **214** with zirconocene dichloride and silver perchlorate,[148] the reaction in both cases proceeding with good yield and stereoselectivity (scheme 43).

Scheme 43

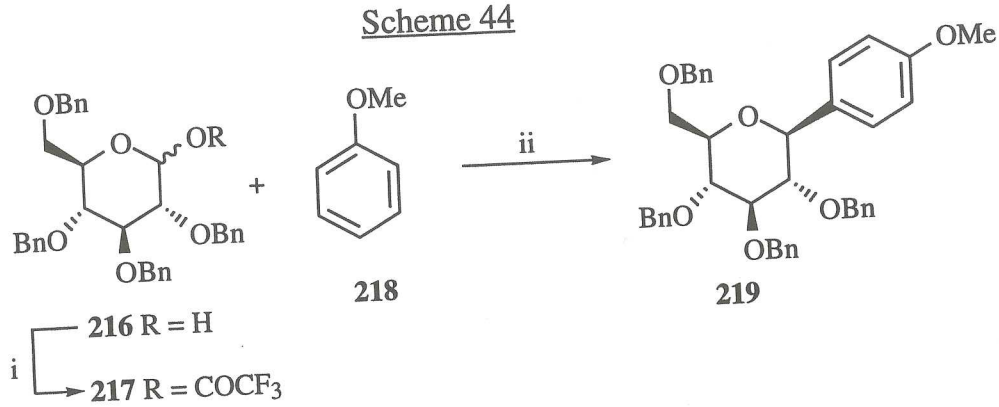


205 **215**

donor	X	promoter	yield (%)
212	$O(C{=}NH)CCl_3$	$BF_3.OEt_2$	76
213	SPy	AgOTf	63
214	F	Cp_2ZrCl_2, $AgClO_4$	80

Allevi *et al.*[149] developed successful methodology for *C*-glycosylation by the *in situ* formation of a pyranosyl trifluoroacetate and its subsequent reaction with a variety of nucleophiles under Lewis acid catalysis. For example, trifluoroacetate **217** was prepared from the pyranose **216** using trifluoroacetic anhydride, then reacted with anisole **218** under boron trifluoride diethyl etherate activation, to afford the β-*C*-glycoside **219** in 50% yield (scheme 44).

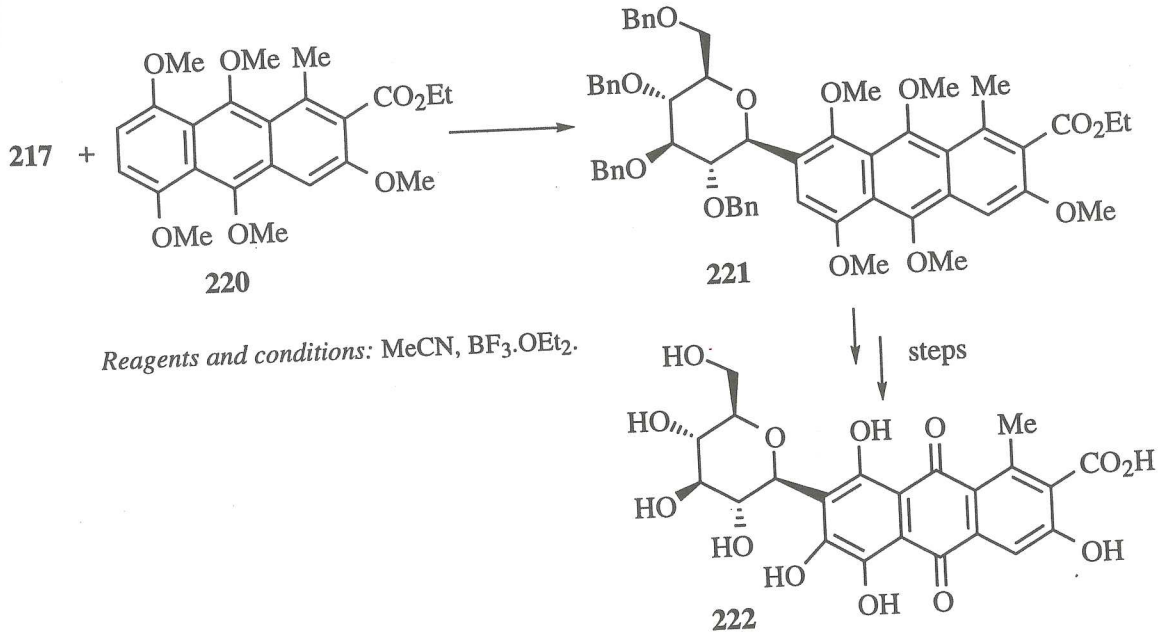
Scheme 44



Reagents and conditions: (i) $(COCF_3)_2O$, CH_2Cl_2, 30 min. (ii) $BF_3.OEt_2$, 20 min.

This methodology was used in the successful total synthesis of carminic acid **222** by the same group.[150] Trifluoroacetate **217** was coupled with anthracene **220**, to give β-*C*-glycoside **221** in 40% yield (scheme 45). A critical modification was the use of acetonitrile rather than dichloromethane as solvent.

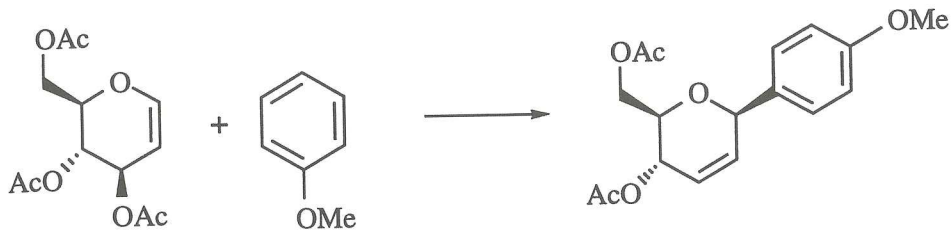
Scheme 45



Reagents and conditions: MeCN, $BF_3.OEt_2$.

Glycals have also been used in Friedel-Crafts *C*-glycosylations. For example, glycal **172** was coupled with anisole **218** in the presence of tin(IV) chloride to give the β-*C*-glycoside **223** (scheme 46).[151] Interestingly, with benzene as the aromatic acceptor the α-*C*-glycoside was formed, highlighting the importance of the nature of aromatic ring substitution.

Scheme 46

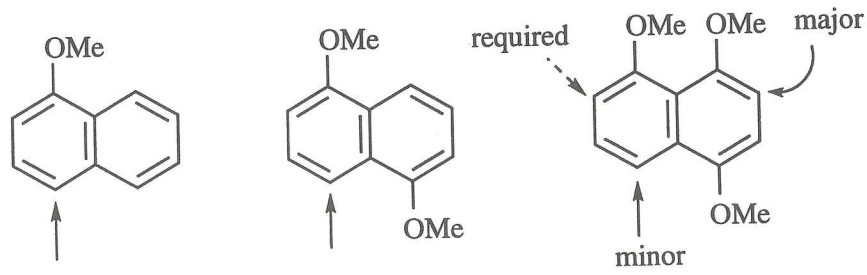


172 **218** **223**

Reagents and conditions: $SnCl_4$.

The main drawback to the Friedel-Crafts approach is the difficulty in controlling the regioselectivity. As for electrophilic substitution reactions, the reaction occurs preferentially at the position with the highest HOMO coefficient, although steric factors are also influential. Significantly, the preferred positions of glycosylation do not correspond with that required for a medermycin precursor (figure 22).

Figure 22

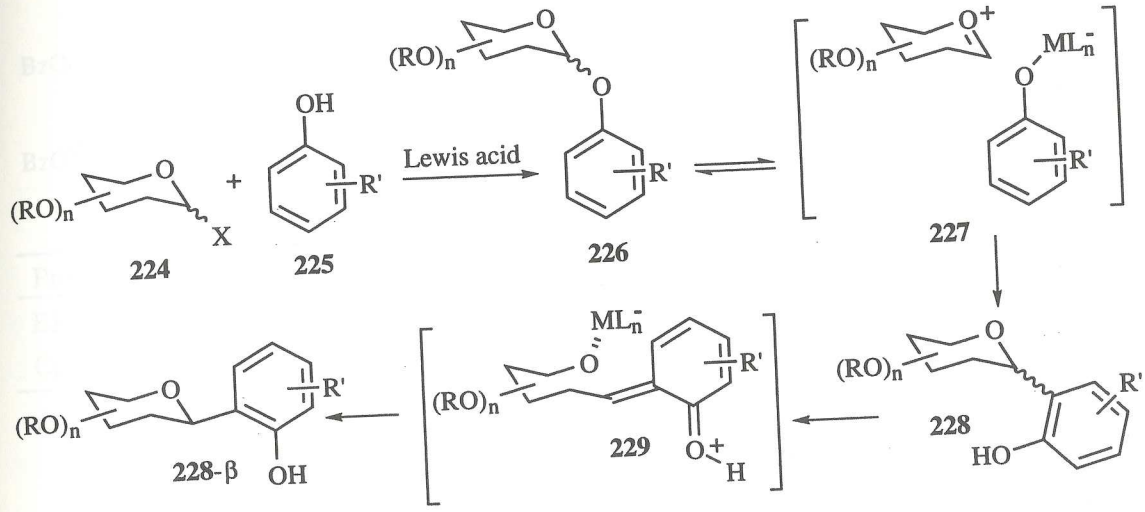


(ii) The O→C-glycoside rearrangement.

A common variation of the Friedel-Crafts approach uses a phenol rather than a fully protected aromatic compound and generally offers superior reactivity and selectivity. The reaction is thought to proceed *via* the intermediacy of an *O*-glycoside, so is termed an *O*→*C*-glycoside rearrangement. A mechanism has been proposed by Suzuki *et al.* (scheme 47).[152]

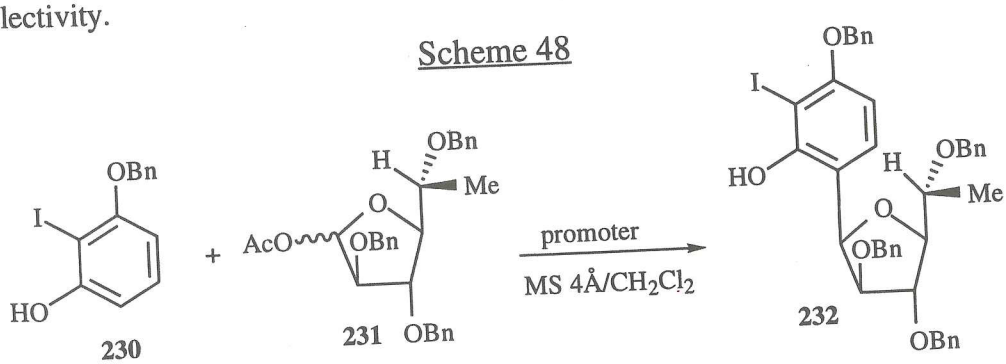
Treatment of phenol **225** with glycosyl donor **224** promoted by a Lewis acid at low temperature affords the *O*-glycoside **226**. On raising the temperature, *C*-glycoside **228** is formed *via* an oxonium phenolate ion pair **227**, although the ion pair can revert to the *O*-glycoside **226** if *C*-glycosylation fails. The anomeric selectivity depends largely on the final temperature of the reaction, with the kinetically formed α/β-mixture **228** undergoing Lewis acid catalyzed conversion to the thermodynamically favoured anomer **228**-β *via* the intermediacy of **229**.

Scheme 47



The temperature dependance of the the α/β selectivity was illustrated by Suzuki *et al.*[153] in the study of a key step in the total synthesis of the gilvocarcins (scheme 48). In the reaction of furanosyl actetate **231** with the phenol **230** to give *C*-glycoside **232**, a difference in the final temperature of as little as 20 °C was enough to reverse the selectivity.

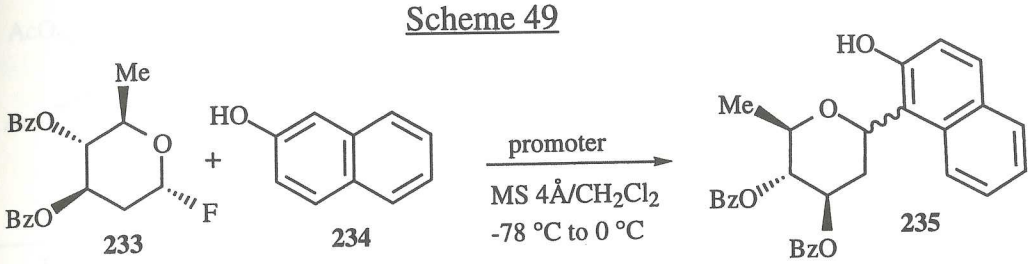
Scheme 48



Promoter	Reaction temp. (°C)	Yield (%)	α/β
$SnCl_4$-$AgClO_4$	-78 to -40	60	5.1/1
$SnCl_4$-$AgClO_4$	-78 to -20	69	1/58
Ph_3SiCl-$AgClO_4$	-78 to -40	91	17/1

Initially Suzuki *et al.* favoured the use of anomeric fluorides. During the investigation of approaches to the antibiotic vineomycin B_2, the reaction of D-olivosyl fluoride **233** with 2-naphthol **234** was examined (scheme 49).[152] Use of boron trifluoride diethyl etherate as the promoter resulted in a 70% yield of the *C*-glycoside **235** (α/β, 3.4/1), as well as a 28% yield of the corresponding *O*-glycoside. In contrast, the hafnocene dichloride-silver perchlorate promoter system gave exclusively the β-C-glycoside **235** in 98% yield.

Scheme 49

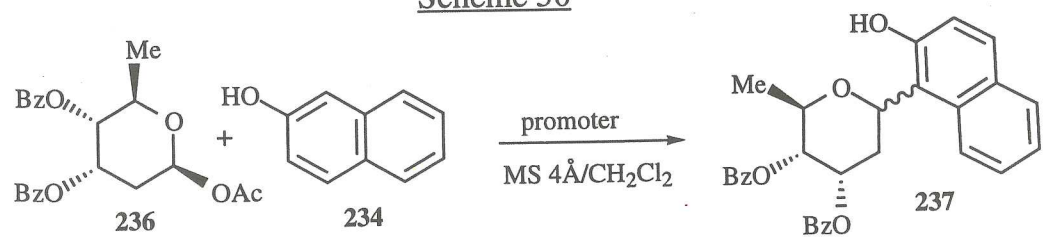


Promoter	Yield (%)	α/β
$BF_3.OEt_2$	70[a]	3.4/1
Cp_2HfCl_2-$AgClO_4$	98	β only

a) *O*-glycoside isolated in 28% yield (α/β = 4.6/1).

In subsequent work, glycosyl acetates were used due to their improved stability. The reaction of the acetate derivative of D-digitoxose **236** with 2-naphthol **234** was investigated (scheme 50).[154] Once again, a quantity of *O*-glycoside was recovered when using boron trifluoride diethyl etherate, although this time the selectivity of the *C*-glycoside **237** favoured the β–anomer. Much better yields and selectivities were obtained using tin(IV) chloride or hafnocene dichloride-silver(I) perchlorate as promoter.

Scheme 50

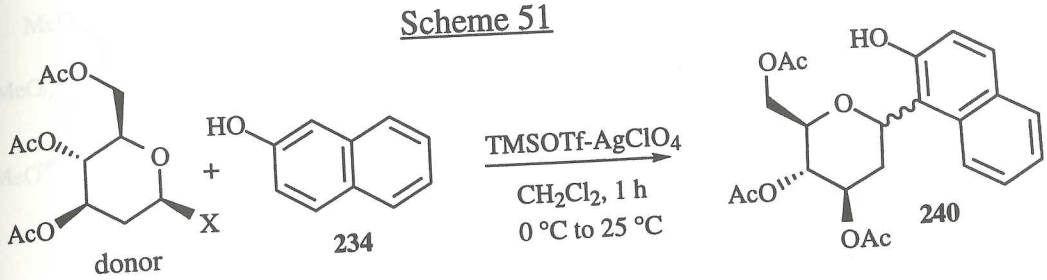


Promoter	Reaction temp. (°C)	Yield (%)	α/β
$BF_3.OEt_2$	-78 to r.t.	75[a]	1/4
$SnCl_4$	-78 to -25	99	1/14
Cp_2HfCl_2-$AgClO_4$	-78 to -15	99	1/10

a) *O*-glycoside isolated in 16% yield (α/β = 1.6/1).

During investigations into the synthesis of medermycin **52**, Toshima *et al.*[155] sought an efficient activator for *C*-glycosylation of inactivated sugars such as methyl glycoside **239**. Excellent results were achieved using the trimethylsilyltriflate-silver perchlorate (1:1) promoter system, with the reaction of **239** (or acetate **238**) and 2-naphthol **234** affording the β-*C*-glycoside **240**.

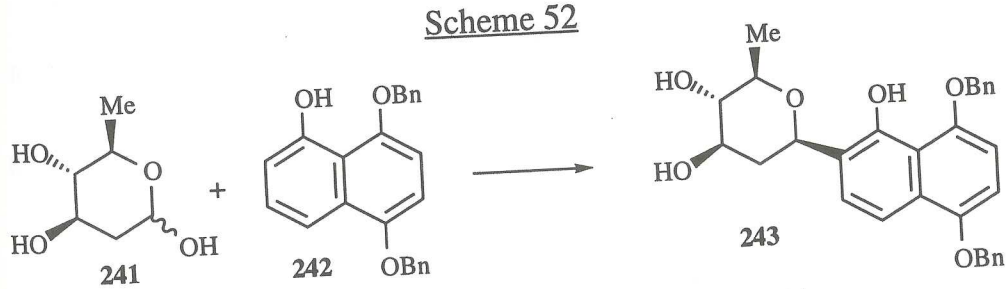
Scheme 51



Donor	X	Yield (%)	α/β
239	OMe (α)	99	1/99
238	OAc (β)	99	1/76

Toshima *et al.*[156] have also examined the use of unprotected sugars in *C*-glycosylation reactions, employing this methodology in the total synthesis of the angucycline antibiotic urdamycinone B1 (scheme 52).[157] It was found that silver perchlorate was unnecessary when the glycosyl moiety lacked acetate or benzoate groups. Reaction of the unprotected D-olivose **241** and naphthol **242** with trimethylsilyl triflate in acetonitrile gave the β-C-glycoside **243** in 78% yield.

Scheme 52

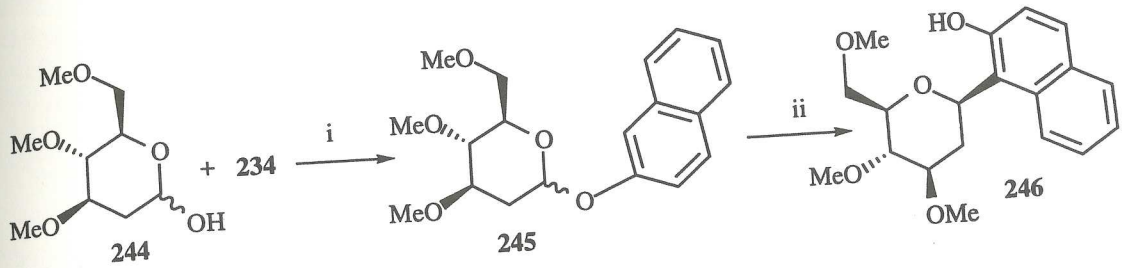


Reagents and conditions: TMSOTf, MeCN, 25°C, 1 h.

Kometani *et al.*[158] employed a different approach in which *O*-glycosides were prepared by Mitsunobu's method[159,160] and then treated with a Lewis acid, effecting rearrangement to the thermodynamically more stable β-*C*-glycosides (scheme 53).

Reaction of pyranose **244** and 2-naphthol **234** with triphenylphosphine and diethylazodicarboxylate gave the *O*-glycoside **245**. Treatment of **245** with boron trifluoride diethyl etherate then afforded the desired β-*C*-glycoside **246** in 74% yield.

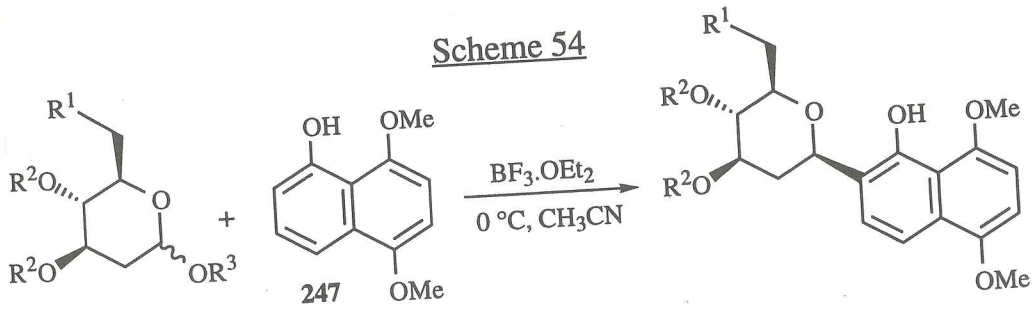
Scheme 53



Reagents and conditions: (i) Ph_3P, DEAD, THF, 72% (ii) $BF_3.OEt_2$, CH_2Cl_2, r.t., 4 h, 74%.

Larsen *et al.*[161] explored a range of methods for *C*-glycosylation during the investigation of synthetic approaches to the angucycline antibiotics. Use of boron trifluoride diethyl etherate as promoter gave the most success, although only after changing the solvent from dichloromethane to acetonitrile. Acetates **238** and **248** reacted with naphthol **247** in the presence of the promoter to give the β-*C*-glycosides **249** and **251**, respectively. The benzyl-protected sugar was first activated as the trifluoroacetate **217** (see scheme 44) and then reacted with naphthol **247** to give the desired β-*C*-glycoside **250**.

Scheme 54

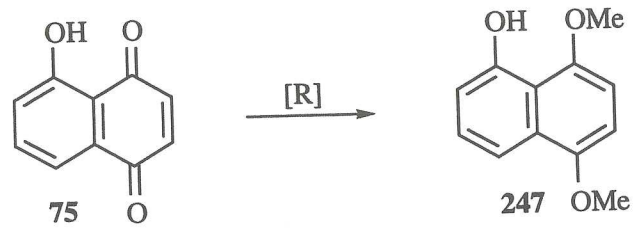


Donor	R	Product	Yield (%)
238	$R^1 = OAc$, $R^2 = R^3 = Ac$	**249**	94
217	$R^1 = OBn$, $R^2 = Bn$, $R^3 = COCF_3$	**250**	81
248	$R^1 = H$, $R^2 = R^3 = Ac$	**251**	75

The aromatic moieties that take part in *O*→*C*-glycoside rearrangement reactions should be electron rich, otherwise the reaction will stop at the *O*-glycoside or never proceed. For this reason hydroxylated quinones such as juglone **75** are unsuitable and

reductive protection is necessary to provide suitable substrates such as **247** for the formation of aryl *C*-glycosides (figure 23).

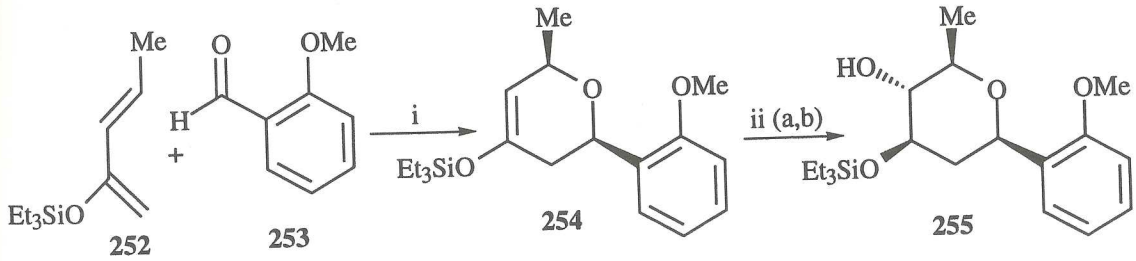
Figure 23



1.3.4 Cycloaddition approach.

Danishefsky *et al.*[162] used cycloaddition methodology to construct the *C*-glycoside moiety of vineomycinone B2. In the model work towards this end, aldehyde **253** was reacted with diene **252** in the presence of a catalytic amount of $Eu(fod)_3$ affording a single cycloaddition product, silyl enol ether **254**. Reduction of **254** with borane dimethylsulfide, followed by oxidation of the intermediate borane, gave the overall hydration product **255** (scheme 55).

Scheme 55



Reagents and conditions: (i) $Eu(fod)_3$, $CHCl_3$, 86% (ii) a. BH_3DMS b. H_2O_2/OH^-, THF, 68%.

CHAPTER TWO

DISCUSSION

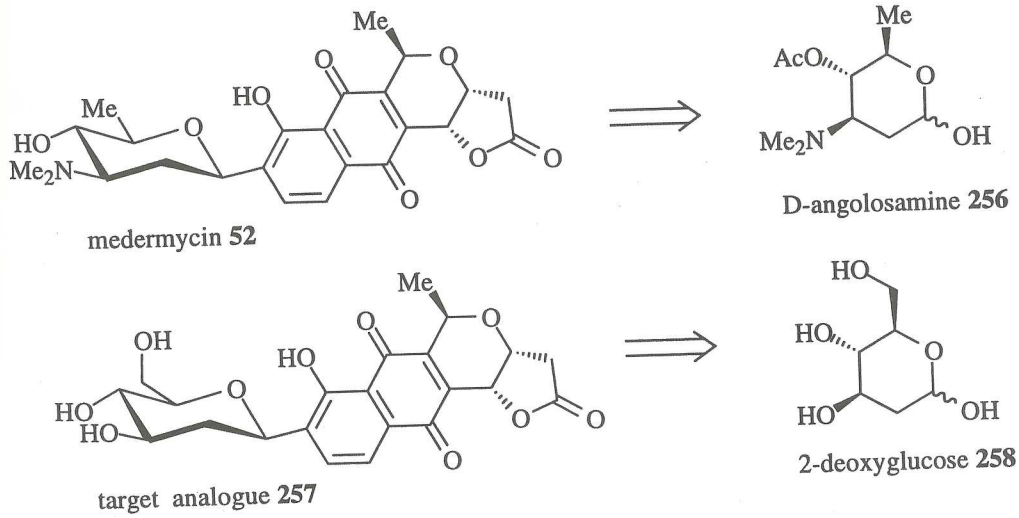
2.1 Aryl *C*-glycosylation studies.

2.1.1 Retrosynthesis and Synthetic Strategy.

The ultimate objective of this research was the synthesis of medermycin **52**. Although the total synthesis of medermycin **52** had previously been reported by Tatsuta *et al.*,[110] that synthesis was lengthy and involved numerous protection and deprotection steps (schemes 24 and 25). In addition, a number of steps in the latter part of the synthesis suffered from poor yields. It was envisaged that a more direct synthesis of medermycin **52** might be possible using the 2-trimethylsilyloxyfuran addition/oxidative rearrangement methodology developed by Brimble *et al.*[103] (see scheme 19). The methodology to be employed for the introduction of the β-*C*-glycosyl functionality was also an important consideration. A number of techniques were reviewed (section **1.3**) and it was decided to focus our investigations on the *O*→*C*-glycoside rearrangement reaction.

Rather than embarking directly on the synthesis of medermycin **52**, it was decided that the feasibility of our approach would be examined using a model system. This would allow the circumvention of some of the pitfalls that arise during any lengthy synthesis. Whereas the natural product medermycin **52** incorporates the amino sugar D-angolosamine **256**, our initial synthetic target was the analogue **257** derived from 2-deoxyglucose **258** (scheme 56).

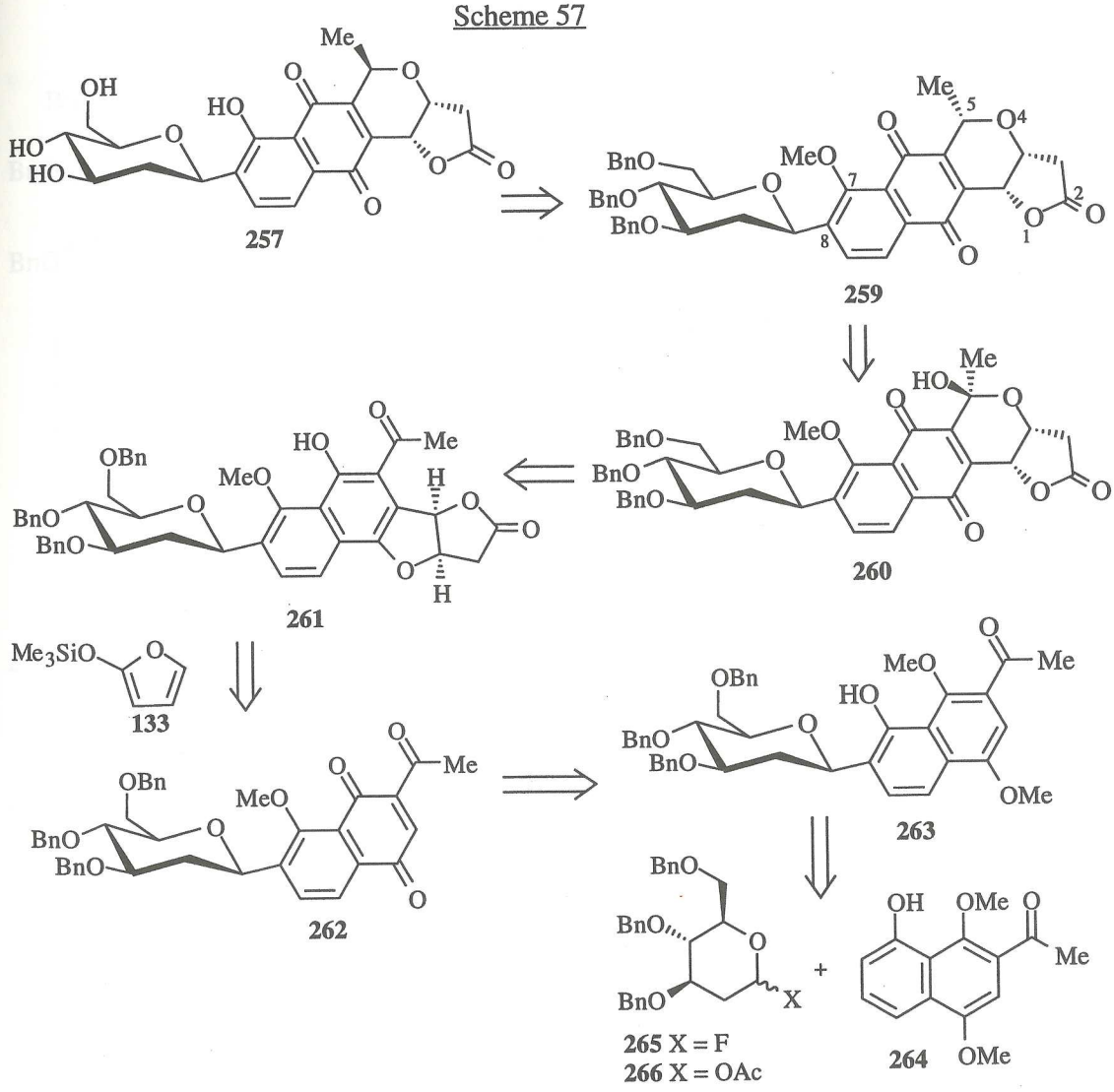
Scheme 56



Based on previous research conducted by the group,[101,102] a retrosynthetic analysis was proposed whereby medermycin analogue **257** would be formed by removal of the methyl and benzyl protecting groups from the cyclic ether **259**, using boron

tribromide, with concomitant *cis/trans* epimerization of the stereocenter at C-5[a] (scheme 57). The methyl ether **259** would be obtained by axial hydride reduction of the lactol **260** according to the procedure of Kraus *et al.*[96] The *cis*-fused 2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran ring system of the hemiacetal **260** would be produced by oxidative rearrangement of the furo[3,2-*b*]naphtho[2,1-*d*]furan **261**, which in turn could be formed by the uncatalyzed Michael addition of 2-trimethylsilyloxyfuran to the activated naphthoquinone **262**. Naphthoquinone **262** would be produced by the methylation of naphthol **263** followed by oxidative demethylation using ceric ammonium nitrate (CAN). β-*C*-Glycoside **263** would be formed by a Lewis acid promoted *O*→*C*-glycoside rearrangement reaction between a suitably activated glycosyl donor (**265**, **266**) and acetylnaphthol **264**.

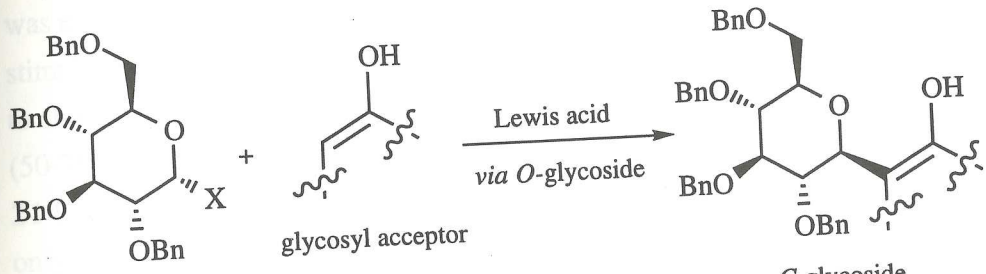
Scheme 57



[a] the numbering has changed from the introduction, where structures were numbered according to general pyranonaphthoquinone convention for consistency.

Having conceived a synthesis, the initial task was to establish suitable reaction conditions for the *O*→*C*-glycoside rearrangement reaction. In light of the multitude of procedures reported for this reaction (see section **1.3**), it was decided to begin our investigations using simple, readily available model compounds. Pyranose **216** and glycosyl fluoride **214** were selected as the glycosyl donors, since they are derived from D-glucose **267** which is inexpensive and available in large quantities. Pyranose **216** has been used by Allevi *et al.*[149,150,163] in glycosylation reactions and glycosyl fluorides have been commonly employed by Suzuki *et al.*[148,152,164] Aryl *C*-glycosylation would then be examined between these glycosyl donors and a variety of simple naphthols using differing conditions and Lewis acids (scheme 58).

Scheme 58



216 X = OH
214 X = F

glycosyl donor

glycosyl acceptor

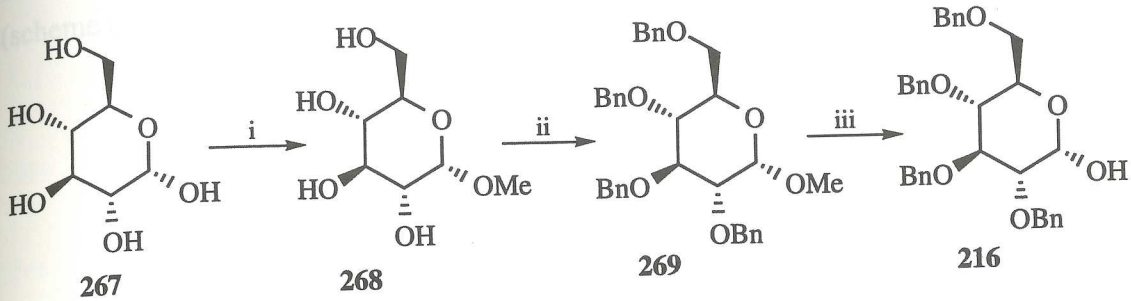
C-glycoside

2.1.2 Synthesis of Coupling Partners.

(i) Synthesis of pyranose 216.

α-Methylglycoside **268** was prepared in 62% yield using the procedure of Patterson and Robertson[165] by treatment of D-glucose **267** with methanolic hydrogen chloride. Pyranose **216** was then synthesized in two steps using the procedure of Glaudemans *et al.*[166] Benzylation of **268** using potassium hydroxide and benzyl chloride afforded the syrupy methylglycoside **269** in 95% yield and acidic hydrolysis at the anomeric position then gave pyranose **216** as white needles in 43% yield (scheme 59).

Scheme 59



267 **268** **269** **216**

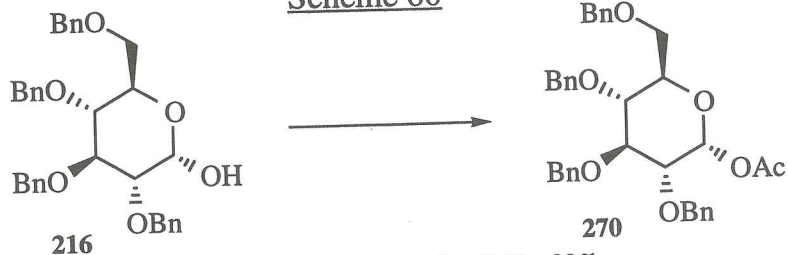
Reagents and conditions: (i) MeOH, 3% HCl, reflux, 4.5 h, 62% (ii) BnCl, KOH, dioxane, reflux, 3 h, 95 % (iii) AcOH, HCl, reflux, 12 h, 43%.

*(ii) Synthesis of glycosyl fluoride **214**.*

With the pyranose **216** in hand, its conversion to the more reactive fluoride **214** was examined. The role glycosyl fluorides have played in *C*-glycoside synthesis[167-170] has stimulated considerable interest in their preparation,[168-172] providing a number of methods to choose from. Two groups have reported the use of pyridinium polyhydrogen fluoride (50-70% hydrogen fluoride in pyridine) to convert pyranose **216** to glycosyl fluoride **214**. Szarek *et al.*[172] reported an 82% yield of α-**214**, while Noyori *et al.*[171] obtained only 63%, reporting an improved yield of 89% with the more activated acetate **270**.

Accordingly, acetate **270** was prepared from pyranose **216**, using pyridine and acetic anhydride, in 82% yield (scheme 60). Both pyranose **216** and acetate **270** were treated with a 70% solution of hydrogen fluoride in pyridine, but in neither case was the desired fluoride formed (scheme 61).

Scheme 60



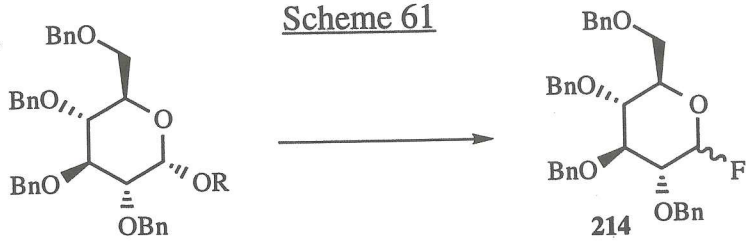
216 **270**

Reagents and conditions: Ac_2O, Py, 82%.

Attention turned to the use of diethylaminosulfur trifluoride (DAST), with which pyranose **216** had been successfully converted to the glycosyl fluoride **214**, initially by Posner and Haines[173] and later by Kovac *et al.*[174] According to the prescribed conditions, a solution of **216** in tetrahydrofuran at -30 °C was treated with DAST, gratifyingly

affording the white crystalline β-fluoride **214** in 83% yield after flash chromatography (scheme 61).

Scheme 61

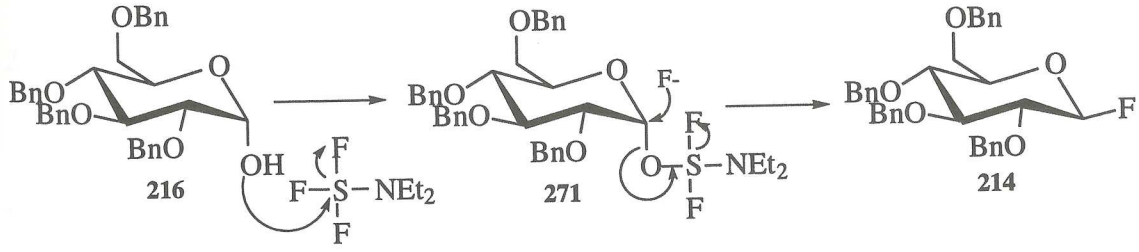


Donor	R	Fluorinating agent	Conditions	Yield (%)	α/β
216	H	70% HF-Py	PhMe, -20 to 0 °C, 6 h	-	-
270	Ac	70% HF-Py	CH_2Cl_2, r.t., 10 h	-	-
216	H	Et_2NSF_3	THF, -30 °C, 30 min	83	β

The reaction is reported[173] to proceed with inversion of configuration at the anomeric position to give exclusively the β-anomer. Our data supported this result, with the ^{1}H nmr spectrum exhibiting a large axial-axial coupling, $J_{1,2}$ 10 Hz, for H-1.

A mechanism has been proposed to explain the observed stereoselectivity (scheme 62).[175] Firstly, nucleophilic displacement of one of the fluorine atoms on sulfur by the anomeric hydroxyl group of the sugar **216** gives the intermediate species **271**. Secondly, S_N2 attack by fluoride on the anomeric carbon results in the observed inversion of configuration.

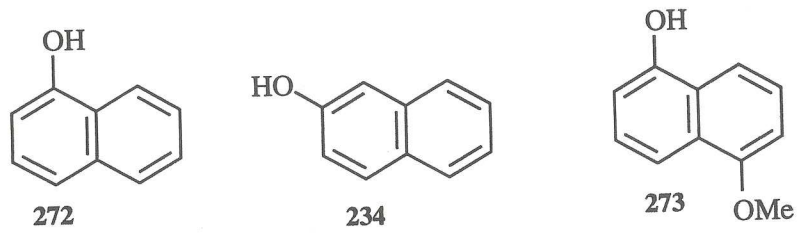
Scheme 62



(iii) Preparation of naphthols.

Naphthols **272**, **234**, and **273** were chosen as the model naphthols for our *C*-glycosylation reactions, since these had the most precedent in the literature (figure 24). While naphthols **272** and **234** were available commercially, it was necessary to synthesize naphthol **273**.

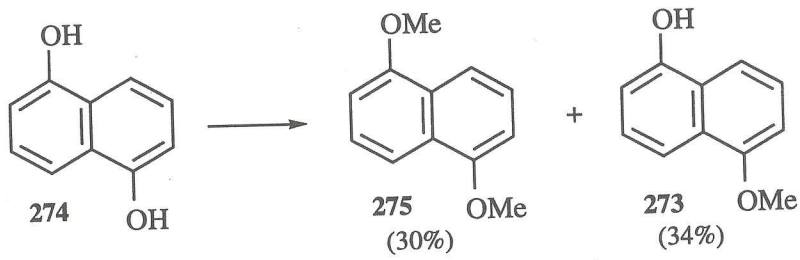
Figure 24



272 234 273

The preparation of 5-methoxynaphthol **273** was carried out according to the procedure of von Krannichfeldt *et al.*[176] (scheme 63), although there is an earlier reference to its preparation by Fischer and Bauer.[177] A solution of 1,5-dihydroxynaphthalene **274** and base was treated with hydrochloric acid then dimethyl sulfate. Unwanted dimethyl ether **275** was removed by filtration, and the solution stirred and heated for a further 4 hours to afford monomethyl ether **273** in 34% yield, on precipitation with hydrochloric acid.

Scheme 63



274

Reagents and conditions: Me_2SO_4, KOH, HCl, H_2O, 4 h, 70 °C.

2.1.3 Investigation of Aryl *C*-Glycosylation Methods.

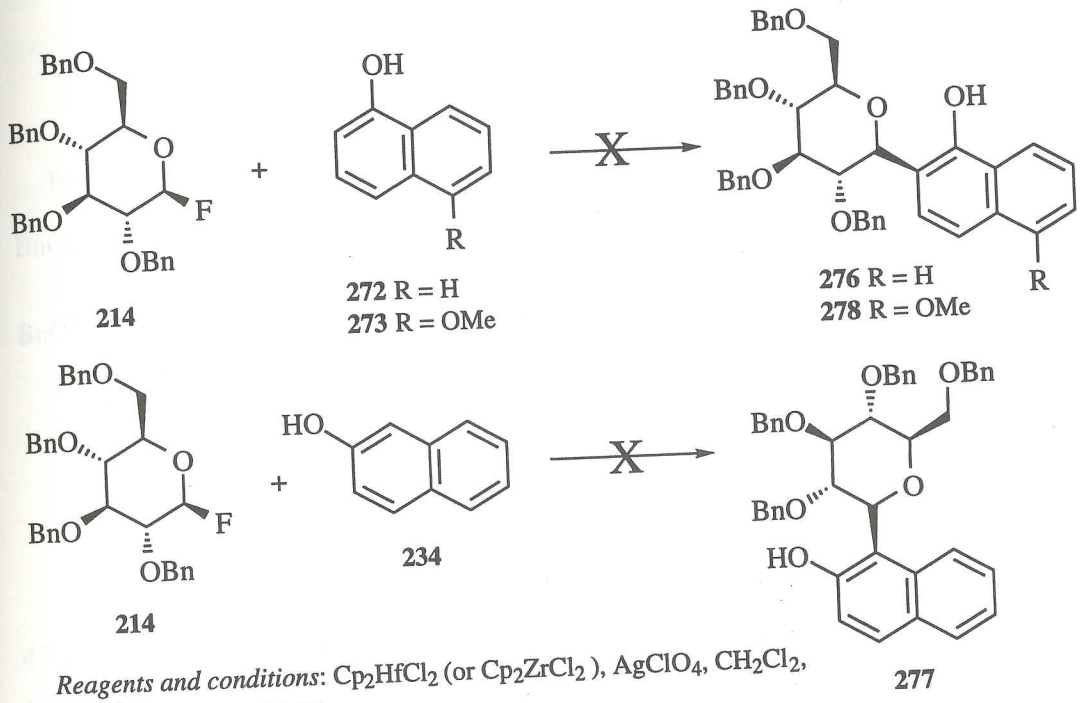
With the model coupling partners in hand, attention turned to an investigation of the various strategies for aryl *C*-glycosylation (reviewed in section **1.3**).

(i) The Suzuki O→C-glycoside rearrangement.

As described in the introduction, the *O→C*-glycoside rearrangement offers a convenient method for *C*-glycosyl bond formation. The reaction of glycosyl fluoride **214** with naphthols **272**, **234** and **273**, was examined using the conditions reported by Suzuki *et al.*[152,154,164] (scheme 64).

A mixture of fluoride **214**, the appropriate naphthol (**272**, **234**, **273**) and 4Å molecular sieves in dry dichloromethane was cooled to -78 °C. The Lewis acid (hafnocene dichloride) and promoter (silver perchlorate) were then added. The solution was allowed to warm to -20 °C and stirred for 1 hour, however, the expected *C*-glycosides (**276**, **277**, **278**) were not observed. Longer reaction times did not result in the formation of the desired product, even when the reaction was allowed to warm to room temperature. Use of an alternative Lewis acid, zirconocene dichloride, was also unsuccessful.

Scheme 64



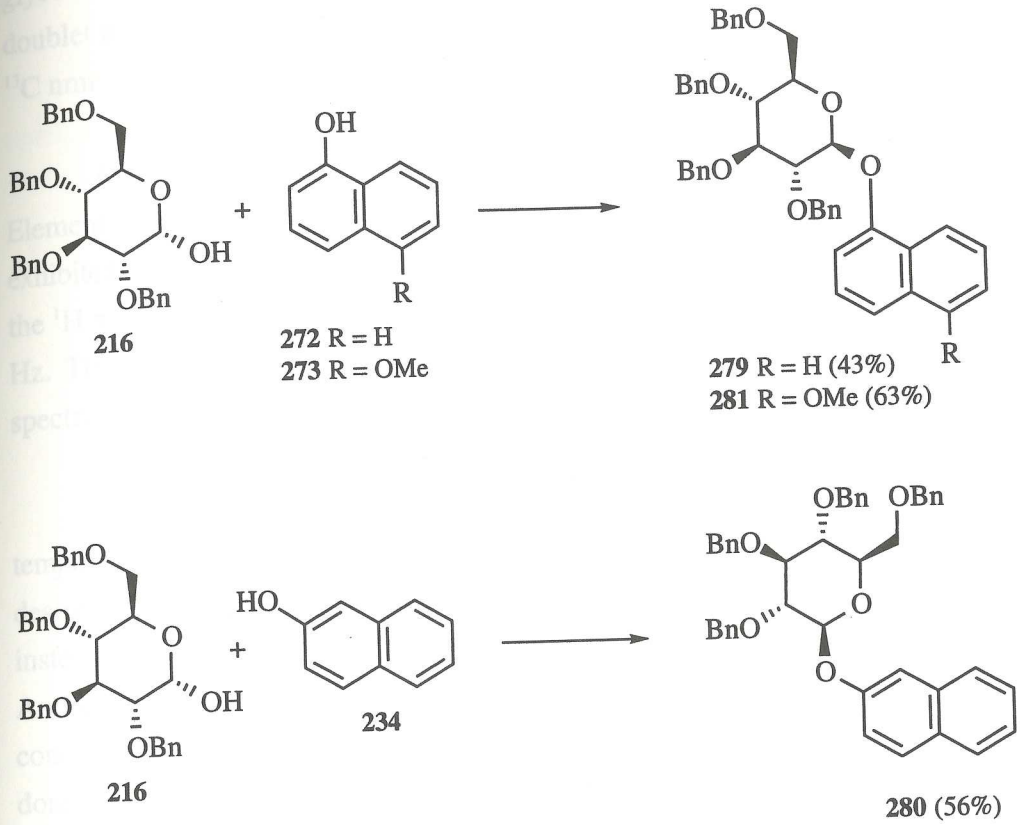
Reagents and conditions: Cp_2HfCl_2 (or Cp_2ZrCl_2), $AgClO_4$, CH_2Cl_2, MS4Å, -78 °C to -20 °C.

(ii) The Kometani O→C-glycoside rearrangement.

Disappointed by the lack of success in effecting *C*-glycosylation using Suzuki's methodology, attention was turned to the two step procedure of Kometani *et al.*[158] As mentioned in the introduction (section **1.3**), this methodology involves the formation of an *O*-glycoside under Mitsunobu conditions[159,160] followed by rearrangement to a β-*C*-glycoside under Lewis acid activation.

Accordingly, a solution of the pyranose **216** and the appropriate naphthol (**272**, **234** or **273**) in tetrahydrofuran at 0 °C was treated with diethyl azodicarboxylate and triphenylphospine to form the corresponding β-*O*-glycosides (**279**, **280**, **281**) in reasonable yields (scheme 65).

Scheme 65



Reagents and conditions: DEAD, PPh_3, THF, 0 °C to r.t., 12 h.

O-Glycoside **279** was obtained as colourless needles (m.p. 131.2-132.2 °C) in 43% yield. The high resolution mass spectrum exhibited a molecular ion at *m/z* 666.2979 consistent with the molecular formula $C_{44}H_{42}O_6$. The ^1H and ^{13}C nmr spectra were also supportive of the proposed structure. In the ^1H nmr spectrum the aliphatic region largely consisted of unresolved multiplets. Notable exceptions were 2'-H, which resonated as a doublet of doublets at δ 3.96 and the anomeric proton 1'-H, which resonated as a doublet at δ 5.23. The coupling constant, $J_{1',2'}$ 7.7 Hz, confirmed the β-stereochemistry about the glycosidic bond. In the ^{13}C nmr spectrum C-1' resonated downfield of the other glycosyl carbons at δ 101.5, characteristic of a β-*O*-glycoside.

O-Glycoside **280** was obtained as colourless needles (m.p. 111.5-112.5 °C) in 56% yield. Elemental analysis confirmed the molecular formula as $C_{44}H_{42}O_6$ and the mass spectrum exhibited a molecular ion at *m/z* 666 further supporting the proposed structure. In the ^1H nmr spectrum the anomeric proton, 1'-H, resonated as a doublet at δ 5.08, $J_{1',2'}$ 7.1 Hz, while C-1' resonated at δ 102.6 in the ^{13}C nmr spectrum.

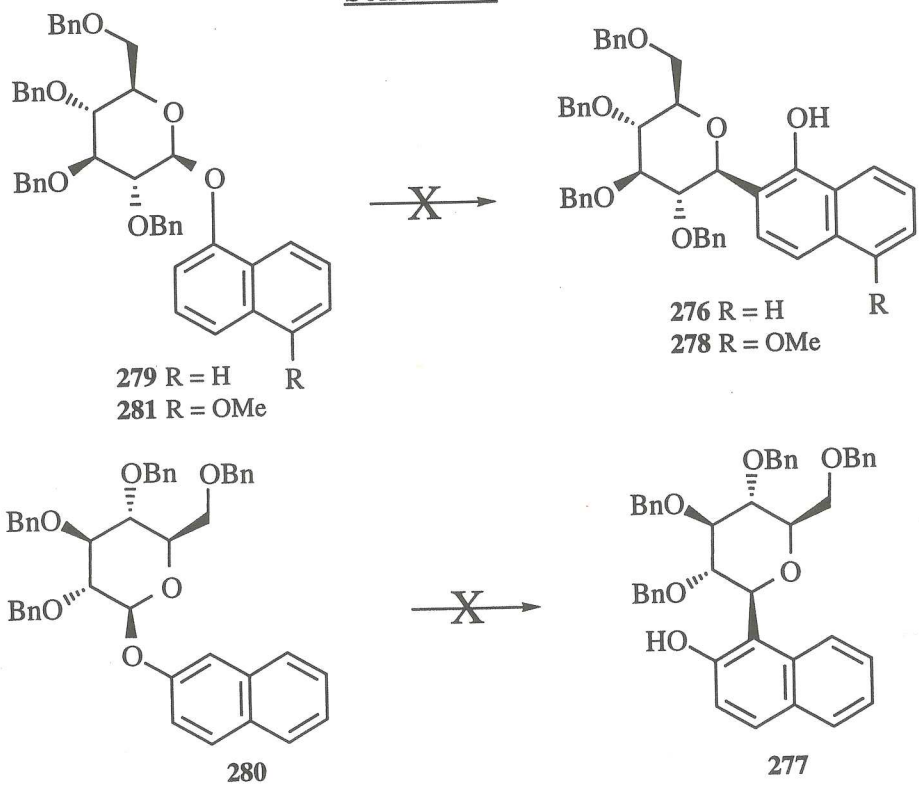
The synthesis of the *O*-glycoside **280** (α:β, 5:1) was recently reported by Larsen and Andrews,[178] with their data supporting the assignment of β-stereochemistry at the

glycosidic linkage for our compound. For comparison, in the α-anomer, 1'-H was a doublet at δ 5.62, with coupling constant, $J_{1',2'}$ 3.5 Hz, and C-1' resonated at δ 95.5 in the ^{13}C nmr spectrum.

O-Glycoside **281** was isolated as tan platelets (m.p. 156-157 °C) in 63% yield. Elemental analysis confirmed the molecular formula as $C_{45}H_{44}O_7$ and the mass spectrum exhibited a molecular ion at *m/z* 696 which further supported the proposed structure. In the ^1H nmr spectrum the anomeric proton, 1'-H, resonated as a doublet at δ 5.21, $J_{1',2'}$ 7.7 Hz. The methoxy group resonated as a three proton singlet at δ 4.00. In the ^{13}C nmr spectrum C-1' resonated at δ 101.6.

Treatment of the *O*-glycosides (**279**, **280**, **281**) in dichloromethane at room temperature with boron trifluoride diethyl etherate failed to effect rearrangement to the desired *C*-glycosides (**276**, **277**, **278**). The glycosidic linkage was eventually cleaved instead, liberating the starting naphthols (**272**, **234**, **273**) (scheme 66). Larsen and Andrews[178] reported the same finding using the α-*O*-glycoside **280**. One of the conclusions derived from their work was that the use of 2-deoxy sugars as glycosyl donors facilitates the formation of *C*-glycosides compared to the use of sugars which are oxygenated at C-2.

Scheme 66

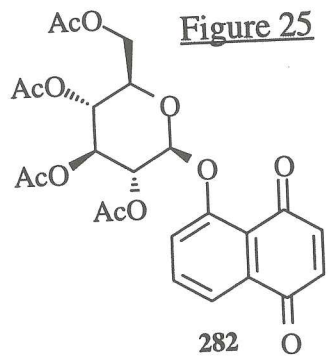


Reagents and conditions: $BF_3.OEt_2$, CH_2Cl_2, r.t., 4 h.

(iii) Rearrangement of an O-Glycoside Prepared From Juglone 75.

Stoodley *et al.*[179,180] used the juglone glucoside **282** in efforts to control the stereochemical outcome of Diels-Alder cycloaddition reactions of juglone derivatives with dienes (figure 25).

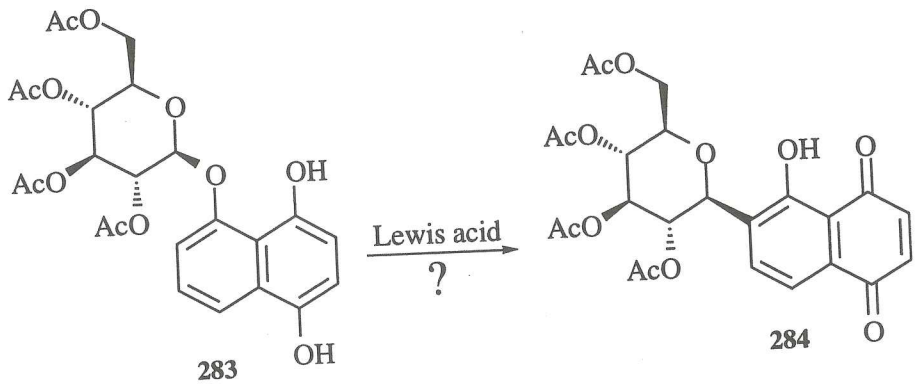
Figure 25



282

Although quinonoid systems are too deactivated to undergo *C*-glycosylation reactions,[181] we proposed that its hydroquinone form **283** might rearrange to the corresponding *C*-glycoside **284** upon treatment with an appropriate Lewis acid (scheme 67).

Scheme 67

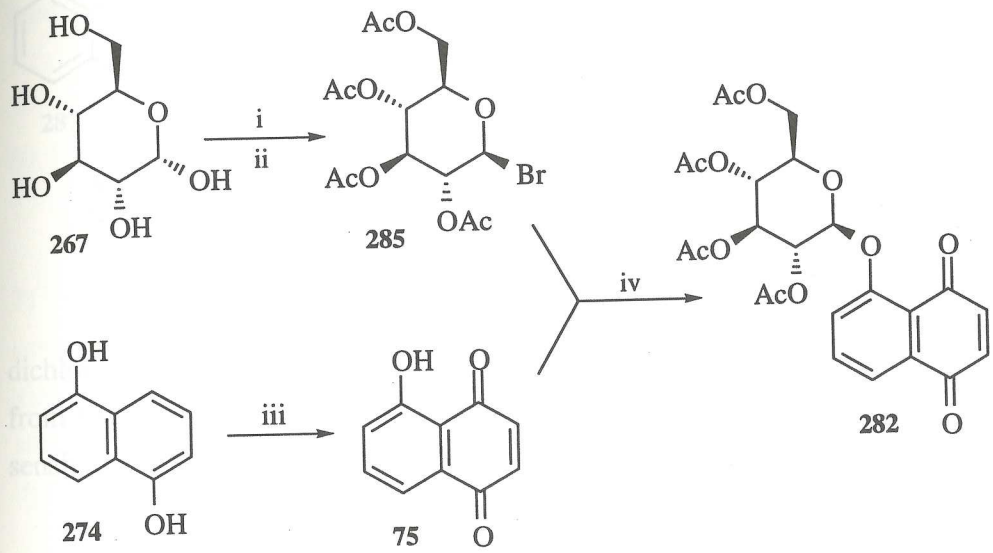


283 **284**

The glycosyl donor, acetobromoglucose **285**, was kindly prepared from glucose **267** by Dr. Mark Bercich (formerly of the University of Auckland, N.Z.) using the procedure of Lemieux *et al.*[182] (scheme 68). Acetobromoglucose **285** is unstable and was purified by flash chromatography (using dichloromethane as eluent) prior to use.

Juglone **75** was synthesized using the method reported by Wakamatsu *et al.*[183] A solution of 1,5-dihydroxynaphthalene **274** and salcomine **286** in tetrahydrofuran underwent Co(II) promoted aerial oxidation to give the orange crystalline juglone **75** in 46% yield after chromatography. This was considerably lower than the reported yield of 80%, although the authors stated that their yield had dropped to 60% when performing the reaction on a gram (instead of milligram) scale.

Scheme 68



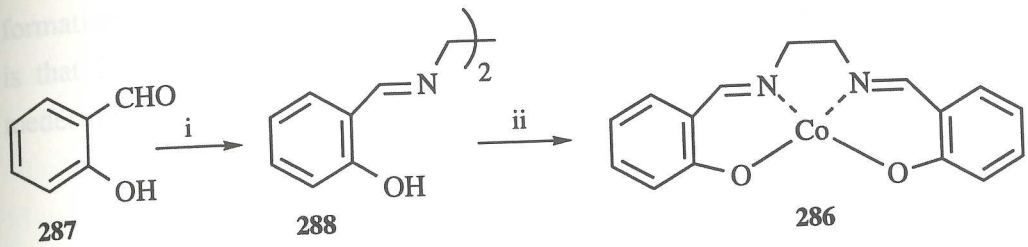
Reagents and conditions: (i) Ac_2O, $HClO_4$ (ii) Br_2, P, H_2O, 70% (iii) O_2, THF, salcomine **286**, 2 h, 46% (iv) Ag_2O, MeCN, ultrasound, 6 h, 36%.

β-*O*-Glycoside **282** was prepared in 36% yield by sonication of juglone **75** and acetobromoglucose **285** with silver(I) oxide in dry acetonitrile.

The data for **282** was in excellent agreement with the literature.[179,180] The infra-red spectrum displayed carbonyl stretches at 1755 and 1745 cm^{-1} consistent with acetate (ester) groups and another at 1670 cm^{-1} consistent with the carbonyl groups of a naphthoquinone whilst there was no evidence of a hydroxyl band. The ^1H nmr further supported the formation of an *O*-glycoside. Four, three proton singlets at δ 2.04, 2.06, 2.07 and 2.11 corresponded with the methyl protons of the four acetate protecting groups on the glycosyl moiety. The anomeric proton, 1'-H, resonated as a doublet at δ 5.14 with the axial-axial coupling, $J_{1',2'}$ 7.5 Hz, confirming formation of a β-*O*-glycoside. In the aromatic region, the presence of five resonances-two doublets at δ 6.84 and 6.89 and three double doublets at δ 7.52, 7.67 and 7.90, further convinced us that we had formed the *O*- and not the *C*-glycoside.

Although salcomine **286** was commercially available, it was also synthesized according to the conditions of Diehl and Hack (scheme 69).[184] Salicylaldehyde **287** was reacted with ethylenediamine to give the Schiff base **288**, which was then treated with cobalt(II) chloride hexahydrate to give salcomine **286** as a brown powder. The yield of juglone **75** was the same using salcomine **286** from the two sources.

Scheme 69



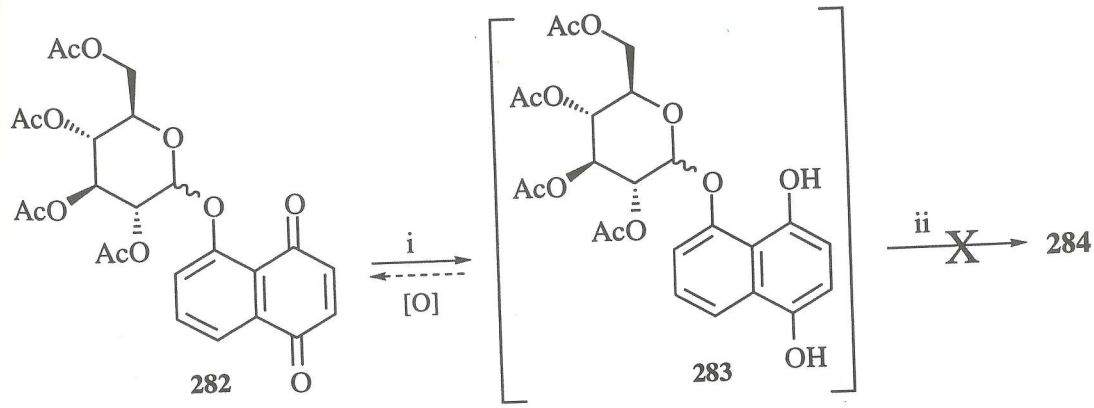
287 **288** **286**

Reagents and conditions: (i) $H_2NCH_2CH_2NH_2$, EtOH, 80 °C, 95%. (ii) NaOH, $NaC_2H_3O_2.3H_2O$, H_2O, 100 °C, $CoCl_2.6H_2O$, 15 min., 90%.

Hydroquinone **283** was readily formed by hydrogenation of the quinone **282** in dichloromethane over 10% palladium on charcoal, the solution rapidly changing colour from deep yellow to almost colourless (scheme 70). Hydroquinone **283** was extremely sensitive, being immediately oxidized to the parent quinone **282** on contact with air.

The solution containing hydroquinone **283** was transferred to a separate flask under hydrogen (by double-ended needle fitted with a filter) and cooled to -30 °C. Subsequent addition of boron trifluoride diethyl etherate (0.1 equiv.) with gradual warming resulted in decomposition of the *O*-glycoside **283**, with none of the desired *C*-glycoside **284** being formed.

Scheme 70



282 **283**

Reagents and conditions: (i) H_2, 10% Pd/C, CH_2Cl_2, 5 min. (ii) $BF_3.OEt_2$, 0.5 h, -30 °C to r.t.

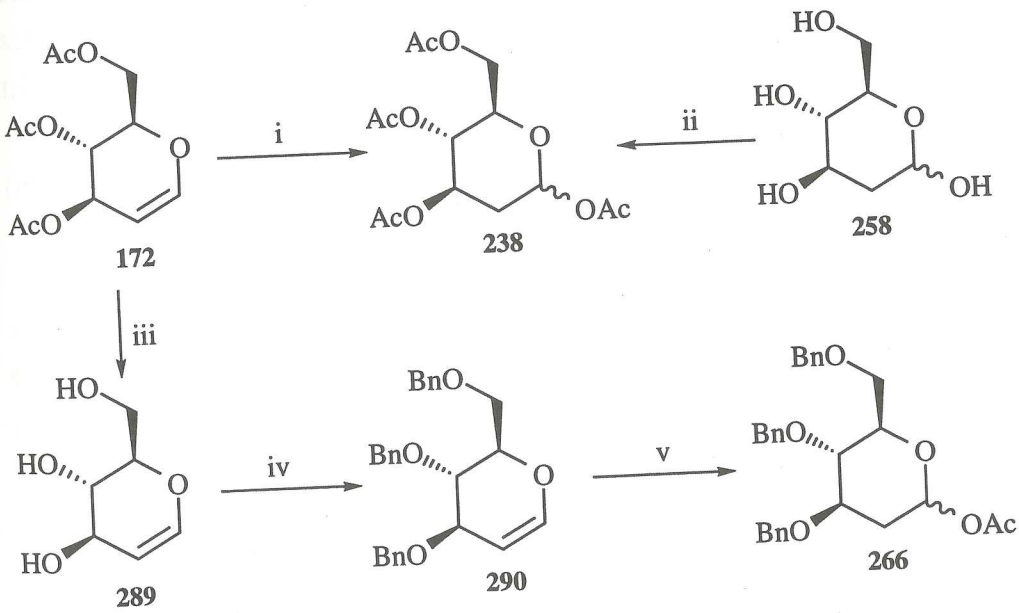
2.1.4 Synthesis of 2-Deoxyglycosyl Donors.

Given the lack of success at forming *C*-glycosides of simple naphthols when using glycosyl donors derived from D-glucose, it was decided to investigate the use of more reactive 2-deoxyglycosyl donors. It was felt that the bulky benzyloxy group at C-2 might be preventing the *O*→*C*-glycoside rearrangement from occurring. Furthermore, 2-deoxy sugar reactants have been reported by Larsen and Andrews[178] to facilitate the formation of *C*-glycosides, compared to sugars oxygenated at C-2. An additional benefit is that 2-deoxyglycosyl donors are closer analogues of the glycosyl component of medermycin **52**.

(i) *Synthesis of glycosyl donor 238.*

The 2-deoxypyranoside **238** was prepared using two different methods (scheme 71). The procedure of Overend *et al.*[185] involved the acetylation of 2-deoxyglucose **258** using pyridine and acetic anhydride at 0 °C, to afford acetate **238** (α:β, 10:1) in 73% yield as colourless needles. The procedure of Mioskowski *et al.*[186] required treatment of a solution of tri-*O*-acetyl-D-glucal **172** in dichloromethane with triphenylphosphine hydrobromide and acetic acid, affording the desired acetate **238** (α:β, 9:1) in 72% yield.

Scheme 71

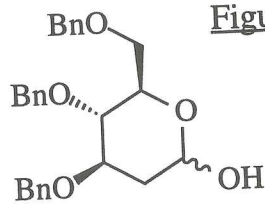


Reagents and conditions: (i) PPh_3.HBr, AcOH, CH_2Cl_2, 2 days, 72% (ii) Ac_2O, Pyr, 0 °C, 4 days, 73% (iii) Na_2CO_3, MeOH, 1 h, 99% (iv) BnCl, DMSO, NaH, 4 h, 46% (v) PPh_3.HBr, AcOH, CH_2Cl_2, 12 h, 86%.

(ii) Synthesis of glycosyl donor 266.

Tri-*O*-benzyl-D-glucal **290** is commercially available (Aldrich™) but was generally prepared from tri-*O*-acetyl-D-glucal **172** in a two step procedure. Deacetylation of **172** was initially carried out in methanol using de-acidite FF-IP (-OH) resin, according to the procedure of Brimbacombe *et al.*,[187] but latterly was found to be faster and more convenient using sodium carbonate and methanol, affording D-glucal **289** as a colourless syrup in quantitative yield. Benzylation of D-glucal **289** was carried out, according to the procedure of Blackburne *et al.*,[188] using benzyl chloride and sodium hydride in dimethylformamide, to afford tri-*O*-benzyl-D-glucal **290** in 46% yield as colourless needles. Acetate **266** was prepared from **290** according to the procedure of Mioskowski *et al.*[186] A solution of the **290** in dichloromethane was treated with triphenylphosphine hydrobromide and acetic acid to afford the acetate **266** (α:β, 9:1) in 86% yield. The useful byproduct pyranose **291** (α:β, 3:1) was also recovered in 6% yield as a white solid (figure 26).

Figure 26



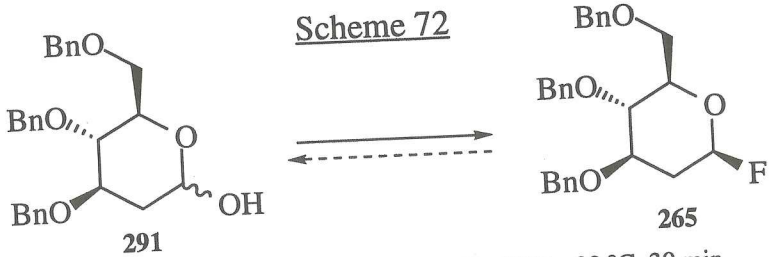
291

Triphenylphosphine hydrobromide was prepared according to the procedure of Jellinek and van den Akker.[189] Anhydrous hydrogen bromide gas was bubbled through a solution of triphenylphoshine in diethyl ether-dichloromethane (1:3) at 0 °C affording triphenylphosphonium hydrogen bromide in 87% yield as a white solid.

(iii) Synthesis of glycosyl fluoride 265.

Pyranose **291** was treated with diethylaminosulfur trifluoride (DAST), in the same manner as the analogous 2-benzyloxy pyranose **216**, to generate the β-glycosyl fluoride **265** (scheme 72). However, purification was problematic with the unstable **265** rapidly decomposing to the pyranose **291**.

Scheme 72



291 **265**

Reagents and conditions: Et_2NSF_3, THF, -30 °C, 30 min.

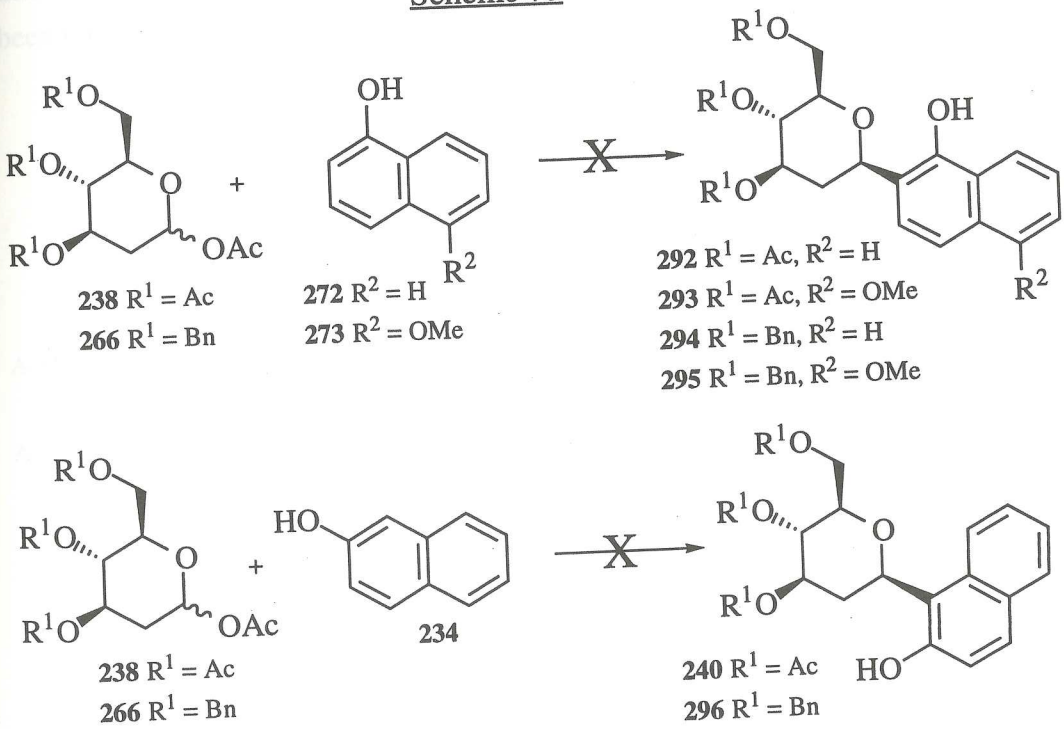
2.1.5 Aryl *C*-Glycosylation Using 2-Deoxyglycosyl Donors.

Suzuki *et al.*[154] reported similar difficulties in purification and storage of the unstable 1-fluoro derivatives of 2-deoxysugars, turning their attention to the more stable 1-*O*-acetyl sugars, which they reported to be just as successful under the reaction conditions. This encouraged us to turn to the acetates **266** and **238** in the current work rather than the problematic glycosyl fluoride **265**.

(i) Glycosylation using Suzuki conditions.

Glycosyl acetates (**266, 238**) were reacted with naphthols (**272, 234, 273**) in dichloromethane using dicyclopentadienylhafnacene dichloride and silver perchlorate in the presence of 4Å molecular sieves (scheme 73). In none of these reactions was *C*-glycoside formation observed.

Scheme 73



Reagents and conditions: Cp_2HfCl_2, $AgClO_4$, CH_2Cl_2, MS4Å, -78 °C to -20 °C.

(ii) C-Glycosylation using Toshima's methodology.

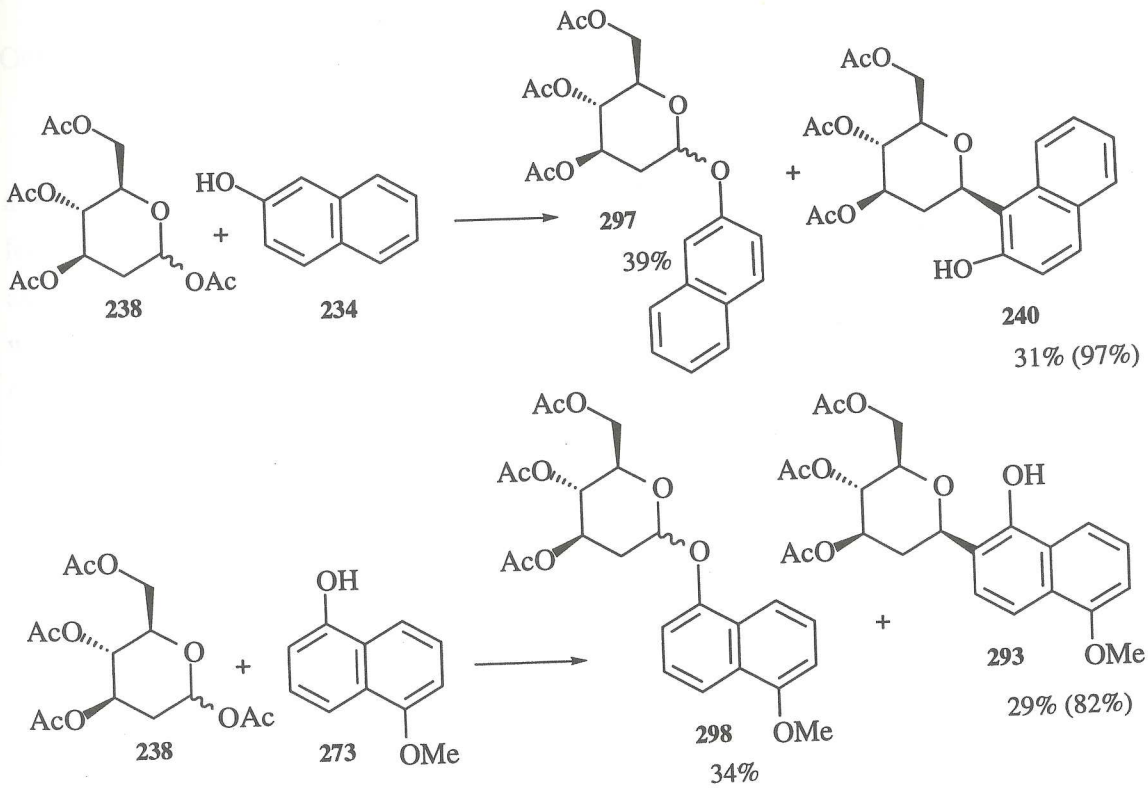
Disappointed by the lack of success using Suzuki's methodology, it was decided to investigate a different strategy reported by Toshima *et al.*[155] This work was cited as

"part of the ongoing program of research in areas such as the first total synthesis of medermycin **52**". Tatsuta, who subsequently achieved that goal,[62] was a co-author. They reported excellent results from the the combined use of trimethylsilyl triflate and silver perchlorate (1:1) as the Lewis acid promoter in the reaction of methyl glycosides and glycosyl acetates with simple naphthols (see scheme 52).

In our hands, naphthols (**234**, **273**) were reacted with glycosyl acetate **238** in dichloromethane at 0 °C using the trimethylsilyl triflate-silver perchlorate promoter system, the reaction then being warmed to room temperature over 1 hour (scheme 74). For both naphthols (**234**, **273**) mixtures of the *O*-glycosides (**297**, **298**) and the desired β-*C*-glycosides (**240**, **293**) were obtained, even after prolonged stirring.

In contrast, when using the more coordinating solvent, acetonitrile, β-*C*-glycosides **240** and **293** were formed exclusively, in yields of 97% and 82% respectively. A similar effect on changing the solvent to acetonitrile, when using boron trifluoride diethyl etherate as the Lewis acid in analogous *C*-glycosylation reactions, has been reported by Larsen *et al.*[161] (scheme 54) and by Allevi *et al.*[150] (schemes 44 and 45).

Scheme 74



Reagents and conditions: TMSOTf, $AgClO_4$, CH_2Cl_2 (or MeCN), 0 °C to r.t.

The α-*O*-glycoside **297** was isolated in 39% yield. The infra-red spectrum lacked a hydroxyl stretch, suggesting an *O*-glycoside. Elemental analysis confirmed the molecular formula as $C_{22}H_{24}O_8$ and the mass spectrum exhibited a molecular ion at *m/z* 416. The ^{1}H nmr spectrum showed three, three proton singlets at δ 1.96, 2.05 and 2.07, attributed to the acetate groups. The anomeric proton 1'-H resonated at δ 5.83 as a broad doublet, with a 2.6 Hz coupling constant indicating the α-anomeric conformation. The anomeric carbon, C-1', resonated at δ 95.3 in the the ^{13}C nmr spectrum, consistent with an α-*O*-glycoside.

The β-*C*-glycoside **240** was isolated in 31% yield (dichloromethane) and 97% (acetonitrile). High resolution mass spectrometry confirmed the molecular formula as $C_{22}H_{22}O_8$. The infra-red spectrum displayed a broad hydroxyl stretch, as expected for the *C*-glycoside. In the ^{1}H nmr spectrum, the anomeric proton 1'-H resonated at δ 5.62 as a doublet of doublets, with coupling constants 11.9 and 2.1 Hz. These represent a large axial-axial coupling with 2'ax-H and a smaller axial-equatorial coupling with 2'eq-H, indicative of the β-stereochemistry of the *C*-glycoside bond. The hydroxyl proton resonated at δ 8.48. In the ^{13}C nmr spectrum, the anomeric carbon, C-1', resonated at 76.6, indicative of a *C*-glycoside.

Compounds **297** and **240** have both been synthesized by other research groups. Our data and assignments agreed well with those reported in the literature.[150,178]

The α-*O*-glycoside **298** was isolated in 34% yield. The infra-red spectrum lacked a hydroxyl stretch and high resolution mass spectrometry confirmed the molecular formula as $C_{23}H_{26}O_9$. In the ^{1}H nmr spectrum, the three proton singlet at δ 3.99 was assigned to the methoxy group. The anomeric proton resonated as a doublet at δ 5.85, with the coupling constant of 2.5 Hz indicating α-stereochemistry. The anomeric carbon, C-1', resonated at δ 95.3, indicative of an *O*-glycoside.

The β-*C*-glycoside **293** was isolated in 29% yield (dichloromethane) and 82% (acetonitrile). High resolution mass spectrometry confirmed the molecular formula as $C_{23}H_{26}O_9$. A broad hydroxyl stretch in the infra-red spectrum was attributed to the phenol of the *C*-glycoside. The ^{1}H nmr spectrum supported the proposed structure. The anomeric proton 1'-H resonated at δ 4.96 as a doublet of doublets, with coupling constants 10.1 and 2.2 Hz indicative of a β-*C*-glycoside. The hydroxyl proton resonated at δ 8.23. The anomeric carbon, C-1', resonated at δ 76.6 in the ^{13}C nmr spectrum, providing further support for the *C*-glycoside structure.

2.1.6 Summary.

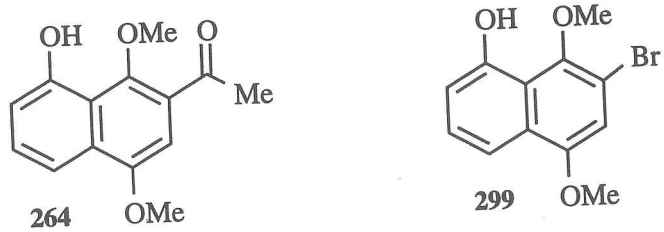
In conclusion, it was found that the more reactive 2-deoxyglucose system was necessary for the *C*-glycosylation reaction to be successful. The best conditions for the coupling were using trimethylsilyl triflate and silver perchlorate as the Lewis Acid catalyst system and with acetonitrile as the solvent. With an effective method for *C*-glycosylation of naphthols with 2-deoxyglycosyl donors at hand, attention was then focused on the use of a more functionalized naphthol in the *C*-glycosylation reaction. First of all, preparation of naphthols suitable for further elaboration to the synthesis of medermycin analogue **257** was required.

2.2 Aryl *C*-Glycosylation Using Naphthols 264 and 299.

2.2.1 Synthetic Strategy for Naphthols 264 and 299.

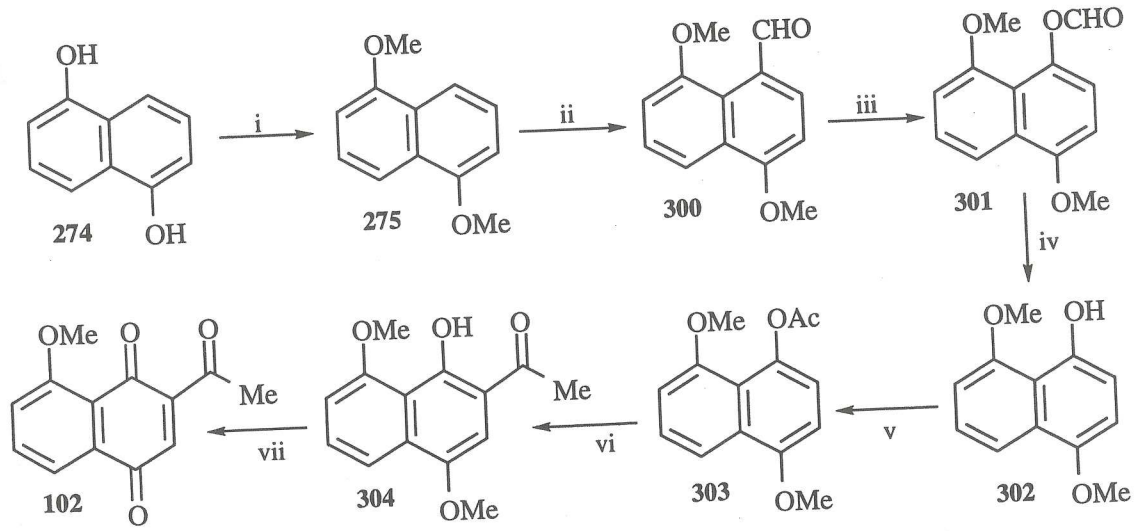
With a successful method for the formation of *C*-glycosides now in hand, it was neccessary to synthesize the more highly substituted naphthols **264** and **299** (figure 27) required for the synthesis of medermycin **52** and the target analogue **257**.

Figure 27



The synthesis of acetylnaphthoquinone **102** by Rapoport *et al.*[190] would be the usual route to this type of ring system (scheme 75). Key steps in this synthesis were introduction of a formyl group *via* the Vilsmeier reaction, Baeyer-Villager oxidation of the resulting aldehyde **300** and hydrolysis of the formate ester **301** to give naphthol **302**. The synthesis was completed by Fries rearrangement of acetate **303** and CAN oxidation of the resultant acetylnaphthol **304** to the naphthoquinone **102**.

Scheme 75

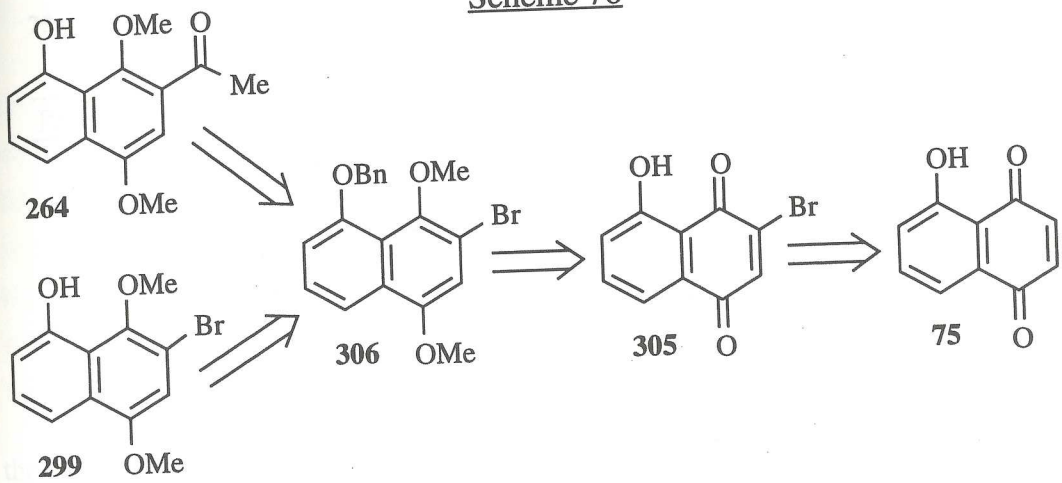


Reagents and conditions: (i) DMSO, Me_2SO_4, KOH, THF, 0 °C (ii) $POCl_3$, DMF, toluene, 10% NaOH, 0 °C (iii) SeO_2, H_2O_2, CH_2Cl_2 (iv) 10% HCl, acetone, reflux (v) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (vi) $BF_3.OEt_2$, heat (vii) aq. CAN, CH_3CN.

In the present work however, we required a free hydroxyl group (at C-5) to facilitate the *O*→*C*-glycoside rearrangement reaction. Thus an easily removable protecting group was required at this position. In addition, since naphthoquinones are too deactivated to undergo *C*-glycosylation, we required the reductively methylated form.

A retrosynthetic analysis of bromonaphthalene **299** and acetylnaphthalene **264** beginning with juglone **75** was proposed with the above points in mind (scheme 76). Regioselective bromination of juglone **75** affords 3-bromojuglone **305**, which is benzylated and reductively methylated to give **306**. Removal of the benzyl ether then affords **299**. Alternatively, the acetyl group is introduced *via* lithiation of **306** and reaction with acetyl chloride. Removal of the benzyl ether then affords **264**.

Scheme 76



2.2.2 Synthesis of 3-Bromonaphthol 299.

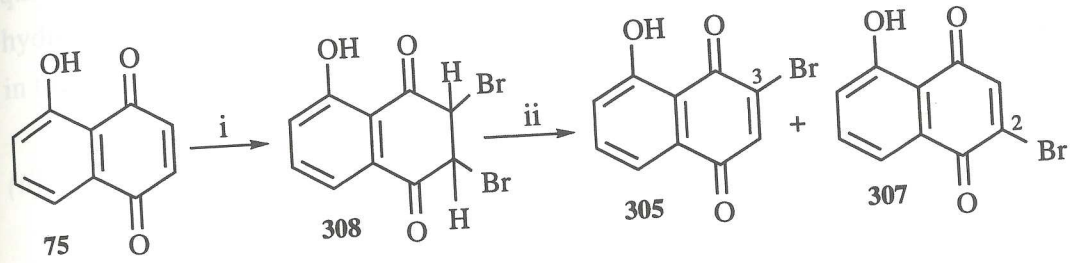
(i) *Synthesis of 3-bromojuglone 305 (and 2-bromojuglone 307).*

The first step in the synthesis was the bromination of juglone **75** (scheme 77). There are a range of methods for this reaction reported in the literature. One reported synthesis involves the reaction of juglone **75** with bromine in glacial acetic acid at 0 °C to form the dibromide **300**, followed by dehydrohalogenation in refluxing ethanol to afford **305** in 85% yield. This procedure was first reported[191,192] to give 2-bromojuglone **307**, but this assignment was shown to be in error.[193] Rapoport *et al.*[190] obtained yields of less than 66% from the same reaction, and the **305** produced was invariably contaminated with di- and tribrominated naphthoquinones. Bromination in chloroform at 0 °C, followed by addition of a trace of acetic acid and dehydrohalogenating in refluxing ethanol was reported to give mostly **305** in 78% yield along with 6-10% of the 2-bromo isomer **307**.

In our hands the latter method of Rapoport *et al.*[190] gave a 3.6:1 mixture of **305** and **307** in an overall yield of 97% (scheme 77).

A modification of the above reaction by Crossley *et al.*[194] involved the addition of boron trifluoride diethyl etherate during the dehydrohalogenation step. Using this method, 3-bromojuglone **305** was obtained as the sole product in 59% yield.

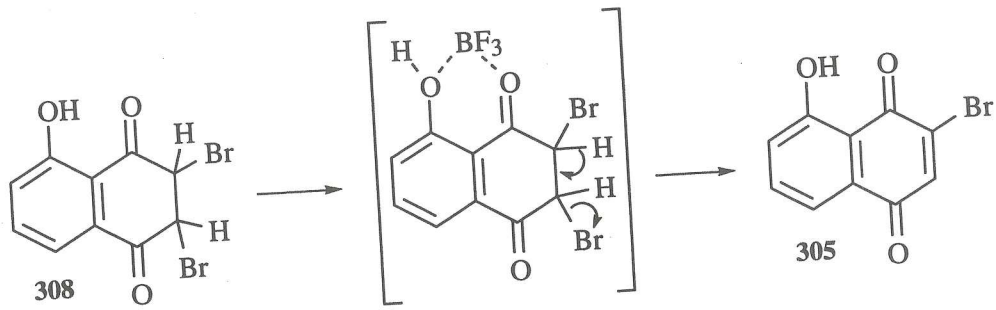
Scheme 77



Procedure	Conditions	Yield (%) **305** : **307**
1.	(i) Br_2, AcOH, $CHCl_3$, 70 min., (ii) EtOH, reflux, 15 min.	76 : 21
2.	(i) Br_2, AcOH, $CHCl_3$, 70 min., (ii) EtOH, $BF_3.OEt_2$, reflux, 15 min.	59 : 0

Crossley *et al.*[194] proposed that boron trifluoride diethyl etherate complexes with the C-5 hydroxyl and C-4 carbonyl groups of the intermediate, juglone dibromide **308**, thereby increasing the acidity of the C-3 proton. This favours the formation of the 3-bromide **305** on elimination of hydrogen bromide (scheme 78).

Scheme 78



3-bromojuglone **305** was the less polar of the two regioisomers and melted at 171-172 °C, in good agreement with the literature.[193] The infra-red spectrum showed a characteristic hydroxyl stretch at 3050 cm^{-1} as well as quinone carbonyl stretches at 1656 and 1631 cm^{-1}. The ^1H nmr spectrum featured a singlet at δ 11.74 due to the hydrogen

bonded hydroxyl group while in the ^{13}C nmr spectrum, C-2 was a methine resonance at δ 141.5. The molecular ion at *m/z* 254/252 in the mass spectrum was consistent with the molecular formula $C_{10}H_5BrO_3$.

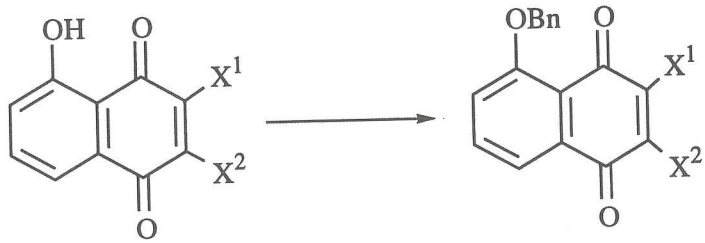
The more polar 2-bromojuglone **307** melted at 135-136 °C and exhibited a molecular ion at *m/z* 254/252 in the mass spectrum, consistent with the molecular formula $C_{10}H_5BrO_3$. Bands at 1675 and 1633 cm^{-1} in the infra-red spectrum were assigned to the quinone carbonyls, but the hydroxyl group was not visible. In the ^1H nmr spectrum, the hydroxyl proton resonated as a singlet at δ 11.77 while the quaternary carbon at δ 140.9 in the ^{13}C nmr spectrum was assigned to C-2. The data agreed well with the literature.[193]

*(ii) Synthesis of benzyl ether **309** (and regioisomer **310**).*

With 3-bromojuglone **305** in hand, attention turned to the benzylation and reductive methylation steps (scheme 79). A solution of 3-bromojuglone **305** in chloroform was treated with benzyl bromide and silver(I) oxide. The yellow crystalline benzyl ether **309** was obtained in 89% yield after work-up and chromatography. When working on a large scale, chromatography was complicated by the presence of benzyl bromide, which co-eluted with the product. The product also tended to crystallize prematurely on the column. In this case recrystallization from hexane-ethyl acetate became the preferred method of purification.

The 2-bromo isomer **307** was subjected to the same conditions, affording the crystalline benzyl ether **310** in 84% yield.

Scheme 79



Naphthol	X	Benzyl ether	Yield (%)
305	X^1= Br, X^2= H	**309**	89
307	X^1= H, X^2= Br	**310**	84

Reagents and conditions: BnBr, Ag_2O, $CHCl_3$, 2 h.

Benzyl ether **309** melted at 107-108 °C. The high resolution mass spectrum (FAB) exhibited a molecular ion at *m/z* 341.9893 consistent with the molecular formula $C_{17}H_{11}{}^{79}BrO_3$. In the infra-red spectrum the single strong band at 1672 cm^{-1} was assigned to the quinone carbonyls, while the absence of a hydroxyl stretch provided further evidence that benzylation had taken place. The ^1H nmr spectrum was also consistent with the introduction of a benzyl group with a singlet at δ 5.30 being assigned to the benzylic methylene group and there was no sign of a hydoxyl peak. The quinone carbonyl carbons, C-1 and C-4, resonated at δ 176.0 and 182.5 in the ^{13}C nmr spectrum.

The 2-bromo isomer **310** melted at 122-123 °C and the high resolution mass spectrum (EI) contained a molecular ion at *m/z* 341.9893 consistent with the molecular formula $C_{17}H_{11}{}^{79}BrO_3$. The infra-red spectrum featured strong bands at 1676 and 1656 cm^{-1} assigned to the quinone carbonyl groups. The ^1H nmr spectrum displayed a two proton singlet at δ 5.30 assigned to the benzylic methylene group. The ^{13}C nmr spectrum provided further evidence for benzylation, with the resonance at δ 70.9 being assigned to the benzylic methylene group. The quinone carbonyl carbons, C-1 and C-4, resonated at δ 178.2 and 181.3.

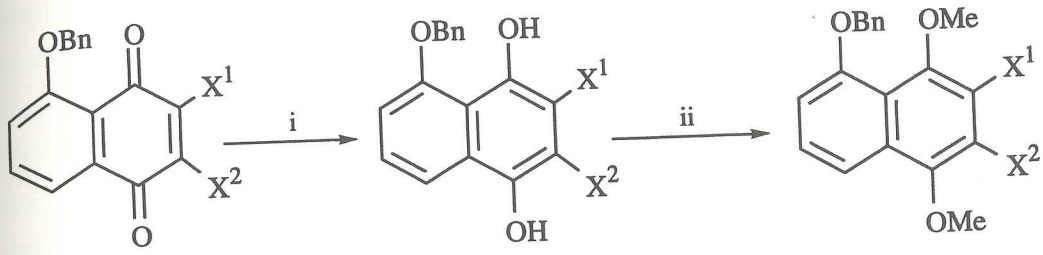
*(iii) Synthesis of naphthalene **306** (and regioisomer **313**).*

With the hydroxy group protected as a benzyl ether, reductive methylation of the quinone was next undertaken. Naphthoquinone **309** was reduced with sodium dithionite solution to give the air sensitive hydroquinone **311**, which was methylated using dimethyl sulfate and potassium carbonate to give the dimethoxynaphthalene **306** in 76% yield (scheme 80).

The 2-bromo isomer **310** reacted under the same conditions to give the dimethylated product **313** in 79% yield, *via* the hydroquinone **312**.

Bromonaphthalene **306** melted at 93.5-94.5 °C and the high resolution mass spectrum (LSIMS) exhibited a molecular ion at *m/z* 372.0363 consistent with the molecular formula $C_{19}H_{17}{}^{79}BrO_3$. There was no sign of a carbonyl band in the infra-red spectrum, confirming reduction of the quinone. The ^1H nmr spectrum was in agreement with the proposed structure, containing two three proton singlets at δ 3.71 and 3.95 assigned to the newly introduced methoxy groups. The C-2 proton resonated as a singlet at δ 6.95, considerably upfield of its position in the quinone **309**. In the ^{13}C nmr spectrum the methoxy groups resonated at δ 56.6 and 62.5, while the quinone carbonyl carbons were no longer present.

Scheme 80



Quinone	X	Hydroquinone	Product	Yield (%)
309	X^1= Br, X^2= H	**311**	**306**	76
310	X^1= H, X^2= Br	**312**	**313**	79

Reagents and conditions: (i) $Na_2S_2O_3/H_2O$, CH_2Cl_2/Et_2O (ii) Me_2SO_4, K_2CO_3, Me_2CO, reflux, 48 h.

The 2-bromo isomer **313** melted at 90.5-100.0 °C and the high resolution mass spectrum exhibited a molecular ion at *m/z* 372.0368 consistent with the molecular formula $C_{19}H_{17}{}^{79}BrO_3$. The infra-red spectrum was characterized by the lack of bands in the carbonyl region, confirming reduction of the naphthoquinone. The ^1H nmr spectrum displayed three proton singlets at δ 3.91 and 3.93 due to the methoxy groups, a two proton singlet at δ 5.20 assigned to the benzylic methylene group and a singlet at δ 6.91 assigned to 3-H. The ^{13}C nmr spectrum featured resonances at δ 55.6 and 61.2 due to the methoxy groups together with a benzylic methylene resonance at δ 71.4.

*(iv) Synthesis of bromonaphthol **299** (and regioisomer **314**).*

The final step in the synthesis of bromonaphthol **299** was the removal of the benzyl protecting group. A solution of the benzyl ether **306** in ethyl acetate was stirred with 10% palladium on charcoal under an atmosphere of hydrogen to give the crystalline bromonaphthol **299** in 98% yield (scheme 81).

Likewise, the 2-bromo isomer **314** was readily afforded by hydrogenolysis of the benzyl ether **313** in 94% yield.

Bromonaphthol **299** melted at 75.5-76.5 °C and analysed correctly for $C_{12}H_{11}BrO_3$. The mass spectrum contained a molecular ion at *m/z* 284/282 further supporting the proposed structure and the infra-red spectrum exhibited a broad band at 3362 cm^{-1} indicative of a hydroxyl group. In the ^1H nmr spectrum, the hydroxyl proton was clearly visible as a downfield singlet at δ 9.39.

Scheme 81



Benzyl ether	X	Product	Yield (%)
306	X^1= Br, X^2= H	**299**	98
313	X^1= H, X^2= Br	**314**	94

Reagents and conditions: EtOAc, H_2, Pd/C, 8 h.

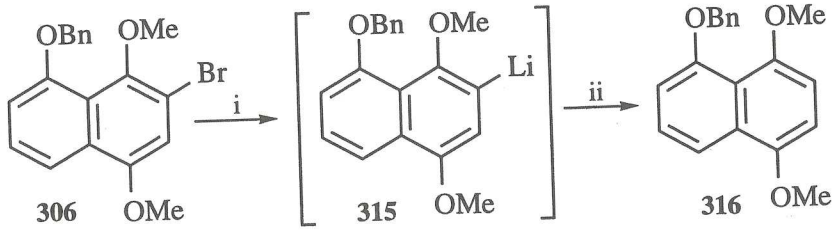
2-Bromonaphthol **314** melted at 140.5-141.5 °C and the high resolution mass spectrum (EI) exhibited a molecular ion at *m/z* 281.9884 consistent with the molecular formula $C_{12}H_{11}{}^{79}BrO_3$. The infra-red spectrum exhibited a broad band at 3362 cm^{-1} indicative of a hydroxyl group. The ^1H nmr spectrum displayed three proton singlets at δ 3.92 and 4.05 assigned to the methoxy groups. A singlet at δ 6.86 was assigned to 3-H and doublet of doublets at δ 6.93, 7.43 and 7.57 were assigned to 6-H, 7-H and 8-H respectively. The resonance at δ 9.19 was assigned to the hydroxyl group. In the ^{13}C nmr spectrum the methoxy groups resonated at δ 56.5 and 61.1.

2.2.3 Synthesis of Acetylnaphthol 264.

(i) Synthesis of alcohol 317 (and regioisomer 318).

It was hoped that the ketone moiety could be installed in one step by the reaction of the lithiated anion of **306** with acetyl chloride. The lithium anion **315** was successfully formed by treatment of a solution of **306** in tetrahydrofuran at -78 °C with *n*-butyllithium (1.35 equiv.). On quenching the reaction with freshly distilled acetyl chloride, however, only the protonated product **316** was recovered (scheme 82).

Scheme 82

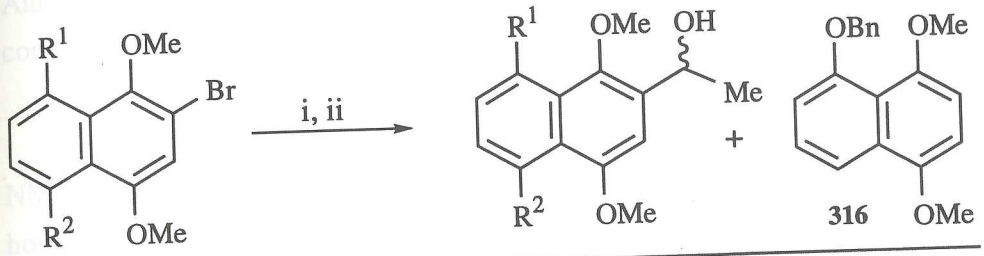


Reagents and conditions: (i) *n*-BuLi, THF, -78 °C, 10 min. (ii) CH_3COCl, 30 min.

It was felt that there would be a greater chance of success using acetaldehyde since acetyl chloride tends to be contaminated with hydrochloric acid. Treatment of bromonaphthalene **306** in tetrahydrofuran at -78 °C with *n*-butyllithium (1.35 equiv.) afforded the naphthyl anion **315**, which was then quenched with acetaldehyde (scheme 83). In addition to the desired product, alcohol **317**, considerable amounts of the protonated compound **316** were also formed. On reducing the amount of time between addition of the lithium reagent and addition of the acetaldehyde (T_1) the yields improved dramatically, affording the benzylic alcohol in 98% yield when the addition was immediate.

The regioisomeric bromide **313** was converted to the alcohol **318** in 97% yield using the optimized conditions.

Scheme 83



Bromide	R	T_1 (min.)	Product	Yield (%)	**316** (%)
306	R^1= OBn, R^2=H	30	**317**	12	82
306	R^1= OBn, R^2=H	10	**317**	45	33
306	R^1= OBn, R^2=H	0.5	**317**	98	0
313	R^1= H, R^2=OBn	0.5	**318**	97	0

Reaction conditions: (i) *n*-BuLi, -78 °C, THF, T_1 (ii) CH_3CHO, T_2 = 15 min.

The infra-red spectrum for **317** exhibited a broad band at 3405 cm^{-1} indicative of a benzylic alcohol and the high resolution mass spectrum (LSIMS) exhibited a molecular ion at *m/z* 338.1520, consistent with the molecular formula $C_{21}H_{22}O_4$. The ^1H nmr spectrum contained a three proton doublet at δ 1.57, J_{vic} 6.4 Hz, assigned to the side chain methyl group. A broad singlet at δ 2.30 was assigned to the hydroxyl proton while the quartet at δ 5.41, J_{vic} 6.4 Hz, was assigned to the benzylic proton.

Formation of the alcohol **318** was confirmed by the presence of a molecular ion at *m/z* 338.1520 in the high resolution mass spectrum (EI), consistent with the molecular formula $C_{21}H_{22}O_4$. The infra-red spectrum exhibited a broad band at 3410 cm^{-1} assigned to the benzylic alcohol. The ^1H nmr spectrum featured a doublet at δ 1.55 and a quartet at

δ 5.41, each with coupling constant J_{vic} 6.5 Hz, assigned to the side chain methyl and benzylic protons respectively. The broad singlet at δ 2.45 was assigned to the hydroxyl proton, while the three proton singlets at δ 3.86 and 3.92 were assigned to the methoxy groups. The methylene protons of the benzyl protecting group appeared as a singlet at δ 5.18 while 3-H also resonated as a singlet at δ 6.92. The ^{13}C nmr spectrum featured resonances at δ 24.2 and 64.7 corresponding respectively to the methyl and methine carbons of the side-chain. The methoxy groups resonated at δ 56.5 and 62.4 and the methylene group at δ 71.5.

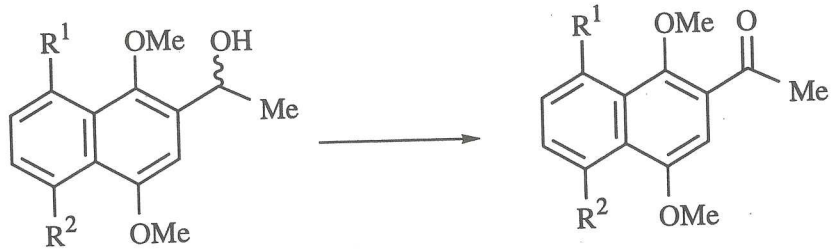
*(ii) Synthesis of ketone **319** (and regioisomer **320**).*

Oxidation of the benzylic alcohol **317** to the ketone **319** was initially attempted using manganese dioxide, however, no reaction took place even after stirring for a day. Attention turned to the use of tetra-*n*-propylammonium perruthenate (TPAP), in combination with *N*-methylmorpholine-*N*-oxide (NMO) as reoxidant.[195,196]

TPAP (5 mol%) was added to a solution of the benzylic alcohol **317** (1.0 equiv.), NMO (1.5 equiv.) and powdered molecular sieves (4Å) in dichloromethane. After 3 hours the reaction was complete and purification by flash chromatography afforded the ketone **319** in 80% yield (scheme 84).

The regioisomeric alcohol **318** was also conveniently oxidized to the ketone **320** in excellent yield using the TPAP/NMO system.

Scheme 84



Alcohol	R	Product	Yield (%)
317	R^1= OBn, R^2=H	**319**	80
318	R^1= H, R^2=OBn	**320**	78

Reaction conditions: TPAP, NMO, MS4Å, CH_2Cl_2, 3 h.

Formation of the ketone **319** was confirmed by the high resolution mass spectrum (LSIMS) which exhibited a molecular ion at *m/z* 336.1363 consistent with the molecular formula $C_{21}H_{20}O_4$. The infra-red spectrum featured a sharp band at 1685 cm^{-1} due to the carbonyl group of the benzylic ketone. The ^1H nmr spectrum displayed a three proton singlet at δ 2.78 assigned to the methyl ketone whilst two three proton singlets at δ 3.71 and 3.99 were assigned to the methoxy groups. The benzylic methylene group resonated as a two proton singlet at δ 5.25 whilst the aromatic protons of the benzyl group and 7-H resonated as a six proton multiplet in the region δ 7.36-7.60. A doublet of doublets at δ 7.06, $J_{6,7}$ 7.8 and $J_{6,8}$ 0.9 Hz, was assigned to 6-H and a singlet at δ 7.09 was assigned to 2-H. The doublet of doublets at δ 7.91, $J_{8,7}$ 8.3 and $J_{8,6}$ 0.9 Hz, was assigned to 8-H. The ^{13}C nmr spectrum was likewise supportive of the proposed structure. A methyl resonance at δ 31.4 and a quaternary carbon at δ 201.3 were assigned to the carbons of the methyl ketone. An upfield shift in the resonance for C-3 at δ 129.1 relative to the benzylic alcohol **317**, where it resonated at δ 134.3, was observed.

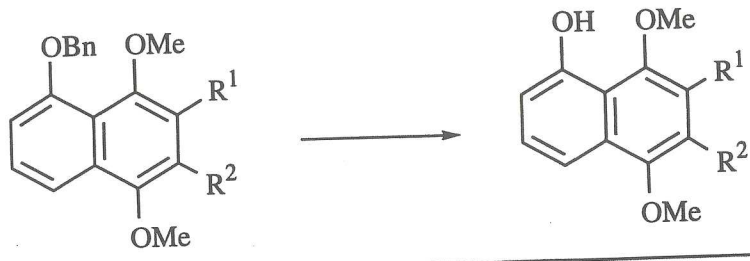
Ketone **320** melted at 109-110 °C and the high resolution mass spectrum (EI) exhibited a molecular ion at *m/z* 336.1363 consistent with the molecular formula $C_{21}H_{20}O_4$. The infra-red spectrum exhibited a strong band at 1668 cm^{-1} assigned to the ketone carbonyl group. The ^1H nmr spectrum featured a three proton singlet at δ 2.79 assigned to the methyl ketone as well as three proton singlets at δ 3.92 and 3.97 due to the methoxy groups. The methylene group resonated as a two proton singlet at δ 5.21 while 6-H was a broad doublet at δ 7.07, $J_{6,7}$ 7.7 Hz and the singlet at δ 7.10 was assigned to 3-H. The ^{13}C nmr spectrum displayed a resonance at δ 30.9 assigned to the methyl carbon of the acetyl group and resonances at δ 56.3 and 63.6 were due to the methoxy groups. The methylene group appeared at δ 71.6 and the quaternary resonance at δ 126.9 was due to C-2.

*(iii) Synthesis of naphthol **264** (and regioisomer **321**).*

With methyl ketone **319** in hand, its debenzylation to naphthol **264** was next examined. Treatment of a solution of **319** in ethyl acetate with palladium on charcoal (50 mg/mmol) under an atmosphere of hydrogen gave acetylnaphthol **264**, in 53% yield, after purification by flash chromatography (scheme 85).

Likewise, the regioisomeric ketone **320** was debenzylated in 58% yield.

Scheme 85



Alcohol	R	Product	Yield (%)	Byprod (%)
319	R^1= COMe, R^2=H	**264**	53	26
320	R^1= H, R^2= COMe	**321**	58	21

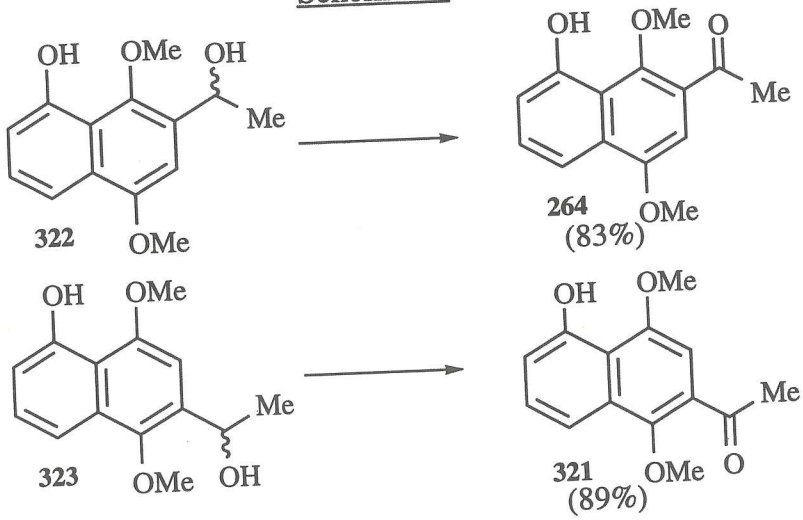
Reaction conditions: EtOAc, 10% Pd/C, H_2, 2 h.

Formation of the acetyl naphthol **264** was confirmed by high resolution mass spectrometry (FAB) which exhibited a molecular ion at *m/z* 246.0894 consistent with the molecular formula $C_{14}H_{14}O_4$. The infra-red spectrum exhibited a broad resonance at 3357 cm^{-1} due to the hydroxyl group and a strong band at 1685 cm^{-1} assigned to the carbonyl group. The ^1H nmr spectrum featured a three proton singlet at δ 2.76 assigned to the methyl ketone as well as two three proton singlets at δ 3.94 and 4.00 due to the methoxy groups. The singlet at δ 6.95 was assigned to 2-H and the doublet of doublets at δ 7.00, $J_{6,7}$ 7.8 and $J_{6,8}$ 0.9 Hz, assigned to 6-H. The two doublet of doublets at δ 7.47 and 7.75 were assigned as 7-H and 8-H respectively and the singlet at δ 9.49 was assigned to the hydroxyl group. The ^{13}C nmr spectrum further confirmed the proposed structure with the methyl resonance at δ 30.3 and the quaternary resonance at δ 199.4 being assigned to the methyl ketone. The lack of methylene resonances provided further evidence for loss of the benzyl group.

The 2-acetylnaphthol **321** melted at 96.5-97.5 °C and the high resolution mass spectrum (FAB) exhibited a molecular ion at *m/z* 246.0894 consistent with the molecular formula $C_{14}H_{14}O_4$. The infra-red spectrum exhibited a broad stretch at 3362 cm^{-1} assigned to the hydroxyl group and a strong band at 1660 cm^{-1} assigned to the ketone carbonyl group. The ^1H nmr spectrum featured a three proton singlet at δ 2.79 due to the methyl ketone as well as three proton singlets at δ 3.93 and 4.01 assigned to the methoxy groups. The doublet at δ 7.01, $J_{6,7}$ 7.7 Hz, was assigned to 6-H while the singlet at δ 7.06 was assigned to 3-H. The doublet of doublets at δ 7.46, $J_{7,6}$ 7.7 and $J_{7,8}$ 8.4 Hz, was assigned to 7-H and the doublet of doublets at δ 7.67, $J_{8,7}$ 8.4 and $J_{8,6}$ 0.6 Hz, was assigned to 8-H. The singlet at δ 9.37 was assigned to the hydroxyl group.

Formation of the byproducts, benzylic alcohols **322** and **323**, accounted for the poor yields from this reaction. Re-oxidation using TPAP and NMO allowed recycling of these unwanted byproducts to the desired ketones **264** and **231**, thereby increasing the overall yield to approximately 70% (scheme 86).

Scheme 86



Reagents and conditions: TPAP, NMO, MS4Å, CH_2Cl_2, 2 h.

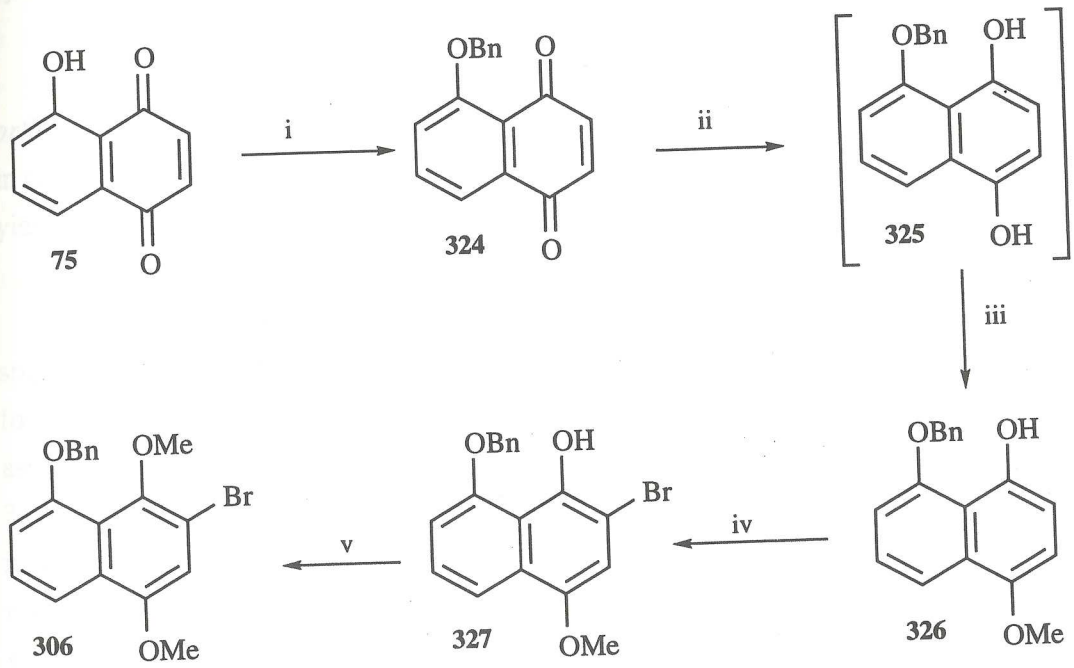
Whilst not fully characterized, alcohol **322** was readily identified on the basis of its ^{1}H nmr spectrum. A doublet at δ 1.54 and a quartet at δ 5.43, J_{vic} 6.4 Hz, corresponded to the methyl and benzylic protons of the side-chain alcohol. The hydroxyl proton resonated as a broad singlet at δ 2.27 while the three proton singlets at δ 3.86 and 4.00 were assigned to the methoxy groups. A singlet at δ 6.82 was assigned to 2-H and three doublet of doublets were observed at δ 6.88, $J_{6,7}$ 7.5 and $J_{6,8}$ 1.2 Hz, (assigned to 6-H) at δ 7.38, $J_{7,6}$ 7.5 and $J_{7,8}$ 8.3 Hz, (assigned to 7-H) and at δ 7.49, $J_{8,7}$ 8.3 and $J_{8,6}$ 1.4 Hz (assigned to 8-H). In addition, the aromatic hydroxyl group resonated as a broad singlet at δ 9.35.

Alcohol **323** was also identified by its ^{1}H nmr spectrum. A doublet at δ 1.52 and a quartet at δ 5.41, each with J_{vic} 6.5 Hz, corresponded to the methyl and benzylic protons of the side-chain alcohol. The hydroxyl proton resonated as a broad singlet at δ 2.68 while the three proton singlets at δ 3.83 and 3.93 were assigned to the methoxy groups. A singlet at δ 6.77 was assigned to 3-H and three doublet of doublets at δ 6.86, $J_{6,7}$ 7.4 and $J_{6,8}$ 1.2 Hz, at δ 7.36, $J_{6,7}$ 7.4 and $J_{7,8}$ 8.3 Hz and at δ 7.45, $J_{8,7}$ 8.3 and $J_{8,6}$ 1.2 Hz, were assigned to 6-H, 7-H and 8-H respectively. The aromatic hydroxyl group resonated as a broad singlet at δ 9.32.

2.2.4 Alternative Synthesis of Bromonaphthalene 306.

Due to the initial problems encountered with the regioselectivity of the bromination of juglone **75**, an alternative synthesis of bromide **306** was developed (scheme 87). Juglone **75** was first protected as a benzyl ether **324** by treatment with benzyl bromide and silver(I) oxide. Purification by flash chromatography afforded the crystalline benzyl ether **324** in 80% yield. As with the benzyl ether **309**, chromatography on a large scale was problematic due to co-elution of benzyl bromide. Recrystallization was therefore routinely used for purification on a large scale.

Scheme 87



Reagents and conditions: (i) BnBr, Ag_2O, $CHCl_3$, 2 h, 80% (ii) $Na_2S_2O_3$, H_2O (iii) Me_2SO_4, K_2CO_3, Me_2CO, reflux, 4 h, 75% (iv) Br_2, CCl_4, 5 min., 99% (v) NaH, MeI, DMF, 12 h, 74%.

The spectroscopic data for benzyl ether **324** were in agreement with the literature.[197] The product **324** melted at 111-111.5 °C with a molecular ion at *m/z* 264 in the mass spectrum confirming the molecular formula $C_{17}H_{12}O_3$. The infra-red spectrum exhibited a strong band at 1659 cm^{-1} due to the quinone carbonyl groups and the ^1H nmr spectrum was consistent with the proposed structure. The benzylic methylene group resonated as a two proton singlet at δ 5.30 while the two proton singlet at δ 6.89 was assigned to 2-H and 3-H.

The reductive methylation of benzyl juglone **324** was then carried out, as for bromide **309**, by reduction to the hydroquinone **325** using aqueous dithionite solution, followed by methylation using dimethyl sulfate and potassium carbonate in acetone under reflux. In this case, the reaction was worked up before methylation of the second more hindered hydroxyl group at C-4 took place, affording methoxynaphthol **326** in 75% yield.

The crystalline methoxynaphthol **326** melted at 108-108.5 °C which, along with the spectroscopic data, was in agreement with that reported in the literature.[197] A hydroxyl stretch was evident in the infra-red spectrum confirming naphthol formation. In the ^{1}H nmr spectrum, the methoxy group resonated as a three proton singlet at δ 3.91 while the hydroxy proton was a singlet at δ 8.98.

Regioselective bromination of naphthol **326** was then possible due to the strong *ortho*-directing effect of the hydroxyl group. Treatment of the naphthol **326** with bromine in carbon tetrachloride gave the crystalline bromonaphthol **327** in essentially quantitative yield after purification by flash chromatography.

Bromonaphthol **327** melted at 132.5-133.5 °C and the high resolution mass spectrum (FAB) exhibited a molecular ion at *m/z* 358.0207 consistent with the molecular formula $C_{18}H_{15}{}^{79}BrO_3$. The infra-red spectrum featured a broad band at 3343 cm^{-1} assigned to the hydroxyl group. The ^{1}H nmr spectrum displayed a three proton singlet at δ 3.86 assigned to the methoxy group and a two proton singlet at δ 5.17 due to the benzylic methylene group. The singlet at δ 6.87 was assigned to 2-H while the hydroxyl group resonated as a singlet at δ 9.58. The ^{13}C nmr spectrum also supported the proposed structure, with the methyl carbon at δ 56.7 assigned to the methoxy group and the methylene resonance at δ 72.6 to the benzyl group. The quaternary resonance at δ 103.6 was assigned to C-3.

The hydroxyl group of bromonaphthol **327** was then methylated by treatment with sodium hydride and methyl iodide in dimethylformamide to give the methyl ether **306** in 74% yield after chromatography. Methyl ether **306** was identical in all respects to the material prepared by the original method.

2.2.5 Aryl *C*-Glycosylation Using Bromonaphthols 299 and 314.

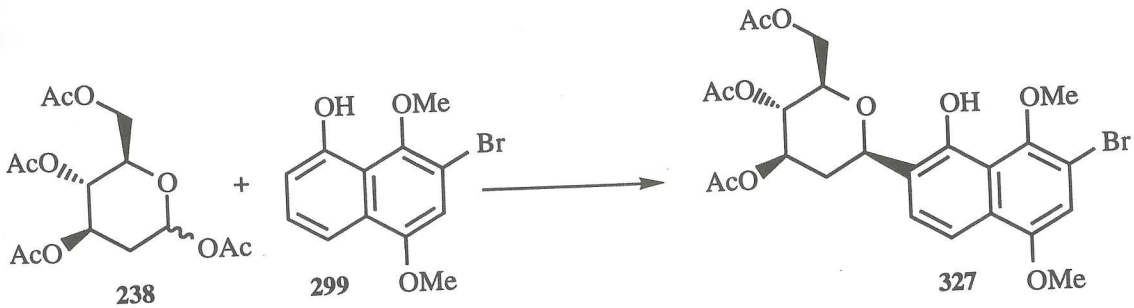
With the bromonaphthol **299** and acetylnaphthol **264** in hand, attention was turned to the glycosylation of these using the conditions that were successful for simpler naphthols (section **2.1.5**). The reactivity of these 3-functionalized naphthols would also be probed by comparison with the regioisomeric 2-functionalized naphthols.

(i) Synthesis of β-C-glycoside 327.

The coupling of bromonaphthol **299** and the glycosyl acetate **238** was investigated (scheme 88). A solution of **299** and **238** in acetonitrile at 0 °C was treated with trimethylsilyl triflate (1.5 equiv.) and silver perchlorate (5 mol%). After 1 hour the reaction was quenched with aqueous sodium bicarbonate solution, affording the desired β-*C*-glycoside **327** in only 5% yield after work-up and chromatography.

The use of boron trifluoride diethyl etherate as the Lewis acid was examined under similar reaction conditions. The use of this promoter in *C*-glycosylation reactions has been reported by several groups.[150,158,161,164] In this instance however, none of the desired β-*C*-glycoside was formed. Instead, much of the starting naphthol **299** was recovered and deacetylation at the anomeric position of the sugar **238** was observed.

Scheme 88



Reagents and conditions: { TMSOTf, $AgClO_4$, CH_3CN, 0 °C, 1 h, 5%. or $BF_3.OEt_2$, CH_3CN, 0 °C, 30 min., 0%.

Formation of the β-*C*-glycoside **327** was confirmed by high resolution mass spectrometry (EI) which exhibited a molecular ion at *m/z* 554.0785 consistent with the molecular formula $C_{24}H_{27}{}^{79}BrO_{10}$. The hydroxyl stretch in the infra-red spectrum was also consistent with *C*-glycoside formation. In the ^1H nmr spectrum, the anomeric proton, 1'-H, resonated at δ 5.12 as a doublets of doublets, with coupling constants $J_{1',2'ax}$ 11.3

and $J_{1',2'eq}$ 2.0 Hz consistent with β-stereochemistry at the anomeric linkage. Doublets of doublets of doublets at δ 1.78 and 2.52 were assigned to 2'ax-H, with coupling constants, J_{gem} 12.7, $J_{2'ax,3'}$ 11.3 and $J_{2'ax,1'}$ 11.3 Hz, and 2'eq-H, with coupling constants, J_{gem} 12.7, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 2.0 Hz, respectively. The three, three proton, singlets at δ 2.02, 2.07 and 2.09 were assigned to the acetate methyl protons of the glycoside and the hydroxyl proton resonated as a singlet at δ 9.70.

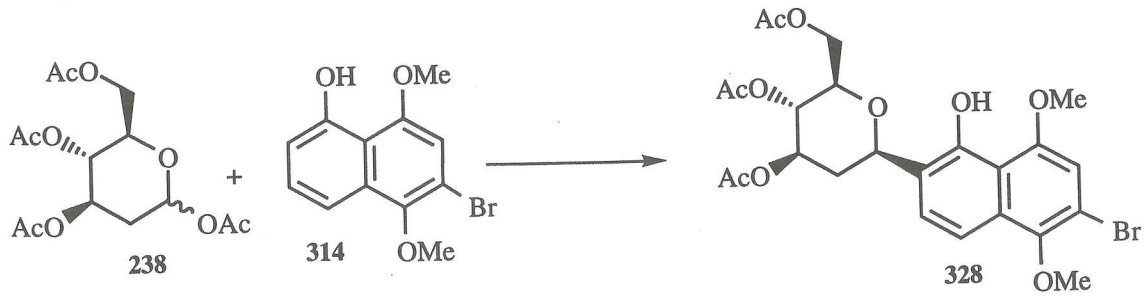
(ii) Synthesis of β-C-glycoside 328.

Despite the poor reactivity shown using the naphthol **249**, it was decided to investigate the reaction of the regioisomeric bromonaphthol **314** with glycosyl acetate **238** under the same conditions(scheme 89).

Accordingly, a solution of the regioisomeric bromonaphthol **314** and the glycosyl acetate **238** in acetonitrile at 0 °C was treated with trimethylsilyl triflate (1.5 equiv.) and silver perchlorate (5 mol%). After 1 hour the reaction was quenched with aqueous sodium bicarbonate solution, affording the desired β-*C*-glycoside **328** in a much improved 57% yield.

Under similar conditions, the use of boron trifluoride diethyl etherate afforded the β-*C*-glycoside **328** in 48% yield. Although this successful *C*-glycosylation using the 2-bromonaphthol **314** was a positive result, this had concerning implications with regard to the reactivity of naphthol **299**.

Scheme 89



Reagents and conditions: { TMSOTf, $AgClO_4$, CH_3CN, 0 °C, 1 h, 57%. or $BF_3.OEt_2$, CH_3CN, 0 °C, 30 min., 48%.

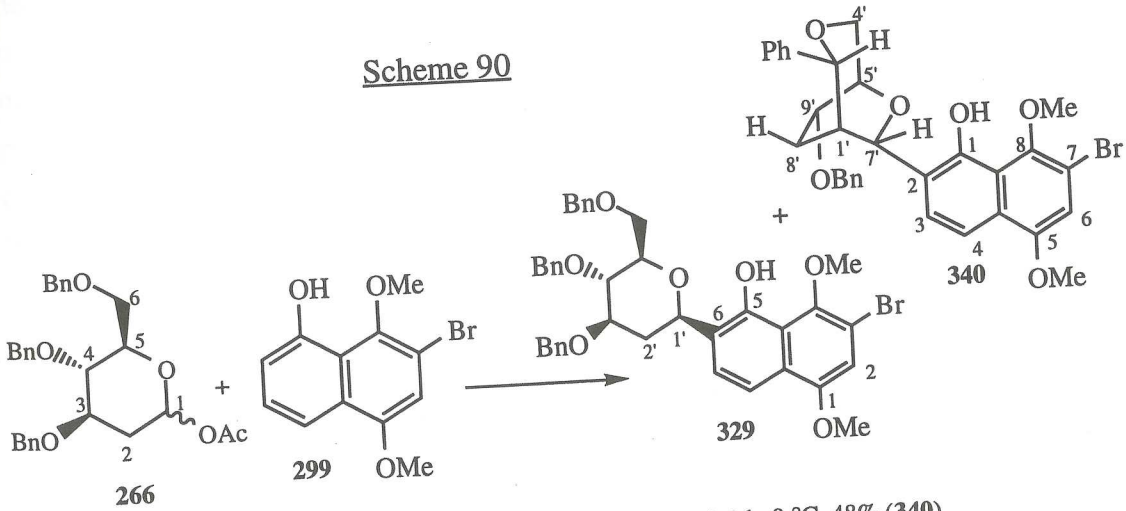
Formation of the β-*C*-glycoside **328** was confirmed by high resolution mass spectrometry (EI) where a molecular ion at *m/z* 554.0777 was exhibited, consistent with

the molecular formula $C_{24}H_{27}{}^{79}BrO_{10}$. The infra-red spectrum displayed a hydroxyl stretch and the ^1H nmr spectrum was similarly supportive of the proposed structure. The anomeric proton, 1'-H, resonated at δ 5.12 as a doublet of doublets, with coupling constants $J_{1',2'ax}$ 11.3 and $J_{1',2'eq}$ 2.0 Hz, while the hydroxyl proton resonated as a singlet at δ 9.49. In the ^{13}C nmr spectrum there were only three methine resonances in the aromatic region indicating that *C*-glycosyl substitution had occurred. In addition, C-1' resonated at δ 71.7 which was consistent with the formation of a *C*-glycoside.

*(iii) Synthesis of β-C-glycoside **329** (and rearranged product **340**).*

Disappointed by the poor recovery of β-*C*-glycoside **327** from glycosylation with acetate **238**, attention was turned to the benzyl protected sugar **266**. Accordingly, trimethylsilyl triflate (1.5 equiv.) and silver perchlorate (5 mol%) were added to a solution of bromonaphthol **299** and glycosyl acetate **266** in dry acetonitrile at 0 °C. After 1 hour the reaction was quenched with aqueous sodium bicarbonate solution and a mixture containing β-*C*-glycoside **329** and the rearranged product **340** (1:6) was isolated after chromatography (scheme 90). On attempting to separate these products by semi-preparative HPLC (0.375% ^{i}PrOH/Hexane, partisil 10 column, 50 cm x 9.4 mm I.D., flow rate 4 mL/min.), the rearranged product **340** was obtained in 48% yield, while the less stable **329** decomposed and was not isolated. The use of an alternative Lewis acid, boron trifluoride diethyl etherate, gave a similar result, affording the rearranged product **340** in a slightly greater yield of 59%.

Scheme 90



Reagents and conditions: { TMSOTf, $AgClO_4$, CH_3CN, 1 h, 0 °C, 48% (**340**). or $BF_3.OEt_2$, CH_3CN, 0 °C, 20 min., 59% (**340**).

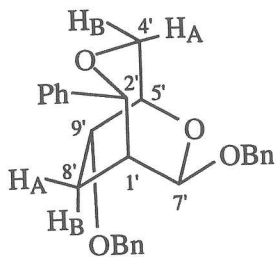
In the ^{1}H nmr spectrum of *C*-glycoside **340**, the presence of two downfield singlets (at δ 5.06 and 5.86) suggested that the structure was not the expected *C*-glycoside. The rest of the aliphatic region also exhibited the wrong pattern for a 2-deoxyglucoside. The mass spectrum confirmed our suspicions with a molecular ion at *m/z* 592/590 instead of *m/z* 701/699.

The high resolution mass spectrum for **340** exhibited a molecular ion at *m/z* 590.1295 consistent with the molecular formula $C_{32}H_{31}{}^{79}BrO_6$. The infra-red spectrum contained a broad stretch at 3329 cm^{-1} indicative of an hydroxyl group. In the ^{1}H nmr spectrum the singlets at δ 5.06 and 5.86 were assigned to 7'-H and 2'-H respectively. Doublets of doublets of doublets at δ 1.43 and 1.98 corresponded to the geminal protons 8'-H_B and 8'-H_A respectively. The doublet of doublets at δ 2.19 was assigned as 1'-H with couplings of $J_{1',8'B}$4.8 and $J_{1',8'A}$2.2 Hz. The resonances at δ 3.85 and 3.94 corresponded to the two methoxy groups. 4'-H_A resonated as a doublet at δ 4.08 with coupling constant, J_{gem}13.4 Hz, while 4'-H_B resonated as a doublet of doublets at δ 4.21 showing an additional coupling constant, $J_{4'B,5'}$5.5 Hz. The 9'-H proton resonated as a doublet of doublets at δ 4.16 with coupling constants, $J_{9',8'A}$9.7 and $J_{9',\ 8'B}$4.8 Hz. 6-H resonated as a singlet at δ 6.70 while 4-H and 3-H resonated as a pair of doublets at δ 7.64 and 8.04 with a coupling constant, $J_{3,4}$8.7 Hz. The ^{13}C nmr spectrum was also consistent with the proposed structure.

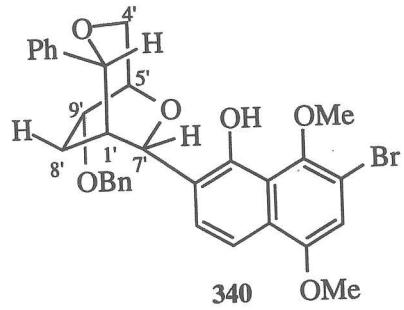
Although the minor product **329** was not isolated, it was readily identifiable in the ^{1}H nmr spectrum of the initial product mixture, giving a series of peaks expected for a 2-deoxy-β-*C*-glycoside. Although the 2'ax-H resonance was obscured, presumably in the region δ 1.60-1.80, the 2'eq-H proton was identifiable resonating as a doublet of doublets of doublets at δ 2.50. The anomeric proton 1'-H was also obscured, but the aromatic protons 8-H and 7-H were evident as doublets at δ 7.59 and 7.66 respectively, with a coupling constant $J_{7,8}$ 8.0 Hz, indicating that *C*-glycosyl substitution had occurred. The 2-H proton of the naphthalene ring resonated as a singlet at δ 6.74 and the hydroxyl proton resonated at δ 9.60.

The assignment of **340** was aided by comparison with compound **342**, which bears essentially the same structure as the rearranged glycosyl moiety of **340** (table 1). However, the literature[198,199] compound **342** has a β-benzyloxy substituent at C-7', whereas in our rearranged product **340** the lack of coupling with 1'-H suggests that 7'-H is *exo* and the aryl moiety is therefore in the α-position. The chemical shift for C-7' in the rearranged product **340** is upfield relative to its position in the bicyclic acetal **342** since the substituent is bonded *via* carbon and not oxygen.

Table 1: NMR Shifts for Bicyclic Acetals **340** and **342.**



342



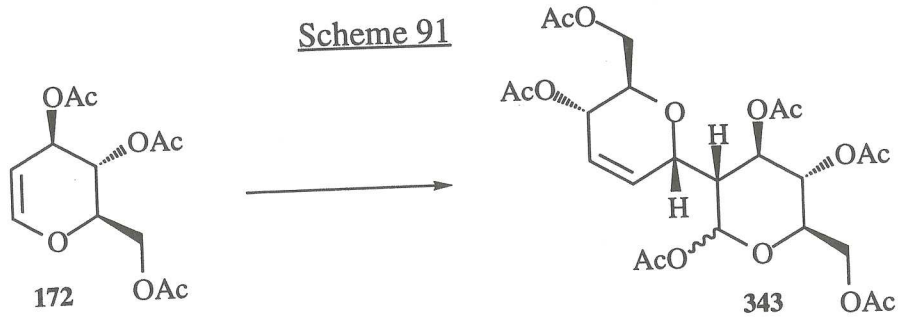
340

C	δ_H (ppm)	m	*J* (Hz)	δ_C(ppm)	δ_H (ppm)	m	*J* (Hz)	δ_C(ppm)
1'	2.35	m	-	44.8	2.19	dd	4.8, 2.2	45.5
2'	5.47	s	-	76.0	5.86	s	-	76.2
4'A	4.00	d	7.1	71.4	4.08	d	13.4	71.1
4'B	4.10	dd	13.1, 5.2	-	4.21	dd	13.4, 5.5	-
5'	4.35	d	5.0	77.4	4.36	d	5.5	76.6
7'	5.18	d	4.4	98.4	5.06	s	-	86.2
8'A	1.44	m	-	25.6	1.43	ddd	14.4, 4.8, 4.8	22.4
8'B	2.38	m	-	-	1.98	ddd	14.4, 9.7, 2.2	-
9'	4.17	dd	9.2, 4.0	73.0	4.16	dd	9.7, 4.8	73.7

(iv) Mechanism of rearrangement.

A precedent for this rearrangement was reported by Steel *et al.*[198,199] while investigating the formation of *C*-disaccharides (such as **343**) by the dimerization of 3-*O*-acyl glycals, upon treatment with acetyl perchlorate (scheme 91).

Scheme 91



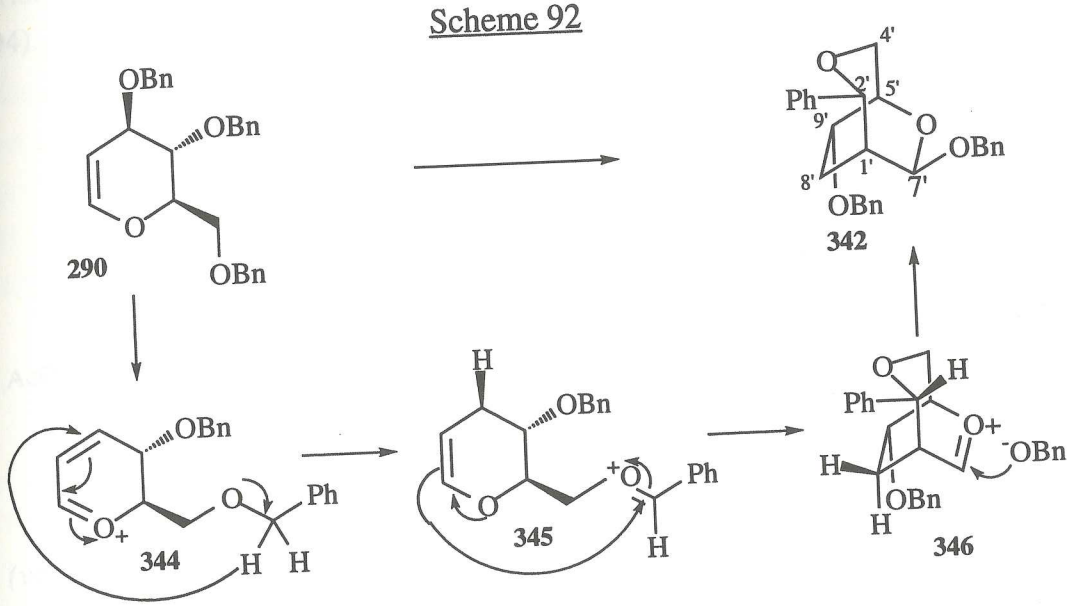
172 **343**

Reagents and conditions: 0.5 eq. $AcClO_4$, CH_2Cl_2, -78 °C, 77%.

Steel *et al.*[198,199] explored the use of the corresponding tri-*O*-benzyl-D-glucal **290**. In this case the major product was the bicyclic acetal **342** (scheme 92). Formation of the

product was rationalized by the initial generation of the oxacarbenium ion **344**. Intramolecular 1,6-hydrogen shift then regenerates the glycal, producing a benzylic oxacarbenium ion **345**. Cyclization through attack of the vinyl ether affords, after trapping of **346** with benzyl alcohol, the observed acetal **342**.

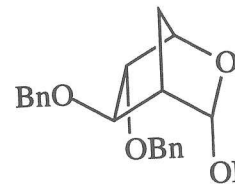
Scheme 92



Reagents and conditions: 0.5 eq. $AcClO_4$, CH_2Cl_2, -78 °C.

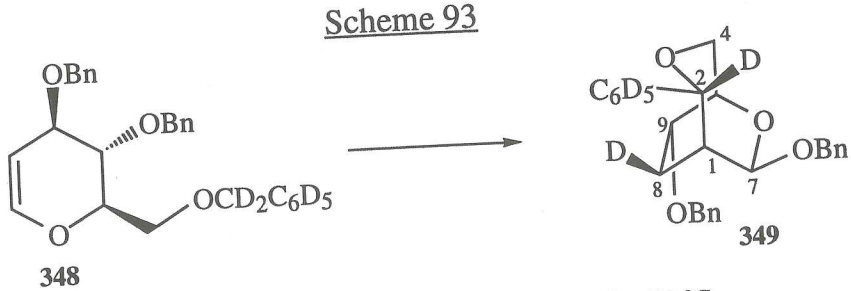
The structure was initially misassigned as **347** (figure 28), but the revised structure **342** was subsequently established by nmr experiments and single-crystal X-ray diffraction. Evidence for the mechanism was provided by an elegant labelling experiment. The deuterium labelled glycal **348** underwent rearrangement to give the bicyclic acetal **349** bearing deuterium at positions 2 and 8, supporting the proposed 1,6-hydrogen shift (scheme 93). The comprehensive nmr data reported (table 1) were invaluable in the structural assignment of compound **340**.

Figure 28



347

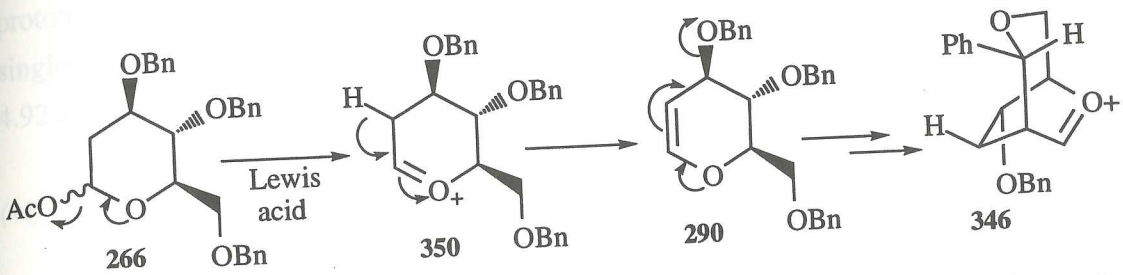
Scheme 93



Reagents and conditions: 0.5 eq. $AcClO_4$, CH_2Cl_2, -78 °C.

A similar fate had evidently befallen our reaction, probably due to the poor reactivity of the bromonaphthol **299**. In light of the above results, it was proposed that the oxonium ion **350**, formed under Lewis acid catalysis from **266**, rearranges to glycal **290** faster than it reacts with naphthol **299**. Rearrangement could then occur as before, with the reactive oxonium species **346** being trapped by bromonaphthol **299** (scheme 94).

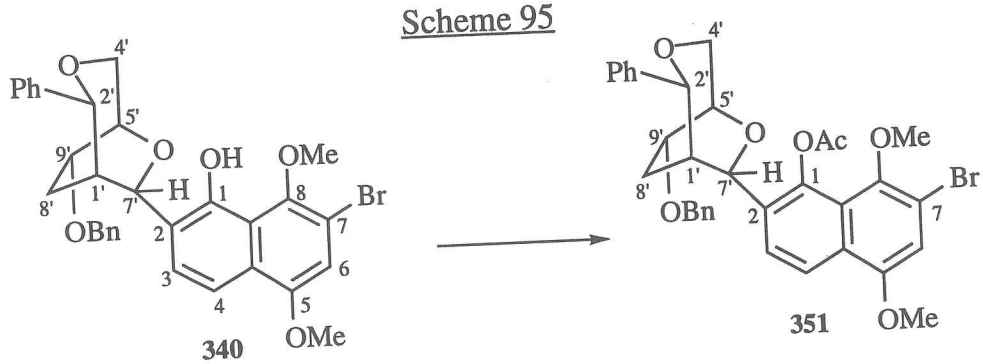
Scheme 94



*(v) Synthesis of acetate **351**.*

Due to difficulty experienced with characterizing the rearranged product **340**, the acetate derivative **351** was prepared in order to obtain crystals for X-ray crystallographic analysis. The acetylation of **340** was effected using triethylamine, acetic anhydride and DMAP to give the crystalline **351** in 94% yield after chromatography (scheme 95).

Scheme 95



Reagents and conditions: Ac_2O, Et_3N, DMAP, CH_2Cl_2, 12 h, 94%.

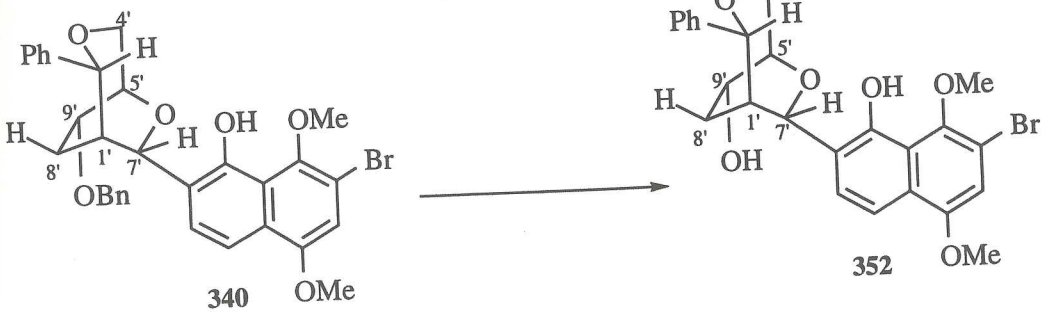
Recrystallization of acetate **351** from hexane-ethyl acetate gave tan needles which melted at 204-205 °C. The high resolution mass spectrum exhibited a molecular ion at *m/z* 632.1422 consistent with the molecular formula $C_{34}H_{33}{}^{79}BrO_7$. The infra-red spectrum showed a carbonyl stretch at 1769 cm^{-1} indicating the presence of an acetate group.

The ^{1}H nmr spectrum exhibited considerable broadening and splitting of many of the peaks, at first leading to concern about the purity of the product, but eventually being attributed to restricted rotation about the *C*-glycosidic bond. Evidence for this phenomenon was obtained by running spectra of acetate **351** at 300 K and 360 K in d_8-toluene (figure 29). As the temperature was elevated peaks sharpened and coalesced until the spectrum resembled that for the parent naphthol **340**. Doublets of doublets of doublets at δ 1.63 and 2.01 were assigned to 8'-H_B and 8'-H_A respectively. The methyl protons of the acetate group resonated as a three proton singlet at δ 2.14, while the protons of the methoxy group resonated, downfield relative to their positions at 300 K, as singlets at δ 3.37 and 3.66. A doublet at δ 4.24 was assigned to 5'-H, while singlets at δ 4.92 and 5.81 were unmistakeable as 7'-H and 2'-H respectively.

(vi) Debenzylation to diol ***352****.*

In an effort to simplify the ^{1}H nmr spectrum for the rearranged product **340**, before the structure had been fully elucidated, it was decided to remove the protecting benzyl groups. Thus a solution of the benzyl ether **340** in ethyl acetate was stirred under hydrogen with 10% palladium on charcoal to give the alcohol **352** in 85% yield after chromatography (scheme 96).

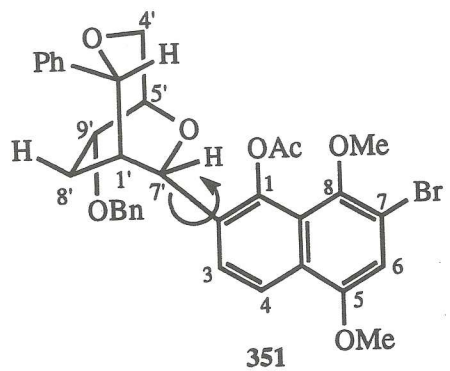
Scheme 96



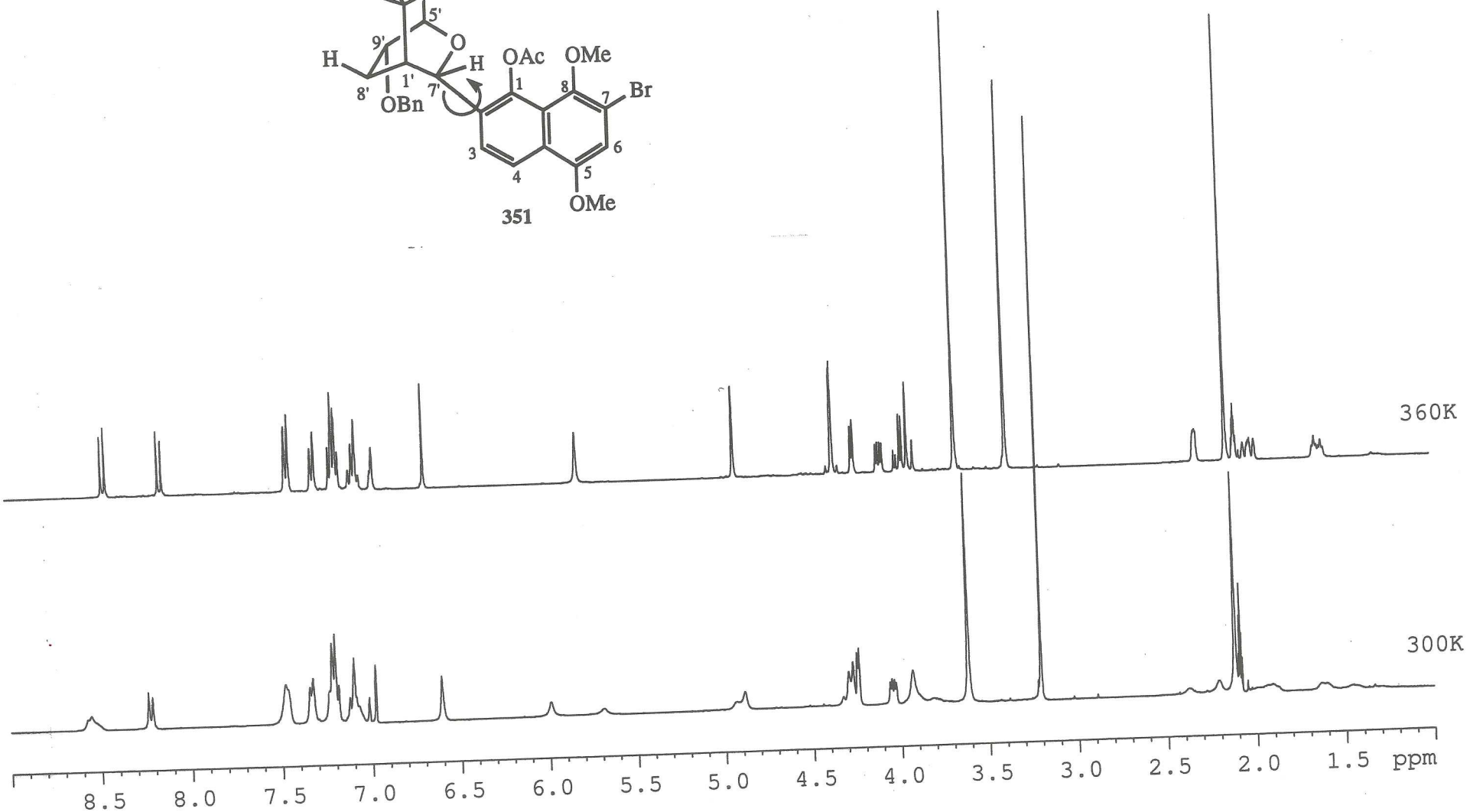
Reagents and conditions: Pd/C (10%), H_2, EtOAc, 1 h, 85%.

The high resolution mass spectrum exhibited a molecular ion at *m/z* 500.0833 consistent with the molecular formula $C_{25}H_{25}{}^{79}BrO_6$. The infra-red spectrum contained a broad hydroxyl stretch at 3334 cm^{-1}. The ^{1}H nmr spectrum was simplified in the methylene and aromatic regions. The ^{13}C nmr spectrum was consistent with the bicyclic acetal structure. The DEPT spectrum contained only 2 methylene resonances at δ 25.7 and 70.1 assigned to C-8' and C-4' respectively. Although comprehensive spectroscopic data was obtained for this compound, we were not able to assign the structure based on these results. Therefore an X-ray crystal structure was obtained of the acetate **351**.

Figure 29: Restricted Rotation Observed for Acetate **351** (VT nmr experiment).



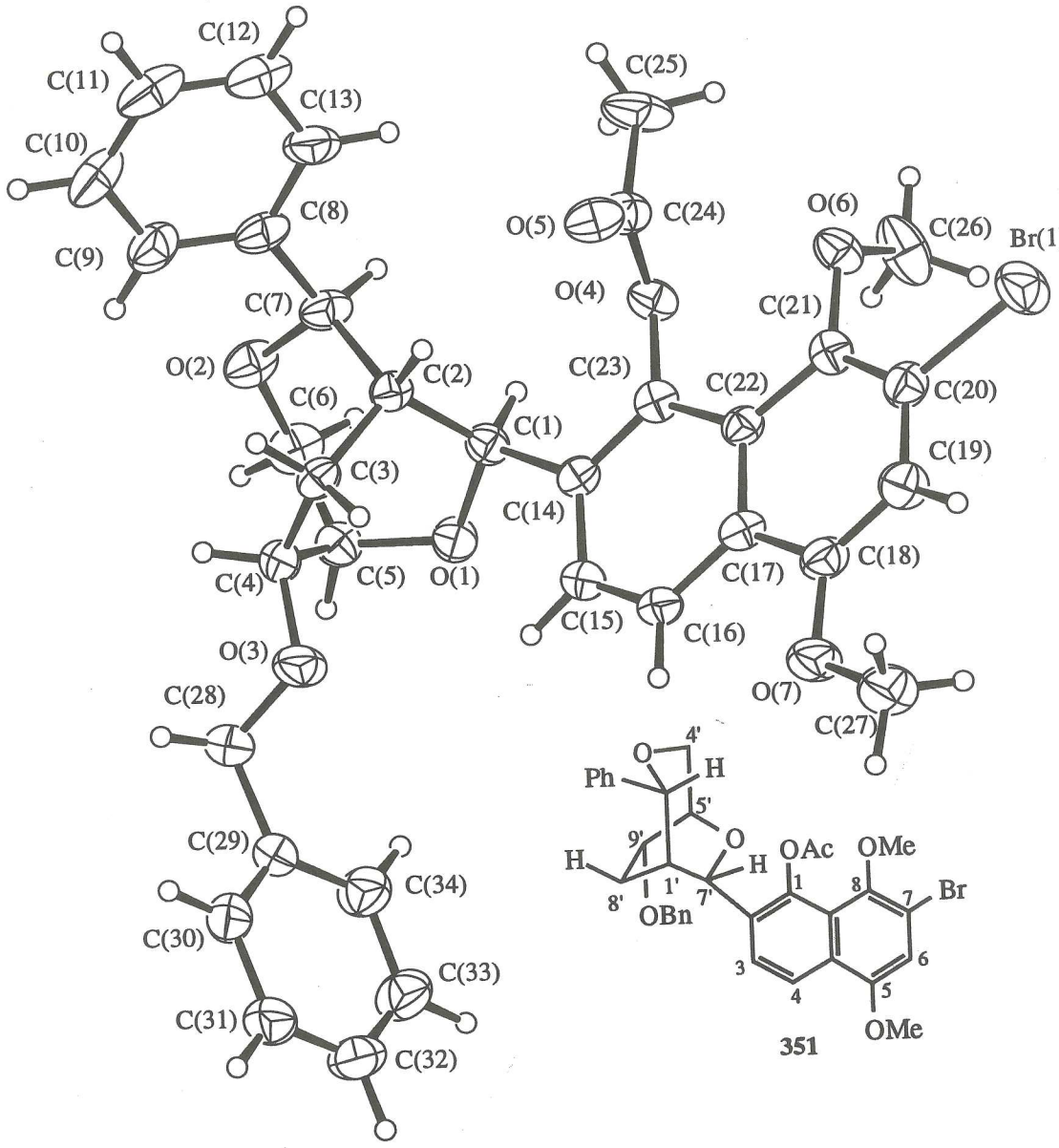
351



(vii) Crystal structure of acetate 351.

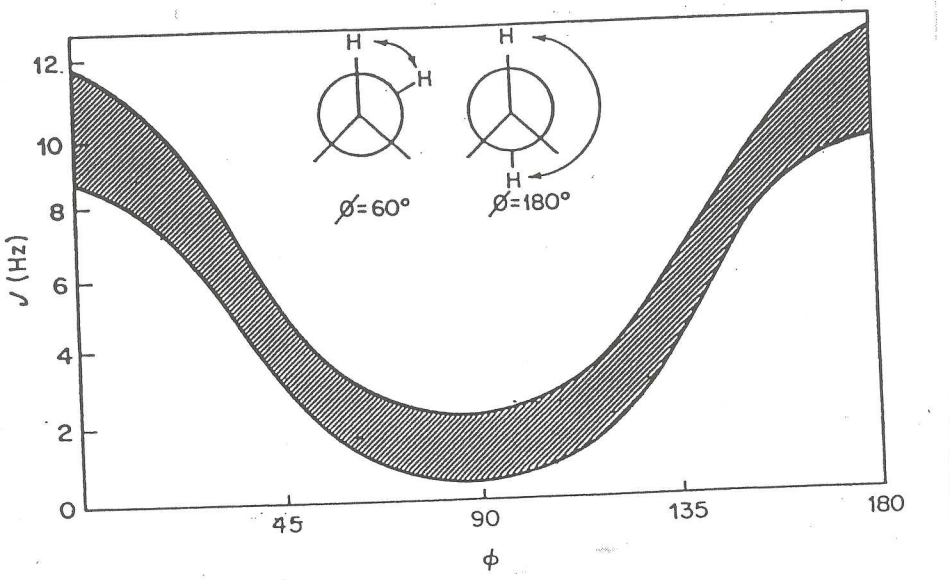
Diffraction quality crystals of acetate **351** were submitted for single-crystal X-ray analysis. The acetate **351** crystallized in a primitive orthorhombic crystal lattice and was solved in the $P2_12_12_1$ space group (#19) by direct methods. Anomalous scattering from bromine was used to determine the absolute configuration of the molecule (ORTEP diagram figure 30, complete data Appendix 1).

Figure 30: X-ray Crystal Structure of Acetate **351.**



The crystal structure of acetate **351** confirms that the naphthalene ring is *endo* to the bicyclic structure. By inspection, it can also be seen that the dihedral angle between the protons 1'-H, 7'-H and 1'-H, 2'-H is close to 90°. This explains the lack of splitting observed in the ^{1}H nmr resonances of 7'-H and 2'-H. In freely rotating alkane systems the dependance of the vicinal coupling constant ($^3J_{H,H}$) on the dihedral angle θ is given approximately by the simple form of the Karplus equation $J = 10\text{Cos}\theta.^{200}$ A dihedral angle of 180° or 0° gives the maximum $^3J_{H,H}$ value, whereas a dihedral angle of 90° gives an extremely small coupling constant (figure 31).

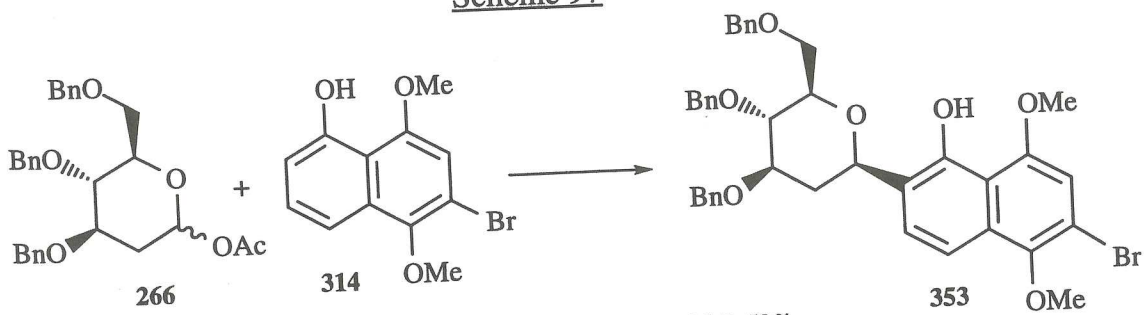
Figure 31



(viii) Synthesis of β-C-glycoside 353.

Interestingly, 2-bromonaphthol **314** coupled smoothly with glycosyl acetate **266** under the standard conditions, using boron trifluoride diethyl etherate as promoter, to give the β-*C*-glycoside **353** in 53% yield after chromatography (scheme 97).

Scheme 97



Reagents and conditions: $BF_3.OEt_2$, CH_3CN, 0 °C, 53%.

The high resolution mass spectrum exhibited a molecular ion at 698.1872 consistent with the molecular formula $C_{39}H_{39}{}^{79}BrO_7$. The infra-red spectrum contained a hydroxyl stretch at 3384 cm^{-1}. The ^1H nmr spectrum was typical for the unrearranged *C*-glycosides, featuring doublet of doublets of doublets at δ 1.63 and 2.59 corresponding to 2'ax-H and 2'eq-H. 1'-H resonated as a doublet of doublets at δ 4.98 with a coupling constant of 10 Hz consistent with the expected β-stereochemistry. The ^{13}C nmr spectrum was also consistent with the proposed structure. The DEPT spectrum contained 5 methylene resonances, assigned to C-2', C-6' and the three benzyl (CH_2) groups.

Just as was observed for glycosylation reactions employing the acetate protected glycosyl donor **358**, the reactivity that 2-bromonaphthol **314** exhibited towards the benzyl protected glycosyl donor **266** was far greater than was displayed by 3-bromonaphthol **299**. The lack of reactivity in the latter case resulted in the Lewis acid catalyzed 1,6-hydride shift rearrangement reaction which gave the unusual bicyclic acetal **340**.

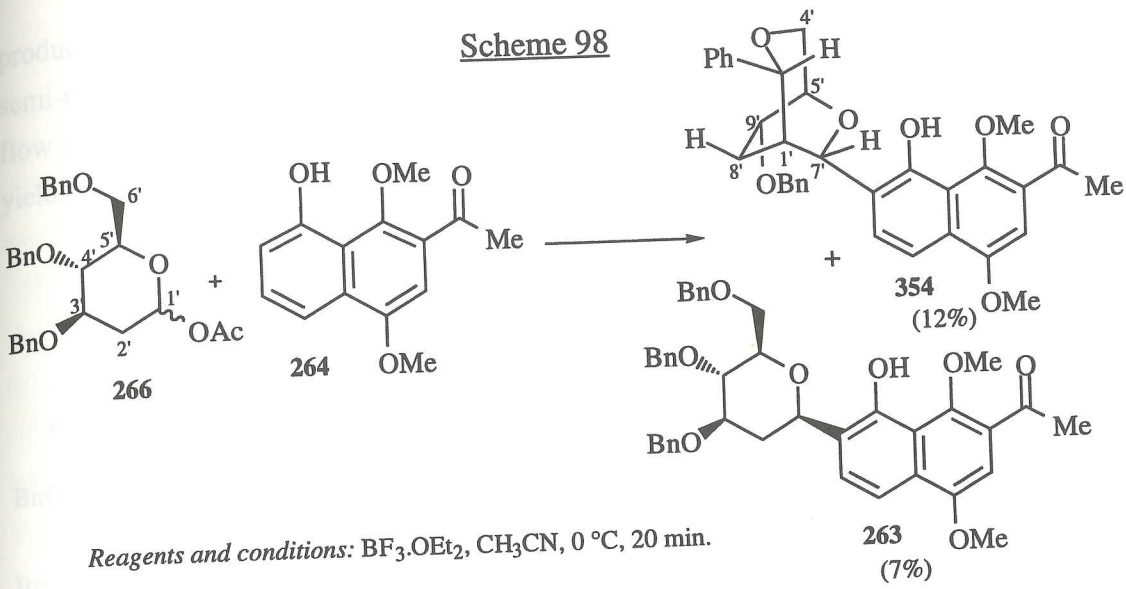
2.2.6 Aryl *C*-Glycosylation Using Acetylnaphthols.

*(i) Synthesis of β-C-glycoside **263** and rearranged product **354**.*

In light of the fact that attempts to couple bromide **299** with glycosyl donor **266** led to the formation of the rearranged *C*-glycoside **340**, it was decided to investigate the *C*-glycosylation of acetylnaphthol **264** with the same glycosyl donor **266**. It was thought that replacement of the bulky bromine atom by an acetyl group may have altered the outcome of the critical *C*-glycosylation reaction.

Boron trifluoride diethyl etherate was added to a solution of the acetylnaphthol **264** and glycosyl acetate **266** in dry acetonitrile at 0 °C. After 20 min., the reaction was quenched with water and a mixture of the desired β-*C*-glycoside **263** and the rearranged product **354** (1:3 by crude ^1H nmr) was isolated after chromatography (scheme 98). Semi-preparative HPLC (1.5% ^{i}PrOH/Hexane, Partisil 10 column, 50 cm x 9.4 mm I.D., flow rate = 4 mL/min.) was required to isolate the pure components, in yields of 7% and 12% respectively.

Scheme 98



Reagents and conditions: $BF_3.OEt_2$, CH_3CN, 0 °C, 20 min.

The major product **354** exhibited a molecular ion in the high resolution mass spectrum at *m/z* 662.2868 consistent with the molecular formula $C_{41}H_{42}O_8$. Characteristic peaks in the infra-red spectrum were a hydroxyl stretch and a ketone carbonyl stretch. The ^1H nmr spectrum featured sharp singlets at δ 5.12 and 5.72, assigned to 7'-H and 2'-H, respectively. In addition, the acetyl methyl group resonated at δ 2.80 and the hydroxyl proton as a singlet at δ 9.69. The ^{13}C nmr spectrum was consistent with the proposed structure, exhibiting a downfield acetyl carbonyl resonance at δ 199.6. The DEPT spectrum revealed 3 methylene groups assigned as C-8', C-4' and a single benzylic (CH_2) group.

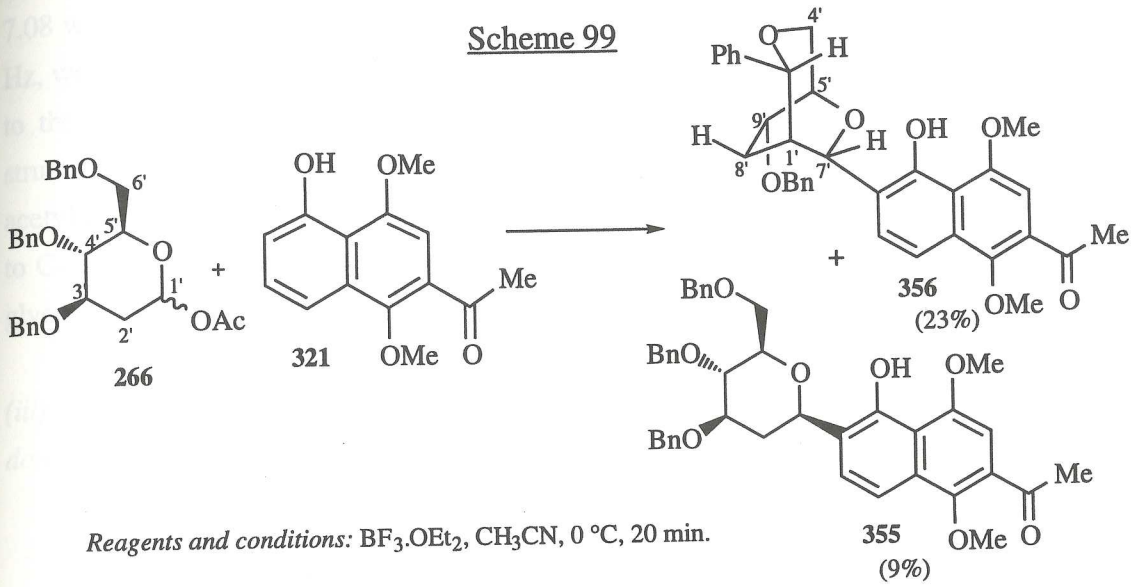
The minor product **263** exhibited a molecular ion in the high resolution mass spectrum at *m/z* 554.2294 consistent with the molecular formula $C_{34}H_{34}O_7$. The infra-red spectrum displayed a hydroxyl stretch and a ketone carbonyl stretch. The ^1H nmr spectrum featured a characteristic pair of doublet of doublets of doublets at δ 1.60 and 2.59 assigned to $2'_{ax}$-H and $2'_{eq}$-H respectively. 1'-H resonated as a doublet of doublets at δ 5.01 with the large axial-axial coupling constant, $J_{1',2'ax}$ 11.5 Hz, confirming β-stereochemistry. The ^{13}C nmr was consistent with the proposed structure containing a downfield acetyl carbonyl resonance at δ 200.0. The DEPT spectrum revealed 5 methylene groups assigned to C-2', C-6' and the three benzyl (CH_2) groups.

(ii) Synthesis of the β-C-glycoside 355 (and the rearranged product 356).

Boron trifluoride diethyl etherate was added to a solution of 2-acetylnaphthol **321** and glycosyl acetate **266** in dry acetonitrile at 0 °C. After 20 min., the reaction was quenched with water and a mixture of the desired β-*C*-glycoside **355** and the rearranged

product **356** (1:3 by ^{1}H nmr) was isolated after chromatography (scheme 99). Once again semi-preparative HPLC (1.5% ^{i}PrOH/Hexane, Partisil 10 column, 50 cm x 9.4 mm I.D., flow rate = 4 mL/min.) was required to isolate the pure components **356** and **355**, in yields of 23% and 9% respectively.

Scheme 99



Reagents and conditions: $BF_3.OEt_2$, CH_3CN, 0 °C, 20 min.

The formation of compound **356** was supported by the high resultion mass spectrum, which confirmed the molecular formula as $C_{41}H_{42}O_8$. The infra-red spectrum featured a carbonyl stretch at 1668 cm^{-1} assigned to the ketone, whilst a broad band at 3366 cm^{-1} was characteristic of the hydroxyl group. The ^{1}H nmr spectrum exhibited three, three proton, singlets at δ 2.79, 3.93 and 4.11 assigned to the methyl protons of the acetyl group and the two methoxy groups respectively. A two proton singlet at δ 4.61 was assigned to the benzylic protons, while sharp singlets at δ 5.12 and 5.72 were assigned to the bicyclic ring protons 7'-H and 2'-H respectively. In the aromatic region, a singlet at δ 7.08 was assigned to 7-H and the hydroxyl proton resonated as a singlet at δ 9.69. The ^{13}C nmr spectrum further confirmed the structure. A methyl carbon at δ 31.6 and a quaternary carbon at δ 199.8 were assigned to the acetyl moiety. Three methylene carbons, at δ 23.2, 71.0 and 71.9, were assigned to C-8', the benzyl group and C-4' respectively. A resonance at δ 86.1 was assigned to C-7', whilst in the aromatic region, methine carbons at δ 102.7 and 114.5 were assigned to C-3 and C-4 respectively.

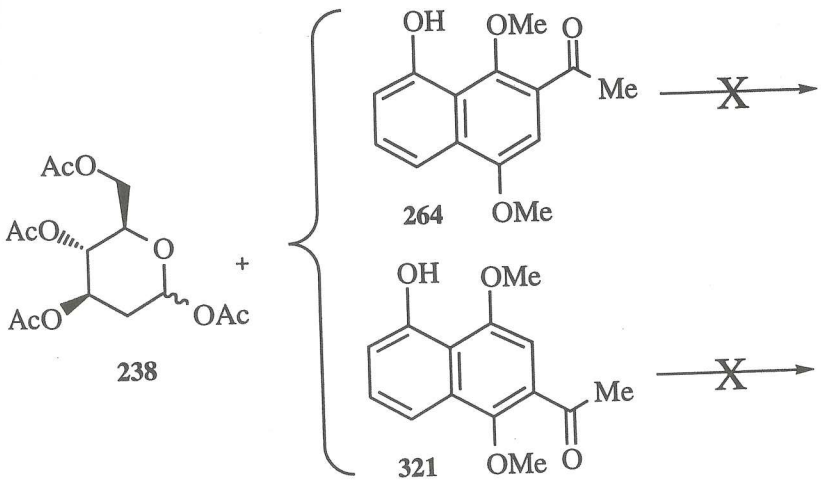
The minor product **355** exhibited a molecular ion in the high resolution mass spectrum at *m/z* 554.2294 consistent with the molecular formula $C_{34}H_{34}O_7$. The infra-red spectrum featured a broad band at 3359 cm^{-1}, corresponding to the hydroxyl group, as well as a strong carbonyl stretch at 1668 cm^{-1} attributed to the ketone. The ^{1}H nmr spectrum displayed doublets of doublets of doublets at δ 1.62 and 2.62, attributed to the

protons 2'$_{ax}$-H and 2'$_{eq}$-H respectively; the former with coupling constants J_{gem} 12.7, $J_{2'ax,3'ax}$ 11.4 and $J_{2'ax,1'ax}$ 11.4 Hz; the latter with coupling constants J_{gem} 12.7, $J_{2'ax,3'ax}$ 4.9 and $J_{2'ax,1'ax}$ 1.7 Hz. The anomeric proton, 1'-H, resonated as a doublet of doublets at δ 5.00, with the large axial-axial coupling constant, $J_{1',2'ax}$ 11.5 Hz, confirming β-stereochemistry with respect to the naphthalene ring. In the aromatic region, a singlet at δ 7.08 was assigned to 3-H. Doublets at δ 7.71 and 7.77, with a coupling constant $J_{7,8}$ 8.7 Hz, were assigned to C-7 and C-8 respectively. Finally, a singlet at δ 9.65 was assigned to the C-5 hydroxyl group. The ^{13}C nmr spectrum further supported the proposed structure, with a methyl carbon at δ 30.9 and quaternary carbon at δ 199.1 assigned to the acetyl group. The five methylene carbons, at δ 37.2, 69.7, 71.2, 73.4 and 75.1, assigned to C-2', C-6' and three benzyl groups respectively, were indicative of the unrearranged glycosyl moiety.

*(iii) Attempted C-Glycosylation using acetylnaphthols **264** and **321** and glycosyl donor **238**.*

Using the acetate protected glycosyl donor **238**, and trimethylsilyl triflate-silver perchlorate as the Lewis acid catalyst system, *C*-glycosylation with acetyl naphthols **264** and **321** was unsuccessful (scheme 100).

Scheme 100



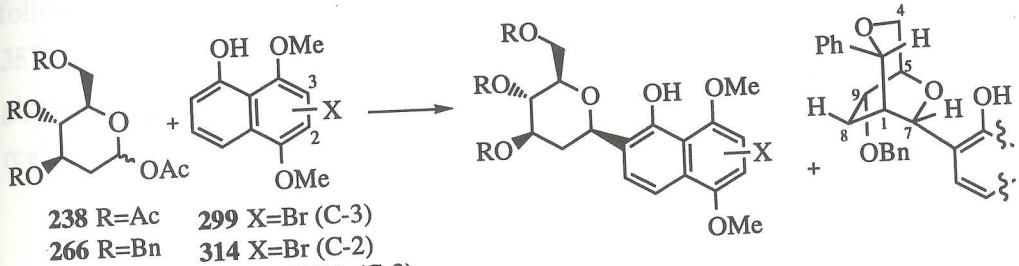
Reagents and conditions: TMSOTf, CH_3CN, 0 °C, 1 h.

2.2.7 Summary.

The table 2 provides an overview of the results from this section. A number of trends can be noted. We observed slightly better results, using the trimethylsilyl triflate-

silver perchlorate system rather than boron trifluoride diethyl etherate, with the acetate protected sugar **238** (entries 1-4). The reverse was true for the benzyl protected sugar **266**, where boron trifluoride diethyl etherate gave slightly improved results (entries 7 & 8). More important, however, was the reactivity of the napthols. Using the acetate protected sugar **238** we observed poor reactivity with the 3-substituted naphthols **299** and **264** (entries 1, 2 & 5) and 2-acetylnaphthol **321** (entry 6), only forming *C*-glycosides in good yields using 2-bromonaphthol **314** (entries 3 & 4). Likewise, using the benzyl protected sugar **266**, poor yields were obtained for the 3-substituted naphthols **299** and **264** (entries 7, 8 & 10) and 2-acetylnaphthol **321** (entry 11), with rearrangement of the sugar occurring to give predominantly the bicyclic compounds. Again, good yields of *C*-glycosides were only obtained using 2-bromonaphthol **314** (entry 9).

Table 2



238 R=Ac
266 R=Bn

299 X=Br (C-3)
314 X=Br (C-2)
264 X=COMe(C-3)
321 X=COMe(C-2)

	Glycosyl Donor	Naphthol	Lewis Acid	2-Deoxyglycoside & Yield(%)	Bicyclic Product & Yield(%)
1	R=Ac	X=Br (C-3)	TMSOTf, $AgClO_4$	**327** 5	-
2	R=Ac	X=Br (C-3)	$BF_3.OEt_2$	-	-
3	R=Ac	X=Br (C-2)	TMSOTf, $AgClO_4$	**328** 57	-
4	R=Ac	X=Br (C-2)	$BF_3.OEt_2$	**328** 48	-
5	R=Ac	X=COMe (C-3)	TMSOTf, $AgClO_4$	-	-
6	R=Ac	X=COMe (C-2)	TMSOTf, $AgClO_4$	-	-
7	R=Bn	X=Br (C-3)	TMSOTf, $AgClO_4$	**329** 5*	**340** 48
8	R=Bn	X=Br (C-3)	$BF_3.OEt_2$	**329** 9*	**340** 59
9	R=Bn	X=Br (C-2)	$BF_3.OEt_2$	**353** 53	-
10	R=Bn	X=COMe (C-3)	$BF_3.OEt_2$	**263** 7	**354** 12
11	R=Bn	X=COMe (C-2)	$BF_3.OEt_2$	**355** 9	**356** 23

* not isolated

It seemed, then, as if we would not be able to use naphthols **299** or **264** for the *C*-glycosylation reaction as we had planned. Rather, we would have to perform the coupling on a naphthol that was unfunctionalized at the C-3 position, and then regioselectively introduce a substituent at a later point in the synthesis. This would be the focus of the next chapter, with a new strategy being required.

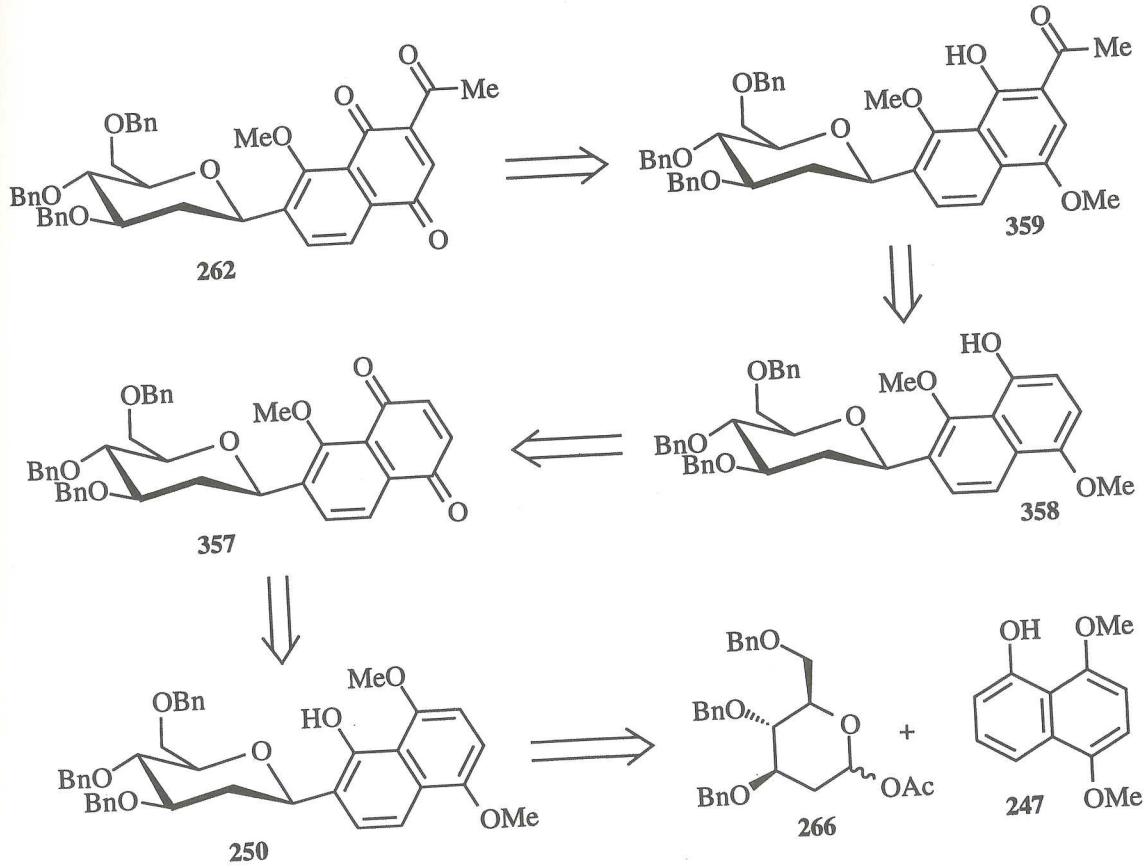
2.3 Synthesis of Acetylnaphthoquinone 262.

2.3.1 Revised Retrosynthesis and Synthetic Strategy.

In light of the glycosyl rearrangement described in chapter 2, which hampered our efforts at the glycosylation of various 3-functionalized naphthols, we decided to investigate an alternative synthesis based on the glycosylation of naphthol **247** (scheme 101). The acetyl group would then have to be regioselectively introduced, with the aryl *C*-glycoside linkage already in place.

A retrosynthetic analysis of the activated naphthoquinone **262** was proposed. The *C*-glycoside **250** would be formed by the Lewis acid promoted reaction of glycosyl acetate **266** and naphthol **247**. Protection of *C*-glycosylnaphthol **250** as the methyl ether followed by oxidative demethylation would then give the *C*-glycosylnaphthoquinone **357**. A key element of this strategy is the reductive methylation of **357** affording the *C*-glycosylnaphthol **358**, with the hydroxyl group providing a convenient handle for regioselective functionalization at the *ortho*-position.

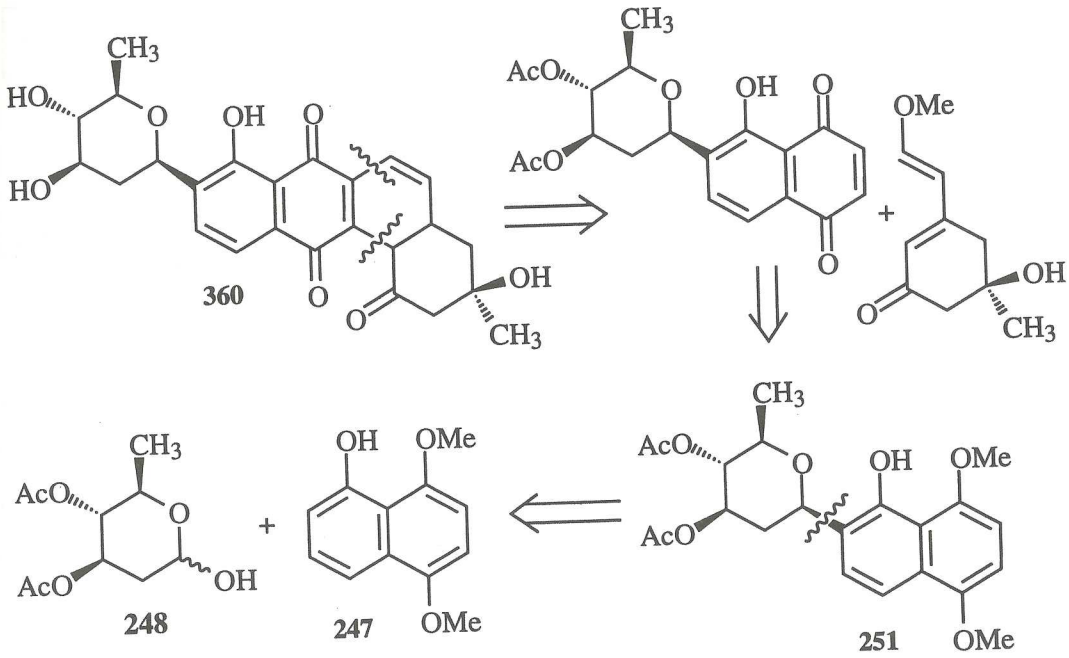
Scheme 101



The latter step was thought possible because methylation of the more sterically hindered C-4 hydroxyl group takes significantly longer than the C-1 hydroxyl group in similar non-glycosylated compounds such as **325** (see section **2.2.4**). The acetyl group could then be introduced by a Fries rearrangement of the acetate of **358** and oxidation of the resultant naphthol **359** would afford the key *C*-glycosylacetylnaphthoquinone **262**.

This particular *C*-glycosylation reaction had precedent in the work reported by Larsen and Andrews[161] (see section **1.3.5**). As part of their investigations towards the synthesis of angucline antibiotics such as urdamycinone B **360** they needed to develop suitable conditions for the formation of the *C*-glycoside **251** (scheme 102).

Scheme 102



During their model work Larsen *et al.*[161,178] experienced several of the same problems that we had encountered, namely:

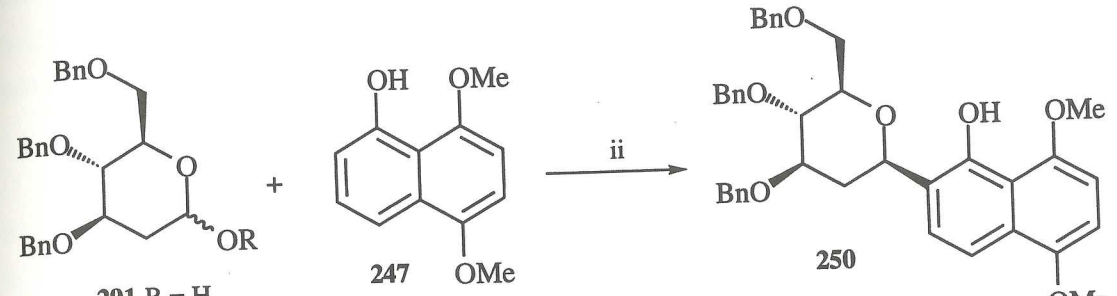
1. Difficulty in rearranging *O*-glycosides, with substituents at the 2-position of the glycosyl moiety, to the corresponding *C*-glycosides using Kometani's methodology.

2. Difficulty with *C*-glycosylation of naphthol **247** using Suzuki's conditions.

3. Success using acetonitrile (instead of dichloromethane) as solvent.

Using the conditions they had developed, Larsen and Andrews[161,178] successfully coupled trifluoroacetate **217**, formed *in situ* from pyranose **291**, with naphthol **247** using boron trifluoride diethyl etherate to afford the β-*C*-glycoside **250** in 81% yield (scheme 103).

Scheme 103



Reagents and conditions: (i) $(COCF_3)_2O$, CH_3CN, r.t., 1 h.
(ii) $BF_3.OEt_2$, CH_3CN, 0 °C, 20 min., 81%.

2.3.2 Synthesis of Naphthol 247.

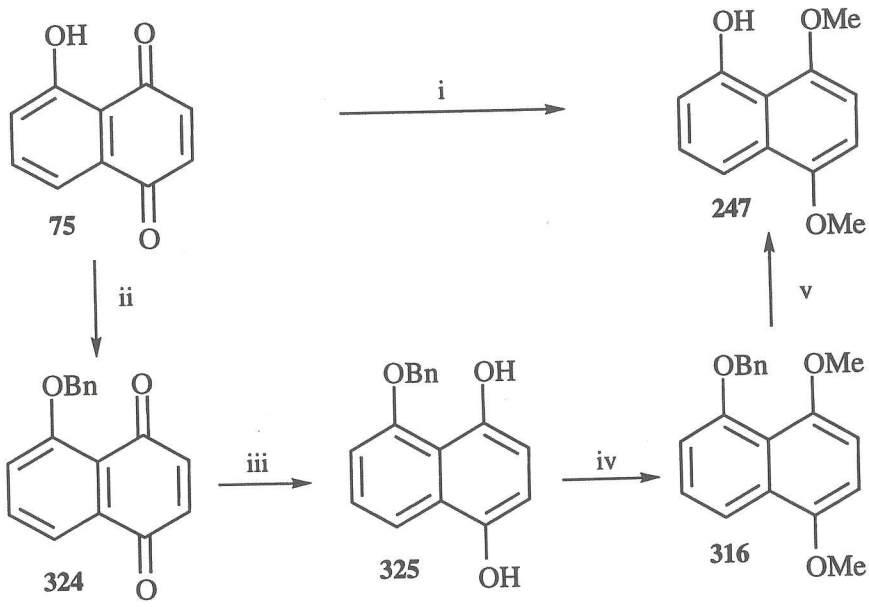
There were two different routes used in the synthesis of naphthol **247** (scheme 104). The first involved three steps, which were high yielding and able to be performed on a large scale. The initial step was benzylation of juglone **75** which was carried out as before (section **2.2.4**) using benzyl bromide and silver(I) oxide in chloroform to give the yellow crystalline benzyl ether **324** in 90% yield.

Reduction of **324** using aqueous sodium dithionite (7 equiv.) gave the hydroquinone **325** as a tan solid after the solvent was removed. The air sensitive hydroquinone **325** was not purified further, but was dissolved immediately in dry acetone then heated at reflux with potassium carbonate (5 equiv.) and dimethyl sulfate (3 equiv.) for 48 hours. The dimethyl ether **316** was obtained as tan needles in 84% yield after work-up and chromatography which was indistinguishable from that prepared previously (section **2.2.3**). The ^{1}H nmr spectrum contained two, three proton, singlets at δ 3.88 and 3.94 assigned as methoxy groups as well as a two proton singlet at δ 5.20 attributable to the benzyl methylene protons.

An ethyl acetate solution of the benzyl ether **316** was then debenzylated using 10% palladium on charcoal under an atmosphere of hydrogen to afford the crystalline naphthol **247** in 98% yield. The physical and spectroscopic data were in agreement with those reported in the literature.[201,202] The ^{1}H nmr spectrum contained two, three proton,

singlets at δ 3.94 and 4.01 assigned to the methoxy groups and a one proton singlet at δ 9.45 corresponding to the hydroxyl group.

Scheme 104



Reagents and conditions: (i) $SnCl_2$, MeOH, conc. H_2SO_4, C_6H_6, reflux, 3 days, 43% (ii) BnBr, Ag_2O, $CHCl_3$, 90% (iii) $Na_2S_2O_4$ (iv) Me_2SO_4, acetone, K_2CO_3, reflux, 48 h, 84% (v) H_2, 10% Pd/C, EtOAc, 2 h, 98%.

A more direct approach to naphthol **247** was reported by Wurm and Goeßler.[201] This involved the addition of juglone **75** and tin(II) chloride to an ice-cooled solution of methanol acidified with concentrated sulfuric acid. The mixture was then heated at reflux for three days. In our hands this procedure gave only a 43% yield of **247** after work-up and chromatography. The naphthol **247** obtained was indistinguishable from that prepared by the previous method.

Subsequently, Larsen and Andrews[178] reported similar poor yields for this reaction which they found to be due to inefficient separation of the crude product from tin residues. The yields reportedly increased when they employed a vigorous aqueous work-up. When benzene was used as a co-solvent, in conjunction with a Dean and Stark apparatus, reproducible yields of 70% were obtained.

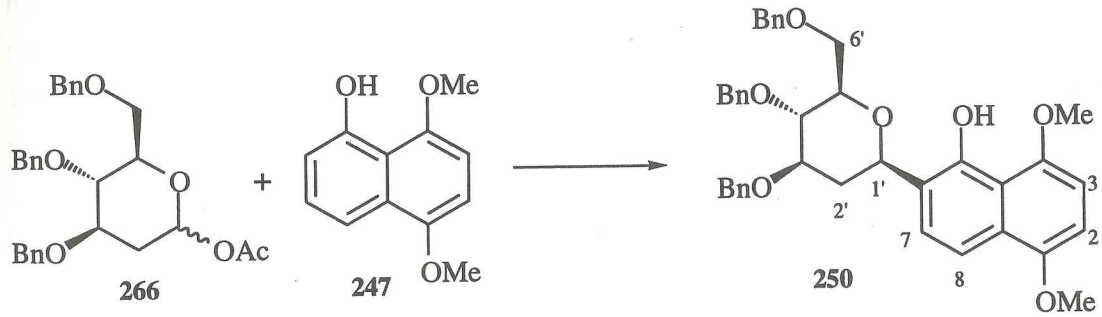
2.3.3 Synthesis of β-*C*-Glycoside 250.

With the naphthol **247** in hand, attention was turned to the glycosylation reaction. Larsen and Andrews[178] had used the trifluoroacetate **217**, formed *in situ* from pyranose **291** on treatment with trifluoroacetic anhydride (see scheme 103). Instability of the acetate **266** on storage was cited as the primary reason for this, with hydrolysis occurring to afford the less reactive pyranose **291**. We found that the acetate **266** gave adequate yields, as long it had been recently prepared.

Thus boron trifluoride diethyl etherate (2.0 equiv.) was added to a solution of the naphthol **247** and the glycosyl acetate **266** (1.2 equiv.) in dry acetonitrile at 0 °C. After 20 min., the solution was quenched with water and the desired β-*C*-glycoside **250** was isolated in 73% yield after chromatography (scheme 105).

The yield for this reaction was improved by avoiding chromatography, which resulted in decomposition of **250**. Hence, the crude product was typically used for the subsequent methylation step.

Scheme 105



Reagents and conditions: $BF_3.OEt_2$, CH_3CN, 0 °C, 20 min., 73%.

The spectral data was consistent with that reported by Larsen and Andrews.[161] In the ^1H nmr spectrum the 2'ax-H and 2'eq-H protons resonated as doublets of doublets of doublets at δ 1.63 and 2.59 respectively, showing a strong geminal coupling constant, J_{gem} 12.8 Hz. Apart from 1'-H, the remainder of the glycosyl protons resonated in the region δ 3.65-4.00 as unresolved multiplets. The two methoxy groups of the naphthalene ring resonated as three proton singlets at δ 3.99 and 4.01. Five of the six benzylic methylene protons resonated as an unresolved multiplet in the region δ 4.60-4.78, while the remaining resonance was a downfield doublet at δ 4.98, coupling constant, J_{gem} 10.7 Hz. The anomeric proton, 1'-H, resonated at δ 5.01, with coupling constants, $J_{1',2'ax}$ 11.0

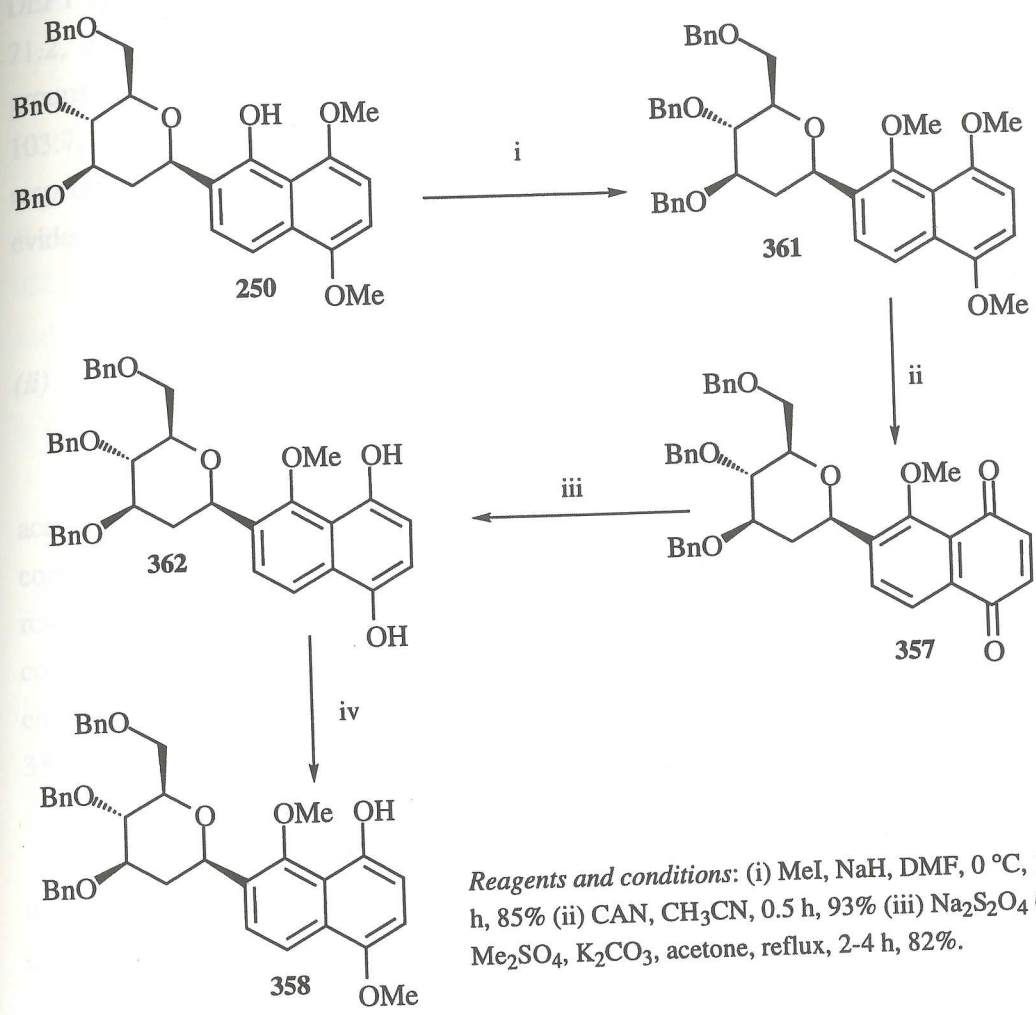
and $J_{1',2'eq}$ 1.8 Hz, providing evidence that 1'-H was axial and hence that the glycosyl linkage was of the desired β-stereochemistry. Doublets at δ 6.61 and 6.68 corresponded to the naphthalene methine protons, 3-H and 2-H respectively, each with a coupling of $J_{2,3}$ 8.4 Hz. The unresolved aromatic region from δ 7.20-7.43 integrated for fifteen protons which was consistent with the presence of three benzyl groups. A second pair of doublets at δ 7.65 and 7.74, with coupling constant, $J_{7,8}$ 8.7 Hz, corresponded to 8-H and 7-H respectively. This was confirmed by positive nOe's between 7-H and 1'-H/2'-H as well as between 8-H and the protons of the methoxy group at C-1. That 8-H is the more upfield resonance seems counter-intuitive since we expect a deshielding influence from the *peri*-methoxy group. One explanation is that the glycosyl moiety is deshielding 7-H to a greater extent. The remaining resonance was a singlet at δ 9.76, characteristic of a naphthalene hydroxyl group.

Likewise, the ^{13}C nmr spectrum agreed well with that reported.[178] Methylene resonances at δ 37.4 and 69.7 were assigned to C-2' and C-6' respectively, with the latter being the more deshielded due to the adjacent oxygen atom. The remaining methylene resonances at δ 71.8, 73.4 and 75.0 were attributed to the three benzyl protecting groups. Resonances at δ 78.5, 79.5 and 81.4 corresponded to the aliphatic carbons C-3', C-4' and C-5' of the glycosyl moiety. Resonances at δ 102.8 and 103.6 were assigned as the naphthyl carbons, C-3 and C-2 respectively (based on comparison with the subsequent methylated product **361** for which a HETCOR spectrum was obtained). Resonances at δ 113.2 and 124.8 were assigned to C-7 and C-8. The benzyl aromatic carbons resonated in the region δ 127.4-128.3, with the exception of the quaternary *ipso*-carbons which resonated at δ 138.7. The remaining resonances were all quaternary. These included the bridgehead carbons C-4a and C-8a at δ 115.1 and 123.7, with C-4a being assigned as the more upfield of the two on the basis of its position adjacent to two electron donating groups (compared with one for C-8a). The C-6 carbon resonance was not observed and was presumed to lie beneath the benzyl aromatic region (δ 127.0-128.3). Support for this was obtained in subsequent steps where the chemical shift for C-6 resonance was in most cases approximately δ 130, and was usually slightly downfield of C-8a. The remaining resonances at δ 149.6, 150.0 and 150.2 were not individually assigned, but were attributed to C-1, C-4 and C-5.

2.3.4 Synthesis of β-*C*-Glycosylnaphthol 358.

With the desired β-*C*-glycosylnaphthol **250** in hand, it was envisaged that, in an analogous fashion to the synthesis of naphthol **326** (section **2.2.4**), glycosylnaphthol **358** could be synthesized in four steps as outlined below (scheme 106).

Scheme 106



Reagents and conditions: (i) MeI, NaH, DMF, 0 °C, 12 h, 85% (ii) CAN, CH_3CN, 0.5 h, 93% (iii) $Na_2S_2O_4$ (iv) Me_2SO_4, K_2CO_3, acetone, reflux, 2-4 h, 82%.

*(i) Synthesis of C-glycosylnaphthol **361**.*

A solution of **250** in dimethylformamide at 0 °C was treated with sodium hydride and methyl iodide. After stirring at room temperature for 12 h the reaction was quenched with water to give, after work-up and chromatography, the methylated product **361** in 85% yield.

Compound **361** analyzed correctly for $C_{40}H_{42}O_7$ and the spectral data was consistent with the proposed structure. The ^1H nmr spectrum displayed three, three proton, singlets at δ 3.82, 3.89 and 3.92 attributable to the three methoxy groups. The resonances for the glycosyl moiety were largely unchanged. The anomeric proton, 1'-H, resonated as a broad doublet at δ 4.91. The ^{13}C nmr spectrum was also consistent with the proposed structure. Resonances at δ 55.7 and 56.6 corresponded to the two methoxy groups attached to C-1 and C-4, with the resonance at δ 62.9 assigned to the newly introduced C-5 methoxy group. The anomeric carbon, C-1', resonated at δ 72.2 while the

DEPT spectrum confirmed the presence of five methylene resonances at δ 38.3, 69.6, 71.2, 73.3 and 75.0 assigned respectively to C-2', C-6' and the three benzyl protecting groups. Analysis of the HETCOR spectrum allowed identification of the resonances at δ 103.7, 106.0, 118.6 and 124.2 as the naphthyl methine carbons C-3, C-2, C-7 and C-8 respectively. The absence of a hydroxyl stretch in the infra-red spectrum provided further evidence that methylation had in fact taken place.

(ii) Synthesis of C-glycosylnaphthoquinone 357.

Castagnoli, Jr. *et al.*[203] have reported that ceric ammonium nitrate in aqueous acetonitrile can be used to oxidize a variety of hydroquinone methyl ethers to the corresponding quinones. Ceric ammonium nitrate has also been used extensively in this research group[102,113] to effect the rearrangement of furonaphthofurans to the corresponding furonaphthopyrans (section **1.2.5**). Based on previous work it was envisaged that the naphthalene **361** would be readily oxidized to the naphthoquinone **357**.

A solution of naphthalene **361** in acetonitrile was oxidatively demethylated using aqueous CAN (2 equiv.) to give the expected naphthoquinone **357** in 93% yield after chromatography.

The high resolution mass spectrum exhibited a molecular ion at *m/z* 604.2453 consistent with the molecular formula $C_{38}H_{36}O_7$. The infra-red spectrum featured a prominent carbonyl stretch at 1665 cm^{-1} indicative of a quinone. Oxidation was evident from the disappearance of two of the methoxy peaks from the ^1H nmr spectrum. The single three proton resonance at δ 3.87 corresponded to the remaining methoxy group at C-5. The aliphatic region exhibited resonances characteristic of a benzyl protected 2-deoxyglycoside, including the anomeric proton, 1'-H, as a doublet of doublets at δ 4.81. The two doublets at δ 6.88 and 6.94 were assigned to 3-H and 2-H respectively with a large coupling of $J_{2,3}$10.3 Hz. In contrast, 7-H and 8-H resonated as a two proton singlet at δ 7.94.

The ^{13}C nmr spectrum was consistent with the proposed structure with the resonance at δ 62.4 attributed to the methoxy group while the quinone carbonyls, C-1 and C-4, resonated at δ 184.4 and 184.7. Most of the naphthalene ring carbons were shifted dramatically downfield due to the deshielding influence of the quinone carbonyls. Striking examples of this phenomenon were C-2 and C-3 shifted from δ 106.0 and 103.7 to δ 136.9 and 140.3 respectively.

(iii) Synthesis of C-glycosylnaphthol 358.

Reduction of the quinone **357** using aqueous sodium dithionite (7 equiv.) gave the hydroquinone **362** as an air sensitive tan solid which was used in crude form for the next step. A solution of **362** in dry acetone was heated at reflux with potassium carbonate (5 equiv.) and dimethyl sulfate (3 equiv.) for 2-4 h to give the monomethylated product **358** in 82% yield after chromatography together with small amounts of the quinone **357** and trimethoxy compound **361**. It was neccessary to carefully monitor the reaction to obtain optimum yields of **358**. Methyl iodide was not a strong enough methylating agent with gradual decomposition occurring rather than the desired methylation.

C-Glycosylnaphthol **358** analyzed correctly for $C_{39}H_{40}O_7$. The mass spectrum included a molecular ion at *m/z* 620 which supported the proposed molecular formula. The infra-red spectrum featured a broad hydroxyl stretch at 3329 cm^{-1}. The ^1H nmr contained two, three proton, singlets at δ 3.85 and 3.86 assigned to the methoxy groups. In addition a singlet was observed at δ 9.53 which was characteristic of an aromatic hydroxyl proton. The ^{13}C nmr spectrum exhibited resonances at δ 56.0 and 64.6 assigned to the two methoxy groups.

2.3.5 Introduction of the Acetyl Group.

(i) Synthesis of acetate 363 and attempted Fries rearrangement.

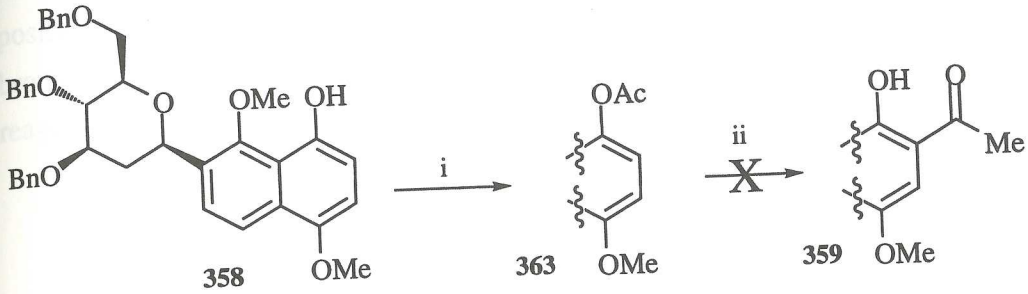
Since introduction of an acetyl group to C-3 of *C*-glycosylnaphthol **358** was our goal, acetylation followed by a Fries rearrangement would be the normal course of action (scheme 107). The presence of benzyl protecting groups on the glycosyl moiety complicated the situation as these have been shown to be labile under Fries conditions.[120]

Acetate **363** was readily formed by treating a dichloromethane solution of *C*-glycosylnaphthol **358** with triethylamine (3 equiv.), acetic anhydride (2 equiv.) and a catalytic amount of 4-dimethylaminopyridine in dichloromethane. After chromatography, acetate **363** was isolated in 85% yield.

Compound **363** analyzed correctly for $C_{41}H_{42}O_8$. The infra-red spectrum featured a carbonyl stretch at 1759 cm^{-1} due to the acetate group and also lacked a hydroxyl group. The mass spectrum exhibited a molecular ion at *m/z* 662 supporting the molecular formula. The ^1H nmr spectrum was consistent with the proposed structure with the acetate group resonating as a three proton singlet at δ 2.29 and the two methoxy groups

resonating at δ 3.73 and 3.90. The ^{13}C nmr spectrum was similarly supportive of the proposed structure. The methyl carbon of the acetate group resonated at δ 20.8 while the methoxy groups resonated at δ 55.8 and 63.2. The acetate carbonyl group resonated downfield at δ 170.1.

Scheme 107



Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t., 6 h, 85 %
(ii) heat, $BF_3.OEt_2$ or (ii) $ScOTf_2$, PhMe, 100 °C, 6 h.

Fries rearrangement of acetate **363** was attempted by heating the neat acetate **363** to 120 °C followed by the addition of boron trifluoride diethyl etherate. None of the rearranged compound **359** was observed, the reaction instead giving a complex mixture of unidentifiable products.

An alternative procedure[204] was investigated, which involved catalytic Fries rearrangement (of acyloxy naphthalenes) using scandium trifluoromethanesulfonate (scandium triflate). Usually in Fries rearrangement reactions, more than a stoichiometric amount of Lewis acid is required because most Lewis acids are deactivated by the free hydroxyl group of the products. It was reported[204] that scandium triflate is not trapped by the carbonyl oxygens of aromatic ketones, and that free hydroxy and carboxylic groups do not decrease the Lewis acidity. Bearing these observations in mind, we examined the Fries rearrangement of acetate **363** using a catalytic amount of scandium triflate.

A solution of acetate **363** and scandium triflate (5 mol%) in toluene was heated at 100 °C for 6 hours. However, the desired acetylnaphthol **359** was not formed, with gradual deacetylation to the naphthol **358** occurring instead.

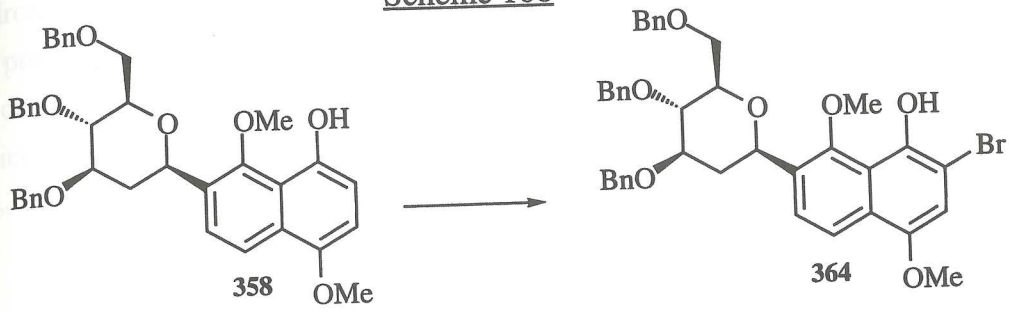
(ii) *Synthesis of C-glycosylbromonaphthol 364.*

In light of the difficulties experienced with the Fries rearrangement reaction, an alternative approach to the synthesis of acetylnaphthol **359** was sought. It was noted that the free hydroxyl group on **358** provided a convenient method for the regioselective introduction of bromine at the *ortho*-position. Competitive bromination at the *para*-position was blocked by the presence of a methoxy substituent at C-1 (scheme 108). The bromine substituent would then provide a suitable handle for use of an organolithium reagent to introduce an acetyl group at C-3.

Various conditions were tried before successful bromination of naphthol **358** was achieved. The addition of bromine in carbon tetrachloride to a solution of naphthol **358** in carbon tetrachloride at 0 °C and subsequent stirring for a period of 0.5 h resulted in the formation of various highly coloured products which were not isolated (thought to be quinonoid by-products resulting from oxidation). The addition of *N*-bromosuccinimide and diisopropylamine to a dichloromethane solution of **358** was similarly unsuccessful. On returning to the initial method, it was discovered that immediate quenching with aqueous sodium thiosulfate following the addition of bromine resulted in isolation of the desired product **364** in 77% yield after chromatography. It was rationalized that bromination was occurring virtually instantaneously and thus secondary oxidation was being avoided by the rapid quench.

Bromonaphthol **364** slowly crystallized in the flask to give tan needles which melted at 116-117 °C and analyzed correctly for $C_{39}H_{39}BrO_7$. The infra-red spectrum contained a broad hydroxyl stretch at 3329 cm^{-1} and the mass spectrum contained a molecular ion at *m/z* 698/700 which supported the proposed structure. The noticeable feature of the ^1H nmr spectrum was that H-2 was now a singlet at δ 6.85 instead of a doublet, since the 3-position was now substituted with bromine. The methoxy protons both resonated at δ 3.85 rather than at δ 3.92 and 3.93 as before, shifted slightly upfield due to the shielding effect of bromine. In contrast the hydroxyl resonance was shifted downfield to δ 9.53. The ^{13}C nmr data also supported the proposed structure, the major changes being that C-4 and C-3 had shifted upfield to δ 143.5 and 103.5 respectively and that C-3 was now quaternary in nature.

Scheme 108



Bromine source	Reaction conditions	Yield (%)
Br_2	CCl_4, 0 °C, 30 min.	quinonoid products
NBS	$^iPr_3N$, 0 °C, 30 min.	quinonoid products
Br_2	CCl_4, 0 °C, 2 min.	77

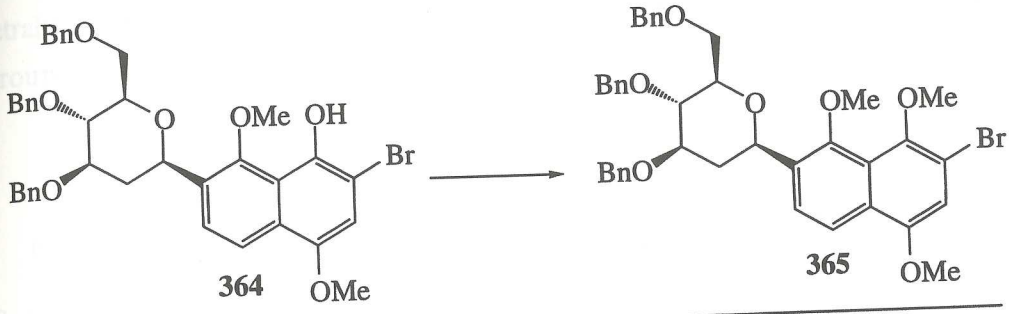
(iii) Synthesis of C-glycosylbromonaphthalene ***365****.*

Methylation of **364** was attempted under a variety of conditions (scheme 109). Using methyl iodide and sodium hydride in dry dimethylformamide only small amounts of the desired product **365** were obtained. A purple by-product was observed which was thought to be the result of oxidation. Using tetrahydrofuran or mixtures of tetrahydrofuran and dimethylformamide as solvent worsened the situation. A slight improvement was noticed on changing to dimethyl sulfate as the methylating agent. Reasonable success was achieved by the addition of a slurry of sodium hydride in dimethylformamide to a solution of **364** and dimethyl sulfate in dimethylformamide at 0 °C under a hydrogen atmosphere, affording a 69% yield of **365** after work-up and chromatography. The rationale for this success is not clear and a more satisfactory method was subsequently developed. This involved the addition of an excess of aqueous sodium hydroxide to a solution of **364** and dimethyl sulfate (2 equiv.) in dry dimethylformamide at 0 °C. After stirring for 15 min. the solution was quenched with water and the product **365** was obtained in 84% yield after chromatography. A key to the success of this reaction was the presence of the methylating agent prior to the addition of the base.

The high resolution mass spectrum exhibited a molecular ion at *m/z* 712.2027 consistent with the molecular formula $C_{40}H_{41}{}^{79}BrO_7$. The lack of a hydroxyl stretch in the infra-red spectrum provided further evidence that methylation was successful. The ^1H nmr spectrum supported the proposed structure, being effectively identical to **364** for the glycosyl resonances, but with several significant changes in the naphthyl region. There were now three methoxy peaks at δ 3.75, 3.76 and 3.88 instead of just two, and the

hydroxyl resonance had disapppeared. The ^{13}C nmr spectrum was likewise supportive of the proposed structure. There was a slight deshielding effect on C-1' and C-2' thought to be due to a buttressing effect from the neighbouring methoxy groups. The naphthyl moiety was affected more dramatically with an additional methoxy resonance being observed at δ 61.9 as well as deshielding of C-3, C-4a and C-6.

Scheme 109

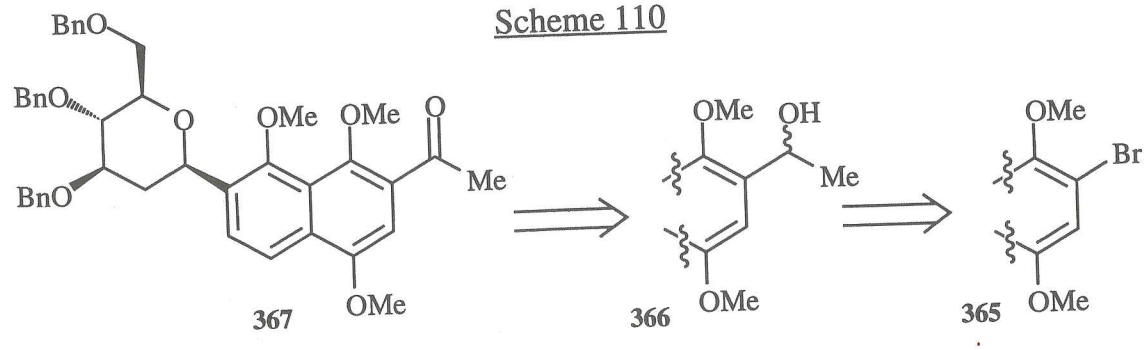


Base	Methylating agent	Conditions	Yield (%)
NaH	MeI	DMF	13
NaH	MeI	DMF/THF, 30 min., 0 °C	7
NaH	Me_2SO_4	DMF, 30 min., 0 °C	34
NaH	Me_2SO_4	DMF, 15 min., 0 °C, H_2	69
NaOH	Me_2SO_4	DMF/H_2O, 15 min., 0 °C	84

*(iv) Attempted synthesis of methyl ketone **367** using an organolithium reagent.*

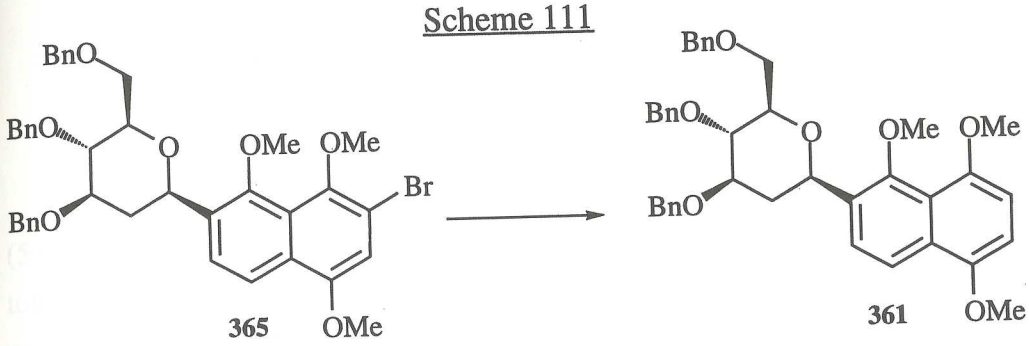
Our initial strategy to effect conversion of bromide **365** to acetylnaphthalene **367** focused on the addition of acetaldehyde to a naphthyl anion (scheme 110). Subsequent oxidation of the resultant alcohol **366** using tetrapropylammonium perruthenate (TPAP) and NMO[6] should then give the desired acetyl compound **367**.

Scheme 110



In practice, the anion formed from *C*-glycosylbromide **365** was extremely reactive and (despite rigorously anhydrous conditions) protonated to give exclusively the dehalogenated **361** (scheme 111). This is thought to be due to the increased basicity of the more highly substituted (and therefore more electron rich) naphthalene relative to the simpler naphthyl bromides used in previous work. It is possible that protons were being abstracted from other molecules of the starting bromide **365** or from acetaldehyde, which was usually added in excess due to its high volatility, or from the solvent, tetrahydrofuran. Similar problems have been encountered previously by this research group.[120]

Scheme 111



Reagents and conditions: CH_3CHO, THF, ^{t}BuLi, -78 °C, 98%.

*(v) Synthesis of methyl ketone **367** using a Stille type coupling.*

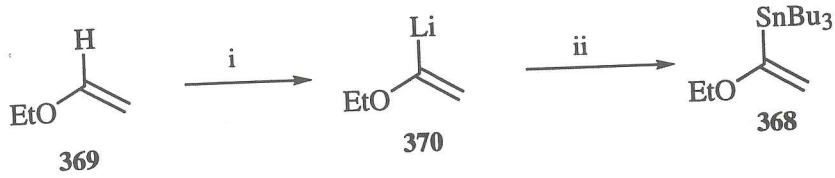
Fortuitously a convenient solution to the dilemma described above was discovered in the literature.[205] This alternative approach employs α-ethoxyvinyltri-*n*-butyl tin as a masked acetylating agent in the palladium(0) catalyzed reaction with various organic halides, including aryl bromides. Hydrolysis of the resulting reaction mixture then affords the corresponding ketones in high yield (scheme 112).

Scheme 112

$$n\text{-}Bu_3SnC(OEt)=CH_2 + R\text{-}X \xrightarrow{[Pd]} RC(OEt)=CH_2 \xrightarrow{H^+} R\text{-}COCH_3$$

The desired tin reagent **368** was readily prepared according to the procedure reported by Soderquist *et al.*[206] (scheme 113). Treatment of a solution of ethyl vinyl ether **369** in tetrahydrofuran at -78 °C with *tert*-butyllithium followed by quenching of the resultant vinyllithium **370** with tributyltin chloride afforded vinyl stannane **368** in 92% yield.

Scheme 113



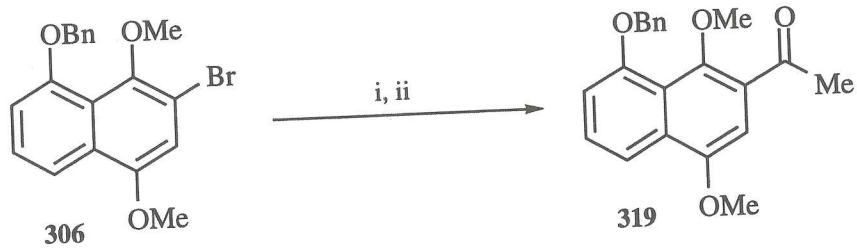
369 **370** **368**

Reagents and Conditions: (i) ^{t}BuLi, THF, -78 °C (ii) Bu_3SnCl, -78 °C to r.t., 92%.

The general acylation procedure involves boiling a solution of the aryl bromide (5.0 equiv.), vinyl stannane **368** (5.5 equiv.) and the palladium catalyst (0.5 equiv.) in toluene for 18 hours followed by hydrolysis with dilute hydrochloric acid. The commercially available bistriphenylphosphino-palladium(II) dichloride was used since palladium(II) catalysts are reduced to the active palladium(0) species under the reaction conditions.[206]

The reaction was trialled on a simple model bromide **306** which afforded the acetyl derivative **319** in 97% yield after chromatography (scheme 114). The ketone **319** was prepared in earlier work in a two step procedure (see section **2.2.3**).

Scheme 114

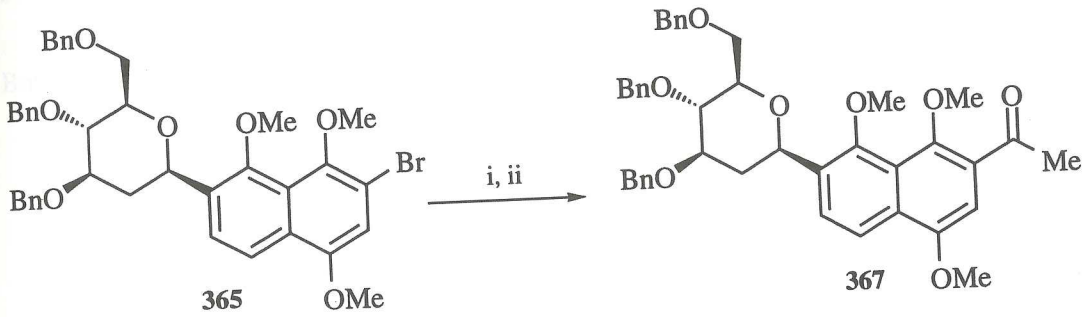


306 **319**

Reagents and Conditions: (i) $Pd(PPh_3)_2Cl_2$, $Bu_3SnC(OEt)=CH_2$, PhMe, 100 °C, N_2, 16 h (ii) H_3O^+, 97%.

The more complex *C*-glycosylbromonaphthalene **365** reacted more slowly than the model compound and it was necessary to add several more portions of both the tin reagent **368** and the palladium catalyst in order for the reaction to proceed to completion (scheme 115). This was probably due to poisoning of the catalyst and meant that in our case the reaction was not catalytic. Hydrolysis of the reaction mixture using dilute hydrochloric acid afforded the desired ketone **367**. Care was needed in order to isolate the product **367** free from tin residues. Washing with aqueous potassium fluoride solution[207] removed the majority of the tin residue and then careful chromatography allowed separation of the product **367** from the small amounts of more polar tin compound that remained. In addition to the desired acetyl compound **367** which was obtained in 90% yield a small amount of the starting bromide **365** was usually recovered and could be recycled. Notably, none of the protonated compound **361** was formed.

Scheme 115



Reagents and Conditions: (i) $Pd(PPh_3)_2Cl_2$, $Bu_3SnC(OEt)=CH_2$, PhMe, 100 °C, N_2, 16 h (ii) H_3O^+, 90%.

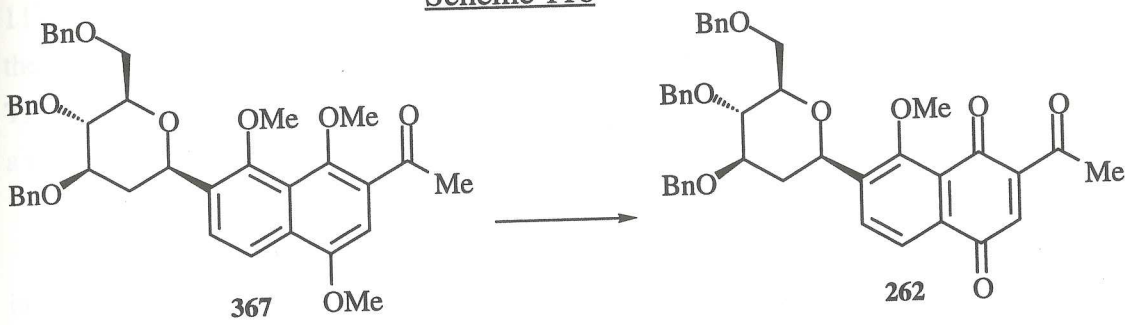
Compound **367** analyzed correctly for $C_{44}H_{42}O_8$. The infra-red spectrum featured a carbonyl stretch due to the ketone at 1667 cm^{-1} and the mass spectrum exhibited a molecular ion at *m/z* 676 further supporting successful acylation. The ^1H nmr spectrum of acetylnaphthol **367** showed little change from the bromide **365** in the glycosyl region, however, a distinctive, three proton, singlet at δ 2.71 was assigned to the protons of methyl ketone. The 2-H proton resonated at δ 6.97, which was downfield of its position (δ 6.85) in the corresponding bromide **365**, due to deshielding from the β-carbonyl group.

The ^{13}C nmr spectrum was also consistent with the proposed structure. A methyl carbon at δ 31.5 and quaternary carbon at δ 201.0 were assigned to the acetyl group.

2.3.5 Synthesis of Acetylnaphthoquinone 262.

With the desired ketone **367** in hand, it remained to effect oxidative demethylation to the activated naphthoquinone **262**. A solution of the ketone **367** in acetonitrile was treated with aqueous ceric ammonium nitrate (CAN) (2 equiv.) and the reaction was monitored by TLC. After stirring for 20 minutes at room temperature no starting material remained. The reaction mixture was then worked-up and filtered. Initially florisil was used as the filter agent but extensive decomposition of the unstable naphthoquinone **262** was observed. Elution through a plug of silica resulted in better purification and less decomposition, affording the quinone **262** in 91% yield (scheme 116).

Scheme 116



Reagents and conditions: CAN, CH_3CN, H_2O, 15 min., 91%
or AgO, HNO_3, dioxane, 20 min., 93%.

An alternative procedure was also used whereby the ketone **367** was oxidized, using silver(II) oxide and nitric acid, in dioxane.[208] After work-up the product **262** was clean enough to use without further purification affording a slightly improved yield of 93%.

Naphthoquinone **262** analyzed correctly for $C_{40}H_{38}O_8$. The infra-red spectrum featured carbonyl stretches assigned as ketone at 1702 cm^{-1} and quinone at 1666 cm^{-1}. The mass spectrum exhibited a molecular ion at *m/z* 648 and the ^1H nmr spectrum was consistent with the proposed structure containing two, three proton, singlets at δ 2.53 and 3.81 assigned to the methyl ketone and remaining methoxy group respectively. In the ^{13}C nmr spectrum, a methyl carbon at δ 30.8 and a quaternary carbon at δ 198.0 were assigned to the methyl ketone. The methoxy group carbon resonated at δ 62.6 while the quinone carbonyls were downfield resonances at δ 183.0 and 184.6.

2.4 Synthesis of Medermycin Analogue 257.

With the key glycosyl naphthoquinone **262** in hand, attention next focused on the furofuran annulation reaction

2.4.1 Synthesis of Furonaphthofurans 261a and 261b.

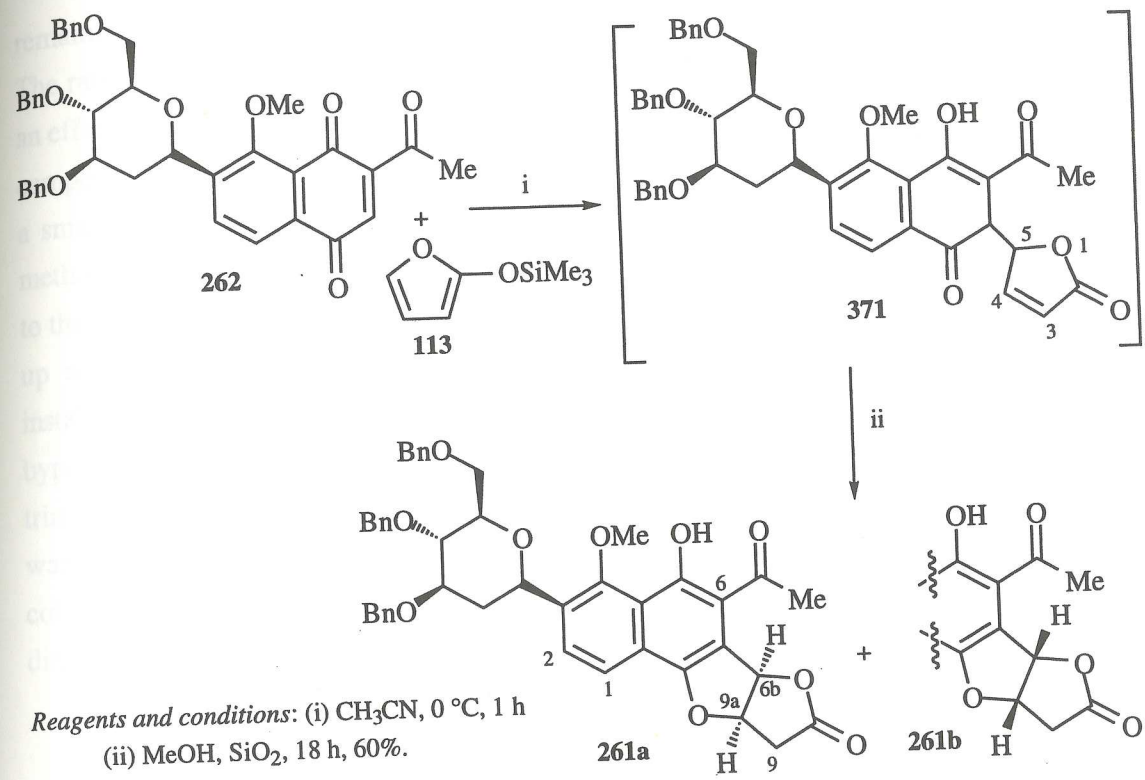
Thus, with acetonitrile as solvent, 2-trimethylsilyloxyfuran **113** (2 equiv.) was added to the naphthoquinone **262** at 0 °C and the reaction monitored by TLC (scheme 117). After an hour the reaction mixture was allowed to warm to room temperature and then stirred for a further eighteen hours. Although there appeared to be one product by TLC, it was apparent from the ^{1}H nmr spectrum of the crude product that there was in fact a mixture of the intermediate **371** and diastereomeric adducts **261a** and **261b**.

The intermediate **371** and products **261a**, **261b** were not readily separable but individual ^{1}H nmr resonances for the two types of compound could be distinguished which allowed establishment of the ratio of product to intermediate. This was important so we could fine tune of the reaction to optimize the yield of the desired product.

Characteristic peaks for the intermediate **371** were the butenolide protons 5-H, 3-H and 4-H which resonated as a doublet of triplets at δ 5.06, a doublet of doublets at δ 6.16 and a doublet of doublets at δ 7.37 respectively.

Adduct (**261a**, **261b**) formation was identified on the basis of the bridgehead protons which have distinctive shifts. The 9a-H proton resonated as a multiplet at δ 5.51, while 6b-H resonated as a pair of doublets at δ 6.47 and δ 6.48*, corresponding to the major and minor* diastereomers respectively.

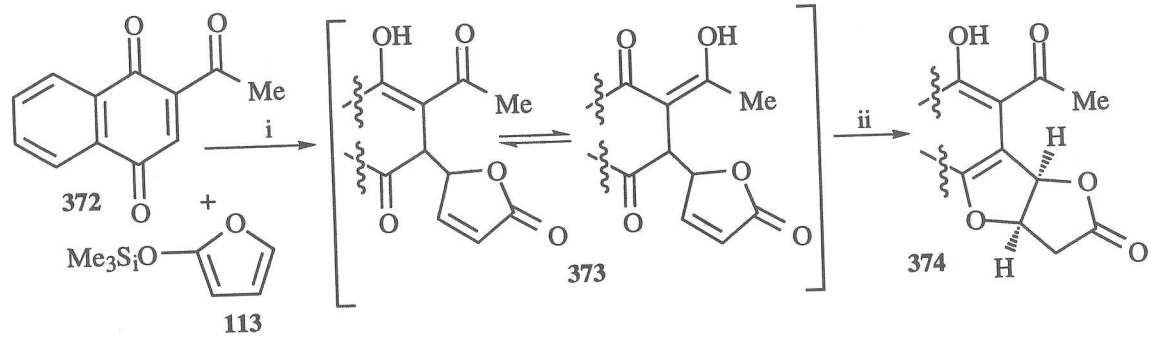
Scheme 117



Reagents and conditions: (i) CH_3CN, 0 °C, 1 h
(ii) MeOH, SiO_2, 18 h, 60%.

Previous work within this research group had established the formation of intermediates similar in structure to **371**.[101] The intermediate **373** was isolated in 5% yield from the reaction of naphthoquinone **372** with 2-trimethylsilyloxyfuran **113** (scheme 118) and was shown to be in the enol rather than methyl ketone form. In this earlier work, the intermediate **373** was isolated due to its lower solubility, although it co-eluted with the product **374**. Cyclization of the butenolide **373** to the desired adduct **374** was achieved through the addition of methanol.

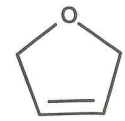
Scheme 118



Reagents and conditions: (i) CH_3CN, -30 °C, 1 h (ii) MeOH, 18 h, 90%.

When methanol was added to the reaction mixture in an attempt to cyclize the remaining butenolide **371** a small increase in the amount of product **261** was observed. The ratio of product **261** to intermediate **371** also improved after flash chromatography, an effect which was attributed to the acidic nature of silica gel. Based on this observation camphorsulfonic acid was added, however, this met with no success. When a small amount of silica was added to the reaction mixture, as well as methanol, and the mixture stirred for 18 hours, almost complete conversion to the desired product **261** was achieved, affording a 60% yield after work-up and chromatography. While rapid elution was preferable due to the instability of **261**, this was hampered by a difficult separation from the butenolide byproduct **375**, formed by elimination of the trimethylsilyloxy group from 2-trimethylsilyloxyfuran **113** (figure 32). The ratio of the two diastereomers of adduct **261** was 5:4 by ^{1}H nmr. Analytical HPLC (optimum conditions 1.5% ^{i}PrOH/hexane, partisil 5 column, 25 cm x 4.6 mm I.D., flow rate 1.5 mL/min.) suggested that separation of the diastereomers by HPLC would be difficult since the resolution was very poor.

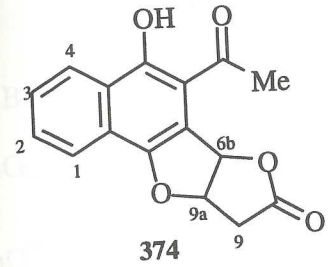
Figure 32



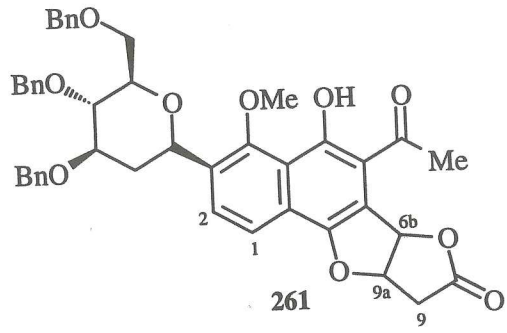
375

The high resolution mass spectrum exhibited a molecular ion at *m/z* 730.2762 consistent with the molecular formula $C_{44}H_{42}O_{10}$. The infra-red spectrum displayed a broad band at 3333 cm^{-1} characteristic of a hydroxyl group as well as strong bands at 1784 and 1642 cm^{-1} indicative of the carbonyl groups of the γ-lactone and *ortho*-hydroxy aryl ketone respectively. As mentioned previously, the ^{1}H nmr spectrum was complicated by the presence of two diastereomers, with the minor diastereomer denoted by an asterisk. In the majority of cases where there were two resonances, the resonances for the minor diastereomer were further upfield, the exception being 6b-H where the resonance for the major diastereomer was the more upfield. In both diastereomers, 2'ax-H resonated as a doublets of doublets of doublets at δ 1.45, whereas 2'eq-H resonated as overlapping doublets of doublets of doublets at δ 2.47* and 2.51 assigned to the minor and major diastereomers respectively. Two proton doublets at δ 3.14* and 3.15 with coupling constant $J_{9,9a}$ 4.1 Hz, were assigned to 9-H, while a doublet of doublets of doublets at δ 5.51 with coupling constants $J_{9a,6b}$ 6.3 Hz, $J_{9a,9}$ 4.1 and $J_{9a,9'}$ 4.1 Hz, was assigned to 9a-H. Resonances at δ 6.47 and 6.48* were assigned to 6b-H and those at δ 14.43* and 14.49 to the aromatic hydroxyl protons. 1-H resonated as a doublet at δ 7.76 with coupling constant $J_{1,2}$ 8.5 Hz, while doublets at δ 7.88* and 7.89 were assigned as the 2-H resonances for the minor and major diastereomers respectively. The bridgehead protons, 6b-H and 9a-H, resonated at similar chemical shifts to those reported for analogous compounds such as adduct **374** (table 3).[101] The bridgehead coupling constant, $J_{9a,6b}$ 6.3 Hz, was consistent with the presence of a *cis*-fused 2*H*-furo[3,2-*b*]naptho[2,3-*d*]pyran ring system.[101,115]

Table 3



374



261

Group	δ_H (ppm)	m	*J* (Hz)	δ_C (ppm)	δ_H (ppm)	m	*J* (Hz)	δ_C (ppm)
COMe	2.84	s	-	30.3	2.83*/2.84	s	-	31.2
9	3.18	d	4.2	35.7	3.14*/3.15	d	4.1	34.0
9a	5.55	ddd	6.6, 4.2, 4.2	80.7	5.51	ddd	6.3, 4.1, 4.1	81.0
6b	6.45	d	6.6	86.0	6.47/6.48*	d	6.3	85.8
OH	14.65	s	-	-	14.43*/14.49	s	-	-
8	-	-	-	174.1	-	-	-	171.7
COMe	-	-	-	202.9	-	-	-	203.0

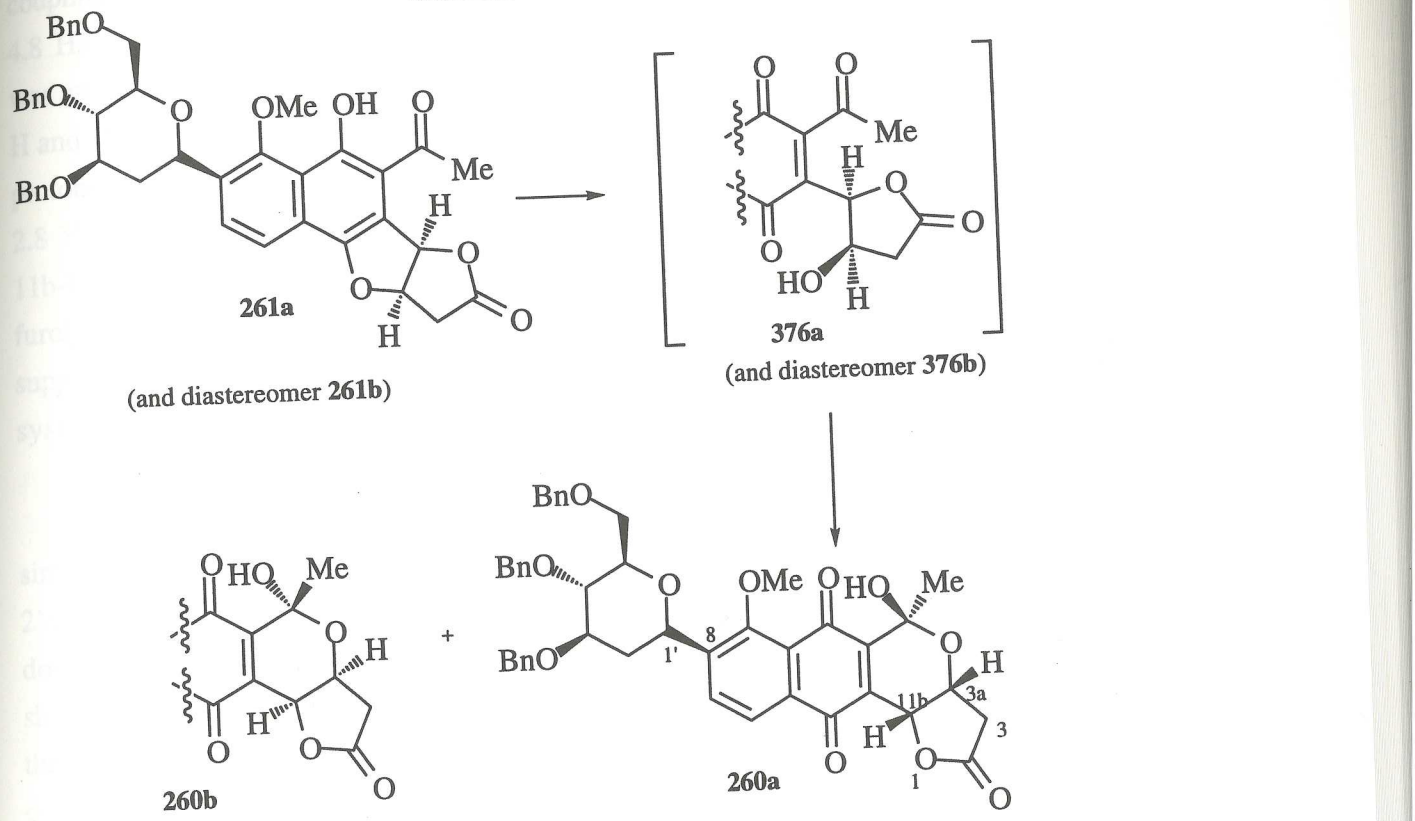
In the ^{13}C nmr spectrum, resonances for the individual diastereomers were not observed. The methyl and quaternary carbons of the methyl ketone of adduct **261** resonated at δ 31.2 and 203.0 respectively, in good agreement with the values for adduct **374**. A methylene resonance at δ 34.0 was assigned to C-9, while the bridgehead carbons, C-9a and C-6b, resonated at δ 81.0 and 85.8 respectively. Methylene resonances at δ 38.2 and 69.7 were characteristic for the glycosyl carbons C-2' and C-6' respectively, while the anomeric carbon, C-1', resonated at δ 72.0.

2.4.2 Synthesis of Furonaphthopyrans 260a and 260b.

With the furo[3,2-*b*]naphtho[2,1-*d*]furans **261** in hand, rearrangement to the corresponding furonaphthopyrans **260** was then investigated (scheme 119). It was anticipated that the diastereomeric lactols **260a** and **260b** would be different enough in polarity to allow separation by column chromatography. A solution of the furonaphthofurans **261** in acetonitrile was treated with an excess of aqueous ceric ammonium nitrate (CAN) (2.0 equiv.) and the reaction monitored by TLC. After 20 min. the reaction had proceeded to completion with the formation of a pair of more polar products. These were identified as the diastereomeric lactols **260** (85% crude yield) and although separation was possible by chromatography, they were extremely unstable on silica gel and the majority of the product decomposed. Thus, except for the purposes of

characterization, the crude mixture of lactols **260** was used in the next step without chromatography.

Scheme 119



Reagents and conditions: CH_3CN, CAN, 20 min., 85%.

Formation of lactol **260** was supported by the high resolution mass spectrum which exhibited a molecular ion at *m/z* 746.2749 confirming the molecular formula as $C_{44}H_{42}O_{11}$. The infra-red spectrum featured a broad stretch at 3276-3624 cm^{-1} indicative of the hydroxyl group as well as carbonyl bands at 1788 cm^{-1} and 1668 cm^{-1} assigned to the γ-lactone and quinone carbonyl groups respectively.

The diastereomers were partially separated by low temperature (-10 °C) chromatography, using hexane-ethyl acetate (1:2) that had been stirred with potassium carbonate as eluent, to afford a 14% yield of lactol **260** enriched in the less polar diastereomer and a 12% yield of lactol **260** enriched in the more polar diastereomer. Assignment of stereochemistry to the two lactols, however, was not possible using the ^1H and ^{13}C nmr data obtained.

The ^{1}H nmr spectrum of the less polar diastereomer featured doublets of doublets of doublets at δ 1.46 and δ 2.46 assigned to 2'ax-H and 2'eq-H respectively, while the three proton singlet at δ 1.73 was assigned to the methyl group. A doublet at δ 2.67, with coupling constant J_{gem} 17.7 Hz, and a doublet of doublets at δ 2.87, J_{gem} 17.7 and $J_{3B,3a}$ 4.8 Hz, were assigned to 3-H_A and 3-H_B respectively. A three proton singlet at δ 3.77 was assigned to the methoxy group and a two proton singlet at δ 7.90 was assigned to 9-H and 10-H. There was a characteristic upfield shift in the resonances of the bridgehead protons relative to the adducts **261**. A doublet of doublets at δ 4.83, $J_{3a,3B}$ 4.7 and $J_{3a,11b}$ 2.8 Hz, was assigned to 3a-H and a doublet at δ 5.20, $J_{11b,3a}$ 2.8 Hz, was assigned to 11b-H. These protons appeared at similar chemical shifts to those reported for analogous furo[3,2-*b*]naphtho[2,3-*d*]pyrans. The bridgehead coupling constant, $J_{3a,11b}$ 2.8 Hz, also supported the presence of a *cis*-fused 2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran system.[101,114,115]

The ^{1}H nmr spectrum of the more polar diastereomer was for the most part very similar to that observed for the less polar diastereomer. While 2'ax-H was unchanged, 2'eq-H shifted upfield resonating at δ 2.40. By contrast the methoxy group was further downfield at δ 3.82. Of the bridgehead protons only 3a-H was noticeably affected, being shifted upfield to δ 4.81, with an additional coupling constant, $J_{3a,3A}$ 2.0 Hz. Likewise, the 3-H_A resonance at δ 2.65 was shifted slightly upfield and the same additional coupling, $J_{3a,3A}$ 2.0 Hz, was observed. The final resonances of note were 10-H and 9-H which for this diastereomer resonated as doublets at δ 7.88 and 7.93 respectively, with coupling constant, $J_{9,10}$ 8.0 Hz.

Since only small quantities of the separated lactols were obtained it proved difficult to obtain good ^{13}C nmr spectra. An additional problem was the instability of the lactols in chloroform, meaning that overnight data collection using a small quantity of sample was not feasible. The ^{13}C nmr data for the mixture of lactols **260** (available in larger quantities) was collected, but was complicated by the doubling up of most of the peaks. Moreover, since the ratio of diastereomers was approximately 1:1 it was not possible to ascertain which peaks belonged to an individual diastereomer of the lactol. The methyl groups resonated at δ 27.5/27.6 and the methoxy groups at δ 62.7/62.9. The resonance at δ 29.7 was assigned to C-3 based on comparison with similar compounds, as were the bridgehead carbons, C-3a and C-11b, resonating at δ 67.1/67.2 and 68.5/68.7 respectively. The chemical shift data obtained was in excellent agreement with that reported for the related literature compounds.[101,114,115]

Future work might involve low temperature ^{13}C nmr as a means of avoiding or slowing decomposition of the sample when long pulse times are required.

Both the ^{1}H nmr and ^{13}C nmr spectra indicated that for each diastereomer only one configuration at the lactol carbon was present. The structure assigned was that in which the hydroxyl group is axial and *cis* with respect to the bridgehead protons 3a-H and 11b-H. This was assignment was made on the basis of the anomeric effect[209] and also by comparison with similar compounds from the literature.[101,114,115]

2.4.3 Reduction of Lactols 260 to Cyclic Ethers 259.

With the desired lactols **260** in hand, albeit as a 1:1 mixture of diastereomers, the next step in the synthesis involved reduction of the hemiacetal to a cyclic ether (scheme 120). This reaction was carried out according to the procedure of Kraus *et al*,[96] who reported axial delivery of hydride from triethylsilane, to afford products with a *cis*-relationship between the protons at C-5 and C-3a.

Thus a solution of lactols **260** in dichloromethane at -30 °C was treated with triethylsilane (10 equiv.) and trifluoroacetic acid (10 equiv.) then allowed to warm to room temperature. After 6 hours none of the desired product (which was expected to be less polar) was observed, but a substantial quantity of baseline material was observed. With stirring for a longer time, all the remaining starting material decomposed.

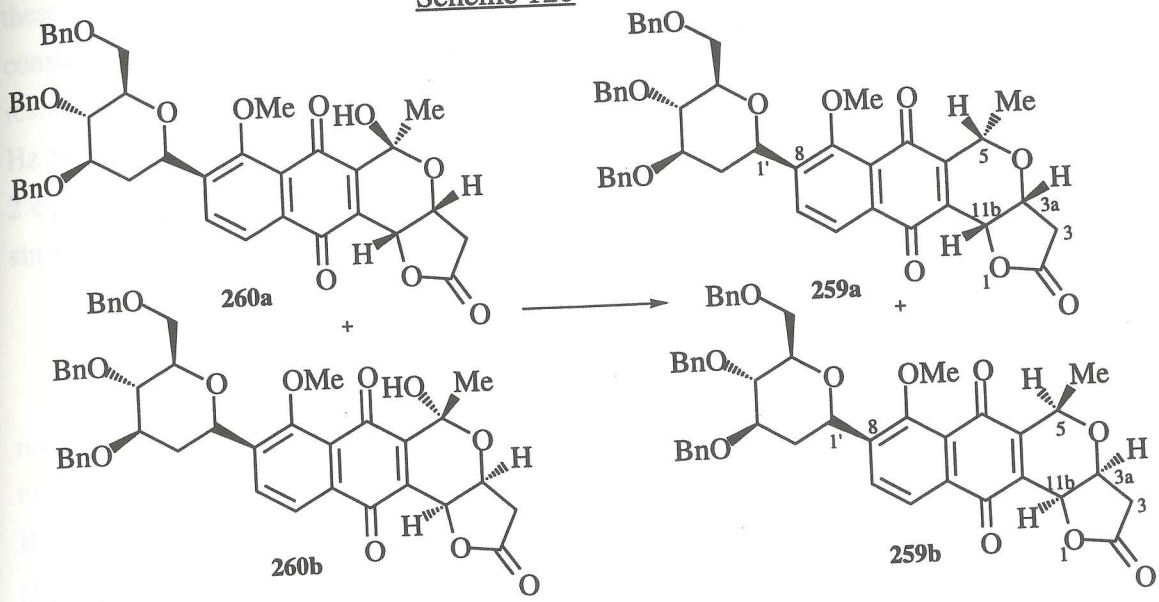
Since decomposition was occurring before the reduction could take place it was decided to carry out the reaction at a lower temperature and over a longer period of time. Thus a solution of lactol **260** in dichloromethane at -30 °C was again treated with triethylsilane (10 equiv.) and trifluoroacetic acid (10 equiv.), allowed to warm to -10 °C and then kept at that temperature with the aid of a cryostat. Using these conditions, decomposition was kept to a minimum and after 3 days the starting material had been entirely consumed and two less polar products were formed which were in fact the cyclic ethers **259a** and **259b**.

Isolation of the cyclic ethers **259a**, **259b** was the next hurdle since the products were highly unstable and the mixture decomposed to an intractable brown tar if the solvent was removed at room temperature. Thus, after the addition of a small amount of Celite™, the solvent was removed at reduced pressure whilst maintaining the temperature at -10 °C.

Chromatography of the cyclic ethers **259a**, **259b** at room temperature resulted in decomposition (presumably initiated by opening of the γ-lactone ring) and methanol was

required to elute the extremely polar decomposition products. Chromatography was then attempted at low temperature (-10 °C) which allowed partial separation of the individual diastereomers and only a small amount of decomposition was observed. This procedure afforded the cyclic ethers **259a**, **259b** in 86% combined yield.

Scheme 120



Reagents and conditions: CF_3CO_2H, Et_3SiH, -10 °C, 72 h, 86%.

High resolution mass spectrometry established the molecular formula $C_{44}H_{42}O_{10}$, whilst the infra-red spectrum featured carbonyl stretches at 1736 and 1665 cm^{-1}, corresponding to the γ-lactone and quinone carbonyls respectively.

In the ^1H nmr spectrum, complex multiplets at δ 1.29-1.38 and 2.40-2.60 were assigned to 2'ax-H and 2'eq-H respectively. A doublet at δ 2.72, with coupling constant J_{gem} 17.3 Hz, was assigned to 3-H_A, while a doublet of doublets at δ 2.90, with coupling constants J_{gem} 17.3 and $J_{3B,3a}$ 4.5 Hz, was assigned to 3-H_B. Multiplets at δ 4.30-4.38 and δ 5.25-5.30 were assigned to the bridgehead protons 3a-H and 11b-H respectively. A doublet of quartets at δ 4.80, with coupling constants, J_{vic} 6.4 and $J_{5,11b}$ 1.8 Hz, was assigned to 5-H. Other resonances of note were a doublet of doublets at δ 5.38, $J_{1',2'ax}$ 10.8 and $J_{1',2'eq}$ 2.9 Hz, assigned to 1'-H, and two apparent singlets at δ 7.94 and 7.96, assigned to 9-H and 10-H.

Some separation of the diastereomers was achieved by low temperature chromatography, and ^1H nmr spectra were obtained for each. Although there were a number of differences observed, assignment of stereochemistry was not possible based on this information. A difference between the chemical shifts for the two diastereomers

was observed in the resonances assigned to the methyl group protons. In the less polar diastereomer, the methyl group protons resonated as a doublet at δ 1.73, J_{vic} 6.2 Hz while in the the more polar diastereomer they resonated as a doublet at δ 1.57, J_{vic} 6.6 Hz. Likewise, differences in the chemical shifts of the protons assigned to the methoxy group and one of the benzylic methylene protons were noticed. In the less polar diastereomer these groups resonated as a singlet at δ 3.88 and a doublet at δ 4.99, with coupling constant J_{gem} 10.7 Hz respectively, while in the the more polar diastereomer, they resonated as a singlet at δ 3.81 and a doublet at δ 4.96, with coupling constant J_{gem} 10.9 Hz respectively. The chemical shift difference observed between the resonances for the 2'eq-H proton in the diastereomeric lactols **260** was not seen for the cyclic ethers **259**, since in the latter case the resonance was an unresolved multiplet, δ 2.40-2.60.

The ^{13}C nmr spectrum was also consistent with the proposed structure. The resonances at δ 20.5/20.3 were assigned to the C-5 methyl group, an upfield shift relative to the analogous protons in the lactol **260**, consistent with reduction to the cyclic ether. Resonances at δ 69.4/69.5 were assigned to C-3a, while those at δ 70.1/70.3 were characteristic of C-11b. The methylene resonances at δ 38.2/38.4 were assigned to C-3 and the resonances at δ 72.4/72.6 assigned to C-5.

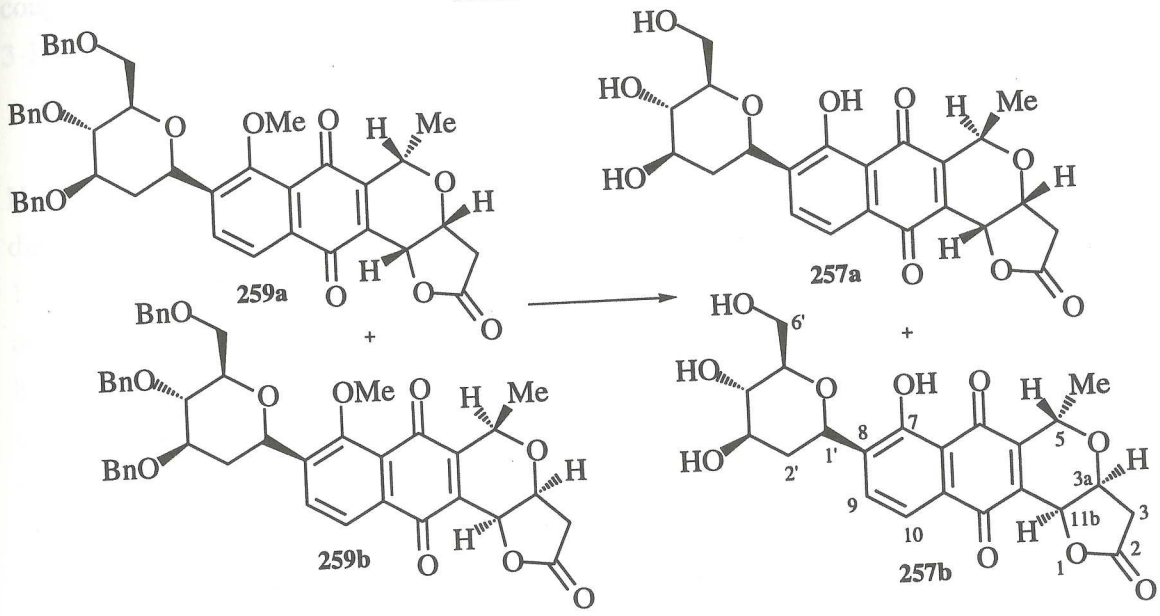
2.4.4 Deprotection and Epimerization of Cyclic Ethers 259 to Give Medermycin Analogue 257.

In the final step of the synthesis of the medermycin analogue **257** it remained to effect deprotection of the methyl ether as well as epimerization of the protons attached to C-3a or C-5 so that they adopted the more thermodynamically favourable *trans* stereochemistry. The benzyl protecting groups on the glycosyl moiety also had to be removed.

Boron tribromide was successfully employed by this research group to to effect the demethylation and epimerization of *epi*-7*O*-methylkalafungin **132** to kalafungin **24** (see scheme 18). While demethylation occurred almost instantaneously, epimerization took much longer. If the reaction was quenched immediately, the *cis*-isomer was obtained, whereas on equilibration at room temperature for 30 minutes, only the *trans*-isomer kalafungin **24** was isolated. A similar result was reported during the synthesis of the arizonins.[113] It was envisaged that the reaction conditions would also result in debenzylation of the glycosyl moiety.

An excess of boron tribromide (6 equiv.) was added to a solution of a mixture of the cyclic ethers **259** (enriched in the more polar diastereomer, 3:1) in dichloromethane at -48 °C (scheme 121). After 5 minutes a red-brown precipitate had formed, presumably because debenzylation of the sugar had rendered the boron tribromide-*C*-glycoside complex insoluble in dichloromethane. When the mixture was allowed to warm to room temperature and still failed to dissolve, acetonitrile was added, affording partial dissolution of the solid material. The stirring was continued for a further 30 minutes in order to allow equilibration to the *trans*-isomer. Aqueous work-up afforded the desired quinone, which was readily freed from benzyl alcohol and benzyl bromide by trituration from hexane and ether, giving the orange crystalline *C*-glycosylpyranonaphthoquinone **257** in 67% yield.

Scheme 121



Reagents and conditions: BBr_3, CH_2Cl_2, -48 °C to r.t., 30 min., 67%.

The formation of compound **257** was supported by the high resolution mass spectrum which exhibited a molecular ion at *m/z* 446.1217, confirming the molecular formula as $C_{22}H_{22}O_{10}$. The infra-red spectrum featured a broad stretch at 3100-3643 cm^{-1} supporting the presence of hydroxyl groups. Prominent carbonyl stretches at 1780, 1652 and 1615 cm^{-1} were assigned to the γ-lactone and two quinone carbonyl groups respectively.

The ^1H nmr spectrum, evidence for the formation of the *trans* isomer in the hydroxynaphthoquinone **257** came from the observation of the characteristic downfield shifts of the resonances assigned to 3a-H and 5-H. The chemical shift of a doublet of

quartets assigned to 5-H shifted from δ 4.80 in the *cis* methyl ether **377** to δ 5.04 in the *trans* product **257**, where it resonated as a quartet, J_{vic} 6.6 Hz. This observed loss of long-range coupling between 5-H and 11b-H is consistent with conversion of the *cis* **259** to the *trans* **257**. The doublet of doublets assigned to the bridgehead proton 3a-H shifted downfield from δ 4.34 in the *cis* methyl ether **259** to δ 4.81-4.84 in the *trans* product **257**, where it resonated as a multiplet. Similar downfield shifts were reported when comparing *epi*-7-*O*-methylkalfungin **132** and kalafungin **24** (see scheme 18).[102]

Resonances at δ 2.49 and 3.19 were assigned to the methylene protons of the γ-lactone ring. The more upfield resonance was a doublet, with geminal coupling $J_{3A,3B}$ 17.5 Hz, and was assigned to the pseudoequatorial proton 3-H_B. The more downfield resonance, a doublet of doublets with geminal coupling, $J_{3A,3B}$ 17.5 Hz, and a smaller coupling to the bridgehead proton, $J_{3A,3a}$ 5.0 Hz, was assigned to the pseudoaxial proton 3-H_A.

Two, three proton, doublets at δ 1.57* and 1.58, with coupling constants J_{vic} 7.0 Hz and J_{vic} 6.8 Hz, were assigned to the methyl protons of the minor* and major diastereomers respectively. The 2'ax-H and 2'eq-H protons resonated as multiplets at δ 1.35 and 2.41, and the anomeric proton, 1'-H, was obscured by the 3a-H multiplet. The aryl protons, 9-H and 10-H, resonated as a pair of doublets at δ 7.63*/7.64 and 8.00*/8.01, with coupling constant $J_{9,10}$ 7.8 Hz. Broad singlets at δ 12.20* and 12.30 were assigned to the protons of the C-7 hydroxyl groups of the minor and major diastereomers respectively.

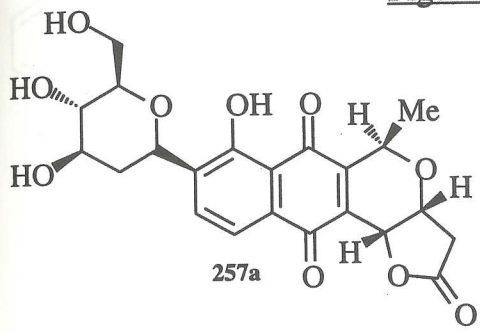
In the ^{13}C nmr spectrum, resonances at δ 18.3/20.6* were assigned to the C-5 methyl carbon. The bridgehead carbons, C-3a and C-11b, were assigned to resonances at δ 66.9*/67.5 and 69.0*/69.5 respectively. Methylene resonances at δ 37.1 and δ 40.4 were assigned to C-3 of the γ-lactone and C-2' of the glycosyl moiety respectively.

Assignment of the individual diastereomers as the medermycin analogue **257a** or the alternative diastereomer **257b**, was not possible using ^1H and ^{13}C nmr spectra of the mixture. Importantly, these final compounds **257a**, **257b** were isolated as a crystalline solid and exhibited much greater stability than both the lactol **260** and cyclic ether **259** precursors. Due to limitations on the amount of **257** available, further investigation of the stereochemistry of the individual diastereomers was not feasible. Future work would involve the synthesis of a greater quantity of the medermycin analogue **257** so that separation of the diastereomers would be possible and individual spectroscopic assignments could be made. Ideally, X-ray crystallographic analysis of each diastereomer would also be obtained, definitively establishing the stereochemistry.

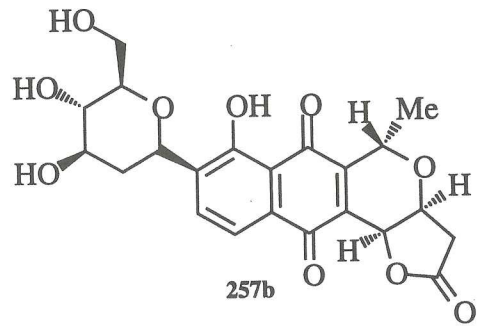
2.5 Conclusions and Future Work.

The synthesis of medermycin analogue **257** has been achieved, although at present as a mixture of diastereomers (figure 33). In the process, the 2-trimethylsilyloxyfuran addition/oxidative rearrangement methodology has been shown to be viable for naphthoquinones bearing a *C*-glycosyl moiety. Additional procedures, such as low temperature reduction of the lactols **260** to the cyclic ethers **259** and low temperature chromatography of both the lactols **260** and cyclic ethers **259**, were developed to compensate for the instability of *C*-glycosyl compounds.

Figure 33



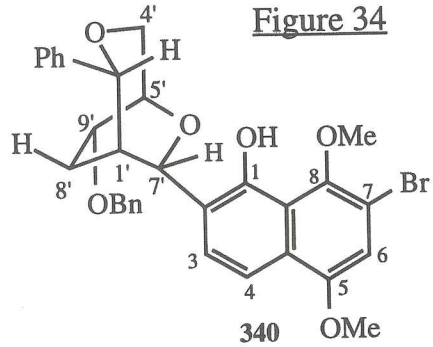
257a



257b

A drawback to the ultimately successful approach using the naphthol **247** is the additional steps required to regioselectively install the functionality at the 3-position. These steps were necessary because of the poor reactivity of 3-functionalized naphthols, which resulted in the rearrangement of benzyl protected sugars to bicylic acetals such as **340** (figure 34). The structure of the unusual bicyclic acetal **340** was elucidated by obtaining an X-ray crystallographic analysis of the acetate **351**.

Figure 34

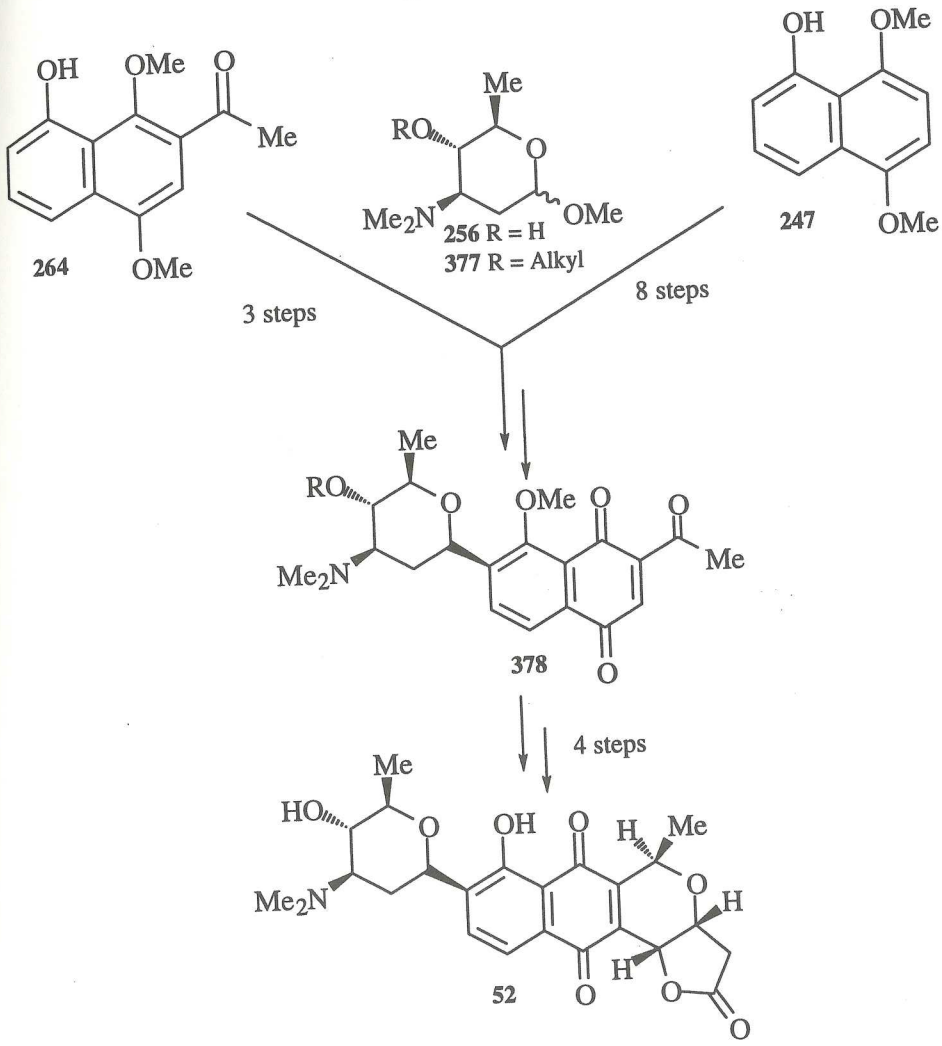


340 OMe

Future work will involve the preparation of larger quantities of the medermycin analogue **257** in order that the diastereomers might be separated and their stereochemistry assigned. Moreover, the synthesis of the natural product, medermycin **52**, will be attempted using the methodology that has been developed (scheme 122). It is possible that

the glycosyl donor used for the synthesis of medermycin **52** might couple where the model sugar did not. This would immediately re-instate the efficiency of the synthesis to that which was originally envisaged. Ideally, D-angolosamine **256** (or the protected form **377**) would undergo *C*-glycosylation with acetylnaphthol **264** to then in six steps afford medermycin **52**. Failing this, the synthetic methodology developed for the preparation of medermycin analogue **257**, involving naphthol **247**, could be employed for the synthesis of the activated naphthoquinone **378** and then ultimately of medermycin **52**.

Scheme 122



It was initially hoped that the chirality of the glycosyl moiety might influence the diastereoselectivity of the 2-trimethylsilyloxyfuran addition reaction, however no significant diastereoselectivity was observed, with the glycosyl linkage probably too far removed from the reactive site to exert such an effect. Recent work in this research group has involved the use of chiral auxiliaries to achieve diastereoselectivity in Diels-Alder reactions similar to the 2-trimethylsilyloxyfuran addition reaction.[210] Such work might eventually lead to the formation of a single diastereomer from this reaction.

CHAPTER THREE

EXPERIMENTAL

3.1 General Details.

Melting points were determined using a Kofler hot stage apparatus or a Reichert heating stage with microscope and are uncorrected.

Elemental analyses were carried out by the Microanalytical Laboratory, University of Otago, Dunedin, New Zealand or the Microanalytical Laboratory, University of New South Wales, Sydney, Australia. The accuracy of the results is within ±0.3%.

Infra-red spectra were recorded using a Perkin-Elmer 1600 Fourier Transform infra-red spectrometer. Compounds were prepared as thin films between sodium chloride plates (oils) or as KBr discs (solids). Absorption maxima are expressed in wavenumbers (cm^{-1}).

^{1}H nuclear magnetic resonance spectra were recorded on a Bruker AC 200 (200.13 MHz), Bruker AM 400 (400.12 MHz), Bruker AMX 400 (400.13 MHz) or Bruker DRX 400 (400.12 MHz) spectrometer at ambient temperature (except where the temperature is stated). Data is expressed as parts per million downfield shift from tetramethylsilane as an internal standard, and reported as a position (δ_H), relative integral, multiplicity (s = singlet, br.s = broad singlet, d = doublet, dd = double douglet, ddd = double double doublet, t = triplet, q = quartet or m = multiplet), coupling constant (*J* Hz) and assignment.

^{13}C nuclear magnetic resonance spectra were recorded on a Bruker AC 200 (50.3 MHz), Bruker AM 400 (100.6 MHz) Bruker AMX 400 (100.4 MHz) or Bruker DRX 400 (100.51 MHz) spectrometer at ambient temperature (except where the temperature is stated) with complete proton decoupling. Data is expressed as parts per million downfield shift from tetramethylsilane as an internal standard, and reported as a position (δ_C), multiplicity (aided by DEPT 135 and DEPT 90 experiments) and assignment.

Low resolution mas spectra were recorded on a VG70-250S, a VG70-SD or an AEI model MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70eV (EI, CI). High resolution mass spectra were recorded at nominal resolution of 5000 or 10000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were (i) electron impact (EI), (ii) chemical ionisation with ammonia as reagent gas (CI), (iii) fast atom bombardment (FAB), (iv) liquid secondary ion mass spectrometry

(LSIMS) using a 4-nitrobenzylalcohol (NBA) and a 5:1 mix (v/v) of dithiothreitol : dithioerythreitol.

Thin layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualised by ultra-violet fluorescence or by staining with vanillin in methanolic sulfuric acid.

High performance liquid chromatography (HPLC) was carried out using a Waters Associates system consisting of a Model M-6000A pump, a millipore model U6K injector, a model 440 ultra-violet detector at 256 nm and a R401 differential refractometer. Separation was carried out using the indicated solvents on a partisil 10 M9 semipreparative column of the following dimensions; outer diameter 12.80 mm, inner diameter 9.40 mm, length 500.0 mm and particle size 10.0 μm.

Flash chromatography was performed according to the procedure of Still *et al.*[211] using Merck Kieselgel 60 or Riedel-de Haen Kieselgel S silica gel (both 230-400 mesh) with the indicated solvents.

Concentration "in vacuo" or at "reduced pressure" refers to concentration using a rotary evaporator connected to a water aspirator. Removal of residual solvent or volatile reagents where desired was achieved by evacuation (0.1-0.01 mm Hg) with a high stage oil sealed vacuum pump.

Unless otherwise noted, moisture sensitive and low temperature reactions were carried out in oven dried glassware under a dry inert atmosphere. Reaction temperatures -100 °C to - 20 °C were obtained by using the following solvent/coolant baths: diethyl ether/CO_2, -100 °C, acetone CO_2, -78 °C, acetonitrile/CO_2, -40 °C. Reactions at 0 °C were maintained using ice/water bath while those at -10 °C were maintained with a cryostat using an ethanol bath.

2-Trimethylsilyloxyfuran, 1,5-dihydroxynaphthalene, tributyltin chloride, dichlorobis-(triphenylphosphine)palladium(II) were purchased from Aldrich Chemical Company and purified as necessary. *n*-Butyllithium was obtained as a solution in hexanes (nominal concentration 1.6 or 2.5 mol dm^{-3}) and the concentration determined before use by titration according to the method of Lipton *et al.*[212] Solvents were dried and purified according to the methods of Perrin, Perrin and Amarego.[213] Ether refers to diethyl ether, dioxane refers to 1,4-dioxane, hexane refers to *n*-hexane (b.p. 65-69 °C), and brine refers to saturated aqueous sodium chloride solution.

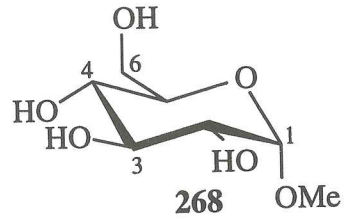
Optical rotations were recorded on an Optical Activity POLAAR 2001 polarimeter using a 5 cm cell. Samples were prepared at the concentration (measured in g/100 cm^3) and in the solvent indicated.

3.2 Aryl *C*-Glycosylation Studies.

3.2.1 Synthesis of Coupling Partners.

methyl-α-D-glucopyranoside 268[165,214]

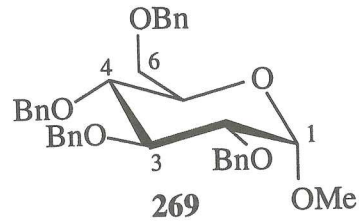
α-D-Glucopyranose **267** (120 g, 667 mmol) was dissolved in an anhydrous solution of hydrochloric acid in methanol (3%, 240 g). The solution was then heated at reflux for 4.5 h and decolourising charcoal (5 g) was added 10 min. before the end of this time. The solution was hot-filtered then cooled on ice-water. The crystals were washed with methanol and filtered. A second crop was recovered from the concentrated mother liquor to give methyl-α-D-glycopyranoside **268** (80 g, 62%) as white needles, m.p. 164-165 °C; $[\alpha]_D^{18}$ = +151.0° (c=1.02, H_2O) {lit.[165] m.p. 165-166 °C; $[\alpha]_D^{12.5}$ = +157.9° (c=1.04, H_2O)}.



268

methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 269[166,215]

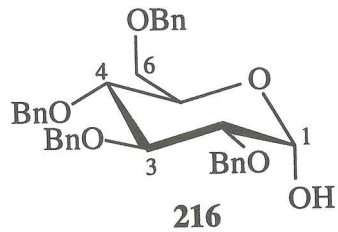
Methyl-α-D-glycopyranoside **268** (50 g, 257 mmol) was suspended with powdered potassium hydroxide (250 g, 4.46 mol) in dry dioxane (150 mL) and the mixture stirred and heated at reflux while benzyl chloride (318 mL, 2.76 mol) was added dropwise over 40 min. The mixture was heated at reflux for a further 0.5 h and the solvent was distilled off over a further 3 h. The residue was cooled and water was added to dissolve the crystalline mass. The crude product was extracted with diethyl ether (3 x 200 mL), washed with water (200 mL), dried (magnesium sulfate) and filtered through charcoal. The solvent was removed at reduced pressure to afford a syrup then benzyl alcohol and benzyl chloride were removed by distillation at 0.05 torr (200 °C bath) to give the methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **269** (135 g, 95%) as a colourless syrup, $[\alpha]_D^{22}$ = +31.9° (c=5, $CHCl_3$) {lit.[215] $[\alpha]_D^{20}$ = +32.2° (c=5, $CHCl_3$)}.



269

2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **216**[166,215]

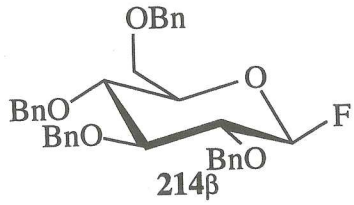
A mixture of acetic acid (120 mL) and methyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **269** (6.0 g, 10.8 mmol) in hydrochloric acid (2 M, 48 mL) was heated at reflux for one day at 80 °C. Part of the product crystallized overnight and was removed by filtration. The filtrate was heated for another day then poured into water affording further product upon cooling. The crude product was recrystallized from methanol to give 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **216** (1.0 g, 43%) as white needles, m.p. 147-148 °C; $[\alpha]_D^{18}$ = +24.12° (c=5.01, $CHCl_3$) {lit.[215] m.p. 151-152 °C; $[\alpha]_D^{20}$ = +21.7° (c=2.19, $CHCl_3$)}.



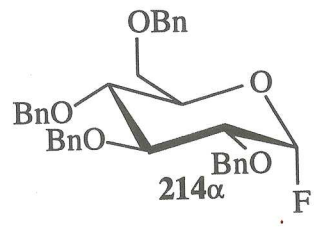
216

2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride **214**[173,174]

To a cold (-30 °C) solution of tetra-*O*-benzylglucopyranose **216** (1.08 g, 2 mmol) in dry tetrahydrofuran (10 mL) was added diethylaminosulfur trifluoride (DAST) (0.3 mL, 2.4 mmol). The mixture was allowed to warm to room temperature and after 30 min. the reaction had proceeded to completion. After cooling to -20 °C, methanol (1 mL) was added and the mixture concentrated at reduced pressure. The residue was partitioned between dichloromethane (50 mL) and a 1:1 mixture of saturated aqueous solutions of sodium chloride and sodium bicarbonate (50 mL). The organic phase was dried and concentrated and the residue purified by flash chromatography using hexane-ethyl acetate (9:1) as eluent to give that was a 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride **214** (α:β, 1:8) as a colourless oil (0.9 g, 83%). Recrystallization from isopropyl ether gave white needles, m.p. 43-44 °C; $[\alpha]_D^{18}$ = +31.0° (c=1.04, $CHCl_3$) {lit.[174] m.p. 48-48.5 °C, $[\alpha]_D^{22}$ = +38° (c=0.8, $CHCl_3$)}. The ^1H nmr data was in agreement with that reported in the literature.[174]



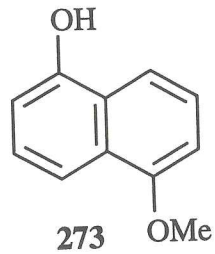
214β



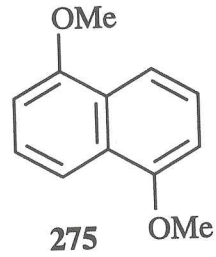
214α

1-hydroxy-5-methoxynaphthalene 273[216]

Hydrochloric acid (1 M, 52.5 mL) was added slowly with mechanical stirring to a cooled solution of 1,5-dihydroxynaphthalene **274** (32 g, 200 mmol), potassium hydroxide (35 g, 624 mmol) and water (35 mL). To this mixture was added dropwise dimethylsulfate (31.5 g, 250 mmol) with the temperature being kept below 30 °C. After 4 h the solution was warmed to 70 °C and dimethyl ether **275** (11.3 g, 30%) that had formed was filtered off. Hydrochloric acid (1 M, *c.a.* 15 mL) was then added to the filtrate to precipitate the product which was then purified by vacuum distillation (15 mmHg, b.p. 190-200 °C) to give the monomethyl ether **273** (11.7 g, 34%). Recrystallization from ethyl acetate gave flaky tan crystals, m.p. 137-138 °C (lit.[216] m.p. 135-136 °C).



273

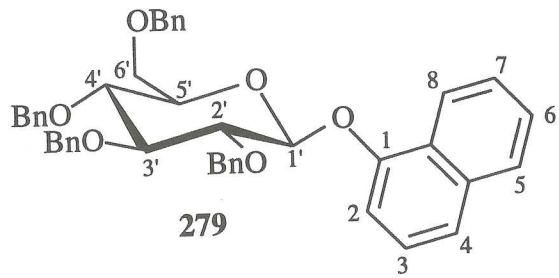


275

3.2.2 Investigation of Aryl *C*-Glycosylation Methods.

(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyloxy)naphthalene 279

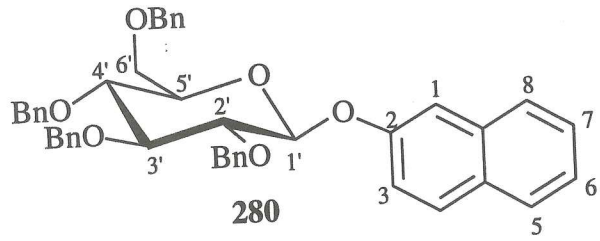
To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **216** (560 mg, 1.04 mmol) and 1-naphthol **272** (100 mg, 0.695 mmol) in dry tetrahydrofuran (3 mL) at 0 °C were added triphenylphosphine (272 mg, 1.04 mmol) and a solution of diethyl azodicarboxylate (DEAD) (181 mg, 1.04 mmol) in dry tetrahydrofuran (1 mL). The mixture was stirred at room temperature for 12 h by which time a more polar species was seen upon analysis by TLC. The solution was concentrated at reduced pressure and the product isolated by flash chromatography using hexane-ethyl acetate (9:1) then ethyl acetate as eluent to afford *(2',3',4',6'-tetra-O-benzyl-β-D-glucopyranosyloxy)naphthalene* **279** (304 mg, 43%). Recrystallization from ethanol gave white needles, m.p. 131.2-132.2 °C; $[\alpha]_D^{18}$ = -42.3° (c=1.06, $CHCl_3$); [Found (EI): M^+, 666.2979. $C_{44}H_{42}O_6$ requires M, 666.2981]; ν_{max} (film) cm^{-1} 3029, 2904, 2869 (C-H), 1579, 1453 (C=C), 1398, 1358 (C-O), 1263, 1240; δ_H (400 MHz; $CDCl_3$) 3.65-3.85 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.96 (1H, dd, $J_{2',3'}$ 8.7 and $J_{2',1'}$ 7.7 Hz, 2'-H), 4.52, 4.60 (each 1H, d, J_{gem} 12.1 Hz, 2 x C<u>H</u>Ph), 4.62, 4.87, 4.89, 4.94, 5.00, 5.17 (each 1H, d, J_{gem} 10.9 Hz, 6 x C<u>H</u>Ph), 5.23 (1H, d, $J_{1',2'}$ 7.7 Hz, 1'-H), 7.14 (1H, d, $J_{2,3}$ 7.8 Hz, 2-H), 7.19-7.34 (20H, m, Ph-H), 7.36 (1H, dd, $J_{4,3}$ 8.3 and $J_{2,3}$ 7.8 Hz, 3-H), 7.43 (1H, ddd, $J_{7,8}$ 8.3, $J_{7,6}$ 8.1 and $J_{7,5}$ 1.3 Hz, 7-H), 7.49 (1H, ddd, $J_{6,7}$ 8.1, $J_{6,5}$ 7.7 and $J_{6,8}$ 1.3 Hz, 6-H), 7.55 (1H, d, $J_{4,3}$ 8.3 Hz, 4-H), 7.82 (1H, d, $J_{5,6}$ 7.7 Hz, 5-H), 8.30 (1H, d, $J_{8,7}$ 8.3 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 68.8 (CH_2, C-6'), 73.5, 75.1 (CH_2, 2 x <u>C</u>H_2Ph), 75.3 (CH, C-5'), 75.4, 75.8 (CH_2, 2 x <u>C</u>H_2Ph), 77.8, 82.2, 84.9 (CH, C-2', C-3', C-4'), 101.5 (CH, C-1'), 109.5 (CH, C-2), 122.1, 122.4, 125.5, 125.8, 126.3 (CH, C-3, C-4, C-5, C-6, C-7), 126.0 (quat., C-4a), 127.5-128.4 (CH, Ph, C-8), 134.6 (quat., C-8a), 138.0, 138.05, 138.1, 138.5 (quat., 4 x *ipso*-Ph), 152.9 (quat., C-1); *m/z* (EI) 666 (M^+, 1%), 522 (M-$C_{10}H_8O$, 4), 415 (3), 325 (3), 181 (15), 91 (C_7H_7, 100).



279

2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyloxy)naphthalene 280

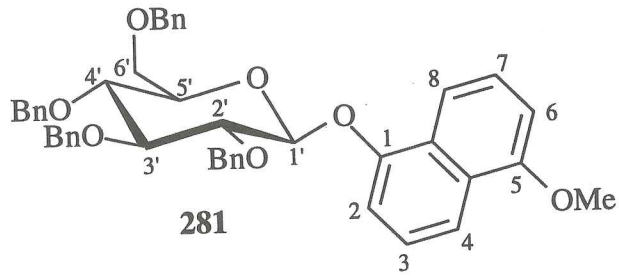
To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **216** (560 mg, 1.04 mmol) and 2-naphthol **234** (100 mg, 0.695 mmol) in dry tetrahydrofuran (3 mL) at 0 °C were added triphenylphosphine (272 mg, 1.04 mmol) and a solution of diethyl azodicarboxylate (181 mg, 1.04 mmol) in dry tetrahydrofuran (1 mL). The mixture was stirred at room temperature for 12 h. The solution was concentrated at reduced pressure and the product isolated by flash chromatography using hexane-ethyl acetate (4:1) then ethyl acetate as eluent to afford 2-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyloxy)naphthalene **280** (390 mg, 56%) which was recrystallized from ethanol to give colourless needles, m.p. 111.5-112.5 °C; the spectroscopic data agreed with that reported in the literature although the melting point (106 °C) was only given for the α-anomer; $[\alpha]_D^{22}$ = -13.0° (c=1.08, $CHCl_3$); (Found: C, 79.25; H, 6.26. $C_{44}H_{42}O_6$ requires C, 79.24; H, 6.35%); ν_{max} (film) cm^{-1} 3061, 3030, 2904, 2867 (C-H), 1630, 1600 (C=C), 1389, 1358 (C-O); δ_H (400 MHz; $CDCl_3$) 3.58-3.77 (6H, m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 4.44-4.53 (3H, m, 3 x C<u>H</u>Ph), 4.75-4.80 (3H, m, 3 x C<u>H</u>Ph), 4.89, 5.01 (each 1H, d, J_{gem} 11.0 Hz, 2 x C<u>H</u>Ph), 5.08 (1H, d, $J_{1',2'}$ 7.1 Hz, 1'-H), 7.13 (1H, dd, $J_{3,4}$ 7.7 and $J_{3,1}$ 2.0 Hz, 3-H), 7.16-7.34 (22H, m, Ph-H, 6-H, 7-H), 7.37 (1H, d, $J_{1,3}$ 2.0 Hz, 1-H), 7.57 (1H, d, $J_{4,3}$ 7.7 Hz, 4-H), 7.69 (1H, d, $J_{8,7}$ 8.7 Hz, 8-H), 7.70 (1H, d, $J_{5,6}$ 7.7 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 69.8 (CH_2, C-6'), 74.3, 75.7, 75.8 (CH_2, 3 x <u>C</u>H_2Ph), 76.0 (CH, C-5'), 76.4 (CH_2, <u>C</u>H_2Ph), 78.5 (CH, C-2', C-3', C-4'), 102.6 (CH, C-1'), 112.3, 119.7, 125.0, 127.0, 128.2, 128.0, 130.1 (CH, C-1, C-3, C-4, C-5, C-6, C-7, C-8), 128.3-129.1 (CH, Ph), 130.7 (quat., C-4a), 135.1 (quat., C-8a), 138.8, 138.9, 139.0, 139.3 (quat., 4 x *ipso*-Ph), 155.9 (quat., C-2); *m/z* (EI) 666 (M^+, 2%), 522 (M-$C_{10}H_8O$, 4), 415 (1), 271 (1), 181 (8), 144 ($C_{10}H_8O$, 4), 115 (C_9H_7, 4), 91 (C_7H_7, 100).



280

1-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyloxy)-5-methoxynaphthalene 281

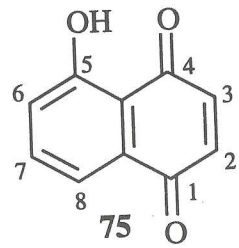
To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **216** (280 mg, 0.52 mmol) and 5-methoxynaphthol **273** (60 mg, 0.35 mmol) in dry tetrahydrofuran (1.5 mL) at 0 °C were added triphenylphosphine (136 mg, 0.52 mmol) and a solution of diethyl azodicarboxylate (90 mg, 0.52 mmol) in dry tetrahydrofuran (0.5 mL). The mixture was stirred at room temperature for 12 h. The solution was concentrated at reduced pressure and the product isolated by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *1-(2',3',4',6'-tetra-O-benzyl-β-D-glucopyranosyloxy)-5-methoxynaphthalene* **281** (226 mg, 63%) as a brown solid that was recrystallized from ethanol to give tan platelets, m.p. 156-157 °C; $[\alpha]_D^{18}$ = -19.7° (c=1.78, $CHCl_3$); (Found: C, 77.25; H, 6.22. $C_{45}H_{44}O_7$ requires C, 77.55; H, 6.37%); ν_{max} (film) cm^{-1} 3061, 3030, 2904, 2867 (C-H), 1630, 1600 (C=C), 1389, 1358 (C-O); δ_H (400 MHz; $CDCl_3$) 3.68-3.81 (4H, m, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.82 (1H, dd, $J_{3',4'}$ 8.7 and $J_{3',2'}$ 8.3 Hz, 3'-H), 3.96 (1H, dd, $J_{2',3'}$ 8.3 and $J_{2',1'}$ 7.7 Hz, 2'-H), 4.00 (3H, s, OCH_3), 4.51, 4.59 (each 1H, d, J_{gem} 12.1 Hz, 2 x C<u>H</u>Ph), 4.60, 4.86, 4.88, 4.92, 4.99, 5.17 (each 1H, d, J_{gem} 10.9 Hz, 6 x C<u>H</u>Ph), 5.21 (1H, d, $J_{1',2'}$ 7.7 Hz, 1'-H), 6.84 (1H, d, $J_{2,3}$ 7.5 Hz, 2-H), 7.18-7.39 (23H, m, Ph-H, 3-H, 4-H, 7-H), 7.89 (1H, d, $J_{6,7}$ 8.4 Hz, 6-H), 7.97 (1H, d, $J_{8,7}$ 8.4 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 68.9 (CH_2, C-6'), 73.6, 75.0 (CH_2, 2 x <u>C</u>H_2Ph), 75.4 (CH, C-5'), 75.4, 75.8 (CH_2, 2 x <u>C</u>H_2Ph), 77.9, 82.3, 85.0 (CH, C-2', C-3', C-4'), 101.6 (CH, C-1'), 104.4, 114.5, 116.5, 125.1, 125.5, 127.5 (CH, C-2, C-3, C-4, C-6, C-7, C-8), 126.9, 127.1 (quat., C-4a, C-8a), 127.5-128.4 (CH, Ph), 138.2, 138.2, 138.2, 138.6 (quat., 4 x *ipso*-Ph), 152.9, 155.3 (quat., C-1, C-5); *m/z* (EI) 696 (M^+, 1%), 522 (M-$C_{10}H_8O$, 28), 325 (6), 181 (6), 91 (C_7H_7, 100).



281

5-hydroxy-1,4-naphthoquinone (juglone) 75[183,217]

N,N'-Bis(salicylidene)ethylenediaminocobalt(II) (salcomine)[184,218] **286** (200 mg, 320 mmol) was added to a solution of 1,5-dihydroxynaphthalene **274** (1.03 g, 624 mmol) in tetrahydrofuran (250 mL) and the mixture stirred at room temperature for 2 h under an atmosphere of oxygen. Celite™ (1.0 g) was then added and the solvent removed at reduced pressure. Purification by flash chromatography using hexane-ethyl acetate (10:1) as eluent gave juglone **75** (500 mg, 46%) as an orange solid. Recrystallization from ethanol gave orange needles, m.p. 160-162 °C (lit.[183] m.p. 161-163 °C); ν_{max} (film) cm^{-1} 3063 (br, OH), 1663, 1644 (C=O, quin.), 1451 (C=C), 1364, 1290 (C-O); δ_H (200 MHz; $CDCl_3$) 6.96 (2H, s, 2-H and 3-H), 7.29 (1H, dd, $J_{6,7}$ 6.5 and $J_{6,8}$ 3.0 Hz, 6-H), 7.60-7.67 (2H, m, 7-H, 8-H), 11.90 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 114.8 (quat., C-4a), 118.9 (CH, C-8), 124.2 (CH, C-6), 131.5 (quat., C-8a), 136.4 (CH, C-7), 138.4 (CH, C-3), 139.3 (CH, C-2), 161.2 (quat., C-5), 183.9 (quat., C-1), 190.0 (quat., C-4). The spectroscopic data was in agreement with that reported in the literature.[183]

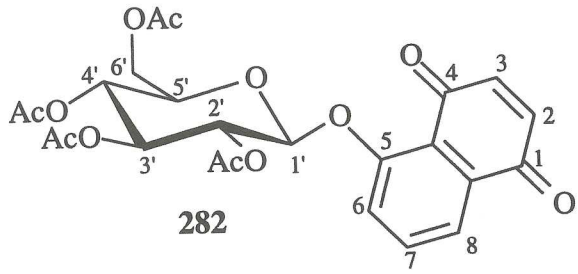


75

5-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone 282[179,180]

Silver(I) oxide (58 mg, 0.25 mmol) was added to a mixture of juglone **75** (44 mg, 0.25 mmol) and acetobromoglucose **285**[182] (100 mg, 0.25 mmol) in dry acetonitrile (1.5 mL) and the mixture was subjected to sonication for 6 h. Celite™ (20 mg) was added and the mixture filtered through silica gel which was then washed with dichloromethane (15 mL) and diethyl ether (15 mL). Concentration of the combined filtrate at reduced pressure gave an orange residue which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent. Recrystallization from dichloromethane-diethyl ether (1:3) gave 5-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone **282** (40 mg, 36%) as yellow needles, m.p. 147-148 °C; $[\alpha]_D^{18}$ = -72.3° (c=0.25, $CHCl_3$) {lit.[179] m.p. 147-148 °C; $[\alpha]_D^{22}$ = -80° (c=1.5, $CHCl_3$)}; ν_{max} (film) cm^{-1} 1755, 1745 (C=O, ester), 1670 (C=O, quin.); δ_H (200 MHz; $CDCl_3$) 2.04, 2.06, 2.07, 2.11 (each 3H, s, 3 x $COC\underline{H}_3$), 3.85-3.91 (1H, m, 5'-H), 4.21 (1H, dd, J_{gem} 12.5 and $J_{6'A,5'}$ 2.5 Hz,

6'-H_A), 4.27 (1H, dd, J_{gem} 12.5 and $J_{6'B,5'}$ 5.5 Hz, 6'-H_B), 5.14 (1H, d, $J_{1',2'}$ 7.5 Hz, 1'-H), 5.20 (1H, dd, $J_{4',3'}$ 9.0 and $J_{4',5'}$ 9.0 Hz, 4'-H), 5.32 (1H, dd, $J_{3',4'}$ 9.0 and $J_{3',2'}$ 9.0 Hz, 3'-H), 5.46 (1H, dd, $J_{2',3'}$ 9.0 and $J_{2',1'}$ 7.5 Hz, 2'-H), 6.84, 6.89 (each 1H, d, $J_{2,3}$ 10.5 Hz, 2-H and 3-H), 7.52 (1H, dd, $J_{6,7}$ 8.5 and $J_{6,8}$ 1.0 Hz, 6-H), 7.67 (1H, dd, $J_{6,7}$ 8.5 and $J_{7,8}$ 7.5 Hz, 7-H), 7.90 (1H, dd, $J_{8,7}$ 7.5 and $J_{6,8}$ 1.0 Hz, 8-H). The spectroscopic data was in agreement with that reported in the literature.[179,180]



282

3.2.3 Synthesis of 2-Deoxyglycosyl Donors.

1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranoside 238

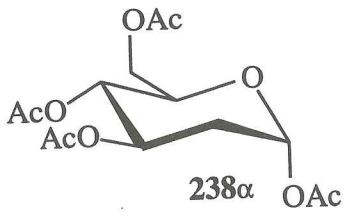
(i) Using 2-deoxyglucose 258.[185]

2-Deoxy-D-glucose **258** (1.5 g, 9.14 mmol) was suspended in dry pyridine (25 mL) at 0 °C and freshly distilled acetic anhydride (20 mL) was added. The reaction mixture was kept at 0 °C for 4 days, at the end of which time the starting material had completely dissolved. The solution was diluted with water and then extracted with chloroform. The combined extracts were washed with sulfuric acid (0.01 M, 3 x 50 mL), dilute sodium bicarbonate solution (50 mL) and water (50 mL). After drying (calcium chloride) the solvent was removed at reduced pressure and the residue was triturated with ethanol-diethyl ether (3:1). The resulting solid was recrystallized several times from ethanol to give 1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranoside **238** (2.21 g, 73%) (α:β, 10:1) as white needles, m.p. 92-93 °C; $[\alpha]_D^{18}$ = +10.9° (c=1.01, ethanol) {lit.[185] m.p. 91°C; $[\alpha]_D^{20}$ = +12.3° (c=0.325, ethanol)}; ν_{max} (film) cm^{-1} 1745 (C=O), 1376 (C-O); The spectroscopic data was in agreement with that reported in the literature;[178]

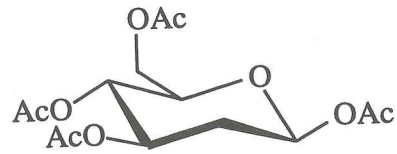
α-anomer: δ_H (200 MHz; $CDCl_3$) 1.87 (1H, ddd, J_{gem} 12.3, $J_{2ax,3}$ 11.3, $J_{2ax,1}$ 10.0 Hz, 2_{ax}-H), 2.04, 2.05, 2.09, 2.12 (each 3H, s, 4 x $COC\underline{H}_3$), 2.36 (1H, ddd, J_{gem} 12.3, $J_{2eq,3}$ 4.7, $J_{2eq,1}$ 2.3 Hz, 2_{eq}-H), 3.75 (1H, ddd, $J_{5,4}$ 9.4, $J_{5,6B}$ 4.7 and $J_{5,6A}$ 2.3 Hz, 5-H),

4.09 (1H, dd, J_{gem} 12.4, $J_{6A,5}$ 2.3 Hz, 6-H_A), 4.32 (1H, dd, J_{gem} 12.4, $J_{6B,5}$ 4.7 Hz, 6-H_B), 4.97-5.14 (2H, m, 3-H, 4-H), 5.80 (1H, dd, $J_{1,2ax}$ 10.0 and $J_{1,2eq}$ 2.3 Hz, 1-H); δ_C (50 MHz; $CDCl_3$) 20.6, 20.7, 20.8, 20.9 (CH_3, 4 x $CO\underline{C}H_3$), 34.7 (CH_2, C-2), 61.9 (CH_2, C-6), 68.2, 70.1, 72.3 (CH, C-3, C-4, C-5), 91.0 (CH, C-1), 168.7, 169.7, 170.0, 170.6 (quat., 4 x $\underline{C}OCH_3$).

β-anomer: δ_H (200 MHz; $CDCl_3$) 5.78 (1H, dd, $J_{1,2ax}$ 10.5 and $J_{1,2eq}$ 2.5 Hz, 1-H).



238α



238β

(i) Using tri-O-acetyl-D-glucal ***172***.[178,186]

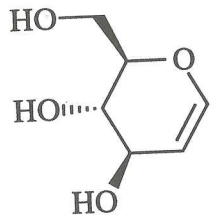
Distilled glacial acetic acid (351 mL, 5.51 mol) was added to a stirred solution of tri-*O*-acetyl-D-glucal **172** (1.002 g, 3.67 mmol) and triphenylphosphine hydrogen bromide (see below) (63 mg, 0.184 mmol) in anhydrous dichloromethane (18 mL). The mixture was allowed to stir for 2 days at room temperature then the solvent was removed at reduced pressure. The resultant oil was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give 1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranoside **238** as a mixture of anomers (α:β, 9:1) (879 mg, 72%). The spectroscopic data was in agreement with that reported in the literature.[178,186]

triphenylphosphine hydrogen bromide[219]

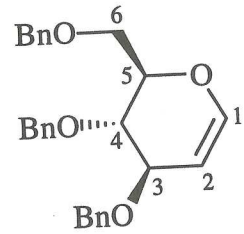
Anhydrous hydrogen bromide was bubbled through an ice-cold solution of triphenylphosphine (0.5 g, 1.9 mmol) in dry dichloromethane-diethyl ether (1:3, 50 mL) for 5 min. The solvent was removed under reduced pressure and the resulting white solid recrystallized several times from dichloromethane-diethyl ether (1:3). The product was dried *in vacuo* to give triphenylphosphine hydrogen bromide (570 mg, 87%) as small colourless needles, m.p. 200-201 °C (lit.[219] m.p. 202 °C).

3,4,6-tri-*O*-benzyl-D-glucal 290[188]

A solution of 3,4,6-tri-*O*-acetyl-D-glucal **172** (2.00 g, 7.35 mmol) in methanol-water (400:1) (15 mL) was treated with sodium carbonate (2.02 g, 19.1 mmol) and the mixture stirred at room temperature for 2 h. Removal of the sodium carbonate by filtration through celite and evaporation of the solvent at reduced pressure afforded D-glucal **289** (990 mg, 99%) as a colourless oil. D-Glucal **289** (990 mg, 6.77 mmol) was dissolved in dry dimethylsulfoxide (10 mL) and a mixture of dry dimethylsulfoxide (10 mL) and oil free sodium hydride (0.65 g, 27.2 mmol) was added dropwise with stirring. The mixture was then stirred for 1 h at room temperature. Benzyl chloride (2.57 g, 20.3 mmol) was added and the mixture stirred for a further 3 h, then poured into ice-water (300 mL), extracted with diethyl ether (3 x 30 mL), and the combined ether layers washed with water (3 x 30 mL) and dried (magnesium sulfate). The solvent was removed at reduced pressure to give a pale yellow syrup which slowly crystallized. Recrystallization from ethanol gave 3,4,6-tri-*O*-benzyl-D-glucal **290** (1.245 g, 46%) as colourless needles, m.p. 56-57 °C; $[\alpha]_D^{18}$ = -2.6° (c=1.02, $CHCl_3$) {lit.[188] m.p. 57-57.5 °C; $[\alpha]_D$ = -2.9° (c=1.2)}.



289



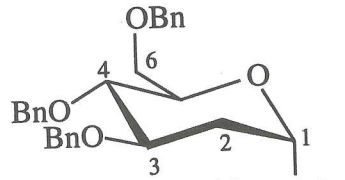
290

3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranosyl acetate 266 and 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranose 291[178,186]

Glacial acetic acid (0.432 g, 7.2 mmol) was added to a stirred solution of tri-*O*-benzyl-D-glucal **290** (2.0 g, 4.80 mmol) and triphenylphosphine hydrogen bromide (82 mg, 0.240 mmol) in dry dichloromethane (35 mL). The mixture was stirred overnight at room temperature. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography using hexane-ethyl acetate (4:1) as eluent gave 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranosyl acetate **266** (α:β, 9:1) (1.97 g, 86%) and 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranose **291** (α:β, 3:1) (125 mg, 6%).

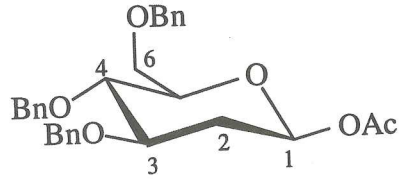
Acetate **266** was a colourless oil, $[\alpha]_D^{20}$ = +71.2° (c=0.876, $CHCl_3$); The spectroscopic data was in agreement with that found in the literature;[178,186]

α anomer: δ_H (200 MHz; $CDCl_3$) 1.84 (1H, ddd, J_{gem} 13.6, $J_{2ax,3}$ 11.4, $J_{2ax,1}$ 3.4 Hz, 2_{ax}-H), 2.03 (3H, s, $COC\underline{H}_3$), 2.28 (1H, ddd, J_{gem} 13.5, $J_{2eq,3}$ 4.9, $J_{2eq,1}$ 1.7 Hz, 2_{eq}-H), 3.53-4.02 (5H, m, 3-H, 4-H, 5-H, 6-H_A, 6-H_B), 4.47-4.71 (5H, m, 5 x C<u>H</u>Ph), 4.91 (1H, d, J_{gem} 10.7 Hz, C<u>H</u>Ph), 6.26 (1H, d, $J_{1,2}$ 1.7 Hz, 1-H), 7.16-7.34 (15H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 21.0 (CH_3, $CO\underline{C}H_3$), 34.1 (CH_2, C-2), 68.3 (CH_2, C-6), 71.7 (CH_2, $\underline{C}H_2Ph$), 73.3 (CH, C-3), 73.4, 75.0 (CH_2, 2 x $\underline{C}H_2Ph$), 76.7 (CH, C-5), 77.4 (CH, C-4), 92.0 (CH, C-1), 127.5-128.5 (CH, Ph), 138.0, 138.1, 138.2 (quat., 3 x *ipso*-Ph), 169.1 (quat., $\underline{C}OCH_3$).



266α

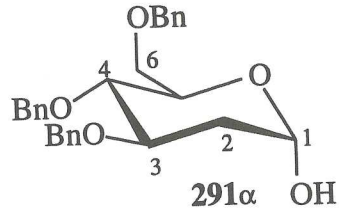
β anomer: δ_H (200 MHz; $CDCl_3$) 1.77 (1H, m, 2_{ax}-H), 2.09 (3H, s, $COC\underline{H}_3$), 2.36 (1H, m, 2_{eq}-H), 3.53-4.02 (5H, m, 3-H, 4-H, 5-H, 6-H_A, 6-H_B), 4.47-4.71 (5H, m, 5 x C<u>H</u>Ph), 4.87 (1H, d, J_{gem}10.8, C<u>H</u>Ph), 5.67 (1H, dd, $J_{1,2ax}$10.0 and $J_{1,2eq}$2.2, 1-H), 7.16-7.34 (15H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 21.1 (CH_3, $CO\underline{C}H_3$), 35.4 (CH_2, C-2), 68.5 (CH_2, C-6), 71.7, 73.5, 75.0 (CH_2, 3 x $\underline{C}H_2Ph$), 75.8 (CH, C-3), 77.3 (CH, C-5), 78.9 (CH, C-4), 92.2 (CH, C-1), 127.5-128.5 (CH, Ph), 138.0, 138.1, 138.2 (quat., 3 x *ipso*-Ph), 169.1 (quat., $\underline{C}OCH_3$).



266β

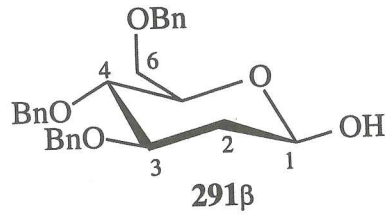
The pyranose **291** (α:β, 3:1) was recrystallized from hexane-ethyl acetate to give colourless needles, m.p. 99-100 °C; $[\alpha]_D^{20}$ = +69.4° (c=0.65, $CHCl_3$); {(lit.[220] m.p. 104-105 °C); lit. $[\alpha]_D^{20}$ = +71.2° (c=1.06, $CHCl_3$)}; The spectroscopic data was in agreement with that found in the literature;[221]

α anomer: δ_H (200 MHz; $CDCl_3$) 1.69 (1H, ddd, J_{gem} 13.0, $J_{2ax,3}$ 12.0, $J_{2ax,1}$ 3.5 Hz, 2_{ax}-H), 2.30 (1H, ddd, J_{gem} 13.0, $J_{2eq,3}$ 5.0, $J_{2eq,1}$ 1.5 Hz, 2_{eq}-H), 3.51 (1H, t, $J_{4,3}$ 9.5 and $J_{4,5}$ 9.5 Hz, 4-H), 3.62-3.73 (2H, m, 6-H_A, 6-H_B), 3.98-4.11 (2H, m, 3-H, 5-H), 4.49-4.68 (5H, m, 5 x C<u>H</u>Ph), 4.89 (1H, d, J_{gem}10.9, C<u>H</u>Ph), 5.40 (1H, br.d, $J_{1,2}$ 2.7 Hz, 1-H), 7.16-7.34 (15H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 35.4 (CH_2, C-2), 70.7 (CH_2, C-6), 71.8 (CH_2, <u>C</u>H_2Ph), 73.4 (CH_2, <u>C</u>H_2Ph), 74.9 (CH_2, <u>C</u>H_2Ph), 77.7, 78.5, 79.2 (CH, C-3, C-4, C-5), 92.1 (CH, C-1), 127.5-128.4 (CH, Ph), 137.9-138.6 (quat., 3 x *ipso*-Ph).



291α

β anomer: δ_H (200 MHz; $CDCl_3$) 1.60 (1H, m, 2_{ax}-H), 2.33 (1H, ddd, J_{gem} 12.5, $J_{2eq,3}$ 4.4, $J_{2eq,1}$ 2.1 Hz, 2_{eq}-H), 3.51 (1H, t, $J_{4,3}$ 9.5 and $J_{4,5}$ 9.5 Hz, 4-H), 3.62-3.73 (2H, m, 6-H_A, 6-H_B), 3.98-4.11 (2H, m, 3-H, 5-H), 4.49-4.68 (5H, m, 5 x C<u>H</u>Ph), 4.72 (1H, dd, $J_{1,2ax}$ 8.2 and $J_{1,2eq}$ 1.7 Hz, 1-H), 4.89 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 7.16-7.34 (15H, m, Ph-H); δ_C (50 MHz; $CDCl_3$) 37.9 (CH_2, C-2), 69.3 (CH_2, C-6), 71.4, 73.4, 74.8 (CH_2, 3 x <u>C</u>H_2Ph), 77.7, 78.5, 79.2 (CH, C-3, C-4, C-5), 94.1 (CH, C-1), 127.5-128.4 (CH, Ph), 137.9-138.6 (quat., 3 x *ipso*-Ph).

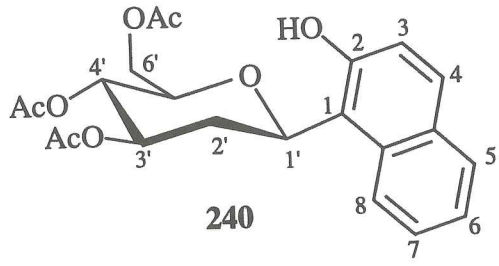


291β

3.2.4 Aryl *C*-Glycosylation Using 2-Deoxyglycosyl Donors.

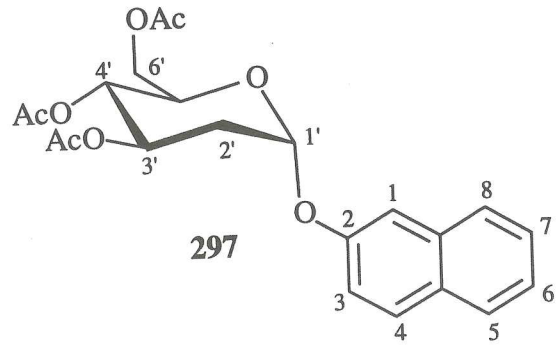
1-(3',4',6'-tri-*O*-acetyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-2-hydroxynaphthalene 240 and 2-(3',4',6'-tri-*O*-acetyl-2'-deoxy-α-D-*arabino*-hexopyranosyloxy)naphthalene 297

Trimethylsilyl trifluoromethanesulfonate (5 μL, 0.023 mmol) was added dropwise to a mixture of 2-naphthol **234** (33 mg, 0.23 mmol), tetra-*O*-acetyl-2-deoxyglucose **238** (38 mg, 0.114 mmol) and silver perchlorate (5 mg, 0.023 mmol) in dry dichloromethane (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h then quenched with saturated aqueous sodium bicarbonate solution (2 mL). The mixture was extracted with diethyl ether (3 x 10 mL) and the combined extracts washed with water (10 mL) and brine (10 mL) then dried (magnesium sulfate). The solvent was removed at reduced pressure, the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give the β-*C*-glycoside **240** (16 mg, 31%) and the α-*O*-glycoside **297** (20 mg, 39%). Repeating the reaction on the same scale but with dry acetonitrile (2 mL) as the solvent gave exclusively the β-*C*-glycoside **240** (49 mg, 97%) which was recrystallized from ethanol to give colourless needles, m.p. 127.5-128.0 °C (lit.[178] m.p. 128 °C); [Found (FAB): M^+, 416.1481. $C_{22}H_{24}O_8$ requires M, 416.1471]; ν_{max} (film) cm^{-1} 3373 (br, OH), 3064, 2962 (C-H), 1747 (C=O, ester), 1622, 1600 (C=C), 1230 (C-O); δ_H (400 MHz; $CDCl_3$) 2.02 (3H, s, $COC\underline{H}_3$), 2.09 (1H, m, $2'_{ax}$-H), 2.11 (3H, s, $COC\underline{H}_3$), 2.16 (3H, s, $COC\underline{H}_3$), 2.50 (1H, ddd, J_{gem} 12.9, $J_{2'eq,3'}$ 3.7 and $J_{2'eq,1'}$ 2.7 Hz, $2'_{eq}$-H), 3.93 (1H, ddd, $J_{5',4'}$ 9.7, $J_{5',6'B}$ 3.2 and $J_{5',6'A}$ 2.3 Hz, 5'-H), 4.20 (1H, dd, J_{gem} 12.5 and $J_{6'A,5'}$ 2.3 Hz, 6'-H_A), 4.22 (1H, dd, J_{gem} 12.5 and $J_{5',6'B}$ 3.2 Hz, 6'-H_B), 5.26-5.32 (2H, m, 3'-H, 4'-H), 5.62 (1H, dd, $J_{1',2'ax}$ 11.9 and $J_{1',2'eq}$ 2.1 Hz, 1'-H), 7.13 (1H, d, $J_{3,4}$ 8.9 Hz, 3-H), 7.33 (1H, ddd, $J_{7,8}$ 7.9, $J_{7,6}$ 7.1 and $J_{7,5}$ 1.0 Hz, H-7), 7.48 (1H, ddd, $J_{6,5}$ 8.6, $J_{6,7}$ 7.1 and $J_{6,8}$ 1.2 Hz, H-6), 7.66 (1H, br.d, $J_{5,6}$ 8.6 Hz, H-5), 7.71 (1H, d, $J_{4,3}$ 8.9 Hz, H-4), 7.76 (1H, br.d, $J_{8,7}$ 7.9 Hz, H-8), 8.48 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 20.67, 20.7, 20.9 (CH_3, 3 x $CO\underline{C}H_3$), 35.7 (CH_2, C-2'), 61.6 (CH_2, C-6'), 68.4, 71.4, 76.0, 76.6 (CH, C-1', C-3', C-4', C-5'), 113.8 (quat., C-4a), 120.0, 120.4, 123.2, 127.1, 129.0, 130.3 (CH, C-3, C-4, C-5, C-6, C-7, C-8), 128.7, 130.5 (quat., C-8a, C-1), 153.6 (quat., C-2), 169.7, 170.3, 170.7 (quat., 3 x $\underline{C}OCH_3$); *m/z* (CI) 416 (M^+, 40%), 181 (100), 43 ($COCH_3$, 74). The spectroscopic data was identical to that reported in the literature.[155,178]



240

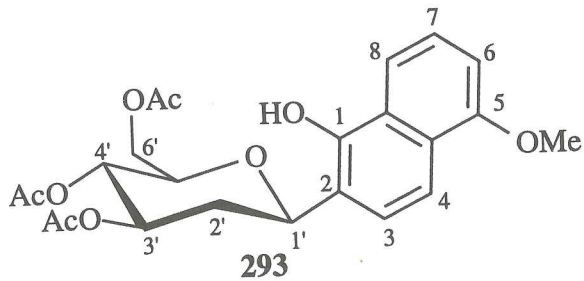
The α-*O*-glycoside **297** was recrystallized from ethanol to give colourless needles, m.p. 98.0-98.5 °C (lit.[178] m.p. 90 °C); [Found: C, 63.52; H, 5.87. $C_{22}H_{24}O_8$ requires C, 63.45; H, 5.81%]; ν_{max} (film) cm^{-1} 3066, 2955 (C-H), 1746 (C=O), 1629, 1600 (C=C), 1367, 1230 (C-O); δ_H (400 MHz; $CDCl_3$) 1.96, 2.05, 2.07 (each 3H, s, 3 x $COC\underline{H}_3$), 2.10 (1H, m, 2'$_{ax}$-H), 2.54 (1H, ddd, J_{gem} 13.1, $J_{2'eq,3'}$ 5.4 and $J_{2'eq,1'}$ 1.2 Hz, 2'$_{eq}$-H), 3.99 (1H, dd, J_{gem} 12.1 and $J_{6'A,5'}$ 2.1 Hz, 6'-H_A), 4.10 (1H, ddd, $J_{5',4'}$ 10.1, $J_{5',6'B}$ 4.7 and $J_{5',6'A}$ 2.1 Hz, 5'-H), 4.32 (1H, dd, J_{gem} 12.1 and $J_{6'B,5'}$ 4.7 Hz, 6'-H_B), 5.12 (1H, dd, $J_{4',5'}$ 10.1 and $J_{4',3'}$ 9.5 Hz, 4'-H), 5.59 (1H, ddd, $J_{3',2'ax}$ 11.5, $J_{3',4'}$ 9.5 and $J_{3',2'eq}$ 5.4 Hz, 3'-H), 5.83 (1H, br.d, $J_{1',2'ax}$ 2.6 Hz, 1'-H), 7.24 (1H, dd, $J_{3,4}$ 9.2 and $J_{3,1}$ 1.9 Hz, 3-H), 7.35 (1H, dd, $J_{5,6}$ 6.9 and $J_{5,7}$ 1.3 Hz, 5-H), 7.41 (1H, d, $J_{1,3}$ 1.8 Hz, 1-H), 7.47 (1H, dd, $J_{8,7}$ 6.7 and $J_{8,6}$ 1.4 Hz, 8-H), 7.72-7.80 (3H, m, 4-H, 6-H, 7-H); δ_C (100 MHz; $CDCl_3$) 20.6, 20.7, 21.0 (CH_3, 3 x $CO\underline{C}H_3$), 35.1 (CH_2, C-2'), 62.0 (CH_2, C-6'), 68.6, 68.9, 69.1 (CH, C-3', C-4', C-5'), 95.3 (CH, C-1'), 110.4, 118.7, 124.3, 126.5, 127.1, 127.6, 129.5 (CH, C-1, C-3, C-4, C-5, C-6, C-7, C-8), 129.5, 134.26 (quat., C-8a, C-4a), 153.8 (quat., C-2), 169.9, 170.3, 170.6 (quat., 3 x $\underline{C}OCH_3$); *m/z* (CI) 416 (M^+, 1%), 356 (2), 273 (M-$C_{10}H_7O$, 1), 213 (18), 144 ($C_{10}H_8O$, 100), 111 (47), 43 ($COCH_3$, 80). The spectroscopic data was identical to that reported in the literature.[178]



297

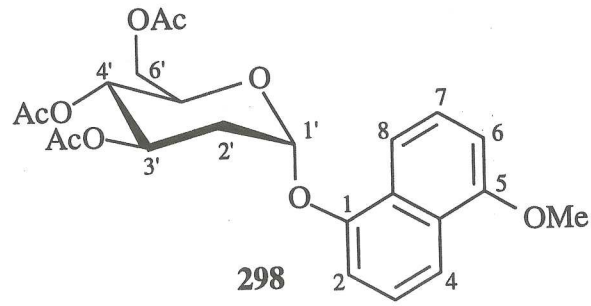
2-(3',4',6'-tri-*O*-acetyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-1-hydroxy-5-methoxynaphthalene 293 and 1-(3',4',5'-tri-*O*-acetyl-2'-deoxy-α-D-*arabino*-hexopyranosyloxy)-5-methoxynaphthalene 298

Trimethylsilyl trifluoromethanesulfonate (5 μL, 0.023 mmol) was added dropwise to a mixture of 5-methoxynaphthol **273** (39 mg, 0.23 mmol), tetra-*O*-acetyl-2-deoxyglucose **238** (38 mg, 0.114 mmol) and silver perchlorate (5 mg, 0.023 mmol) in dry dichloromethane (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h then quenched with saturated aqueous sodium bicarbonate solution (2 mL). The mixture was extracted with diethyl ether (3 x 10 mL) and the extracts were washed with water (10 mL), brine (10 mL) then dried (magnesium sulfate). The solvent was removed at reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give the β-*C-glycoside* **293** (10 mg, 29%) and the α-*O-glycoside* **298** (17 mg, 34%). Repeating the reaction on the same scale using dry acetonitrile (2 mL) as the solvent gave exclusively the β-*C-glycoside* **293** (28 mg, 82%) which was recrystallized from ethanol to give colourless needles, m.p. 140.3-140.9 °C; $[\alpha]_D^{19}$ = +80.0 (c=0.1, $CHCl_3$); [Found (FAB): M^+, 446.1572. $C_{23}H_{26}O_9$ requires M, 446.1577]; ν_{max} (film) cm^{-1} 3469 (OH), 1746 (C=O, ester), 1230 (C-O); δ_H (200 MHz; $CDCl_3$) 2.04, 2.09, 2.18 (each 3H, s, 3 x $COC\underline{H}_3$), 2.10 (1H, m, 2'$_{ax}$-H), 2.51 (1H, ddd, J_{gem} 13.9, $J_{2'eq,3'}$ 3.7 and $J_{2'eq,1'}$ 2.7 Hz, 2'$_{eq}$-H), 3.88 (1H, ddd, $J_{5',4'}$ 10.1, $J_{5',6'B}$ 4.4 and $J_{5',6'A}$ 2.3 Hz, 5'-H), 3.98 (3H, s, OCH_3), 4.22 (1H, dd, J_{gem} 12.3 and $J_{6'A,5'}$ 2.3 Hz, 6'-H_A), 4.35 (1H, dd, J_{gem} 12.3 and $J_{5',6'B}$ 4.4 Hz, 6'-H_B), 4.96 (1H, dd, $J_{1',2'ax}$ 10.1 and $J_{1',2'eq}$ 2.2 Hz, 1'-H), 5.20 (2H, m, 3'-H, 4'-H), 6.83 (1H, d, $J_{6,7}$ 7.5 Hz, 6-H), 7.02 (1H, d, $J_{3,4}$ 8.7 Hz, 3-H), 7.39 (1H, dd, $J_{7,8}$ 8.5 and $J_{7,6}$ 7.5 Hz, 7-H), 7.74 (1H, dd, $J_{8,7}$ 8.5 and $J_{8,6}$ 0.3 Hz, 8-H), 7.85 (1H, d, $J_{4,3}$ 8.7 Hz, 4-H), 8.23 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 20.7, 20.9, 21.0 (CH_3, 3 x $CO\underline{C}H_3$), 36.7 (CH_2, C-2'), 55.4 (CH_3, OCH_3), 63.3 (CH_2, C-6'), 68.4 (CH, C-5'), 69.4, 73.2, 76.2 (CH, C-1', C-3', C-4'), 108.6 (quat., C-4a), 106.5, 108.7, 122.9, 124.9, 129.2 (CH, C-3, C-4, C-6, C-7, C-8), 126.2, 129.2 (quat., C-8a, C-2), 151.0, 152.5 (quat., C-1, C-5), 169.8, 170.2, 170.3 (quat., 3 x $\underline{C}OCH_3$); *m/z* (CI) 446 (M^+, 3%), 253 (1), 174 (100), 159 (9), 111 (25), 43 ($COCH_3$, 62).



293

The α-*O-glycoside* **298** was recrystallized from ethanol to give white needles, m.p. 128-131 °C; $[\alpha]_D^{20}$ = +119.0° (c=0.65, $CHCl_3$); [Found (FAB): M^+, 446.1572. $C_{23}H_{26}O_9$ requires M, 446.1577]; ν_{max} (film) cm^{-1} 2958 (C-H), 1746 (C=O, ester), 1592 (C=C), 1229 (C-O); δ_H (400 MHz; $CDCl_3$) 2.02, 2.04, 2.09 (each 3H, s, 3 x $COC\underline{H}_3$), 2.10 (1H, m, 2'$_{ax}$-H), 2.64 (1H, ddd, J_{gem} 13.1, $J_{2'eq,3'}$ 5.3 and $J_{2'eq,1'}$ 1.2 Hz, 2'$_{eq}$-H), 3.99 (1H, dd, J_{gem} 12.1 and $J_{6'A,5'}$ 2.1 Hz, 6'-H_A), 3.99 (3H, s, OCH_3), 4.09 (1H, ddd, $J_{5',4'}$ 10.1, $J_{5',6'B}$ 4.6 and $J_{5',6'A}$ 2.1 Hz, 5'-H), 4.30 (1H, dd, J_{gem} 12.1 and $J_{6'B,5'}$ 4.6 Hz, 6'-H_B), 5.16 (1H, dd, $J_{4',5'}$ 10.1 and $J_{4',3'}$ 9.5 Hz, 4'-H), 5.68 (1H, ddd, $J_{3',2'ax}$ 11.5, $J_{3',4'}$ 9.5 and $J_{3',2'eq}$ 5.4 Hz, 3'-H), 5.85 (1H, d, $J_{1',2'ax}$ 2.5 Hz, 1'-H), 6.85 (1H, d, $J_{6,7}$ 9.2 Hz, 6-H), 7.20 (1H, d, $J_{2,3}$ 7.5 Hz, 2-H), 7.34 (1H, dd, $J_{3,4}$ 8.4 and $J_{3,2}$ 7.5 Hz, 3-H), 7.42 (1H, dd, $J_{7,8}$ 8.5 and $J_{7,6}$ 7.7 Hz, 7-H), 7.84 (1H, d, $J_{8,7}$ 8.5 Hz, 8-H), 7.92 (1H, d, $J_{4,3}$ 8.4 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 20.6, 20.9, 20.9 (CH_3, 3 x $CO\underline{C}H_3$), 35.2 (CH_2, C-2'), 55.5 (CH_3, OCH_3), 61.9 (CH_2, C-6'), 68.7 (CH, C-5'), 68.9, 69.0 (CH, C-3', C-4'), 95.3 (CH, C-1'), 104.5, 108.9, 113.8, 116.0, 124.9, 125.7 (CH, C-2, C-3, C-4, C-6, C-7, C-8), 126.5, 126.6 (quat., C-8a, C-4a), 151.3, 155.2 (quat., C-1, C-5), 169.8, 170.2, 170.3 (quat., 3 x $\underline{C}OCH_3$); *m/z* (CI) 446 (M^+, 5%), 174 (100), 111 (28), 43 ($COCH_3$, 62).



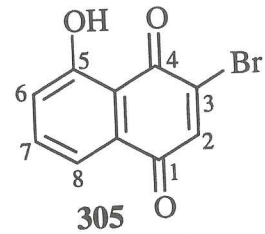
298

3.3 Aryl *C*-Glycosylation Using Naphthols 264 and 299.

3.3.1 Synthesis of 3-Bromonaphthol 299.

3-bromo-5-hydroxy-1,4-naphthoquinone (3-bromojuglone) 305 and 2-bromo-5-hydroxy-1,4-naphthoquinone (2-bromojuglone) 307[194]

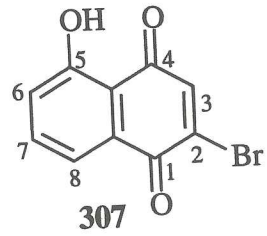
A solution of bromine (400 mg, 2.50 mmol) in chloroform (5 mL) was added to a stirred solution of juglone **75** (400 mg, 2.30 mmol) and acetic acid (4 drops) in chloroform (5 mL). Stirring was continued for 70 min. after which the solvent was removed at reduced pressure. Flash chromatography of the resulting orange solid (juglone dibromide **308**) using toluene-hexane (4:1) as eluent afforded 3-bromojuglone **305** (442 mg, 76%) and the less polar 2-bromojuglone **307** (122 mg, 21%). Alternatively, the orange solid **308** was redissolved in a mixture of ethanol (10 mL) and boron trifluoride diethyl etherate (1 mL) and heated for 15 min. on a steam bath. The reaction mixture was cooled, diluted with water (10 mL) and chloroform (30 mL), then filtered and the residue washed well with chloroform (15 mL). The phases were separated and the aqueous phase extracted with chloroform (2 x 40 mL). The combined organic fractions were washed with water (100 mL), dried (sodium sulfate) and the solvent removed at reduced pressure. Purification of the residue by flash chromatography using toluene-hexane (4:1) as eluent gave 3-bromojuglone **305** (343 mg, 59%) as the sole product which was recrystallized from ethanol to give orange needles, m.p. 171-172 °C (lit.[193] m.p. 172 °C); ν_{max} (film) cm^{-1} 3050 (OH), 1656, 1631 (C=O, quin.), 1459 (C-O); δ_H (200 MHz; $CDCl_3$) 7.31 (1H, dd, $J_{6,7}$ 6.9 and $J_{6,8}$ 2.8 Hz, 6-H), 7.50 (1H, s, 2-H), 7.62-7.72 (2H, m, 7-H and 8-H), 11.74 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 114.2 (quat., C-4a), 119.8 (CH, C-8), 124.6 (CH, C-6), 131.9 (quat., C-8a), 137.3 (CH, C-7), 141.5 (CH, C-2), 142.4 (quat., C-3), 162.2 (quat., C-5), 181.7 (quat., C-1), 183.1 (quat., C-4); *m/z* (EI) 254, 252 (M^+, 26%), 173 (M-Br, 100).



305

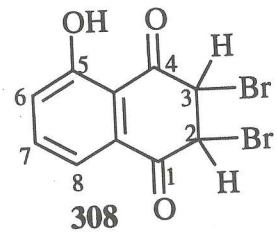
2-Bromojuglone **307** (442 mg, 76%) was recrystallized from hexane to give orange plates, m.p. 135-136 °C (lit.[193] 136 °C); ν_{max} (film) cm^{-1} 1675, 1633 (C=O, quin.), 1589 (C-O); δ_H (200 MHz; $CDCl_3$) 7.32 (1H, dd, $J_{6,7}$ 8.3 and $J_{6,8}$ 1.4 Hz, 6-H), 7.50

(1H, s, 3-H), 7.64 (1H, dd, $J_{7,6}$ 8.3 and $J_{7,8}$ 7.4 Hz, 7-H), 7.75 (1H, dd, $J_{8,7}$ 7.4 and $J_{8,6}$ 1.4 Hz, 8-H), 11.77 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 114.6 (quat., C-4a), 121.0 (CH, C-8), 125.1 (CH, C-6), 130.7 (quat., C-8a), 136.4 (CH, C-7), 140.3 (CH, C-3), 140.9 (quat., C-2), 161.7 (quat., C-5), 176.0 (quat., C-1), 187.5 (quat., C-4); *m/z* (EI) 254, 252 (M^+, 25%), 173 (M-Br, 100).



307

The intermediate 2,3-dibromo-2,3-dihydro-5-hydroxy-1,4-naphthoquinone (juglone dibromide) **308** could be isolated by filtration as an orange solid, m.p. 104 °C (lit.[191] 109 °C); δ_H (200 MHz; $CDCl_3$) 4.92, 4.96 (1H, d, $J_{2,3}$ 3.2 Hz, 2-H and 3-H), 7.36 (1H, dd, $J_{6,7}$ 8.0 and $J_{6,8}$ 1.4 Hz, 6-H), 7.65 (1H, dd, $J_{8,7}$ 7.4 and $J_{8,6}$ 1.4 Hz, 8-H), 7.74 (1H, dd, $J_{7,6}$ 8.0 and $J_{7,8}$ 7.4 Hz, 7-H), 11.42 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 45.4, 45.5 (CH, C-2 and C-3), 113.0 (quat., C-4a), 120.2 (CH, C-8), 125.4 (CH, C-6), 130.2 (quat., C-8a), 138.0 (CH, C-7), 162.6 (quat., C-5), 185.7, 192.7 (quat., C-1 and C-4); *m/z* (EI) 336, 334, 332 [M^+, 20, 40, 20%], 255, 254, 253, 252 (M-Br, 100], 173 (M-2Br, 95), 145 (75), 118 (40), 63 (60).

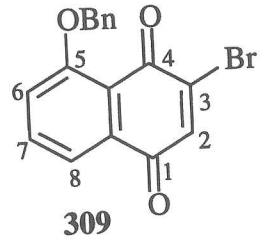


308

5-benzyloxy-3-bromo-1,4-naphthoquinone 309

Silver(I) oxide (5.5 g, 23.7 mmol) was added to a stirred solution of 3-bromojuglone **305** (1.50 g, 5.93 mmol) and benzyl bromide (1.41 mL, 11.9 mmol) in chloroform (15 mL). After 2 h the solution was filtered through a celite pad to remove silver salts and the solvent removed at reduced pressure. The resultant orange oil was purified by flash chromatography using hexane-ethyl acetate (18:1-9:1) as eluent to afford *5-benzyloxy-3-bromo-1,4-naphthoquinone* **309** (1.82 g, 89%) which was recrystallized from ethanol to give orange needles, m.p. 107-108 °C; [Found (FAB): M^+, 343.9875, 341.9893. $C_{17}H_{11}BrO_3$ requires M, 343.9871, 341.9892]; ν_{max} (film) cm^{-1} 1672 (C=O, quin.), 1583 (C-O); δ_H (400 MHz; $CDCl_3$) 5.30 (2H, s, C<u>H</u>$_2$Ph), 7.34 (1H, d, J_{ortho} 7.3 Hz, *p*-Ph), 7.35 (1H, dd, $J_{6,7}$ 8.7 and $J_{6,8}$ 0.7 Hz, 6-H), 7.43 (2H, t, J_{ortho} 7.3 Hz, *m*-

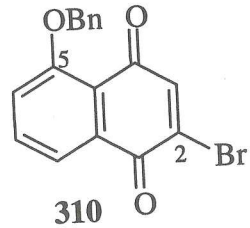
Ph), 7.45 (1H, s, 2-H), 7.58 (2H, d, J_{ortho} 7.3 Hz, *o*-Ph), 7.66 (1H, dd, $J_{7,6}$ 8.1 and $J_{7,8}$ 8.1 Hz, 7-H), 7.73 (1H, dd, $J_{8,7}$ 7.8 and $J_{8,6}$ 1.0 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 70.1 (CH_2, $\underline{C}H_2Ph$), 119.6, 119.7 (CH, C-6, C-8), 126.7 (CH, *o*-Ph), 128.1 (CH, *p*-Ph), 128.7 (CH, *m*-Ph), 135.4 (CH, C-7), 135.7 (quat., *ipso*-Ph), 138.3 (CH, C-2), 142.6 (quat., C-3), 159.2 (quat., C-5), 176.0, 182.5 (quat., C-1, C-4); *m/z* (EI) 344, 342 (M^+, 9%), 253, 251 (M-C_7H_7, 12), 91 (C_7H_7, 100).



309

5-benzyloxy-2-bromo-1,4-naphthoquinone 309

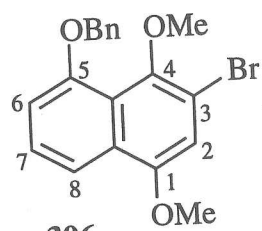
Silver(I) oxide (9.25 g, 39.9 mmol) was added to a stirred solution of 2-bromojuglone **307** (2.02 g, 7.98 mmol) and benzyl bromide (7.8 mL, 11.2 mmol) in chloroform (15 mL). After 2 h the solution was filtered through a celite pad to remove silver salts and the solvent removed at reduced pressure. The resultant orange oil was purified by flash chromatography using hexane-ethyl acetate (18:1-9:1) as eluent to afford *5-benzyloxy-2-bromo-1,4-naphthoquinone* **310** (2.30 g, 84%) which was recrystallized from ethanol to give yellow needles, m.p. 122-123 °C; [Found (EI): M^+, 343.9875, 341.9893. $C_{17}H_{11}BrO_3$ requires M, 343.9871, 341.9892]; ν_{max} (film) cm^{-1} 1676, 1656 (C=O, quin.); δ_H (400 MHz; $CDCl_3$) 5.30 (2H, s, $C\underline{H}_2Ph$), 7.33-7.43 (5H, m, 6-H, 3-H, *p*-Ph, *m*-Ph), 7.58 (2H, dd, J_{ortho} 7.3 and J_{meta} 0.8 Hz, *o*-Ph), 7.66 (1H, dd, $J_{7,8}$ 8.5 and $J_{7,6}$ 8.1 Hz, 7-H), 7.73 (1H, dd, $J_{8,7}$ 8.5 and $J_{8,6}$ 1.1 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 70.9 (CH_2, $\underline{C}H_2Ph$), 119.8 (quat., C-4a), 120.9, 120.1 (CH, C-6, C-8), 126.7 (CH, *o*-Ph), 128.1 (CH, *p*-Ph), 128.7 (CH, *m*-Ph), 133.1 (quat., C-8a), 135.9 (CH, C-7), 135.7, 136.9 (quat., C-2, *ipso*-Ph), 142.3 (CH, C-3), 158.8 (quat., C-5), 178.2, 181.3 (quat., C-1, C-4); *m/z* (EI) 344, 342 (M^+, 90%), 91 (C_7H_7, 100).



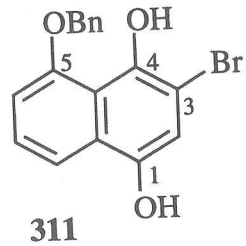
310

5-benzyloxy-3-bromo-1,4-dimethoxynaphthalene 306

Naphthoquinone **309** (2.7 g, 7.87 mmol) was dissolved in dichloromethane-diethyl ether (1:3) (200 mL) and shaken with a freshly prepared solution of sodium dithionite (12 g, 55 mmol) in water (120 mL) for 10 min. The organic layer was separated, washed with brine (80 mL) and dried (magnesium sulfate). The solvent was removed under reduced pressure to give the crude hydroquinone **311** as a pale brown oil. This was dissolved in dry acetone (45 mL) and transferred by double-ended needle to a reaction vessel containing a stirred suspension of potassium carbonate (13.0 g, 94 mmol) in dry acetone (130 mL). Dimethyl sulfate (5.2 mL, 55 mmol) was added in one portion and the solution stirred and heated at reflux for 48 h. The mixture was then cooled, filtered through celite and the solvent removed at reduced pressure. The resultant red oil was redissolved in diethyl ether (100 mL) and stirred with triethylamine (8.78 mL, 63 mmol). After 20 min. the solution was washed with hydrochloric acid (1 M, 2 x 50 mL), water (50 mL) and brine (50 mL). The organic extract was then dried (sodium sulfate) and concentrated *in vacuo* to give an oily residue which was purified by flash chromatography using hexane-ethyl acetate (6:1) as eluent to afford *5-benzyloxy-3-bromo-1,4-dimethoxynaphthalene* **306** (2.16 g, 76%) as a brown solid which was recrystallized from hexane-ethyl acetate to give tan needles, m.p. 93.5-94.5 °C; [Found (FAB): M^+, 372.0363. $C_{19}H_{17}{}^{79}BrO_3$ requires M, 372.0361); ν_{max} (film) cm^{-1} 1577, 1508 (C-O); δ_H (400 MHz; $CDCl_3$) 3.71, 3.95 (each 3H, s, 2 x OCH_3), 5.19 (2H, s, $C\underline{H}_2Ph$), 6.95 (1H, s, 2-H), 7.03 (1H, d, $J_{6,7}$ 7.7 Hz, 6-H), 7.30-7.46 (4H, m, 7-H, *m*-Ph, *p*-Ph), 7.58 (2H, d, J_{ortho} 7.8 Hz, *o*-Ph), 7.85 (1H, dd, $J_{8,7}$ 8.4 and $J_{8,6}$ 0.8 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 56.6, 62.5 (CH_3, 2 x OCH_3), 72.4 (CH_2, $\underline{C}H_2Ph$), 109.7 (CH, C-2), 110.1 (CH, C-6), 115.0 (quat., C-3), 116.1 (CH, C-7), 122.3 (quat., C-4a), 126.7 (CH, C-8), 128.4-129.2 (CH, Ph), 128.9 (quat., C-8a), 137.6 (quat., *ipso*-Ph), 147.5 (quat., C-5), 152.5, 155.2 (quat., C-1, C-4); *m/z* (EI) 374, 372 (M^+, 4%), 283, 281 (M-C_7H_7, 6), 202 (M-C_7H_7-Br, 11), 174 (10), 91 (C_7H_7, 67), 83 (17), 72 (55), 59 (100).



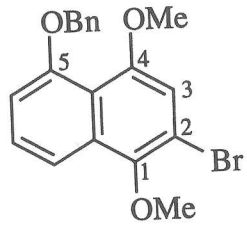
306



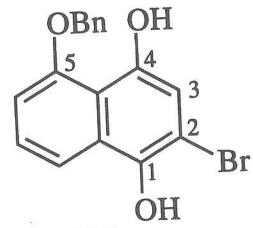
311

5-benzyloxy-2-bromo-1,4-dimethoxynaphthalene 313

Using the above conditions, 2-bromonaphthoquinone **310** (1.35 g, 3.94 mmol) was reduced to the hydroquinone **312** and then methylated. Purification by flash chromatography using hexane-ethyl acetate (6:1) as eluent afforded *5-benzyloxy-2-bromo-1,4-dimethoxynaphthalene* **313** (1.12 g, 79%) as a tan solid which was recrystallized from hexane-ethyl acetate to give colourless needles, m.p. 90.4-90.9 °C; [Found (EI): M^+, 374.0330, 372.0368. $C_{19}H_{17}BrO_3$ requires M, 374.0341, 372.0361]; ν_{max} (film) cm^{-1} 1578 (C-O); δ_H (400 MHz; $CDCl_3$) 3.91, 3.93 (each 3H, s, 2 x OCH_3), 5.20 (2H, s, $C\underline{H}_2Ph$), 6.91 (1H, s, 3-H), 6.97 (1H, d, $J_{6,7}$ 7.7 Hz, 6-H), 7.33 (1H, t, J_{ortho} 7.4 Hz, *p*-Ph), 7.40 (2H, t, J_{ortho} 7.4 Hz, *m*-Ph), 7.45 (1H, dd, $J_{6,7}$ 7.7 and $J_{7,8}$ 8.4 Hz, 7-H), 7.57 (1H, br.d, J_{ortho} 7.4 Hz, *o*-Ph), 7.71 (1H, br.d, $J_{8,7}$ 8.4 Hz, 8-H); δ_C (400 MHz; $CDCl_3$) 55.6, 61.2 (CH_3, 2 x OCH_3), 71.4 (CH_2, $\underline{C}H_2Ph$), 109.2 (CH, C-3), 109.7 (CH, C-6), 115.1 (CH, C-8), 118.1 (quat., C-4a), 126.9 (CH, *o*-Ph), 127.5, 127.6 (CH, *p*-Ph, C-7), 128.4 (CH, *m*-Ph), 131.8 (quat., C-8a), 137.3 (quat., *ipso*-Ph), 146.6 (quat., C-1), 154.0, 156.5 (quat., C-4, C-5); *m/z* (EI) 374, 372 (M^+, 27%), 283, 281 (M-C_7H_7, 10), 174 (15), 91 (C_7H_7, 100).



312

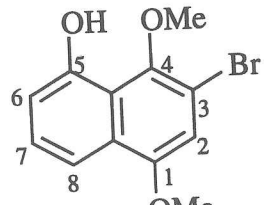


313

3-bromo-1,4-dimethoxy-5-hydroxynaphthalene 299

A solution of benzyl ether **306** (1.00 g, 2.68 mmol) in ethyl acetate (15 mL) was stirred under an atmosphere of hydrogen gas over palladium on charcoal (10%, 140 mg, 50 mg/mmol). After 8 h the reaction was complete and the mixture was filtered through celite. The solvent was removed at reduced pressure and the resultant green oil purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *3-bromo-1,4-dimethoxy-5-hydroxynaphthalene* **299** (745 mg, 98%) as a pale green solid which was recrystallized from ethanol to give colourless needles, m.p. 75.5-76.5 °C; (Found: C, 51.42; H, 3.71. $C_{12}H_{11}O_3Br$ requires C, 51.07; H, 3.93%); ν_{max} (film) cm^{-1} 3362 (br, OH), 1595, 1583 (C=C), 1381, 1335 (C-O); δ_H (400 MHz; $CDCl_3$) 3.95, 4.01 (each 3H, s, 2 x OCH_3), 6.84 (1H, s, 2-H), 6.99 (1H, dd, $J_{6,7}$ 7.7 and $J_{6,8}$ 1.1 Hz, 6-H), 7.39 (1H, dd, $J_{7,6}$ 7.7 and $J_{7,8}$ 8.3 Hz, 7-H), 7.70 (1H, dd, $J_{8,7}$ 8.3 and $J_{8,6}$ 1.1 Hz, 8-H), 9.39 (1H,

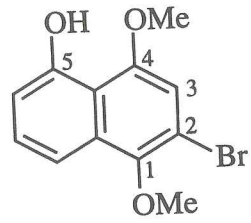
s, OH); δ_C (100 MHz; $CDCl_3$) 56.6, 63.2 (CH_3, 2 x OCH_3), 108.9 (CH, C-2), 111.1 (quat., C-3), 113.1, 114.4 (CH, C-6, C-7), 118.7 (quat., C-4a), 127.5 (quat., C-8a), 128.1 (CH, C-8), 146.8 (quat., C-5); 153.5, 153.6 (quat., C-1, C-4); *m/z* (EI) 284, 282 (M^+, 70%), 269, 267 (M-CH_3, 100), 173 [M-CH_3-CH_3-Br, 30].



299

2-bromo-5-hydroxy-1,4-dimethoxynaphthalene 314

A solution of benzyl ether **313** (500 mg, 1.34 mmol) in ethyl acetate (8 mL) was stirred over palladium on charcoal (10%, 67 mg, 50 mg/mmol) under an atmosphere of hydrogen gas. After 8 h the reaction was complete and the mixture was filtered through celite. The solvent was removed at reduced pressure and the resultant green oil purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *2-bromo-5-hydroxy-1,4-dimethoxynaphthalene* **314** (356 mg, 94%) as a pale green solid which was recrystallized from ethanol to give colourless needles, m.p. 140.5-141.5 °C; [Found (EI): M^+, 283.9874, 281.9884. $C_{12}H_{11}BrO_3$ requires M, 283.9871, 281.9892]; ν_{max} (film) cm^{-1} 3362 (br, OH); δ_H (200 MHz; $CDCl_3$) 3.92, 4.05 (each 3H, s, 2 x OCH_3), 6.86 (1H, s, 3-H), 6.93 (1H, dd, $J_{6,7}$ 7.7 and $J_{6,8}$ 1.1 Hz, 6-H), 7.43 (1H, dd, $J_{7,8}$ 8.3 and $J_{7,6}$ 7.7 Hz, 7-H), 7.57 (1H, dd, $J_{8,7}$ 8.3 and $J_{8,6}$ 1.1 Hz, 8-H), 9.19 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 56.5, 61.1 (CH_3, 2 x OCH_3), 107.7 (CH, C-3), 111.5 (CH, C-6, quat., C-2), 113.1 (CH, C-8), 114.9 (quat., C-4a), 128.7 (CH, C-7), 131.1 (quat., C-8a), 147.7, (quat., C-1), 152.6, 154.9 (quat., C-4, C-5); *m/z* (EI) 284, 282 (M^+, 70%), 269 (100), 267 (100), 173 (30).

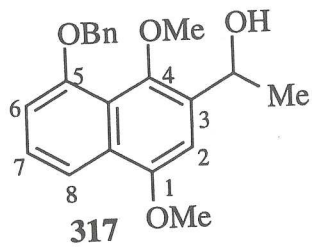


314

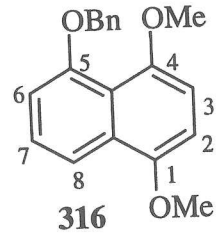
3.3.2 Synthesis of 3-Acetylnaphthol 264.

5-benzyloxy-3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene 317

A solution of 3-bromo-5-benzyloxy-1,4-dimethoxynaphthalene **306** (300 mg, 0.804 mmol) in tetrahydrofuran (10 mL) was stirred at -78 °C under an atmosphere of nitrogen. *n*-Butyllithium (1.36 M solution in hexane, 800 μL, 1.09 mmol) was added, followed immediately by an excess of acetaldehyde (>32 μL) [any delay before the addition of acetaldehyde resulted in the formation of considerable amounts of the protonated byproduct, 5-benzyloxy-1,4-dimethoxynaphthalene **316**]. The solution was allowed to warm to room temperature over 1 h then quenched with saturated ammonium chloride solution (5 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic fractions were washed with water (30 mL) and dried (sodium sulfate). The solvent was removed at reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (4:1-2:1) as eluent to afford *5-benzyloxy-3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene* **317** (266 mg, 98%) as a colourless oil which slowly turned yellow on standing; [Found (FAB): M^+, 338.1526. $C_{21}H_{22}O_4$ requires M, 338.1518]; ν_{max} (film) cm^{-1} 3405 (br, OH), 2968, 2929 (C-H), 1600, 1579, 1510 (C=C), 1361, 1262, 1067 (C-O); δ_H (200 MHz; $CDCl_3$) 1.57 (3H, d, J_{vic} 6.4 Hz, CH_3), 2.30 (1H, br.s, OH), 3.68, 3.98 (each 3H, s, 2 x OCH_3), 5.20 (2H, s, $C\underline{H}_2Ph$), 5.50 (1H, q, J_{vic} 7.1 Hz, C<u>H</u>OH), 6.94 (1H, s, 2-H), 6.99 (1H, dd, $J_{6,7}$ 7.7 and $J_{6,8}$ 0.9 Hz, 6-H), 7.30-7.46 (4H, m, *m*-Ph, *p*-Ph, 7-H), 7.56 (2H, dd, J_{ortho} 7.6 and J_{meta} 1.5 Hz, *o*-Ph), 7.88 (1H, dd, $J_{8,7}$ 8.4 and $J_{8,6}$ 0.9 Hz, 8-H); δ_C (50 MHz; $CDCl_3$) 24.4 (CH_3, CH_3), 55.7 (CH_3, OCH_3), 63.3 (CH, <u>C</u>HOH), 64.6 (CH_3, OCH_3), 71.5 (CH_2, $\underline{C}H_2Ph$), 102.0 (CH, C-2), 109.2 (CH, C-6), 115.3 (CH, C-8), 120.7 (quat., C-4a), 125.5 (CH, C-7), 127.6 (CH, *o*-Ph), 127.8 (CH, *p*-Ph), 128.4 (quat., C-8a), 128.5 (CH, *m*-Ph), 134.3 (quat., C-3), 137.1 (quat., *ipso*-Ph), 146.0 (quat., C-4), 151.9, 155.0 (quat., C-1, C-5); *m/z* 338 (M^+, 100%), 217(M-C_7H_7-Me-Me, 65), 91 (C_7H_7, 100).



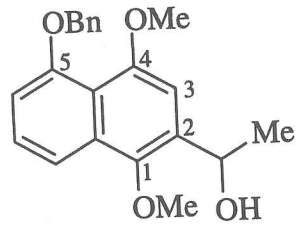
317



316

5-benzyloxy-2-(1-hydroxyethyl)-1,4-dimethoxynaphthalene 318

Using the conditions reported for **317**, 2-bromo-5-benzyloxy-1,4-dimethoxynaphthalene **313** (300 mg, 0.804 mmol) afforded *5-benzyloxy-2-(1-hydroxyethyl)-1,4-dimethoxynaphthalene* **318** (287 mg, 97%) as a tan oil; [Found (EI): M^+, 338.1520. $C_{21}H_{22}O_4$ requires M, 338.1518]; ν_{max} (film) cm^{-1} 3410 (br, OH), 1583 (C-O), 1511, 1454, 1385; δ_H (400 MHz; $CDCl_3$) 1.55 (3H, d, J_{vic} 6.5 Hz, CH_3), 2.45 (1H, br.s, OH), 3.86, 3.92 (each 3H, s, 2 x OCH_3), 5.18 (2H, s, C$\underline{H}_2$Ph), 2.41 (1H, q, J_{vic} 6.5 Hz, C$\underline{H}$OH), 6.92 (1H, s, 3-H), 6.92 (1H, br.d, $J_{6,7}$ 7.7 Hz, 6-H), 7.30-7.45 (4H, m, *m*-Ph, *p*-Ph, 7-H), 7.58 (2H, br.d, J_{ortho} 7.5 Hz, *o*-Ph), 7.65 (1H, dd, $J_{8,7}$ 8.5 and $J_{8,6}$ 0.9 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 24.2 (CH_3, CH_3), 56.5, 62.4 (CH_3, 2 x OCH_3), 64.7 (CH, $\underline{C}$HOH), 71.5 (CH_2, $\underline{C}H_2$Ph), 103.4 (CH, C-3), 108.9 (CH, C-6), 115.2 (CH, C-8), 118.4 (quat., C-4a), 126.7 (CH, C-7), 126.9 (CH, *o*-Ph), 127.5 (CH, *p*-Ph), 128.3 (CH, *m*-Ph), 131.2 (quat., C-8a), 133.8 (quat., C-2), 137.5 (quat., *ipso*-Ph), 145.5 (quat., C-1), 154.0, 156.4 (quat., C-4, C-5); *m/z* 338 (M^+, 100%), 217 (65), 91 (C_7H_7, 100), 43 (12).

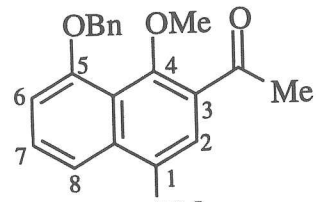


58

3-acetyl-5-benzyloxy-1,4-dimethoxynaphthalene 319

Tetrapropylammonium perruthenate (26 mg, 0.074 mmol) was added to a stirred solution of benzylic alcohol **317** (290 mg, 0.858 mmol), *N*-methylmorpholine-*N*-oxide (NMO) (260 mg, 2.22 mmol) and powdered molecular sieves (4Å, 30 mg) in dry dichloromethane (3 mL). When the reaction was complete (2-3 h) the mixture was filtered through a pad of silica using dichloromethane as eluent. The solvent was evaporated and the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *3-acetyl-5-benzyloxy-1,4-dimethoxynaphthalene* **319** (230 mg, 80%) as a pale yellow oil; [Found (EI): M^+, 336.1361. $C_{21}H_{20}O_4$ requires M, 336.1362]; ν_{max} (film) cm^{-1} 2933, 2842 (C-H), 1685 (C=O, ketone), 1615, 1573, 1508, 1410 (C=C), 1366, 1265, 1224, 1065 (C-O); δ_H (200 MHz; $CDCl_3$) 2.78 (3H, s, COC$\underline{H}_3$), 3.71, 3.99 (each 3H, s, 2 x OCH_3), 5.25 (2H, s, C$\underline{H}_2$Ph), 7.06 (1H, dd, $J_{6,7}$ 7.8 and $J_{6,8}$ 0.9 Hz, 6-H), 7.07 (1H, s, 2-H), 7.36-7.60 (6H, m, Ph-H, 7-H), 7.91 (1H, dd, $J_{8,7}$ 8.3 and $J_{8,6}$ 0.9 Hz, 8-

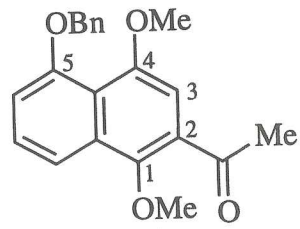
H); δ_C (50 MHz; $CDCl_3$) 31.4 (CH_3, $CO\underline{C}H_3$), 55.7, 64.1 (CH_3, 2 x OCH_3), 71.4 (CH_2, $\underline{C}H_2Ph$), 103.2 (CH, C-2), 109.3 (CH, C-6), 115.2 (CH, C-8), 120.6 (quat., C-4a), 127.6 (CH, *o*-Ph, *p*-Ph), 128.0 (CH, C-7), 128.5 (CH, *m*-Ph), 129.1 (quat., C-3), 131.2 (quat., C-8a), 136.7 (quat., *ipso*-Ph), 151.3, 152.2, 156.1 (quat., C-1, C-4, C-5), 201.3 (quat., $\underline{C}OCH_3$); *m/z* (EI) 336 (M^+, 65%), 245 (M-C_7H_7, 38), 203 (M-$COCH_3$, 40), 91 (C_7H_7, 100), 43 ($COCH_3$, 18).



319

2-acetyl-5-benzyloxy-1,4-dimethoxynaphthalene 320

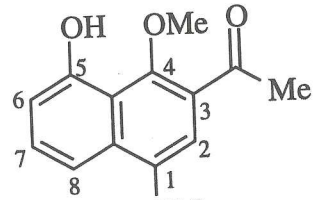
Using the conditions reported for **319**, benzylic alcohol **318** (290 mg, 0.858 mmol) was oxidized to afford *2-acetyl-5-benzyloxy-1,4-dimethoxynaphthalene* **320** (224 mg, 78%) as a yellow solid which was recrystallized from ethanol to give colourless needles, m.p. 109-110 °C; [Found (EI): M^+, 336.1363. $C_{21}H_{20}O_4$ requires M, 336.1362]; ν_{max} (film) cm^{-1} 2934 (C-H), 1668 (C=O, ketone), 1593 (C=C), 1375 (C-O); δ_H (400 MHz; $CDCl_3$) 2.79 (3H, s, $COC\underline{H}_3$), 3.92, 3.97 (each 3H, s, 2 x OCH_3), 5.21 (2H, s, $C\underline{H}_2Ph$), 7.07 (1H, br.d, $J_{6,7}$ 7.7 Hz, 6-H), 7.10 (1H, s, 3-H), 7.34 (1H, t, J_{ortho} 7.4 Hz, *p*-Ph), 7.42 (2H, t, J_{ortho} 7.4 Hz, *m*-Ph), 7.47 (1H, dd, $J_{7,8}$ 8.4 and $J_{7,6}$ 7.7 Hz, 7-H), 7.59 (2H, br.d, J_{ortho} 7.4 Hz, *o*-Ph), 7.82 (1H, dd, $J_{8,7}$ 8.4 and $J_{8,6}$ 0.7 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 30.9 (CH_3, $CO\underline{C}H_3$), 56.3, 63.6 (CH_3, 2 x OCH_3), 71.6 (CH_2, $\underline{C}H_2Ph$), 103.9 (CH, C-3), 111.3 (CH, C-6), 116.4 (CH, C-8), 121.2 (quat., C-4a), 126.9 (CH, *o*-Ph), 126.9 (quat., C-2), 127.3 (CH, C-7), 127.6 (CH, *p*-Ph), 128.4 (CH, *m*-Ph), 131.8 (CH, C-8a), 137.2 (quat., *ipso*-Ph), 151.2, 153.5, 156.4 (quat., C-1, C-4, C-5), 199.9 (quat., $\underline{C}OCH_3$); *m/z* (EI) 336 (M^+, 59%), 245 (M-C_7H_7, 35), 203 (M-$COCH_3$, 52), 91 (C_7H_7, 100), 43 ($COCH_3$, 12).



321

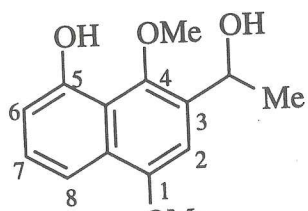
3-acetyl-5-hydroxy-1,4-dimethoxynaphthalene 264 and 5-hydroxy-3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene 322

A solution of benzyl ether **319** (223 mg, 0.664 mmol) in ethyl acetate (5 mL) was stirred under an atmosphere of hydrogen over palladium on charcoal (10%, 33 mg, 50 mg/mmol). After 2 h the reaction was incomplete, hence, the mixture was filtered through celite and the solvent removed *in vacuo*. The residue was redissolved in ethyl acetate and the hydrogenation procedure repeated with the reaction going to completion almost immediately. The mixture was filtered through celite and the solvent evaporated at reduced pressure. The oily green residue was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *ketone* **264** (86 mg, 53%) and *diol* **322** (43 mg, 26%); *Ketone* **264** was a pale yellow oil; [Found (FAB): M^+, 246.0894. $C_{14}H_{14}O_4$ requires M, 246.0892]; ν_{max} (film) cm^{-1} 3357 (br, OH), 2939, 2843 (C-H), 1672 (C=O), 1627, 1598, 1512 (C=C), 1367, 1240, (C-O); δ_H (200 MHz; $CDCl_3$) 2.76 (3H, s, $COC\underline{H}_3$), 3.94, 4.00 (3H, s, 2 x OCH_3), 6.95 (1H, s, 2-H), 7.00 (1H, dd, $J_{6,7}$ 7.8 and $J_{6,8}$ 0.9 Hz, 6-H), 7.47 (1H, dd, $J_{7,6}$ 7.8 and $J_{7,8}$ 8.3 Hz, 7-H), 7.75 (1H, dd, $J_{8,7}$ 8.3 and $J_{8,6}$ 0.9 Hz, 8-H), 9.49 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 30.3 (CH_3, $CO\underline{C}H_3$), 55.7, 65.5 (CH_3, 2 x OCH_3), 102.4 (CH, C-2), 112.4, 113.5 (CH, C-6, C-8), 117.1 (quat., C-4a), 126.6 (quat., C-3), 129.3 (CH, C-7), 130.2 (quat., C-8a), 151.3, 152.2, 154.7 (quat., C-1, C-4, C-5), 199.4 (quat., $\underline{C}OCH_3$); *m/z* (EI) 246 (M^+, 70%), 231 (M-CH_3, 100), 203 (M-$COCH_3$, 45), 175 (25), 145 (20), 115 (30), 89 (18), 43 ($COCH_3$, 27).



264

Diol **322**, a colourless oil, although not characterized, was identified on the basis of its ^1H nmr spectrum; δ_H (200 MHz; $CDCl_3$) 1.54 (3H, d, J_{vic} 6.4 Hz, CH_3), 2.27 (1H, br.s, CHO$\underline{H}$), 3.86, 4.00 (3H, s, 2 x OCH_3), 5.43 (1H, q, J_{vic} 6.4 Hz, C$\underline{H}$OH), 6.82 (1H, s, 2-H), 6.88 (1H, dd, $J_{6,7}$ 7.5 and $J_{6,8}$ 1.2 Hz, 6-H), 7.38 (1H, dd, $J_{7,8}$ 8.3 and $J_{7,6}$ 7.5 Hz, 7-H), 7.49 (1H, dd, $J_{8,7}$ 8.3 and $J_{8,6}$ 1.2 Hz, 8-H), 9.35 (1H, s, OH).



322

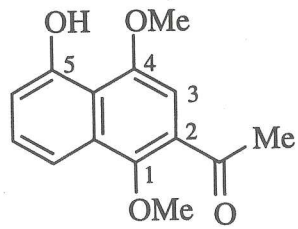
Oxidation of diol ***322*** *to ketone* ***264****.*

A solution of diol **322** (43 mg, 0.173 mmol) in dry dichloromethane (1 mL) was treated with tetrapropylammonium perruthenate (3 mg, 0.009 mmol), *N*-methylmorpholine-*N*-oxide (30 mg, 0.260 mmol) and molecular sieves (4Å, 10 mg) and stirred for 2 h. The mixture was filtered through silica and the solvent removed at reduced pressure. Purification by flash chromatography using hexane-ethyl acetate (4:1) as eluent afforded ketone **264** (35 mg, 83%).

2-acetyl-5-hydroxy-1,4-dimethoxynaphthalene 321 and 5-hydroxy-3-(1-hydroxy-ethyl)-1,4-dimethoxynaphthalene 323

A solution of benzyl ether **320** (205 mg, 0.610 mmol) was debenzylated using the conditions reported for **319** to afford *ketone* **321** (87 mg, 58%) and *diol* **323** (32 mg, 21%);

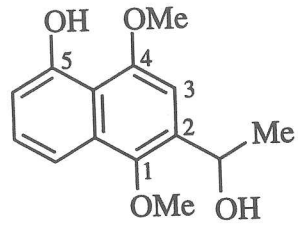
Ketone **321** was recrystallized from hexane-ethyl acetate to give colourless needles, m.p. 96.5-97.5 °C; [Found (FAB): M^+, 246.0894. $C_{14}H_{14}O_4$ requires M, 246.0892]; ν_{max} (film) cm^{-1} 3362 (br, OH), 1660 (C=O, ketone), 1611 (C=C), 1375, 1214 (C-O); δ_H (400 MHz; $CDCl_3$) 2.79 (3H, s, $COC\underline{H}_3$), 3.93, 4.01 (each 3H, s, 2 x OCH_3), 7.01 (1H, br.d, $J_{6,7}$ 7.7 Hz, 6-H), 7.06 (1H, s, 3-H), 7.47 (1H, dd, $J_{7,8}$ 8.4 and $J_{7,6}$ 7.7 Hz, 7-H), 7.67 (1H, dd, $J_{8,7}$ 8.4 and $J_{8,6}$ 0.6 Hz, 8-H), 9.37 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 30.9 (CH_3, $CO\underline{C}H_3$), 56.4, 63.6 (CH_3, 2 x OCH_3), 102.0 (CH, C-3), 113.6, 114.6 (CH, C-6, C-8), 117.8 (quat., C-4a), 126.9 (quat., C-2), 128.6 (CH, C-7), 131.1 (quat., C-8a), 152.4, 152.8, 154.9 (quat., C-1, C-4, C-5), 199.3 (quat., $\underline{C}OCH_3$); *m/z* (EI) 246 (M^+, 70%), 231 (M-CH_3, 100), 203 (M-$COCH_3$, 45), 175 (25), 145 (20), 115 (30), 89 (18), 43 ($COCH_3$, 27).



321

Diol **323**, a colourless oil, was identified on the basis of its ^1H nmr spectrum; δ_H (200 MHz; $CDCl_3$) 1.52 (3H, d, J_{vic} 6.5 Hz, Me), 2.68 (1H, br.s, CHO$\underline{H}$), 3.83, 3.93 (3H, s, 2 x OCH_3), 5.41 (1H, q, J_{vic} 6.5 Hz, C$\underline{H}$OH), 6.77 (1H, s, 3-H), 6.86 (1H, dd,

$J_{6,7}$ 7.4 and $J_{6,8}$ 1.2 Hz, 6-H), 7.36 (1H, dd, $J_{7,8}$ 8.3 and $J_{7,6}$ 7.4 Hz, 7-H), 7.45 (1H, dd, $J_{8,7}$ 8.3 and $J_{8,6}$ 1.2 Hz, 8-H), 9.32 (1H, s, OH).



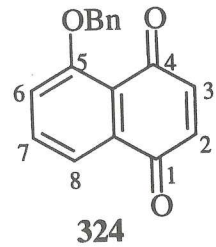
323

Diol **323** (32 mg, 0.129 mmol) was oxidized as for **322** to give ketone **321** (28 mg, 89%).

3.3.3 Alternative Synthesis of Bromonaphthalene 306.

5-benzyloxy-1,4-naphthoquinone 324[197,222]

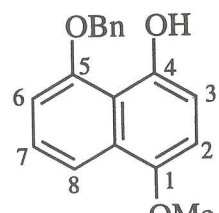
Silver(I) oxide (14 g, 62 mmol) was added to a stirred solution of juglone **75** (2.70 g, 15.5 mmol) and benzyl bromide (5.5 mL, 46.6 mmol) in chloroform (50 mL). After 2 h, the solution was filtered through a celite pad to remove silver salts and the solvent removed at reduced pressure. The oily residue was purified by flash chromatography using hexane-ethyl acetate (18:1-9:1) as eluent to afford 5-benzyloxy-1,4-naphthoquinone **324** (3.28 g, 80%) as fine orange needles, m.p. 111-111.5 °C (lit.[197] m.p. 113 °C, and lit.[222] m.p. 108-109 °C); ν_{max} (film) cm^{-1} 1659 (C=O, quin.); δ_H (400 MHz; $CDCl_3$) 5.30 (2H, s, $C\underline{H}_2Ph$), 6.89 (2H, s, 2-H and 3-H), 7.33-7.37 (2H, m, 6-H, *p*-Ph), 7.42 (2H, t, J_{ortho} 7.3 Hz, *m*-Ph), 7.58 (2H, d, J_{ortho} 7.3 Hz, *o*-Ph), 7.65 (1H, dd, $J_{6,7}$ 8.0 and $J_{7,8}$ 7.6 Hz, 7-H), 7.74 (1H, dd, $J_{8,7}$ 7.6 and $J_{8,6}$ 0.9 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 70.9 (CH_2, $\underline{C}H_2Ph$), 119.5, 119.6 (CH, C-7, C-8), 126.6 (CH, *o*-Ph), 128.0 (CH, *p*-Ph), 128.7 (CH, *m*-Ph), 120.2, 134.1, (quat., C-8a, C-4a), 134.8, 136.2, 140.9 (CH, C-6, C-2, C-3), 136.0 (quat., *ipso*-Ph), 158.5 (quat., C-5), 184.1, 185.2 (quat., C-1, C-4); *m/z* (EI) 264 (M^+, 25%), 91 (C_7H_7, 100).



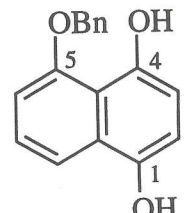
324

5-benzyloxy-4-hydroxy-1-methoxynaphthalene 326[197]

Naphthoquinone **324** (1.01 g, 3.78 mmol) was dissolved in dichloromethane-diethyl ether (1:3) (60 mL) and shaken with a freshly prepared solution of sodium dithionite (4.6 g, 26.5 mmol) in water (30 mL) for 10 min. The organic layer was washed with water (30 mL), dried (magnesium sulfate) and the solvent removed under reduced pressure to give the crude hydroquinone **325** as a brown foam. This was dissolved in dry acetone (50 mL) and transferred by double-ended needle to a reaction vessel containing a slurry of potassium carbonate (1.57 g, 11.3 mmol) and dry acetone (20 mL). Dimethyl sulfate (1.43 mL, 15.0 mmol) was added and the solution stirred and then heated at reflux until the reaction was complete (2-3 h). The mixture was then cooled, filtered through celite and the solvent removed at reduced pressure. The resultant red oil was dissolved in diethyl ether (100 mL) and stirred with triethylamine (2.3 mL, 16.6 mmol) for 20 min. The ethereal solution was washed with hydrochloric acid (1 M, 2 x 50 mL), water (50 mL), brine (50 mL) then dried (sodium sulfate) and concentrated *in vacuo*. The oily residue was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford 5-benzyloxy-4-hydroxy-1-methoxynaphthalene **326** (761 mg, 75%) as a brown solid which was recrystallized from ethanol to give tan needles, m.p. 108-108.5 °C (lit.[197] m.p. 108 °C); ν_{max} (film) cm^{-1} 3407 cm^{-1} (br, OH); δ_H (200 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 5.23 (2H, s, $C\underline{H}_2Ph$), 6.75 (2H, s, 2-H and 3-H), 6.90 (1H, d, $J_{7,6}$ 7.9 Hz, 6-H), 7.31 (1H, dd, $J_{7,8}$ 8.1 and $J_{6,7}$ 7.9 Hz, 7-H), 7.34-7.50 (5H, m, Ph), 7.86 (1H, dd, $J_{7,8}$ 8.1 and $J_{8,6}$ 0.8 Hz, 8-H), 8.98 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 56.0 (CH_3, OCH_3), 71.7 (CH_2, $\underline{C}H_2Ph$), 106.3 (CH, C-2 and C-3), 109.1, 116.2, 125.1 (CH, C-6, C-7, C-8), 115.7 (quat., C-4a), 126.0 (quat., C-8a), 128.0 (CH, *o*-Ph), 128.8 (CH, *p*-Ph), 129.0 (CH, *m*-Ph), 135.3 (quat., *ipso*-Ph), 147.9 (quat., C-1), 148.1 (quat., C-5), 155.1 (quat., C-4); *m/z* (EI) 280 (M^+, 20%), 189 (M-C_7H_7, 100), 91 (C_7H_7, 40).



326

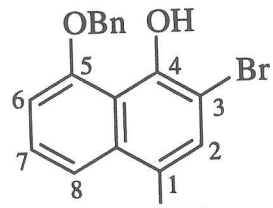


325

5-benzyloxy-3-bromo-4-hydroxy-1-methoxynaphthalene 327

A solution of bromine (190 mg, 1.18 mmol) in carbon tetrachloride (1.0 mL) was added dropwise to a solution of naphthol **326** (300 mg, 1.07 mmol) in carbon tetrachloride (6.0 mL) at 0 °C. The reaction mixture was stirred for a further 2 min. before

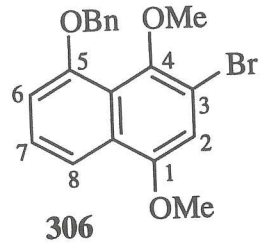
being quenched with saturated aqueous sodium thiosulfate solution (5 mL) and diluted with dichloromethane (50 mL). The organic layer was washed with water (50 mL) and the aqueous layer extracted twice with dichloromethane (2 x 50 mL). The combined organic extracts were dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was purified by flash chromatography using hexane-ethyl acetate (6:1) as eluent to afford *5-benzyloxy-3-bromo-4-hydroxy-1-methoxynaphthalene* **327** (380 mg, 99%) which was recrystallized from hexane-ethyl acetate to give red needles, m.p. 132.5-133.5 °C; [Found (FAB): M^+, 358.0207. $C_{18}H_{15}{}^{79}BrO_3$ requires M, 358.0205]; ν_{max} (film) cm^{-1} 3343 (br, OH); δ_H (400 MHz; $CDCl_3$) 3.86 (3H, s, OCH_3), 5.17 (2H, s, $C\underline{H}_2Ph$), 6.87 (1H, s, 2-H), 6.91 (1H, dd, $J_{7,6}$ 7.8 and $J_{6,8}$ 1.0 Hz, 6-H), 7.28 (1H, dd, $J_{6,7}$ 8.9 and $J_{8,7}$ 7.8 Hz, 7-H), 7.33-7.43 (5H, m, Ph-H), 7.77 (1H, dd, $J_{8,7}$ 8.9 and $J_{8,6}$ 1.0 Hz, 8-H), 9.58 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 56.7 (CH_3, OCH_3), 72.6 (CH_2, $\underline{C}H_2Ph$), 103.6 (quat., C-3), 107.9 (CH, C-2), 110.8, 117.0, 126.2 (CH, C-6, C-7, C-8), 116.4 (quat., C-4a), 128.0 (quat., C-8a), 128.9 (CH, *o*-Ph), 129.7 (CH, *p*-Ph), 129.7 (CH, *m*-Ph), 135.4 (quat., *ipso*-Ph), 145.0, (quat., C-1), 148.8 (quat., C-5), 155.0 (quat., C-4); *m/z* (EI) 360, 358 (M^+, 15%), 279 (M-Br, 20), 269, 267 (M-C_7H_7, 100), 91 (C_7H_7, 60).



327

5-benzyloxy-3-bromo-1,4-dimethoxynaphthalene 306

A slurry of oil free sodium hydride (259 mg, 10.8 mmol) in dry dimethylformamide (2 mL) was added dropwise to a stirred solution of bromonaphthol **327** (1.94 g, 5.40 mmol) in dimethylformamide (15 mL) at 0 °C. The mixture was stirred for 15 min. at 0 °C then iodomethane (3.36 mL, 54 mmol) was added and the reaction mixture allowed to warm to room temperature overnight. The reaction was then quenched with water (1 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water (50 mL), dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *5-benzyloxy-3-bromo-1,4-dimethoxynaphthalene* **306** (1.49 g, 74%) which was recrystallized from hexane-ethyl acetate to give tan needles, m.p. 93.5-94 °C. The spectroscopic data was identical to that reported previously.

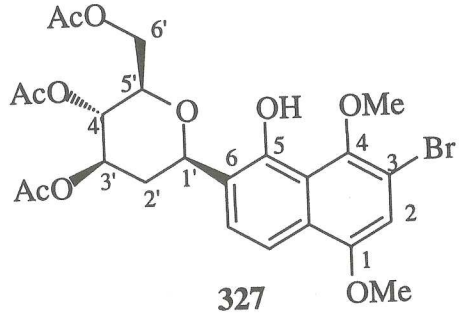


306

3.3.4 Aryl *C*-Glycosylation Using Bromonaphthols 299 and 314.

6-(3',4',6'-tri-*O*-acetyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-5-hydroxy-1,4-dimethoxynaphthalene 327

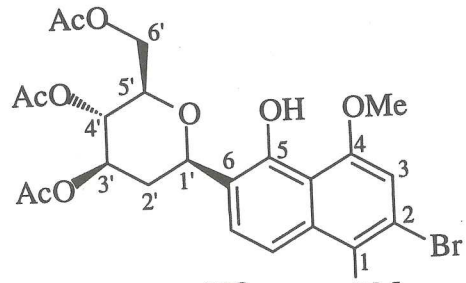
Trimethylsilyl trifluoromethanesulfonate (51 μL, 0.266 mmol) and silver perchlorate (2 mg, 5 mol%) were added to a stirred solution of 3-bromo-1,4-dimethoxy-5-hydroxynaphthalene **299** (50 mg, 0.177 mmol) and tetra-*O*-acetyl-2-deoxy-D-glucoside **238** (100 mg, 210 mmol) in dry acetonitrile (5 mL) at 0 °C. The mixture was stirred for 1 hour then quenched with aqueous bicarbonate solution (5 mL). The reaction mixture was extracted with dichloromethane (3 x 50 mL), washed with water (100 mL) and dried (magnesium sulfate). The solvent was removed at reduced pressure and the oily residue purified by flash chromatography using hexane-ethyl acetate (6:1) as eluent to give *6-(3',4',6'-tri-O-acetyl-2'-deoxy-β-D-arabino-hexopyranosyl)-3-bromo-5-hydroxy-1,4-dimethoxynaphthalene* **327** (5 mg, 5%) as a colourless oil; [Found (EI): M^+, 554.0785. $C_{24}H_{27}{}^{79}BrO_{10}$ requires M, 554.0788]; ν_{max} (film) cm^{-1} 3345 (OH), 1741 (C=O), 1631 (C=C), 1391 (C-O); δ_H(200 MHz; $CDCl_3$) 1.78 (1H, ddd, J_{gem} 12.7, $J_{2'ax,1'}$ 11.3 and $J_{2'ax,3'}$ 11.3 Hz, 2'$_{ax}$-H), 2.02, 2.07, 2.09 (each 3H, s, 3 x COC$\underline{H}_3$), 2.52 (1H, ddd, J_{gem} 12.7, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 2.0 Hz, 2'$_{eq}$-H), 3.84 (1H, ddd, $J_{5',4'}$ 9.7, $J_{5',6'B}$ 4.8 and $J_{5',6'A}$ 2.3 Hz, 5'-H), 3.95, 3.99 (each 3H, s, 2 x OCH_3), 4.20 (1H, dd, J_{gem} 12.2 and $J_{6'A,5'}$ 2.3 Hz, 6'-H_A), 4.35 (1H, dd, J_{gem} 12.2 and $J_{6'B,5'}$ 4.8 Hz, 6'-H_B), 5.12 (1H, dd, $J_{1',2'ax}$ 11.3 and $J_{1',2'eq}$ 2.0 Hz, 1'-H), 5.14 (1H, dd, $J_{4',3'}$ 9.7 and $J_{4',5'}$ 9.7 Hz, 4'-H), 5.25 (1H, ddd, $J_{3',2'ax}$ 11.3, $J_{3',4'}$ 9.7 , $J_{3',2'eq}$ 4.8 Hz, 3'-H), 6.83 (1H, s, 2-H), 7.57 (1H, d, $J_{8,7}$ 8.8 Hz, 8-H), 7.72 (1H, d, $J_{7,8}$ 8.8 Hz, 7-H) 9.70 (1H, s, OH); *m/z* (EI) 556, 554 (M^+, 38%), 43 (100).



327

6-(3',4',6'-tri-*O*-acetyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-2-bromo-5-hydroxy-1,4-dimethoxynaphthalene 328

Under the same conditions as for **327**, 2-bromo-5-hydroxy-1,4-dimethoxynaphthalene **314** (50 mg, 0.177 mmol) and tetra-*O*-acetyl-2-deoxy-D-glucoside **238** (100 mg, 210 mmol) were reacted to afford *6-(3',4',6'-tri-O-acetyl-2'-deoxy-β-D-arabino-hexopyranosyl)-2-bromo-5-hydroxy-1,4-dimethoxynaphthalene* **328** (71 mg, 57%) as a colourless oil; $[\alpha]_D^{22}$ = +17.49° (c=0.27, $CHCl_3$); [Found (EI): M^+, 556.0774 and 554.0777. $C_{24}H_{27}BrO_{10}$ requires M, 556.0767 and 554.0788]; ν_{max} (film) cm^{-1} 3346 (OH), 2938 (C-H), 1742 (C=O), 1631 (C=C), 1391 (C-O); δ_H (200 MHz; $CDCl_3$) 1.26 (1H, ddd, J_{gem} 12.7, $J_{2'ax,1'}$ 11.3 and $J_{2'ax,3'}$ 11.3 Hz, 2'$_{ax}$-H), 2.02, 2.08, 2.10 (each 3H, s, 3 x $COC\underline{H}_3$), 2.52 (1H, ddd, J_{gem} 12.7, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 2.0 Hz, 2'$_{eq}$-H), 3.84 (1H, ddd, $J_{5',4'}$9.7, $J_{5',6'B}$ 4.8 and $J_{5',6'A}$ 2.3 Hz, 5'-H), 3.91, 4.04 (each 3H, s, 2 x OCH_3), 4.20 (1H, dd, J_{gem} 12.2 and $J_{6'A,5'}$ 2.3 Hz, 6'-H_A), 4.35 (1H, dd, J_{gem} 12.2 and $J_{6'B,5'}$ 4.8 Hz, 6'-H_B), 5.12 (1H, dd, $J_{1',2'ax}$ 11.3 and $J_{1',2'eq}$ 2.0 Hz, 1'-H), 5.14 (1H, dd, $J_{4',3'}$ 9.7 and $J_{4',5'}$ 9.7 Hz, 4'-H), 5.25 (1H, ddd, $J_{3',2'ax}$ 11.3, $J_{3',4'}$ 9.7 , $J_{3',2'eq}$ 4.8 Hz, 3'-H), 6.86 (1H, s, 3-H), 7.58 (1H, d, $J_{8,7}$ 8.8 Hz, 8-H), 7.64 (1H, d, $J_{7,8}$ 8.8 Hz, 7-H), 9.49 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 20.8, 20.9, 21.0 (CH_3, 3 x $CO\underline{C}H_3$), 36.7 (CH_2, C-2'), 56.7, 61.2 (CH_3, 2 x OCH_3), 62.9 (CH_2, C-6'), 69.6 (CH, C-4'), 71.7 (CH, C-1'), 72.5 (CH, C-3'), 76.2 (CH, C-5'), 108.2 (CH, C-3), 113.4 (CH, C-7), 114.5 (quat., C-2), 122.5 (quat., C-4a), 125.9 (CH, C-8), 130.1 (quat., C-8a), 133.5 (quat., C-6), 147.8, 150.5, 152.7 (quat., C-1, C-4, C-5), 170.0, 170.4, 170.9 (quat., 3 x $\underline{C}OCH_3$); *m/z* (EI) 556, 554 (M^+, 42%), 321, 319 (48), 43 ($COCH_3$, 100).



328

(1'*R*,2'*R*,5'*S*,7'*R*,9'*S*)-2-(9'-benzyloxy-2'-phenyl-3',6'-dioxabicyclo-[3.2.2]nonan-7'-yl)-7-bromo-1-hydroxy-5,8-dimethoxynaphthalene 340

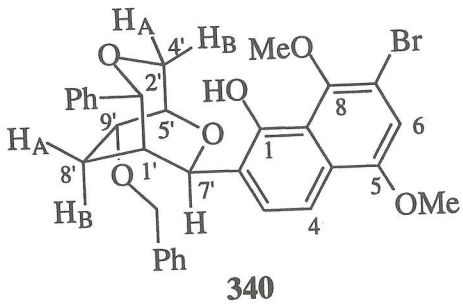
and

6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-5-hydroxy-1,4-dimethoxynaphthalene 329

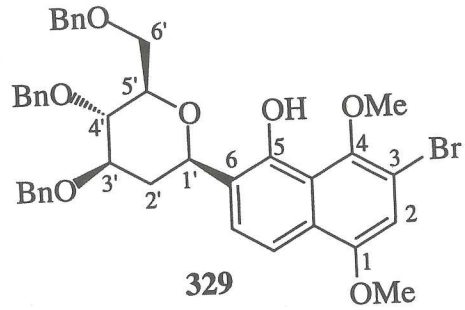
Trimethylsilyl trifluoromethanesulfonate (51 μL, 0.266 mmol) and silver perchlorate (2 mg, 5 mol%) were added to a stirred solution of 3-bromo-1,4-dimethoxy-5-hydroxynaphthalene **299** (50 mg, 0.177 mmol) and tri-*O*-benzyl-2-deoxy-D-glucosyl acetate **266** (101 mg, 210 mmol) in dry acetonitrile (5 mL) at 0 °C. The mixture was stirred for 1 hour then quenched with aqueous bicarbonate solution (5 mL). The reaction mixture was extracted with dichloromethane (3 x 50 mL), washed with water (100 mL) and dried (magnesium sulfate). The solvent was removed at reduced pressure and the oily residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give a mixture of the *rearranged compound* **340** and the desired *β-C-glycoside* **329** (71 mg, 6:1). These were subjected to HPLC. Analytical HPLC established the optimal separation conditions (0.375% ^{i}PrOH/hexane, partisil 5 column, 25 cm x 4.6 mm I.D., flow rate 1.5 mL/min.), but on a semi-preparative scale (0.375% ^{i}PrOH/hexane, partisil 10 column, 50 cm x 9.4 mm I.D., flow rate 4 ml/min.) the unstable β-*C*-glycoside **329** decomposed.

The more stable rearranged product **340** (59 mg, 48%) was recovered as a colourless oil; $[\alpha]_D^{22}$ = -105° (c=0.24, $CHCl_3$); [Found (LSIMS): M^+, 590.1295. $C_{32}H_{31}{}^{79}BrO_6$ requires M, 590.1304]; ν_{max} (film) cm^{-1} 3329 (OH), 2934 (C-H), 1591 (C=C), 1508, 1453 (C-O); δ_H(400 MHz; $CDCl_3$) 1.43 (1H, ddd, J_{gem} 14.4, $J_{8'B,9'}$ 4.8 and $J_{8'B,1'}$ 4.8 Hz, 8'-H_B), 1.98 (1H, ddd, J_{gem} 14.4, $J_{8'A,9'}$ 9.7 and $J_{8'A,1'}$ 2.2 Hz, 8'-H_A), 2.19 (1H, dd, $J_{1',8'B}$ 4.8 and $J_{1',8'A}$ 2.2 Hz, 1'-H), 3.85 (3H, s, 5-OCH_3), 3.94 (3H, s, 8-OCH_3), 4.08 (1H, d, J_{gem} 13.4 Hz, 4'-H_A), 4.16 (1H, dd, $J_{9',8'A}$ 9.7 and $J_{9',8'B}$ 4.8 Hz, 9'-H), 4.21 (1H, dd, J_{gem} 13.4 and $J_{4'B,5'}$ 5.5 Hz, 4'-H_B), 4.36 (1H, d, $J_{5',4'B}$ 5.5 Hz, 5'-H), 4.48 (1H, d, J_{gem} 11.9 Hz, C<u>H</u>Ph), 4.52 (1H, d, J_{gem} 11.9 Hz, C<u>H</u>Ph), 5.06 (1H, s, 7'-H), 5.86 (1H, s, 2'-H), 6.70 (1H, s, 6-H), 7.14 (1H, t, J_{ortho} 7.2 Hz, *p*-Ph), 7.24 (2H, t, J_{ortho} 7.2 Hz, *m*-Ph), 7.29-7.35 (7H, m, *o*-Ph, CH_2<u>Ph</u>), 7.64 (1H, d, $J_{4,3}$ 8.7 Hz, 4-H), 8.04 (1H, d, $J_{3,4}$ 8.7 Hz, 3-H) 9.68 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 22.4 (CH_2, C-8'), 45.5 (CH, C-1'), 55.9 (CH_3, 5-OCH_3), 62.6 (CH_3, 8-OCH_3), 70.2 (CH_2, <u>C</u>H_2Ph), 71.1 (CH_2, C-4'), 73.7 (CH, C-9'), 76.2 (CH, C-2'), 76.6 (CH, C-5'), 86.2 (CH, C-7'), 107.6 (CH, C-3), 110.3 (quat., C-7), 113.0 (CH, C-4), 117.4 (quat., C-8a), 125.5 (CH, Ph), 126.1 (CH, C-6), 126.4, 126.6 (quat., C-2, C-4a), 127.0-128.4

(CH, Ph), 138.6 (quat., *ipso*-Ph), 142.4 (quat., *ipso*-Ph), 146.0 (quat., C-1), 148.5, 152.8 (quat., C-5, C-8); *m/z* (EI) 592, 590 (M^+, 27%), 321 (11), 91 (C_7H_7, 100).



340

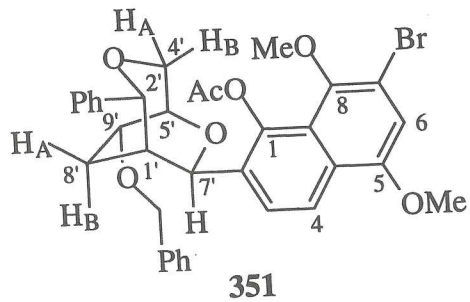


329

Although not able to be fully characterized,^{1}H nmr shifts for β-*C*-glycoside **329** were identified from the spectrum of the mixture; δ_H (400 MHz; $CDCl_3$) *inter alia.* 2.50 (1H, ddd, J_{gem} 12.7, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 1.8 Hz, 2_{eq}'-H), 7.59 (1H, d, $J_{8,7}$ 8.0 Hz, 8-H), 6.74 (1H, s, 2-H), 7.66 (1H, d, $J_{7,8}$ 8.0 Hz, 7-H), 9.60 (1H, s, OH).

(1'*R*,2'*R*,5'*S*,7'*R*,9'*S*)-2-(9'-benzyloxy-2'-phenyl-3',6'-dioxabicyclo-[3.2.2]nonan-7'-yl)-7-bromo-5,8-dimethoxynaphthalen-1-yl acetate 351

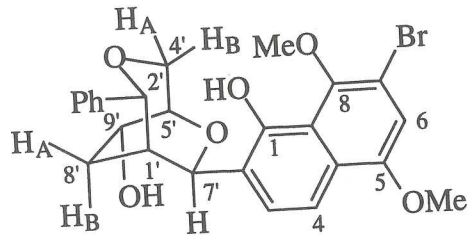
Triethylamine (0.50 mL, 3.59 mmol), acetic anhydride (0.25 mL, 2.65 mmol) and a catalytic quantity of dimethylaminopyridine were added to a solution of *C*-glycoside **340** (98 mg, 0.166 mmol) in dichloromethane (2 mL). The solution was stirred overnight then the solvent removed at reduced pressure. The residue was purified by flash chromatography using hexane-ethyl acetate (4:1) to give the *acetate* **351** (99 mg, 94%) which was recrystallized from hexane-ethyl acetate to give white needles, m.p. 204-205 °C (from which a crystal structure was obtained); $[\alpha]_D^{20}$ = -192° (c=0.45, $CHCl_3$); [Found (LSIMS): M^+, 632.1422. $C_{34}H_{33}{}^{79}BrO_7$ requires M, 632.1410]; ν_{max} (film) cm^{-1} 2933 (C-H), 1769 (C=O, ester), 1587 (C=C), 1506, 1453, 1411 (C-O); δ_H (400 MHz; 360K; C_7D_8) 1.63 (1H, ddd, J_{gem} 14.4, $J_{8'B,9'}$ 4.6 and $J_{8'B,1'}$ 4.6 Hz, 8'-H_B), 2.01 (1H, ddd, J_{gem} 14.4, $J_{8'A,9'}$ 9.7 and $J_{8'A,1'}$ 2.2 Hz, 8'-H_A), 2.14 (3H, s, $COCH_3$), 2.31 (1H, dd, $J_{1',8'B}$ 4.6 and $J_{1',8'A}$ 2.2 Hz, 1'-H), 3.37, 3.66 (each 3H, s, 2 x OCH_3), 3.91 (1H, d, J_{gem} 13.4 Hz, 4'-H_A), 3.98 (1H, dd, J_{gem} 13.4 and $J_{4'B,5'}$ 5.1 Hz, 4'-H_B), 4.09 (1H, dd, $J_{9',8'A}$ 9.7 and $J_{9',8'B}$ 4.6 Hz, 9'-H), 4.24 (1H, d, $J_{5',4'B}$ 5.1 Hz, 5'-H), 4.34 (1H, d, J_{gem} 12.2 Hz, CHPh), 4.37 (1H, d, J_{gem} 12.2 Hz, CHPh), 4.92 (1H, s, 7'-H), 5.81 (1H, s, 2'-H), 6.68 (1H, s, 6-H), 7.03-7.09 (2H, m, *p*-Ph), 7.15-7.20 (4H, m, *m*-Ph), 7.30 (2H, d, J_{ortho} 7.7 Hz, *o*-Ph), 7.44 (2H, d, J_{ortho} 7.7 Hz, *o*-Ph), 8.14 (1H, d, $J_{4,3}$ 8.9 Hz, 4-H), 8.45 (1H, d, $J_{3,4}$ 8.9 Hz, 3-H); *m/z* (CI) 634, 632 (M^+, 10%), 91 (C_7H_7, 100).



351

(1'*R*,2'*R*,5'*S*,7'*R*,9'*S*)-7-bromo-1-hydroxy-2-(9'-hydroxy-2'-phenyl-3',6'-dioxabicyclo-[3.2.2]nonan-7'-yl)-5,8-dimethoxynaphthalene 352

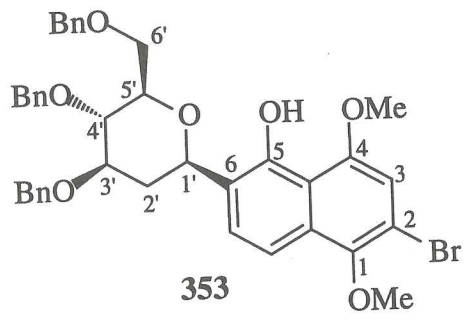
A solution of benzyl ether **340** (25 mg, 0.042 mmol) in ethyl acetate (1 mL) was stirred under an atmosphere of hydrogen over palladium on charcoal (10%, 2 mg, 50 mg/mmol). After 1 h (longer reaction times resulted in debromination) the reaction mixture was filtered through celite. The solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent to afford the *title compound* **352** (18 mg, 85%) as a colourless oil; $[\alpha]_D^{20}$ = -171° (c=0.32, $CHCl_3$); [Found (LSIMS): M^+, 500.0833. $C_{25}H_{25}{}^{79}BrO_6$ requires M, 500.0834]; ν_{max} (film) cm^{-1} 3334 (OH), 2936, 2853 (C-H), 1591 (C=C), 1513, 1451 (C-O); δ_H (400 MHz; $CDCl_3$) 1.27 (1H, ddd, J_{gem} 14.7, $J_{8'B,9'}$ 4.8 and $J_{8'B,1'}$ 4.8 Hz, 8'-H_B), 2.18 (1H, ddd, J_{gem} 14.4, $J_{8'A,9'}$ 9.7 and $J_{8'A,1'}$ 2.2 Hz, 8'-H_A), 2.27 (1H, dd, $J_{1',8'B}$ 4.8 and $J_{1',8'A}$ 2.2 Hz, 1'-H), 3.85 (3H, s, 5-OCH_3), 4.04 (3H, s, 8-OCH_3), 4.17 (1H, d, J_{gem} 13.4 Hz, 4'-H_A), 4.36 (1H, d, $J_{5',4'B}$ 5.5 Hz, 5'-H), 4.34 (1H, dd, J_{gem} 13.4 and $J_{4'B,5'}$ 5.5 Hz, 4'-H_B), 4.53 (1H, dd, $J_{9',8'A}$ 9.7 and $J_{9',8'B}$ 4.8 Hz, 9'-H), 5.14 (1H, s, 7'-H), 5.95 (1H, s, 2'-H), 6.80 (1H, s, 6-H), 7.23 (1H, t, J_{ortho} 7.3 Hz, *p*-Ph), 7.32 (2H, t, J_{ortho} 7.3 Hz, *m*-Ph), 7.94 (2H, d, J_{ortho} 7.3 Hz, *o*-Ph), 7.74 (1H, d, $J_{4,3}$ 8.7 Hz, 4-H), 7.94 (1H, d, $J_{3,4}$ 8.7 Hz, 3-H), 9.83 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 25.7 (CH_2, C-8'), 45.4 (CH, C-1'), 55.9 (CH_3, 5-OCH_3), 62.6 (CH_3, 8-OCH_3), 67.2 (CH, C-9'), 70.1 (CH_2, C-4'), 76.4 (CH, C-2'), 80.1 (CH, C-5'), 86.1 (CH, C-7'), 107.7 (CH, C-3), 110.6 (quat., C-7), 113.2 (CH, C-4), 117.6 (quat., C-8a), 125.1 (CH, C-6), 125.4 (CH, *o*-Ph), 126.0, 126.6 (quat., C-2, C-4a), 127.1 (CH, *p*-Ph), 128.1 (CH, *m*-Ph), 142.3 (quat., *ipso*-Ph), 146.0 (quat., C-1), 148.7, 152.8 (quat., C-5, C-8); *m/z* (CI) 501, 499 (M^+, 64%), 423 (M-Br, 100), 397, 395 (27), 345 (25), 297, 295 (21), 255 (20), 219, 217 (20), 61 (18).



352

6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-2-bromo-5-hydroxy-1,4-dimethoxynaphthalene 353

Boron trifluoride diethyl etherate (43 μL, 0.350 mmol) was added dropwise to a stirred solution of 2-bromonaphthol **314** (50 mg, 0.177 mmol) and tri-*O*-benzyl-2-deoxy-D-glucosyl acetate **266** (100 mg, 210 mmol) in dry acetonitrile (5 mL) at 0 °C. The mixture was stirred for 20 min. then quenched with water (5 mL). The reaction mixture was extracted with dichloromethane (3 x 50 mL), washed with water (100 mL) and dried (magnesium sulfate). The solvent was removed at reduced pressure and the oily residue purified by flash chromatography using hexane-ethyl acetate (6:1) as eluent to give the *title compound* **353** (65 mg, 53%) as a colourless glass; $[\alpha]_D^{22}$ = +29.3° (c=0.3, $CHCl_3$); [Found (FAB): M^+, 700.1855, 698.1872. $C_{39}H_{39}BrO_7$ requires M, 700.1859, 698.1879]; ν_{max} (film) cm^{-1} 3384 (OH), 3056, (C-H), 1643 (C=C), 1419 (C-O); δ_H (200 MHz; $CDCl_3$) 1.63 (1H, ddd, J_{gem} 12.9, $J_{2'ax,1'}$ 11.6 and $J_{2'ax,3'}$ 11.6 Hz, 2_{ax}'-H), 2.59 (1H, ddd, J_{gem} 12.9, $J_{2'eq,3'}$ 5.0 and $J_{2'eq,1'}$ 1.0 Hz, 2_{eq}'-H), 3.66-4.02 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.90, 3.98 (each 3H, s, 2 x OCH_3), 4.58-4.74 (5H, m, 5 x C<u>H</u>Ph), 4.97 (1H, d, J_{gem} 10.8 Hz, C<u>H</u>Ph), 4.98 (1H, dd, $J_{1',2'ax}$ 10.0 and $J_{1',2'eq}$ 1.0 Hz, 1'-H), 6.82 (1H, s, 3-H), 7.21-7.41 (15H, m, Ph-H), 7.59 (1H, d, $J_{8,7}$ 8.7 Hz, 8-H), 7.73 (1H, d, $J_{7,8}$ 8.7 Hz, 7-H), 9.47 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 38.5 (CH_2, C-2'), 56.5, 61.1 (CH_3, 2 x OCH_3), 69.6 (CH_2, C-6'), 71.1 (CH_2, <u>C</u>H_2Ph), 71.6 (CH, C-1'), 73.4, 75.0 (CH_2, 2 x <u>C</u>H_2Ph), 78.4, 79.4, 81.3 (CH, C-3', C-4', C-5'), 108.0 (CH, C-7), 111.1 (quat., C-2), 113.3 (CH, C-8), 114.5 (quat., C-4a), 124.0 (quat., C-8a), 126.4 (CH, C-3), 127.4-128.3 (CH, Ph), 130.2 (quat., C-6), 138.5, 138.6, 138.6 (quat., 3 x *ipso*-Ph), 147.8, 150.1, 152.7 (quat., C-1, C-4, C-5); *m/z* (EI) 700, 698 (M^+, 12%), 592, 590 (20), 91 (C_7H_7, 100).



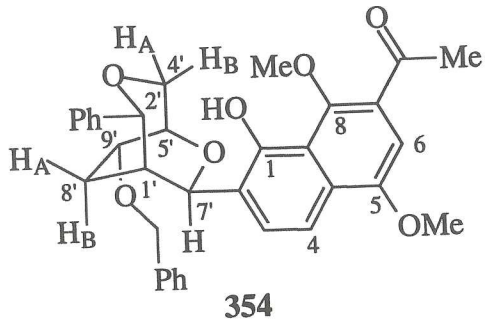
353

3.3.5 Aryl *C*-Glycosylation Using Acetylnaphthols.

(1'*R*,2'*R*,5'*S*,7'*R*,9'*S*)-7-acetyl-2-(9'-benzyloxy-2'-phenyl-3',6'-dioxabicyclo[3.2.2]nonan-7'-yl)-1-hydroxy-5,8-dimethoxynaphthalene 354 and 3-acetyl-6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-1,4-dimethoxynaphthalene 263

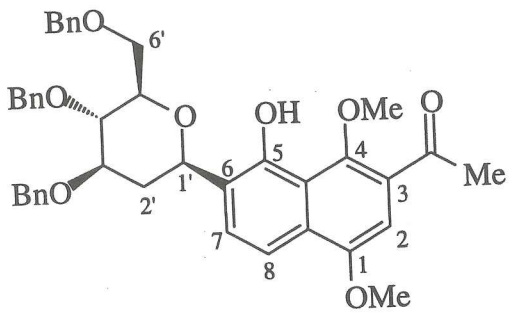
Boron trifluoride diethyl etherate (40 μL, 0.325 mmol) was added dropwise to a stirred solution of tri-*O*-benzyl-2-deoxy-D-glucosyl acetate **266** (93 mg, 0.195 mmol) and 3-acetylnaphthol **264** (40 mg, 0.163 mmol) in dry acetonitrile (3 mL) at 0 °C. The mixture was allowed to stir for 1 h at 0 °C, then quenched with water (2 mL). The crude reaction mixture was extracted with dichloromethane (3 x 25 mL), washed with water (50 mL) and dried (magnesium sulfate). The solvent was removed at reduced pressure and the oily residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give the starting naphthol **264** (24 mg, 60%) as well as a (1:2) mixture of the *β-C-glycoside* **263** and the *rearranged product* **354** (29 mg). These products were separated by semipreparative HPLC (1.5% ^{i}PrOH/hexane, partisil 10 column, 50 cm x 9.4 mm I.D., flow rate 4 mL/min.) to give:

(1'R,2'R,5'S,7'R,9'S)-7-acetyl-2-(9'-benzyloxy-2'-phenyl-3',6'-dioxabicyclo[3.2.2]-nonan-7'-yl)-1-hydroxy-5,8-dimethoxynaphthalene **354** (11 mg, 12%) as a yellow oil; $[\alpha]_D^{22}$ = -147.5° (c=0.24, $CHCl_3$); [Found (EI): M^+, 554.2294. $C_{34}H_{34}O_7$ requires M, 554.2305]; ν_{max} (film) cm^{-1} 3328 (br, OH), 2956, 2917, 2851 (C-H), 1667 (C=O), 1602, 1514 (C=C), 1366 (s, C-O); δ_H (400 MHz; $CDCl_3$) 1.52 (1H, ddd, J_{gem} 14.5, $J_{8'B,1'}$ 4.9 and $J_{8'B,9'}$ 4.8 Hz, 8'-H_B), 2.09 (1H, ddd, J_{gem} 14.5, $J_{8'A,9'}$ 9.7 and $J_{8'A,1'}$ 2.3 Hz, 8'-H_A), 2.29 (1H, dd, $J_{1',8'B}$ 4.9 and $J_{1',8'A}$ 2.3 Hz, 1'-H), 2.76 (3H, s, $COC\underline{H}_3$), 3.96, 3.99 (each 3H, s, 2 x OCH_3), 4.17 (1H, d, J_{gem} 13.5 Hz, 4'-H_A), 4.25 (1H, dd, $J_{9',8'A}$ 9.7 and $J_{9',8'B}$ 4.8 Hz, 9'-H), 4.31 (1H, dd, J_{gem} 13.5 and $J_{4'B,5'}$ 5.3 Hz, 4'-H_B), 4.45 (1H, d, $J_{5',4'B}$ 5.3 Hz, 5'-H), 4.58 (1H, d, J_{gem} 11.9 Hz, C$\underline{H}$Ph), 4.62 (1H, d, J_{gem} 11.9 Hz, C$\underline{H}$Ph), 5.15 (1H, s, 7'-H), 5.98 (1H, s, 2'-H), 6.91 (1H, s, 6-H), 7.24 (1H, t, J_{ortho} 7.4 Hz, *p*-Ph), 7.33 (2H, t, J_{ortho} 7.4 Hz, *m*-Ph), 7.38-7.46 (7H, m, Ph-H), 7.78 (1H, d, $J_{4,3}$ 8.7 Hz, 4-H), 8.21 (1H, d, $J_{3,4}$ 8.7 Hz, 3-H), 9.88 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 22.4 (CH_2, C-8'), 30.5 (CH_3, $CO\underline{C}H_3$), 45.5 (CH, C-1'), 55.8, 65.6 (CH_3, 2 x OCH_3), 70.2 (CH_2, $\underline{C}H_2$Ph), 71.2 (CH_2, C-4'), 73.7 (CH, C-9'), 76.2 (CH, C-2'), 76.6 (CH, C-5'), 86.2 (CH, C-7'), 101.9 (CH, C-3), 112.9 (CH, C-4), 116.6 (quat., C-8a), 125.5 (CH, Ph), 126.4, 126.7 (quat., C-2, C-4a), 127.0, 127.5, 127.6, 128.1, 128.2, 128.4 (CH, Ph, C-6), 129.3 (quat., C-7), 138.6 (quat., *ipso*-Ph), 142.5 (quat., *ipso*-Ph), 150.4, 151.3, 152.4 (quat., C-1, C-5, C-8), 199.6 (quat., $\underline{C}OCH_3$); *m/z* (EI) 554 (M^+, 4%), 285 (17), 91 (C_7H_7, 100).



354

3-acetyl-6-(3',4',6'-tri-O-benzyl-2-deoxy-β-D-arabino-hexopyranosyl)-5-hydroxy-1,4-dimethoxynaphthalene **263** (8 mg, 7%) as a yellow oil; $[\alpha]_D^{22}$ = +40.0° (c=0.40, $CHCl_3$); [Found (EI): M^+, 662.2868. $C_{41}H_{42}O_8$ requires M, 662.2880]; ν_{max} (film) cm^{-1} 3327 (br, OH), 2921, 2853 (C-H), 1672 (C=O), 1604, 1514, 1453 (C=C), 1368 (s, C-O); δ_H (400 MHz; $CDCl_3$) 1.65 (1H, ddd, J_{gem} 12.7, $J_{2'ax,3'}$ 11.5 and $J_{2'ax,1'}$ 11.5 Hz, 2'$_{ax}$-H), 2.57 (1H, ddd, J_{gem} 12.7, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 1.8 Hz, 2'$_{eq}$-H), 2.76 (3H, s, $COC\underline{H}_3$), 3.65-4.20 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.93, 3.99 (each 3H, s, 2 x OCH_3), 4.61 (1H, d, J_{gem} 12.4 Hz, C$\underline{H}$Ph), 4.65 (1H, d, J_{gem} 11.6 Hz, C$\underline{H}$Ph), 4.66 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 4.70 (1H, d, J_{gem} 12.4 Hz, C$\underline{H}$Ph), 4.74 (1H, d, J_{gem} 11.6 Hz, C$\underline{H}$Ph), 4.97 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 5.04 (1H, dd, $J_{1',2'ax}$ 11.4 and $J_{1',2'eq}$ 1.6 Hz, 1'-H), 6.92 (1H, s, 2-H), 7.20-7.50 (15H, m, Ph-H), 7.75 (1H, d, $J_{8,7}$ 8.7 Hz, 8-H), 7.79 (1H, d, $J_{7,8}$ 8.7 Hz, 7-H), 9.78 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 30.5 (CH_3, $CO\underline{C}H_3$), 37.4 (CH_2, C-2'), 55.8, 65.6 (CH_3, 2 x OCH_3), 69.6 (CH_2, C-6'), 71.3 (CH_2, $\underline{C}H_2Ph$), 71.7 (CH, C-1'), 73.4, 75.1 (CH_2, 2 x $\underline{C}H_2Ph$), 78.5, 79.5, 81.4 (CH, C-3', C-4', C-5'), 102.3 (CH, C-2), 113.7 (CH, C-8), 116.8 (quat., C-4a), 124.9, 125.5 (quat., C-3, C-6), 127.1 (CH, C-7), 127.5-128.3 (CH, Ph), 129.4 (quat., C-8a), 138.5, 138.6, 138.6 (quat., 3 x *ipso*-Ph), 150.1, 151.3, 152.3 (quat., C-1, C-4 , C-5), 199.7 (quat., $\underline{C}OCH_3$); *m/z* (EI) 662 (M^+, 0.5%), 554 (1), 272 (12), 91 (C_7H_7, 100).

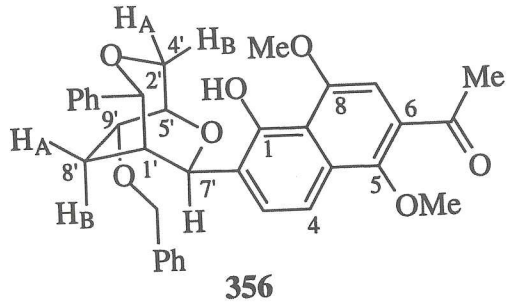


263

(1'*R*,2'*R*,5'*S*,7'*R*,9'*S*)-6-acetyl-2-(9'-benzyloxy-2'-phenyl-3',6'-dioxabicyclo[3.2.2]nonan-7'-yl)-1-hydroxy-5,8-dimethoxynaphthalene 356 and 2-acetyl-6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyran-osyl)-5-hydroxy-1,4-dimethoxynaphthalene 355

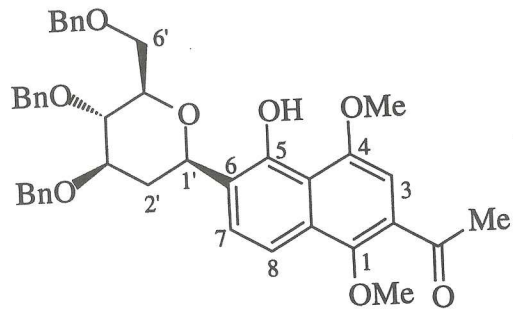
Boron trifluoride diethyl etherate (40 μL, 0.325 mmol) was added dropwise to a stirred solution of tri-*O*-benzyl-2-deoxy-D-glucosyl acetate **266** (93 mg, 0.195 mmol) and 2-acetyl-1,4-dimethoxy-5-hydroxynaphthalene **321** (40 mg, 0.163 mmol) in dry acetonitrile (3 mL) at 0 °C. The mixture was allowed to stir for 1 h at 0 °C then quenched with water (2 mL). The crude reaction mixture was extracted with dichloromethane (3 x 25 mL), washed with water (50 mL) and dried (magnesium sulfate). The solvent was removed at reduced pressure and the oily residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give the starting naphthol **321** (17 mg, 43%) as well as a (1:2) mixture of *β-C-glycoside* **355** and the *rearranged product* **356** (60 mg). These were separated by HPLC (1.5% ^{i}PrOH/hexane, partisil 5 column, r.t. 45 min.) to give:

(1'R,2'R,5'S,7'R,9'S)-6-acetyl-2-(9'-benzyloxy-2'-phenyl-3',6'-dioxabicyclo[3.2.2]-nonan-7'-yl)-1-hydroxy-5,8-dimethoxynaphthalene **356** (21 mg, 23%) as a colourless oil; $[\alpha]_D^{22}$ = -201° (c=0.38, $CHCl_3$); [Found (EI): M^+, 554.2317. $C_{34}H_{34}O_7$ requires M, 554.2305]; ν_{max} (film) cm^{-1} 3366 (br, OH), 2938, 2855 (C-H), 1668 (C=O), 1608 (C=C), 1371 (C-O); δ_H (400 MHz; $CDCl_3$) 1.52 (1H, ddd, J_{gem} 14.3, $J_{8'B,9'}$ 4.7 and $J_{8'B,1'}$ 4.6 Hz, 8'-H_B), 2.09 (1H, ddd, J_{gem} 14.3, $J_{8'A,9'}$ 9.6 and $J_{8'A,1'}$ 2.3 Hz, 8'-H_A), 2.29 (1H, dd, $J_{1',8'B}$ 4.6 and $J_{1',8'A}$ 2.3 Hz, 1'-H), 2.79 (3H, s, $COC\underline{H}_3$), 3.93, 4.11 (each 3H, s, 2 x OCH_3), 4.17 (1H, d, J_{gem} 13.5 Hz, 4'-H_A), 4.26 (1H, dd, $J_{9',8'A}$ 9.6 and $J_{9',8'B}$ 4.7 Hz, 9'-H), 4.31 (1H, dd, J_{gem} 13.5 and $J_{4'B,5'}$ 5.4 Hz, 4'-H_B), 4.46 (1H, d, $J_{5',4'B}$ 5.4 Hz, 5'-H), 4.61 (2H, s, $C\underline{H}_2Ph$), 5.14 (1H, s, 7'-H), 5.94 (1H, s, 2'-H), 7.08 (1H, s, 7-H), 7.24 (1H, t, J_{ortho} 7.4 Hz, *p*-Ph), 7.33 (2H, t, J_{ortho} 7.4 Hz, *m*-Ph), 7.35-7.45 (7H, m, Ph-H), 7.70 (1H, d, $J_{4,3}$ 8.7 Hz, 4-H), 8.21 (1H, d, $J_{3,4}$ 8.7 Hz, 3-H) 9.72 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 23.2 (CH_2, C-8'), 31.6 (CH_3, $CO\underline{C}H_3$), 45.9 (CH, C-1'), 57.1, 64.3 (CH_3, 2 x OCH_3), 71.0 (CH_2, $\underline{C}H_2Ph$), 71.9 (CH_2, C-4'), 74.5 (CH, C-9'), 76.9 (CH, C-2'), 77.2 (CH, C-5'), 86.1 (CH, C-7'), 102.7 (CH, C-3), 114.5 (CH, C-4), 118.1 (quat., C-8a), 126.2 (CH, Ph), 127.0 (quat., C-2), 127.7, 128.0, 128.2, 128.3 (CH, Ph, C-7), 128.4 (quat., C-4a), 128.7, 129.1 (CH, Ph), 130.8 (quat., C-6), 139.3 (quat., *ipso*-Ph), 143.1 (quat., 3 x *ipso*-Ph), 151.3, 153.1, 153.8 (quat., C-1, C-5, C-8), 199.8 (quat., $\underline{C}OCH_3$); *m/z* (EI) 554 (M^+, 3%), 285 (18), 91 (C_7H_7, 100).



356

2-acetyl-6-(3',4',6'-tri-O-benzyl-2'-deoxy-β-D-arabino-hexopyranosyl)-5-hydroxy-1,4-dimethoxynaphthalene **355** (10 mg, 9%) as a colourless oil; $[\alpha]_D^{22}$ = +45.0° (c=0.16, $CHCl_3$); [Found (EI): M^+, 662.2898. $C_{41}H_{42}O_8$ requires M, 662.2880]; ν_{max} (film) cm^{-1} 3359 (br, OH), 2955, 2922, 2863 (C-H), 1668 (C=O), 1610 (C=C), 1454, 1372 (C-O); δ_H (400 MHz; $CDCl_3$) 1.62 (1H, ddd, J_{gem} 12.7, $J_{2'ax,3'}$ 11.4 and $J_{2'ax,1'}$ 11.4 Hz, 2'$_{ax}$-H), 2.62 (1H, ddd, J_{gem} 12.7, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 1.7 Hz, 2'$_{eq}$-H), 2.79 (3H, s, $COC\underline{H}_3$), 3.65-3.92 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.93, 4.08 (each 3H, s, 2 x OCH_3), 4.61 (1H, d, J_{gem} 12.4 Hz, C$\underline{H}$Ph), 4.65 (1H, d, J_{gem} 11.6 Hz, C$\underline{H}$Ph), 4.66 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 4.71 (1H, d, J_{gem} 12.4 Hz, C$\underline{H}$Ph), 4.73 (1H, d, J_{gem} 11.6 Hz, C$\underline{H}$Ph), 4.97 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 5.00 (1H, dd, $J_{1',2'ax}$ 11.4 and $J_{1',2'eq}$ 1.7 Hz, 1'-H), 7.08 (1H, s, 3-H), 7.25-7.40 (15H, m, Ph-H), 7.71 (1H, d, $J_{8,7}$ 8.7 Hz, 8-H), 7.77 (1H, d, $J_{7,8}$ 8.7 Hz, 7-H), 9.65 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 30.9 (CH_3, $CO\underline{C}H_3$), 37.2 (CH_2, C-2'), 56.4, 63.6 (CH_3, 2 x OCH_3), 69.7 (CH_2, C-6'), 71.2 (CH_2, $\underline{C}H_2Ph$), 71.7 (CH, C-1'), 73.4, 75.1 (CH_2, 2 x $\underline{C}H_2Ph$), 78.4, 79.5, 81.3 (CH, C-3', C-4', C-5'), 102.4 (CH, C-3), 114.8 (CH, C-8), 117.5 (quat., C-4a), 126.2 (CH, C-7), 126.3, 126.6 (quat., C-2, C-6), 127.5-128.4 (CH, Ph), 130.2 (quat., C-8a), 138.6, 138.6, 138.6 (quat., 3 x *ipso*-Ph), 150.2, 152.5, 152.9 (quat., C-1, C-4 , C-5), 199.1 (quat., $\underline{C}OCH_3$); *m/z* (EI) 662 (M^+, 0.5%), 554 (0.2), 272 (8), 181 (5), 149 (7), 91 (C_7H_7, 100).



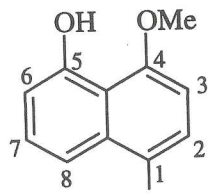
355

3.4 Synthesis of Acetylnaphthoquinone 262.

5-hydroxy-1,4-dimethoxynaphthalene 247

(i) From juglone 75 using sulphuric acid and methanol.[201]

Concentrated sulphuric acid (12.5 mL) was added slowly to ice-cooled dry methanol (75 mL). Anhydrous tin(II) chloride (7.50 g, 39.6 mmol) was then added and the mixture left for 2 min. before the addition of juglone **75** (1.50 g, 8.62 mmol) and benzene (200 mL). The mixture was heated at reflux for 3 days after which time most of the solvent was removed under reduced pressure. The mixture was then poured onto water and extracted with dichloromethane (3 x 200 mL). The extracts were washed with water (3 x 600 mL) and dried (magnesium sulfate). The crude material was then purified by flash chromatography using dichloromethane as eluent. The product, 5-hydroxy-1,4-dimethoxynaphthalene **247** (756 mg, 43%) was obtained as a pale green solid. Recrystallization from ethanol gave fine white needles, m.p. 101-102 °C (lit.[202] m.p. 103-104 °C); ν_{max} (film) cm^{-1} 3342 (OH), 2936, 2834 (C-C), 1630, 1613 (C=C), 1517, 1462, 1451, 1400 (C-O); δ_H (200 MHz; $CDCl_3$) 3.94, 4.02 (each 3H, s, 2 x OCH_3), 6.56 (1H, d, $J_{3,2}$ 8.0 Hz, 3-H), 6.68 (1H, d, $J_{2,3}$ 8.0 Hz, 2-H), 6.92 (1H, dd, $J_{6,7}$ 7.7 and $J_{6,8}$ 1.0 Hz, 6-H), 7.37 (1H, dd, $J_{7,8}$ 8.3 and $J_{7,6}$ 7.7 Hz, 7-H), 7.71 (1H, dd, $J_{8,7}$ 8.3 and $J_{8,6}$ 1.0 Hz, 8-H); *m/z* (EI) 204 (M^+, 12%), 149 (100).



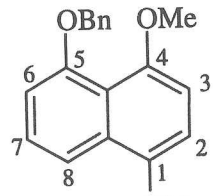
247

(ii) From juglone 75 via 324, 325 and 316.

5-benzyloxy-1,4-dimethoxynaphthalene 316

Juglone benzyl ether **324** (3.56 g, 13.5 mmol) (prepared previously) was dissolved in dichloromethane-diethyl ether (1:3) (300 mL) and shaken with a freshly prepared solution of sodium dithionite (17.5 g, 101 mmol) in water (200 mL) for 10 min. The organic layer was separated, washed with brine (140 mL), dried (magnesium sulfate) and the solvent removed at reduced pressure to give the crude hydroquinone **325** as a pale brown oil. This was dissolved in dry acetone (75 mL) and transferred by double-

ended needle to a reaction vessel containing a stirred suspension of potassium carbonate (22 g, 160 mmol) in dry acetone (220 mL). Dimethyl sulfate (6.36 mL, 67 mmol) was added in one portion and the solution heated at reflux for 48 h. The mixture was then cooled, filtered through celite and the solvent removed at reduced pressure. The resultant red oil was dissolved in diethyl ether (170 mL) and stirred with triethylamine (10.3 mL, 74 mmol). After 20 min. the solution was washed with hydrochloric acid (1 M, 2 x 85 mL), water (85 mL) and brine (85 mL). It was then dried (sodium sulfate) and concentrated *in vacuo* to give an oily residue that was purified by flash chromatography using hexane-ethyl acetate (6:1) as eluent to afford 5-benzyloxy-1,4-dimethoxynaphthalene **316** (3.33 g, 84%) as tan needles, m.p. 108-109 °C (lit.[222,223] m.p. 108-109 °C); δ_H (200 MHz; $CDCl_3$) 3.88, 3.94 (each 3H, s, 2 x OCH_3), 5.20 (2H, s, $C\underline{H}_2Ph$), 6.74 (1H, d, $J_{3,2}$ 8.4 Hz, 3-H), 6.79 (1H, d, $J_{2,3}$ 8.4 Hz, 2-H), 6.99 (1H, dd, $J_{6,7}$ 7.5, $J_{6,8}$ 1.0 Hz, 6-H), 7.23-7.42 (4H, m, 7-H, Ph-H), 7.59 (2H, d, J_{ortho} 7.5 Hz, *o*-Ph), 7.89 (1H, dd, $J_{8,7}$ 8.6 and $J_{8,6}$ 1.0 Hz, 8-H); δ_C (50 MHz; $CDCl_3$) 55.8, 57.2 (CH_3, 2 x OCH_3), 71.6 (CH_2, $\underline{C}H_2Ph$), 104.2, 106.8, 109.6, 115.2 (CH, C-2, C-3, C-6, C-7), 119.0 (quat., C-4a), 125.9 (CH, C-8), 127.0 (CH, *o*-Ph), 127.5 (CH, *p*-Ph), 128.3 (CH, *m*-Ph), 128.9 (quat., C-8a), 137.6 (quat., *ipso*-Ph), 149.5, 151.0, 155.7 (quat., C-1, C-4, C-5); *m/z* (EI) 294 (M^+, 13%), 91 (C_7H_7, 100). The data was in agreement with the literature.[222,223]



316

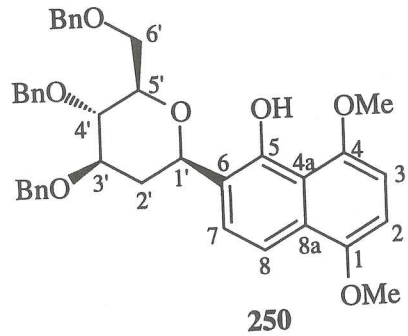
5-hydroxy-1,4-dimethoxynaphthalene 247

A solution of benzyl ether **316** (1.21 g, 4.11 mmol) in ethyl acetate (15 mL) was stirred under an atmosphere of hydrogen over palladium on charcoal (10%, 206 mg, 50 mg/mmol). After 4 h the reaction was complete. The mixture was filtered through celite and the solvent removed at reduced pressure. The crude green oil was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford the title compound **247** (823 mg, 98%) as a pale green solid. Recrystallization from ethanol gave fine white needles, m.p. 101-102 °C (lit.[202] m.p. 103-104 °C). The data for **247** was identical to that for **247** prepared by the previous method.

6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-1,4-dimethoxynaphthalene 250[161]

*(i) Using acetate **266**.*

Boron trifluoride diethyl etherate (241 μL, 1.96 mmol) was added dropwise to a solution of naphthol **247** (200 mg, 0.980 mmol) and 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucosyl acetate **266** (562 mg, 1.18 mmol) in dry acetonitrile (18 mL) at 0 °C. The mixture was stirred for 20 min. then quenched with water (5 mL). The reaction mixture was extracted with dichloromethane (3 x 150 mL), washed with water (250 mL) and dried (magnesium sulfate). The solvent was removed at reduced pressure and the oily residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give 6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-1,4-dimethoxynaphthalene **250** (444 mg, 73%) as a colourless oil, $[\alpha]_D^{22}$ = +45.6° (c=1.14, $CHCl_3$) {lit.[161] $[\alpha]_D^{25}$ = +33.13° (c=0.32, CH_2Cl_2)}; ν_{max} (film) cm^{-1} 3384 (OH), 3056, (C-H), 1643 (C=C), 1419 (C-O); δ_H (200 MHz; $CDCl_3$) 1.63 (1H, ddd, J_{gem} 12.8, $J_{2'ax,1'}$ 11.0 and $J_{2'ax,3'}$ 11.0 Hz, 2'$_{ax}$-H), 2.59 (1H, ddd, J_{gem} 12.8, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 1.8 Hz, 2'$_{eq}$-H), 3.65-4.00 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.99, 4.01 (each 3H, s, 2 x OCH_3), 4.60-4.78 (5H, m, 5 x C<u>H</u>Ph), 4.98 (1H, d, J_{gem} 10.7 Hz, C<u>H</u>Ph), 5.01 (1H, dd, $J_{1',2'ax}$ 11.0 and $J_{1',2'eq}$ 1.8 Hz, 1'-H), 6.61 (1H, d, $J_{3,2}$ 8.4 Hz, 3-H), 6.68 (1H, d, $J_{2,3}$ 8.4 Hz, 2-H), 7.20-7.43 (15H, m, Ph-H), 7.65 (1H, d, $J_{8,7}$ 8.7 Hz, 8-H), 7.74 (1H, d, $J_{7,8}$ 8.7 Hz, 7-H), 9.76 (1H, s, OH); δ_C (50 MHz; $CDCl_3$) 37.4 (CH_2, C-2'), 55.7, 56.4 (CH_3, 2 x OCH_3), 69.7 (CH_2, C-6'), 71.1 (CH, C-1'), 71.8, 73.4, 75.0 (CH_2, 3 x <u>C</u>H_2Ph), 78.5, 79.5, 81.4 (CH, C-3', C-4', C-5'), 102.8, 103.6 (CH, C-2, C-3), 113.2 (CH, C-7), 115.1 (quat., C-4a), 123.7 (quat., C-8a), 124.8 (CH, C-8), 127.4-128.3 (CH, Ph), 138.6, 138.7, 138.7 (quat., 3 x *ipso*-Ph), 149.6, 150.0, 150.2 (quat., C-1, C-4, C-5); *m/z* (EI) 620 (M^+, 12%), 91 (C_7H_7, 100). The data was in agreement with that reported in the literature.[161]



250

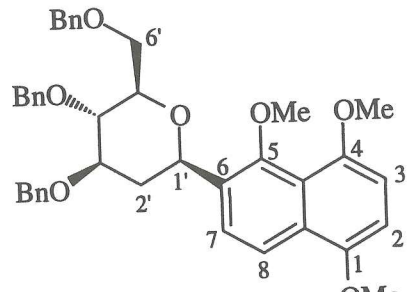
(ii) Using trifluoroacetate 217.

Trifluoroacetic anhydride (235 uL, 1.67 mmol) was added to a stirred solution of 3,4,6-tri-*O*-benzyl-2-deoxy-D-hexopyranose **266** (511 mg, 1.18 mmol) and dry acetonitrile (10 mL). After 1 h, naphthol **247** (200 mg, 0.98 mmol) dissolved in acetonitrile (8 mL) was added to the reaction mixture. After cooling to 0 °C, boron trifluoride diethyl etherate (120 mg, 0.98 mmol) was added to the stirred solution. The mixture was stirred for 20 min. and then quenched with water (10 mL). The crude reaction mixture was extracted with dichloromethane (3 x 150 mL) and washed with water (250 mL). The combined organic fractions were dried (magnesium sulfate) and the solvent removed at reduced pressure. Purification of the residue by flash chromatography using hexane-ethyl acetate (4:1) as eluent afforded the *C*-glycoside **250** (432 mg, 71%) as a colourless oil.

6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-1,4,5-trimethoxynaphthalene 361

A slurry of sodium hydride (60 mg, 2.52 mmol) in dry dimethylformamide (2 mL) was added to a stirred solution of the *C*-glycosylnaphthol **250** (1.04 g, 1.68 mmol) in dimethylformamide (15 mL) at 0 °C. After an interval of 5 min. iodomethane (0.54 mL, 16.8 mmol) was added and the mixture allowed to warm to room temperature and stirred overnight. The solvent was removed at reduced pressure and the mixture redissolved in dichloromethane (50 mL). This was washed with water (50 mL) and the aqueous layer extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried (magnesium sulfate) and the solvent removed at reduced pressure. The crude product was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *6-(3',4',6'-tri-O-benzyl-2'-deoxy-β-D-arabino-hexopyranosyl)-1,4,5-trimethoxynaphthalene* **361** (904 mg, 85%) as a tan oil; $[\alpha]_D^{19}$ = +13.9° (c=0.718, $CHCl_3$); (Found: C, 75.26; H, 7.08. $C_{40}H_{42}O_7$ requires C, 75.67; H, 6.67%); ν_{max} (film) cm^{-1} 2925, 2863 (C-H), 1621, 1602, 1584 (C=C), 1453 (C-O); δ_H (200 MHz; $CDCl_3$) 1.74 (1H, ddd, J_{gem} 12.5, $J_{2'ax,1'}$ 11.5 and $J_{2'ax,3'}$ 11.5 Hz, 2'$_{ax}$-H), 2.51 (1H, ddd, J_{gem} 12.5, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 1.6 Hz, 2'$_{eq}$-H), 3.55-3.95 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.82, 3.89, 3.92 (each 3H, s, 3 x OCH_3), 4.54-4.73 (5H, m, 5 x C<u>H</u>Ph), 4.90 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 4.91 (1H, br.d, $J_{1,2}$ 9.9 Hz, 1'-H), 6.63 (1H, d, $J_{3,2}$ 8.5 Hz, 3-H), 6.69 (1H, d, $J_{2,3}$ 8.5 Hz, 2-H), 7.16-7.37 (15H, m, Ph-H), 7.59 (1H, d, $J_{8,7}$ 8.9v Hz, 8-H), 7.99 (1H, d, $J_{7,8}$ 8.9 Hz, 7-H); δ_C (50 MHz; $CDCl_3$) 38.3 (CH_2, C-2'), 55.7, 56.6 (CH_3, 1-OCH_3, 4-OCH_3), 62.9 (CH_3, 5-OCH_3), 69.6 (CH_2, C-6'), 71.2 (CH_2, <u>C</u>H_2Ph), 72.2 (CH, C-1'), 73.3, 75.0 (CH_2, 2 x <u>C</u>H_2Ph), 78.3, 79.5, 81.4 (CH, C-3', C-4', C-5'), 103.7 (CH, C-3), 106.0 (CH, C-2), 118.6 (CH, C-7), 120.4 (quat.,

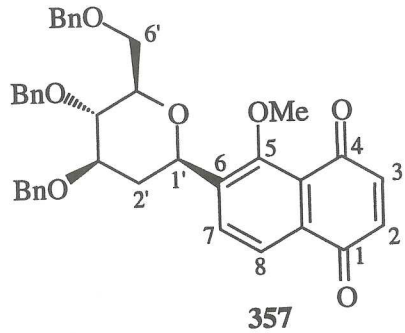
C-4a), 124.2 (CH, C-8), 127.4-128.4 (CH, Ph), 128.4 (quat., C-8a), 132.1 (quat., C-6), 138.6, 138.6, 138.7 (quat., 3 x *ipso*-Ph), 149.8, 149.8, 152.3 (C-1, C-4, C-5); *m/z* (EI) 634 (M^+, 50%), 526 (50), 436 (18), 294 (10), 189 (13), 105 (52), 91 (C_7H_7, 100).



361

6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone 357

A solution of ceric ammonium nitrate (1.49 g, 2.72 mmol) in water (1 mL) was added dropwise to a stirred solution of *C*-glycosylnaphthalene **361** (863 mg, 1.36 mmol) in acetonitrile (15 mL). The reaction mixture was allowed to stir for 0.5 h then diluted with dichloromethane (50 mL) and washed with water (50 mL). The combined organic extracts were dried (magnesium sulfate) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent to afford *6-(3',4',6'-tri-O-benzyl-2'-deoxy-β-D-arabino-hexopyranosyl)-5-methoxy-1,4-naphthoquinone* **357** (765 mg, 93%) as an orange oil; $[\alpha]_D^{19}$ = -29.6° (c=1.02, $CHCl_3$); [Found (FAB): M^+, 604.2453. $C_{38}H_{36}O_7$ requires M, 604.2461]; ν_{max} (film) cm^{-1} 3029, 2919, 2864 (C-H), 1665 (C=O, quin.) 1496, 1453, 1362, 1288 (C-O), 1090; δ_H (200 MHz; $CDCl_3$) 1.51 (1H, ddd, J_{gem} 12.5, $J_{2'ax,1}$ 11.4, and $J_{2'ax,3}$ 11.4 Hz, $2'_{ax}$-H), 2.52 (1H, ddd, J_{gem} 12.5, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 1.6 Hz, $2'_{eq}$-H), 3.53-4.01 (5H, m, 3'-H, 4'-H, 5'-H, 6-H_A, 6-H_B), 3.87 (3H, s, OCH_3), 4.75-4.95 (5H, m, 5 x C<u>H</u>Ph), 4.81 (1H, dd, $J_{1',2'ax}$ 11.4 and $J_{1',2'eq}$ 1.6 Hz, 1'-H), 4.96 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 6.88 (1H, d, $J_{3,2}$ 10.3 Hz, 3-H), 6.94 (1H, d, $J_{2,3}$ 10.3 Hz, 2-H), 7.21-7.37 (15H, m, Ph-H), 7.94 (2H, s, 8-H and 7-H); δ_C (50 MHz; $CDCl_3$) 37.8 (CH_2, C-2'), 62.4 (CH_3, OCH_3), 69.6 (CH_2, C-6'), 71.3, 73.3, 75.0 (CH_2, 3 x <u>C</u>H_2Ph), 71.9 (CH, C-1'), 78.0, 79.3, 80.9 (CH, C-3', C-4', C-5'), 123.2, 132.5 (CH, C-2, C-3), 123.4 (quat., C-4a), 127.6 (CH, *o*-Ph), 127.9 (CH, *p*-Ph), 128.7 (CH, *m*-Ph), 133.0 (quat., C-8a), 136.9, 140.3 (CH, C-7, C-8), 138.2, 138.3, 138.4 (quat., 3 x *ipso*-Ph), 143.5 (quat., C-6), 156.5 (quat., C-5), 184.4, 184.7 (quat., C-1, C-4); *m/z* (EI) 606 (MH_2^+, 4%), 604 (M^+, 2), 513 (7), 498 (2), 407 (47), 299 (8), 215 (7), 91 (C_7H_7, 100).

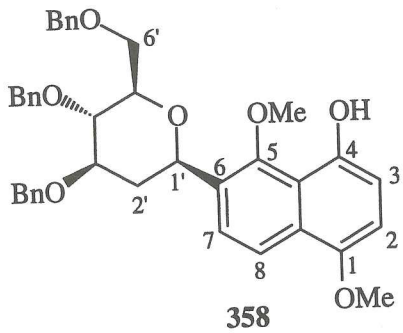


357

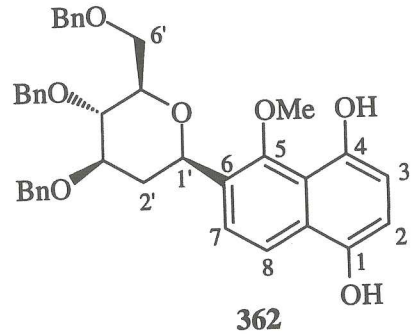
6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-4-hydroxy-1,5-dimethoxynaphthalene 358

C-Glycosylnaphthoquinone **357** (765 mg, 1.27 mmol) was dissolved in dichloromethane-diethyl ether (1:3) (100 mL) and shaken with a solution of sodium dithionite (1.545 g, 8.88 mmol) in water (100 mL) for 10 min. The organic layer was washed with water (50 mL), dried (magnesium sulfate) and the solvent removed under reduced pressure to give the crude hydroquinone **362** as a brown foam. This was dissolved in dry acetone (20 mL) and transferred by double-ended needle to a reaction vessel containing potassium carbonate (875 mg, 6.33 mmol) and dry acetone (5 mL). Dimethyl sulfate (360 μL, 3.80 mmol) was added, the mixture stirred and heated at reflux until the reaction was complete (2-3 h). The mixture was then cooled, filtered through celite and the solvent removed at reduced pressure. The residue was dissolved in diethyl ether (50 mL) and stirred with triethylamine (706 μL, 5.07 mmol). After 20 min. the solution was washed with hydrochloric acid (1 M, 2 x 50 mL), water (50 mL) and brine (50 mL). It was then dried (sodium sulfate) and concentrated *in vacuo* to give an oily residue that was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford *6-(3',4',6'-tri-O-benzyl-2'-deoxy-β-D-arabino-hexopyranosyl)-4-hydroxy-1,5-dimethoxynaphthalene* **358** (643 mg, 82%) as a tan oil; $[\alpha]_D^{19}$ = +1.08° (c=0.372, $CHCl_3$); (Found: C, 74.83; H, 6.36. $C_{39}H_{40}O_7$ requires C, 75.45; H, 6.50%); ν_{max} (film) cm^{-1} 3381 (br, OH), 3029, 2925, 2863 (C-H), 1634, 1608 (C=C), 1496, 1469, 1452, 1409, 1355 (C-O); δ_H (400 MHz; $CDCl_3$) 1.95 (1H, ddd, J_{gem} 13.0, $J_{2'ax,1'}$ 11.5 and $J_{2'ax,3'}$ 11.5 Hz, 2'$_{ax}$-H), 2.32 (1H, ddd, J_{gem} 13.0, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 1.9 Hz, 2'$_{eq}$-H), 3.68-4.00 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.92, 3.92 (each 3H, s, 2 x OCH_3), 4.53, 4.62 (each 1H, d, J_{gem} 12.3 Hz, 2 x C<u>H</u>Ph), 4.65 (1H, d, J_{gem} 11.7 Hz, C<u>H</u>Ph), 4.66 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 4.72 (1H, d, J_{gem} 11.7 Hz, C<u>H</u>Ph), 4.89 (1H, dd, $J_{1',2'ax}$ 11.5 and $J_{1',2'eq}$ 1.9 Hz, 1'-H), 4.98 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 6.74 (1H, d, $J_{3,2}$ 8.4 Hz, 3-H), 6.82 (1H, d, $J_{2,3}$ 8.4 Hz, 2-H), 7.23-7.34 (15H, m, Ph-H), 7.57 (1H, d, $J_{8,7}$ 8.9 Hz, 8-H), 8.05 (1H, d, $J_{7,8}$ 8.9 Hz, 7-H), 8.94 (1H, s, OH); δ_C

(100 MHz; $CDCl_3$) 37.6 (CH_2, C-2'), 55.9 (CH_3, 1-OCH_3), 64.3 (CH_3, 5-OCH_3), 69.6 (CH_2, C-6'), 71.4 (CH, C-1'), 71.5, 73.4, 75.1 (CH_2, 3 x $\underline{C}H_2Ph$), 78.3, 79.8, 81.3 (CH, C-3', C-4', C-5'), 106.0 (CH, C-3), 109.5 (CH, C-2), 117.0 (quat., C-4a), 119.9 (CH, C-7), 124.3 (CH, C-8), 127.5-128.4 (CH, Ph, quat., C-8a), 129.3 (quat., C-6), 138.4, 138.4, 138.5 (quat., 3 x *ipso*-Ph) 147.0, 148.5, 152.5 (quat., C-1, C-4, C-5) *m/z* (EI) 620 (M^+, 20%), 230 (30), 91 (C_7H_7, 100).



358

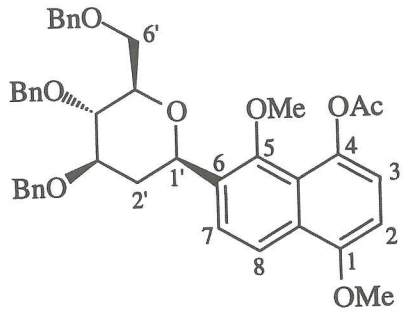


362

4-acetoxy-6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-1,5-dimethoxynaphthalene 363

Triethylamine (128 μL, 0.919 mmol), acetic anhydride (58 μL, 0.613 mmol) and a catalytic quantity of DMAP were added to a solution of **358** (190 mg, 0.306 mmol) in dichloromethane (10 mL). The solution was stirred overnight and then the solvent removed at reduced pressure. The residue was purified by flash chromatography using hexane-ethyl acetate (4:1) to give *4-acetoxy-6-(3',4',6'-tri-O-benzyl-2'-deoxy-β-D-arabino-hexopyranosyl)-1,5-dimethoxynaphthalene* **363** (172 mg, 85%) as a tan oil; (Found C, 74.12; H, 6.45. $C_{41}H_{42}O_8$ requires C, 74.30; H, 6.39%); ν_{max} (film) cm^{-1} 2927, 2862 (C-H), 1759 (C=O, ester), 1603 C=C), 1352, 1207 (C-O); δ_H (400 MHz; $CDCl_3$) 1.77 (1H, ddd, J_{gem} 13.1, $J_{2'ax,1'}$ 11.6 and $J_{2'ax,3'}$ 11.6 Hz, 2'$_{ax}$-H), 2.26 (1H, ddd, J_{gem} 13.1, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,1'}$ 1.9 Hz, 2'$_{eq}$-H), 2.90 (3H, s, $COC\underline{H}_3$), 3.50-3.90 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.73, 3.90 (each 3H, s, 2 x OCH_3), 4.47 (1H, d, J_{gem} 12.3 Hz, C$\underline{H}$Ph), 4.55-4.59 (3H, m, 3 x C$\underline{H}$Ph), 4.64 (1H, d, J_{gem} 11.6 Hz, C$\underline{H}$Ph), 4.87 (1H, dd, $J_{1',2'ax}$ 11.6 and $J_{1',2'eq}$ 1.9 Hz, 1'-H), 4.90 (1H, d, J_{gem} 11.0 Hz, C$\underline{H}$Ph), 6.68 (1H, d, $J_{3,2}$ 8.3 Hz, 3-H), 6.94 (1H, d, $J_{2,3}$ 8.3 Hz, 2-H), 7.17-7.26 (15H, m, Ph-H), 7.56 (1H, d, $J_{8,7}$ 8.9 Hz, 8-H), 8.03 (1H, d, $J_{7,8}$ 8.9 Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 20.8 (CH_3, $COC\underline{H}_3$), 37.9 (CH_2, C-2'), 55.8, 63.2 (CH_3, 2 x OCH_3), 69.7 (CH_2, C-6'), 71.4 (CH_2, $\underline{C}H_2Ph$), 71.7 (CH, C-1'), 73.4, 75.1 (CH_2, 2 x $\underline{C}H_2Ph$), 78.5, 79.7, 81.4 (CH, C-3', C-4', C-5'), 103.5 (CH, C-2), 119.4, 119.4 (CH, C-3, C-7), 121.7 (quat., C-4a), 124.6 (CH, C-8), 127.4-128.4 (CH, Ph, quat., C-8a), 132.3 (quat., C-6), 138.6 (quat., C-4), 138.6, 138.7, 138.8 (quat., 3 x *ipso*-Ph), 151.4, 153.8 (quat., C-1,

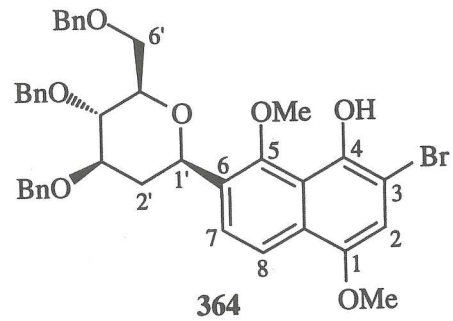
C-5), 170.1 (quat., $\underline{C}OCH_3$); *m/z* (EI) 662 (M^+, 4%), 620 (M-$COCH_3$, 1), 230 (26), 91 (C_7H_7, 100).



6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-4-hydroxy-1,5-dimethoxynaphthalene 364

A solution of bromine (148 mg, 0.92 mmol) in carbon tetrachloride (1.0 mL) was added dropwise to a stirred solution of *C*-glycosylnaphthol **358** (477 mg, 0.77 mmol) in carbon tetrachloride (4.0 mL) at 0 °C. The reaction mixture was allowed to stir for a further 5 min. then quenched with saturated aqueous sodium thiosulfate solution (5 mL) and diluted with dichloromethane (50 mL). The organic layer was washed with water (50 mL) and the aqueous layer extracted twice with dichloromethane (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed at reduced pressure. The crude product was purified by flash column chromatography using hexane-ethyl acetate (4:1) as eluent to afford *6-(3',4',6'-tri-O-benzyl-2'-deoxy-β-D-arabino-hexopyranosyl)-3-bromo-4-hydroxy-1,5-dimethoxynaphthalene* **364** as a pale brown solid (416 mg, 77%) which was recrystallized from hexane-ethyl acetate to give tan needles, m.p. 116-117 °C; $[\alpha]_D^{19}$ = -4.06° (c=0.394, $CHCl_3$); (Found: C, 66.90; H, 5.41. $C_{39}H_{39}BrO_7$ requires C, 66.95; H, 5.62%); ν_{max} (film) cm^{-1} 3329 (br, OH), 3029, 2862 (C-H), 1663, 1604 (C=C), 1496, 1453, 1403, 1352 (C-O); δ_H (400 MHz; $CDCl_3$) 1.86 (1H, ddd, J_{gem} 13.0 and $J_{2'ax,1'}$ 11.5 and $J_{2'ax,3'}$ 11.5 Hz, 2'$_{ax}$-H), 2.23 (1H, ddd, J_{gem} 13.0, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 1.8 Hz, 2'$_{eq}$-H), 3.59-3.87 (5H, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_A), 3.85, 3.85 (each 3H, s, 2 x OCH_3), 4.45, 4.53 (each 1H, d, J_{gem} 12.2 Hz, 2 x C$\underline{H}$Ph), 4.58 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 4.58 (1H, d, J_{gem} 11.7 Hz, C$\underline{H}$Ph), 4.64 (1H, d, J_{gem} 11.7 Hz, C$\underline{H}$Ph), 4.80 (1H, dd, $J_{1',2'ax}$ 11.5 and $J_{1',2'eq}$ 1.8 Hz, 1'-H), 4.90 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 6.85 (1H, s, H-2), 7.17-7.26 (15H, m, Ph-H), 7.52 (1H, d, $J_{8,7}$ 8.9 Hz, H-8), 7.94 (1H, d, $J_{7,8}$ 8.9 Hz, H-7), 9.53 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 37.6 (CH_2, C-2'), 56.0, 64.6 (CH_3, 2 x OCH_3), 69.6 (CH_2, C-6'), 71.4 (CH_2, $\underline{C}H_2Ph$), 71.5 (CH, C-1'), 73.4, 75.1 (2 x $\underline{C}H_2Ph$), 78.3, 79.8, 81.2 (CH, C-3', C-4', C-5'), 103.5 (quat., C-3), 109.9 (CH, C-2), 117.6 (quat., C-4a), 120.1, 124.8 (CH, C-7, C-8), 127.0 (quat., C-8a), 127.5-128.4 (CH, Ph), 130.5 (quat., C-6), 138.3, 138.4,

138.5 (quat., 3 x *ipso*-Ph), 143.5, 148.5, 151.9 (quat., C-1, C-4, C-5); *m/z* (EI) 700, 698 (M^+, 3%), 621 (14), 530 (6), 309 (14), 230 (30), 91 (C_7H_7, 100).



364

6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene 365

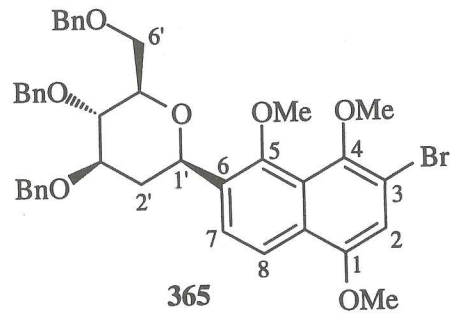
(i) Using sodium hydride/hydrogen atmosphere.

To a solution of *C*-glycosylbromonaphthol **364** (251 mg, 0.359 mmol) in dimethylformamide (5 mL) at 0 °C (which had been degassed and flushed with nitrogen) was added dropwise with stirring a slurry of oil free sodium hydride (17 mg, 0.718 mmol) in dimethylformamide (1 mL) followed by dimethyl sulfate (68 μL, 0.718 mmol). The reaction mixture was allowed to stir for 5 min. then quenched with water (5 mL), extracted with dichloromethane (3 x 50 mL) and the combined organic extracts washed with water (50 mL). The organic phase was dried (magnesium sulfate), the solvent evaporated at reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford the *title compound* **365** (177 mg, 69%) as a colourless oil;

(ii) Using sodium hydroxide.

To a solution of *C*-glycosylbromonaphthol **364** (250 mg, 0.358 mmol) in dimethylformamide (5 mL) at 0 °C was added dimethyl sulfate (68 μL, 0.715 mmol) followed by aqueous sodium hydroxide solution (2M, 1.79 mL). The mixture was stirred for 0.5 h at room temperature and then quenched with dilute aqueous ammonium hydroxide solution (2M, 5 mL). The mixture was extracted with dichloromethane (3 x 150 mL), washed with water (100 mL) and dried (sodium sulfate). The solvent was removed at reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford the *title compound* **365** (214 mg, 84%) as a colourless oil;

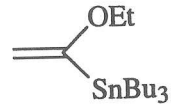
$[\alpha]_D^{19}$ = +11.4° (c=0.980, $CHCl_3$); [Found (FAB): M^+, 712.2027. $C_{40}H_{41}{}^{79}BrO_7$ requires M, 712.2036]; ν_{max} (film) cm^{-1} 2927, 2861 (C-H), 1587 (C=C), 1496, 1452, 1408, 1360, 1328 (C-O); δ_H (400 MHz; $CDCl_3$) 1.74 (1H, ddd, J_{gem} 13.0, $J_{2'ax,1'}$ 11.5 and $J_{2'ax,3'}$ 11.5 Hz, 2'$_{ax}$-H), 2.51 (1H, ddd, J_{gem} 13.0, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 1.8 Hz, 2'$_{eq}$-H), 3.60-3.87 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.88, 3.75, 3.76 (each 3H, s, 3 x OCH_3), 4.50 (1H, d, J_{gem} 12.3 Hz, C<u>H</u>Ph), 4.56-4.67 (4H, m, 4 x C<u>H</u>Ph) 4.90 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 4.94 (1H, dd, $J_{1',2'ax}$ 11.5 and $J_{1',2'eq}$ 1.8 Hz, 1'-H), 6.85 (1H, s, 2-H), 7.17-7.27 (15H, m, Ph-H), 7.59 (1H, d, $J_{8,7}$ 8.8 Hz, 8-H), 8.00 (1H, d, $J_{7,8}$ 8.8 Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 38.5 (CH_2, C-2'), 55.9, 61.9, 63.4 (CH_3, 3 x OCH_3), 69.6 (CH_2, C-6'), 71.5 (CH_2, <u>C</u>H_2Ph), 71.9 (CH, C-1'), 73.4, 75.1 (CH_2, 2 x <u>C</u>H_2Ph), 78.4, 79.6, 81.4 (CH, C-3', C-4', C-5'), 108.6 (CH, C-2), 114.9 (quat., C-3), 119.2 (CH, C-7), 124.6 (CH, C-8), 123.1 (quat., C-4a), 127.5-128.4 (CH, Ph), 127.8 (quat., C-8a), 133.3 (quat., C-6), 138.5, 138.6, 138.6 (quat., 3 x *ipso*-Ph), 145.7, 152.2, 152.2 (quat., C-1, C-4, C-5); *m/z* (EI) 714, 712 (M^+, 34%), 624, 622 (M-C_7H_7, 12), 324 (30), 309 (21), 279 (48), 167 (16), 149 (42), 105 (17), 91 (C_7H_7, 100).



365

(α-ethoxyvinyl)tributyltin 368[206]

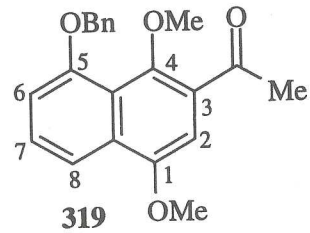
Ethyl vinyl ether **369** (100 mmol) was dissolved in tetrahydrofuran (450 mL) at -78 °C. *tert*-Butyllithium (12 mL, 2.0 M, 75 mmol) was added dropwise over 90 min. The mixture was slowly allowed to warm to 0 °C over 3 h and subsequently recooled to -78 °C. Tributyltin chloride (16.3 g, 50 mmol) was then added dropwise and the mixture allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution, extracted with water (6 x 5 mL), dried (potassium carbonate) and distilled to give the title compound **368** (13.0 g, 85%) as a colourless oil, b.p. 105-107 °C (0.4 mmHg) [lit.[206] b.p. 106 °C (0.4 mmHg)]; ν_{max} (film) cm^{-1} 1575 (C=C); δ_H (200 MHz; $CDCl_3$) 0.77-1.03 (30H, m, 3 x *n*-Bu and C<u>H</u>$_3$CH_2O-), 3.60 (2H, q, J_{vic} 8 Hz, CH_3C<u>H</u>$_2$O-) 4.30, 4.83 (each 1H, d, J_{gem} 2 Hz, 2 x vinylic-H). The data was in agreement with the literature.[206]



368

3-acetyl-5-benzyloxy-1,4-dimethoxynaphthalene 319

A mixture of α-ethoxyvinyltributyltin **368** (306 mg, 1.00 mmol), bromonaphthalene **306** (340 mg, 0.911 mmol), dichlorobis(triphenylphosphine)palladium (6 mg, 0.009 mmol) and dry toluene (5 mL) was heated at 100 °C for 20 h. After hydrolysis of the reaction mixture by dilution with dichloromethane (5 mL) and stirring with hydrochloric acid (1 M, 2 mL) for 0.5 h, the organic layer was extracted with diethyl ether and dried (sodium sulfate). The solvent was removed at reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford the title compound **319** (297 mg, 97 %) as a pale yellow oil. The spectroscopic data was identical to that for **319** prepared previously.

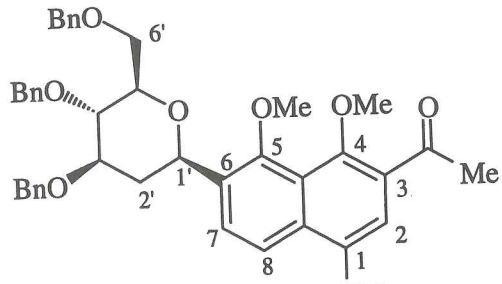


319

3-acetyl-6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-1,4,5-trimethoxynaphthalene 367

A mixture of α-ethoxyvinyltributyltin **368** (52 mg, 0.171 mmol), *C*-glycosylbromonaphthalene **365** (111 mg, 0.156 mmol), dichlorobis-(triphenylphosphine)palladium (11 mg, 1.56 x 10^{-2} mmol) and dry toluene (2 mL) was heated at 100 °C. Over the course of 20 h, two more portions of **368** (52 mg, 0.171 mmol) and the palladium catalyst (11 mg, 1.56 x 10^{-2} mmol) were added due to the sluggishness of the reaction. After hydrolysis of the reaction mixture by dilution with dichloromethane (5 mL) and vigorous stirring with hydrochloric acid (1 M, 2 mL) for 0.5 h, the organic layer was extracted with diethyl ether (3 x 100 mL). The combined organic fractions were washed with water (150 mL), dilute aqueous potassium fluoride solution (100 mL) and water (150 mL). After drying (sodium sulfate) the solvent was removed at reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford the *title compound* **367** (95 mg, 90%) as a pale yellow oil; $[\alpha]_D^{19}$ = +21.8° (c=0.330, $CHCl_3$); (Found: C, 74.28; H, 6.66. $C_{42}H_{44}O_8$ requires C,

74.52; H 6.56%); ν_{max} (film) cm^{-1} 3063, 3029, 2927, 2862 (C-H), 1667 (C=O, ketone), 1603, 1568 (C=C), 1510, 1496, 1454, 1415, 1360 (C-O); δ_H (400 MHz; $CDCl_3$) 1.72 (1H, ddd, J_{gem} 12.9, $J_{2'ax,3'}$ 11.5 and $J_{2'ax,1'}$ 11.5 Hz, 2'$_{ax}$-H), 2.31 (1H, ddd, J_{gem} 12.9, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 1.9 Hz, 2'$_{eq}$-H), 2.71 (3H, s, $COC\underline{H}_3$), 3.55-3.97 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.74, 3.76, 3.92 (each 3H, s, 3 x OCH_3), 4.50, 4.59 (each 1H, d, J_{gem} 12.3 Hz, 2 x C$\underline{H}$Ph), 4.59 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 4.61, 4.66 (each 1H, d, J_{gem} 11.6 Hz, 2 x C$\underline{H}$Ph), 4.90 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 4.95 (1H, dd, $J_{1',2'ax}$ 11.5 and $J_{1',2'eq}$ 1.7 Hz, 1'-H), 6.97 (1H, s, 2-H), 7.18-7.27 (15H, m, Ph-H), 7.67 (1H, d, $J_{8,7}$ 8.8 Hz, 8-H), 8.01 (1H, d, $J_{7,8}$ 8.8 Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 31.5 (CH_3, $CO\underline{C}H_3$), 38.6 (CH_2, C-2'), 55.8 (CH_3, 1-OCH_3), 63.3 (CH_3, 5-OCH_3), 63.8 (CH_3, 4-OCH_3), 69.7 (CH_2, C-6'), 71.6 (CH_2, $\underline{C}H_2$Ph), 71.9 (CH, C-1'), 73.4, 75.1 (CH_2, 2 x $\underline{C}H_2$Ph), 78.4, 79.6, 81.4 (CH, C-3', C-4', C-5'), 102.8 (CH, C-2), 119.2, 126.5 (CH, C-7, C-8), 122.5 (quat., C-4a), 127.5-128.4 (CH, Ph), 129.4, 130.7, 133.2 (quat., C-8a, C-3, C-6), 138.5, 138.6, 138.6 (quat., 3 x *ipso*-Ph), 151.0, 151.8, 152.2 (quat., C-1, C-4, C-5), 201.0 (quat., $\underline{C}OCH_3$); *m/z* (CI) 676 (M^+, 48%), 286 (16), 91 (C_7H_7, 100).



367

3-acetyl-6-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone 262

(i) Using CAN.

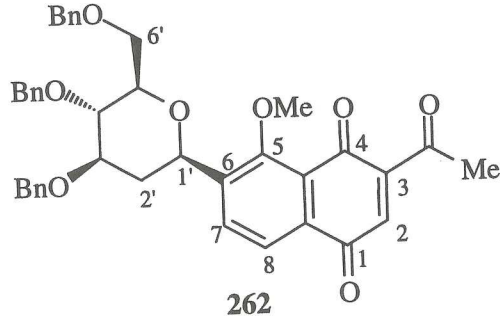
A solution of ceric ammonium nitrate (308 mg, 0.562 mmol) in water (1.0 mL) was added dropwise to a solution of *C*-glycosylnaphthalene **367** (190 mg, 0.281 mmol) in acetonitrile (5.0 mL) and the mixture stirred for 10 min. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic fractions were washed with water (50 mL), dried (sodium sulfate) and the solvent removed at reduced pressure to give an orange oil. Flash chromatography

using hexane-ethyl acetate (1:1) as eluent afforded the *title compound* **262** (166 mg, 91%) as a yellow oil.

(i) Using silver(II) oxide and nitric acid.

To a solution of *C*-glycosylnaphthalene **367** (200 mg, 0.296 mmol) in dioxane (10 mL) was added freshly prepared silver(II) oxide[208] (146 mg, 1.18 mmol) followed by nitric acid (11.1 M, 106 μL). After stirring for 10 min. further portions of silver(II) oxide (146 mg, 1.18 mmol) and nitric acid (11.1 M, 106 μL) were added. After stirring for an additional 15 min. the reaction mixture was quenched with water (5 mL) and extracted into dichloromethane (3 x 100 mL). The organic layer was washed with water (2 x 50 mL), dried (sodium sulfate) and the solvent removed under reduced pressure to yield the *title compound* **262** (178 mg, 93%) as an orange oil.

(Found: C, 73.98; H, 6.21. $C_{40}H_{38}O_8$ requires C, 74.27; H, 5.93%); ν_{max} (film cm^{-1} 3060, 3030, 2925, 2863 (C-H), 1702 (C=O, ketone), 1666 (C=O, quin.), 1605, 1585, 1573 (C=C), 1496, 1453, 1365 (C-O); δ_H (400 MHz; $CDCl_3$) 1.72 (1H, ddd, J_{gem} 12.9, $J_{2'ax,3'}$ 12.0 and $J_{2'ax,1'}$ 12.0 Hz, 2_{ax}-H), 2.31 (1H, ddd, J_{gem} 12.9, $J_{2'eq,3'}$ 5.0 and $J_{2'eq,1'}$ 1.0 Hz, 2_{eq}-H), 2.53 (3H, s, $COC\underline{H}_3$), 3.47-3.90 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A, 6'-H_B), 3.81 (3H, s, OCH_3), 4.47-4.60 (4H, m, 4 x C<u>H</u>Ph), 4.63 (1H, d, J_{gem} 11.8 Hz, C<u>H</u>Ph), 4.74 (1H, dd, $J_{1',2'ax}$ 11.6 and $J_{1',2'eq}$ 1.0 Hz, 1'-H), 4.89 (1H, d, J_{gem} 11.2 Hz, C<u>H</u>Ph), 6.96 (1H, s, 2-H), 7.15-7.28 (15H, m, Ph-H), 7.85 (1H, d, $J_{8,7}$ 8.1 Hz, 8-H), 7.91 (1H, d, $J_{7,8}$ 8.1 Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 30.8 (CH_3, $CO\underline{C}H_3$), 38.0 (CH_2, C-2'), 62.6 (CH_3, OCH_3), 69.8 (CH_2, C-6'), 71.5 (CH_2, <u>C</u>H_2Ph), 72.0 (CH, C-1'), 73.5, 75.0 (CH_2, 2 x <u>C</u>H_2Ph), 78.2, 79.6, 81.0 (CH, C-3', C-4', C-5'), 123.0, 123.5 (quat., C-4a, C-3), 127.6-128.5 (CH, Ph, C-7), 133.1 (CH, C-8), 134.8 (quat., C-8a), 138.6, 138.6, 138.6 (quat., 3 x *ipso*-Ph), 147.3 (quat., C-6), 157.1 (quat., C-5), 183.0, 184.6 (quat., C-1, C-4), 198.0 (quat., <u>C</u>OCH_3); *m/z* (CI) 648 (M^+, 12%), 286 (16), 258 (21), 181 (16), 91 (C_7H_7, 100), 43 ($COCH_3$, 55).



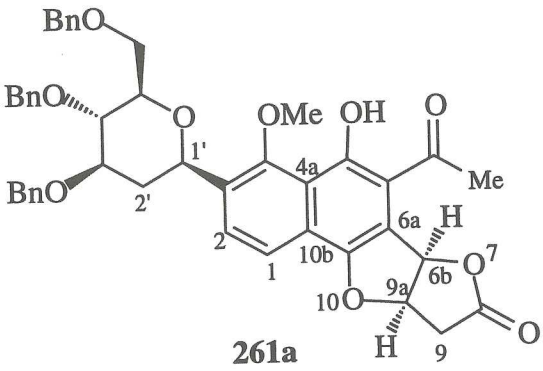
262

3.5 Synthesis of Medermycin Analogue 257.

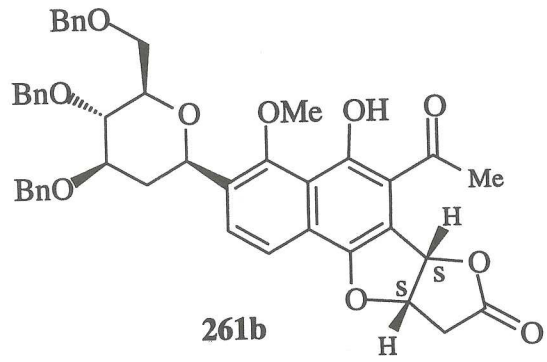
(6b*R*,9a*R*)-6-acetyl-3-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-4-methoxy-6b,9a-dihydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one 261a and (6b*S*,9a*S*)-6-acetyl-3-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-4-methoxy-6b,9a-dihydro-furo[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one 261b

A solution of 2-trimethylsilyloxyfuran **113** (33 mg, 0.21 mmol) in dry acetonitrile (0.5 mL) was added dropwise to an ice-cooled solution of *C*-glycosylnaphthoquinone **262** (69 mg, 0.107 mmol) in dry acetonitrile (1.5 mL) under an atmosphere of nitrogen. After 1 h the reaction mixture was allowed to warm to room temperature and methanol (0.5 mL) and silica (50 mg) were added. After a further 18 h, dichloromethane (10 mL) was added and the solution washed with water (2 x 5 mL) and dried (sodium sulfate). Removal of the solvent at reduced pressure yielded a crude oil that was adsorbed onto celite (100 mg) and then purified by flash chromatography using hexane-ethyl acetate (2:1) as eluent to afford the *title compound* **261** (47 mg, 60%) as an orange oil that was a mixture of diastereomers (5:4, ^{1}H nmr); [Found (LSIMS): M^+, 730.2762. $C_{44}H_{42}O_{10}$ requires M, 730.2778]; ν_{max} (film) cm^{-1} 3333 (br, OH), 2924, 2868 (C-H), 1784 (C=O, γ-lactone), 1742 (C=O, ketone), 1666 (C=O, quin.), 1630 (C=C), 1565, 1517, 1496, 1453, 1396 (C-O); δ_H(400 MHz; $CDCl_3$) 1.45 (1H, ddd, J_{gem} 12.9, $J_{2'ax,3'}$ 11.0 and $J_{2'ax,1'}$ 11.0 Hz, 2'$_{ax}$-H), 2.47*, 2.51 (1H, ddd, J_{gem} 12.9, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 1.8 Hz, 2'$_{eq}$-H), 2.83*, 2.84 (3H, s, COC$\underline{H}_3$), 3.14*, 3.15 (2H, d, $J_{9,9a}$ 4.1 Hz, 9-CH_2), 3.61-3.71 (2H, m, 6'-CH_2), 3.79-3.84 (2H, m, 4'-H, 5'-H), 3.86-3.95 (1H, m, 3'-H), 3.91*, 3.93 (3H, s, OCH_3), 4.56, 4.58* (1H, d, J_{gem} 12.3 Hz, C$\underline{H}$Ph), 4.61-4.68 (3H, m, 3 x C$\underline{H}$Ph), 4.72 (1H, d, J_{gem} 11.8 Hz, C$\underline{H}$Ph), 4.94 (1H, dd, $J_{1',2'ax}$ 7.0 and $J_{1',2'eq}$ 1.8 Hz, 1'-H), 4.98 (1H, d, J_{gem} 10.9 Hz, C$\underline{H}$Ph), 5.51 (1H, dt, $J_{9a,6b}$ 6.3 and $J_{9a,9}$ 4.1 Hz, 9a-H), 6.47, 6.48* (1H, d, $J_{9a,6b}$ 6.3 Hz, 6b-H), 7.25-7.35 (15H, m, Ph-H), 7.76 (1H, d, $J_{1,2}$ 8.5 Hz, 1-H), 7.88*, 7.89 (1H, d, $J_{2,1}$ 8.5 Hz, 2-H), 14.43*, 14.49 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 31.2 (CH_3, CO$\underline{C}H_3$), 34.0 (CH_2, C-9), 38.2 (CH_2, C-2'), 63.3 (CH_3, OCH_3), 69.7 (CH_2, C-6'), 71.3 (CH_2, $\underline{C}H_2$Ph), 72.0 (CH, C-1'), 73.4, 75.0 (CH_2, 2 x $\underline{C}H_2$Ph), 78.2, 79.4, 81.2 (CH, C-3', C-4', C-5'), 81.0 (CH, C-9a), 85.8 (CH, C-6b), 107.3, 116.5 (CH, C-1, C-2), 108.4, 116.6, 121.0, 126.9 (quat., C-4a, C-6, C-6a, C-10b), 127.5-127.4 (CH, Ph), 130.0 (quat., C-3), 138.3, 138.4, 138.6 (quat., 3 x *ipso*-Ph), 150.2, 156.1, 162.6 (quat., C-4, C-5, C-10a), 171.7 (quat., C-8),

203.0 (quat., $\underline{C}OCH_3$); *m/z* (CI) 731 (MH^+, 92%), 730 (M^+, 100), 685 (10), 640 (15), 547 (35), 391 (80), 341 (40), 305 (88), 91 (C_7H_7, 63).*



261a



261b

(3a*R*,11b*R*,5*S*)-8-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-7-methoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-furo[3,2-*b*]naphtho[2,1-*d*]pyran-2,6,11-trione 260a and (3a*S*,11b*S*,5*R*)-8-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-7-methoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-furo[3,2-*b*]naphtho[2,1-*d*]pyran-2,6,11-trione 260b

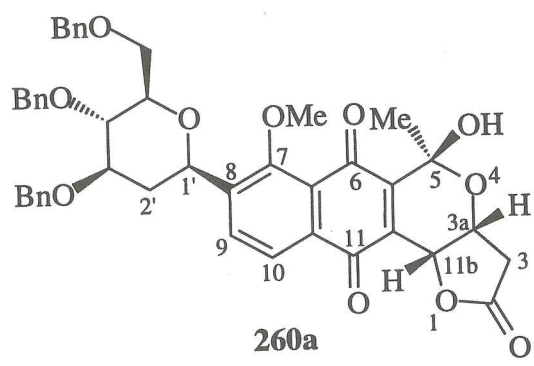
A solution of ceric ammonium nitrate (71 mg, 0.13 mmol) in water (0.5 mL) was added dropwise to a stirred solution of adduct **261** (47 mg, 0.064 mmol) in acetonitrile (5.0 mL) until no starting material could be detected by TLC (*ca.* 10 min.). The mixture was diluted with dichloromethane (10 mL), washed with water (2 x 5 mL) and dried (sodium sulfate). The solvent was removed at reduced pressure and the resultant oil filtered through a plug of silica using dichloromethane as eluent. Removal of the solvent at reduced pressure afforded a mixture of *title lactols* **260** (41 mg, 85%) as an orange oil that was a mixture of diastereomers (1:1, ^1H nmr); [Found (LSIMS): M^+, 746.2749. $C_{44}H_{42}O_{11}$ requires M, 746.2727]; δ_C (100 MHz; $CDCl_3$) 27.5, 27.6 (CH_3, CH_3, CH_3*), 29.7 (CH_2, C-3), 37.9 (CH_2, C-2'), 62.7, 62.9 (CH_3, OCH_3, OCH_3*), 67.1, 67.2 (CH, C-3a), 68.5, 68.7 (CH, C-11b), 69.6 (CH_2, C-6'), 71.4 (CH_2, $\underline{C}H_2Ph$), 71.8, 72.0 (CH, C-1'), 73.4, 75.1 (CH_2, 2 x $\underline{C}H_2Ph$), 78.0, 79.4, 80.9 (CH, C-3', C-4', C-5'), 93.2 (quat., C-5), 123.4, 123.5 (CH, C-9, C-10), 127.6-128.4 (CH, Ph and quat, C-5a, C-6a, C-10a, C-11a), 138.2, 138.63, 138.4 (quat., 3 x *ipso*-Ph), 166.4, 166.5 (quat., C-2, C-2*), 171.2, 174.2 (quat., C-6, C-11); *m/z* (CI) 744 (M^+, 1%), 686 (2), 296 (3), 105 (6), 91 (C_7H_7, 100).

* denotes resonance for minor diastereomer.

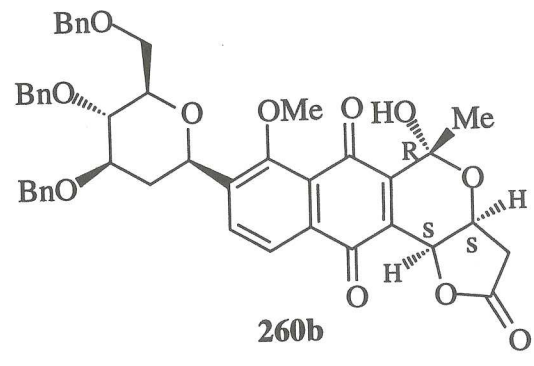
Flash chromatography at -10 °C using hexane-ethyl acetate (1:2) treated with potassium carbonate, as eluent, allowed separation of the diastereomers to give:

The less polar lactol **260** (6 mg, 14%) as a yellow oil; ν_{max} (film) cm^{-1} 3276-3624 (OH), 1788 (C=O, γ-lactone) and 1668 (C=O, quin.); δ_H (200 MHz; $CDCl_3$) 1.46 (1H, ddd, J_{gem} 12.7, $J_{2'ax,3'}$ 11.7 and $J_{2'ax,1'}$ 11.2 Hz, $2'_{ax}$-H), 1.64-1.90 (1H, br.s, OH), 1.73 (3H, s, CH_3), 2.46 (1H, ddd, J_{gem} 12.7, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,1'}$ 2.0 Hz, $2'_{eq}$-H), 2.67 (1H, d, J_{gem} 17.7 Hz, 3-H_A), 2.87 (1H, dd, J_{gem} 17.7, $J_{3B,3a}$ 4.8 Hz, 3-H_B), 3.46-3.62 (2H, m, 6'-H_B, 6'-H_A), 3.68-3.75 (2H, m, 4'-H, 5'-H), 3.76-3.84 (1H, m, 3'-H), 3.77 (3H, s, OCH_3), 4.45-4.68 (5H, m, 5 x C<u>H</u>Ph), 4.73 (1H, dd, $J_{1',2'ax}$ 11.2 and $J_{1',2'eq}$ 2.0 Hz, 1'-H), 4.83 (1H, dd, $J_{3a,3B}$ 4.8 and $J_{3a,11b}$ 2.7 Hz, 3a-H), 4.89 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 5.20 (1H, d, $J_{11b,3a}$ 2.7 Hz, 11b-H), 7.13-7.29 (15H, m, Ph-H), 7.90 (2H, s, 9-H and 10-H).

The more polar lactol **260** (5 mg, 12%) as a yellow oil; ν_{max} (film) cm^{-1} 3587-3182 (OH), 3062, 3023, 2925, 2866 (C-H), 1788 (C=O, γ-lactone), 1671 (C=O, quin.); δ_H (200 MHz; $CDCl_3$) 1.45 (1H, ddd, J_{gem} 13.0, $J_{2'ax,3'}$ 11.7 and $J_{2'ax,1'}$ 11.7 Hz, $2'_{ax}$-H), 1.64-1.90 (1H, br.s, OH), 1.72 (3H, s, CH_3), 2.40 (1H, ddd, J_{gem} 13.0, $J_{2'eq,3'}$ 5.0 and $J_{2'eq,1'}$ 2.0 Hz, $2'_{eq}$-H), 2.65 (1H, dd, J_{gem} 17.5 and $J_{3A,3a}$ 2.0 Hz, 3-H_A), 2.87 (1H, dd, J_{gem} 17.7, $J_{3B,3a}$ 4.7 Hz, 3-H_B), 3.46-3.68 (2H, m, 6'-H_A, 6'-H_B), 3.68-3.75 (2H, m, 4'-H, 5'-H), 3.76-3.84 (1H, m, 3'-H), 3.82 (3H, s, OCH_3), 4.45-4.68 (5H, m, 5 x C<u>H</u>Ph), 4.72 (1H, dd, $J_{1',2'ax}$ 11.7 and $J_{1',2'eq}$ 2.0 Hz, 1'-H), 4.81 (1H, ddd, $J_{3a,3B}$ 4.7, $J_{3a,11b}$ 2.8 and $J_{3a,3A}$ 2.0 Hz, 3a-H), 4.89 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 5.19 (1H, d, $J_{11b,3a}$ 2.8 Hz, 11b-H), 7.13-7.29 (15H, m, Ph-H), 7.88 (1H, d, $J_{10,9}$ 8.0 Hz, 10-H), 7.93 (1H, d, $J_{9,10}$ 8.0 Hz, 9-H).



260a



260b

(3a*R*,11b*R*,5*S*)-8-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-7-methoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-furo[3,2-*b*]naphtho[2,1-*d*]pyran-2,6,11-trione 259a and (3a*S*,11b*S*,5*R*)-8-(3',4',6'-tri-*O*-benzyl-2'-deoxy-β-D-*arabino*-hexopyranosyl)-7-methoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-furo[3,2-*b*]naphtho[2,1-*d*]pyran-2,6,11-trione 259b

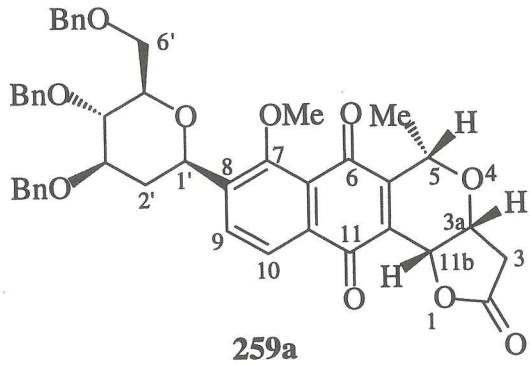
To a solution of lactols **260** (42 mg, 0.056 mmol) in dichloromethane (4 mL), cooled to -30 °C under an atmosphere of nitrogen, were added trifluoroacetic acid (43 μL, 0.56 mmol) and triethylsilane (90 μL, 0.56 mmol). The mixture was slowly allowed to warm to -10 °C and then stirred at this temperature for 72 h with the aid of a cryostat. Celite (250 mg) was added and the solvent removed at reduced pressure while maintaining the temperature at -10 °C. The unstable residue was purified by flash chromatography at -10 °C using hexane-ethyl acetate (1:1) that had been stirred over potassium carbonate as eluent to give the *title lactols* **259** (35 mg, 86%) as an orange oil that was a mixture of diastereomers (1:1, ^{1}H nmr); [Found (LSIMS): MH^+, 731.2823. $C_{44}H_{42}O_{10}$ requires MH, 731.2778]; ν_{max} (film) cm^{-1} 3027, 2923, 2865 (C-H) 1736 (C=O, γ-lactone), 1665 (C=O, quin.), 1575 (C=C), 1453, 1362, 1270, 1095 (C-O); The ^{13}C nmr spectrum was obtained for a mixture of diastereomers enriched in the more polar diastereomer (less polar diastereomer marked with asterisk); δ_C (100 MHz; $CDCl_3$) 20.5, 20.3* (CH_3, Me), 37.8 (CH_2, C-2'), 38.4, 38.2* (CH_2, C-3), 63.5, 63.2* (CH_3, OMe), 69.5, 69.4* (CH, C-3a), 69.9 (CH_2, C-6'), 70.3, 70.1* (CH, C-11b), 71.8 (CH_2, $\underline{C}H_2Ph$), 71.9 (CH, C-1'), 72.4, 72.6* (CH, C-5), 73.9, 75.8 (CH_2, 2 x $\underline{C}H_2Ph$), 78.4, 79.7, 81.4 (CH, C-3', C-4', C-5'), 122.2, 124.7 (CH, C-9 and C-10), 123.9, 124.7* (quat., C-11a), 133.0, 132.9*, 133.4, 133.5* (quat., C-10a and C-6a), 138.6, 138.6, 138.7 (quat., 3 x *ipso*-Ph), 144.2, 143.9* (quat., C-8), 152.7, 153.8* (quat., C-5a), 156.9, 157.0* (quat., C-7), 175.4, 175.3* (quat., C-2), 182.8, 182.4*, 184.4, 185.5* (quat., C-6 and C-11); *m/z* (CI) 732 (MH_2^+, 24%), 702 (M-CO, 20), 181 (30), 91 (C_7H_7, 100).

More careful chromatography at -10 °C allowed some degree of separation of the diastereomers with considerable loss of material to afford;

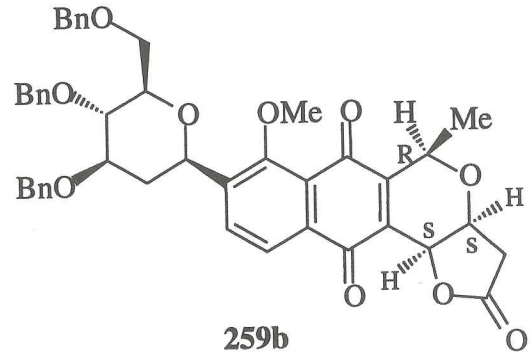
The less polar diastereomer **259** (8 mg, 19%) as an orange glass; δ_H (200 MHz; $CDCl_3$) 1.73 (3H, d, J_{vic} 6.2 Hz, CH_3), 1.29-1.38 (1H, m, 2'ax-H), 2.40-2.60 (1H, m, 2'eq-H), 2.72 (1H, d, J_{gem} 17.3 Hz, 3-H_A), 2.90 (1H, dd, J_{gem} 17.3, $J_{3B,3a}$ 4.5 Hz, 3-H_B), 3.46-3.84 (5H, m, 3'H, 4'-H, 5'-H, 6'-H_A and 6'-H_B), 3.88 (3H, s, OCH_3), 4.30-4.38 (1H, m, 3a-H), 4.55-4.75 (5H, m, 5 x C$\underline{H}$Ph), 4.80 (1H, d.q, J_{vic} 6.2, $J_{5,11b}$ 1.8 Hz, 5-H), 4.99 (1H, d, J_{gem} 10.7 Hz, C$\underline{H}$Ph), 5.27 (1H, br.s, 11b-H), 5.38 (1H, dd,

$J_{1',2'ax}$ 10.8, $J_{1',2'eq}$ 2.9 Hz, 1'-H), 7.24-7.35 (15H, m, Ar-H), 7.94 (1H, apparent s, 9-H), 7.96 (1H, apparent s, 10-H);

The more polar diastereomer **259** (10 mg, 24%) as an orange glass; δ_H (200 MHz; $CDCl_3$) 1.57 (3H, d, J_{vic} 6.6 Hz, CH_3), 1.29-1.38 (1H, m, 2'ax-H), 2.40-2.60 (1H, m, 2'eq-H), 2.72 (1H, d, J_{gem} 17.3 Hz, 3-H_A), 2.90 (1H, dd, J_{gem} 17.3, $J_{3B,3a}$ 4.5 Hz, 3-H_B), 3.46-3.84 (5H, m, 3'-H, 4'-H, 5'-H, 6'-H_A and 6'-H_B), 3.81 (3H, s, OCH_3), 4.30-4.38 (1H, m, 3a-H), 4.55-4.75 (5H, m, 5 x C<u>H</u>Ph), 4.80 (1H, d.q, J_{vic} 6.6, $J_{5,11b}$ 1.8 Hz, 5-H), 4.96 (1H, d, J_{gem} 10.9 Hz, C<u>H</u>Ph), 5.27 (1H, br.s, 11b-H), 5.38 (1H, dd, $J_{1',2'ax}$ 10.8, $J_{1',2'eq}$ 2.9 Hz, 1'-H), 7.24-7.35 (15H, m, Ar-H), 7.94 (1H, apparent s, 9-H), 7.96 (1H, apparent s, 10-H).



259a

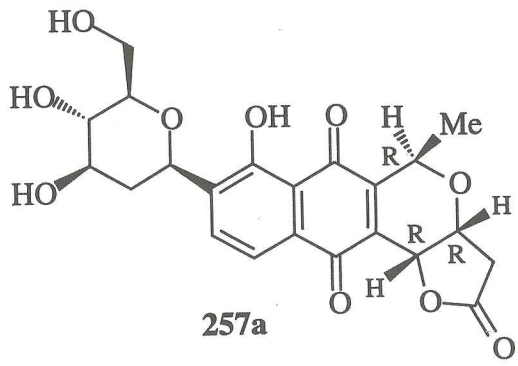


259b

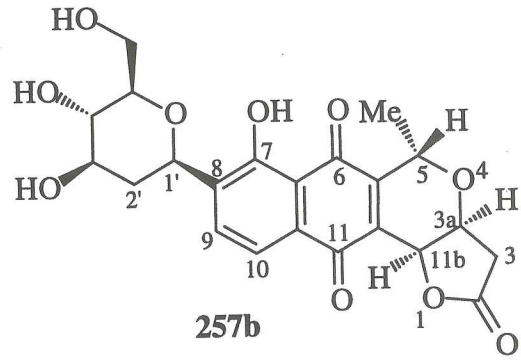
(3a*R*,11R,5*R*)-8-(2'-deoxy-β-D-*arabino*-hexopyranosyl)-7-hydroxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-furo[3,2-*b*]naphtho[2,1-*d*]pyran-2,6,11-trione 257a and (3a*S*,11b*S*,5*S*)-8-(2'-deoxy-β-D-*arabino*-hexopyranosyl)-7-hydroxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-furo[3,2-*b*]naphtho[2,1-*d*]pyran-2,6,11-trione 257b

A solution of boron tribromide in dichloromethane (0.27 mL, 0.27 mmol) was added dropwise to a solution of ethers **259** (33 mg, 0.045 mmol) (more polar diastereomer : less polar diastereoisomer, 3:1) in dichloromethane (1 mL) cooled to -48 °C under an atmosphere of nitrogen. After 5 min., acetonitrile (1 mL) was added and the reaction mixture allowed to warm to room temperature. Stirring was continued for a further 0.5 h. The reaction mixture was treated with water (1 mL), stirred for 5 min. and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The organic phases were combined, dried and the solvent removed at reduced pressure to afford **257** (13 mg, 67%) as an orange solid that was a mixture of diastereomers (3:1, ^{1}H nmr); m.p. 151-152 °C; [Found (LSIMS): M^+, 446.1217. $C_{22}H_{22}O_{10}$ requires M, 446.1213]; ν_{max} (film) cm^{-1} 3100-3643 (OH), 2934, 2890 (C-H) 1780 (C=O, γ-lactone), 1652, 1615 (C=O, quin.),

1434, 1282, 1088, 1039; δ_H [400 MHz; $(CD_3)_2CO$] 1.57 (3H, d, J_{vic} 7.0 Hz, CH_3*), 1.58 (3H, d, J_{vic} 6.6 Hz, CH_3), 1.31-1.39 (1H, m, 2'ax-H), 2.36-2.47 (1H, m, 2'eq-H), 2.49 (1H, d, J_{gem} 17.5 Hz, 3-H_A), 3.19 (1H, dd, J_{gem} 17.5, $J_{3,3a}$ 5.0 Hz, 3-H_B), 4.81-4.99 (2H, m, 3a-H, 1'-H), 5.04 (1H, q, J_{vic} 6.6 Hz, 5-H), 5.34 (1H, d, $J_{11b,3a}$ 1.6 Hz, 11b-H), 5.78 (1H, br.s, OH), 7.63 (1H, d, $J_{9,10}$ 7.8 Hz, 9-H*), 7.64 (1H, d, $J_{9,10}$ 7.8 Hz, 9-H), 8.00 (1H, d, $J_{9,10}$ 7.8 Hz, 10-H*), 8.01 (1H, d, $J_{9,10}$ 7.8 Hz, 10-H), 12.20 (1H, br.s, ArOH*), 12.30 (1H, br.s, ArOH); δ_C [100 MHz; $(CD_3)_2CO$] 18.3 (CH_3, Me), 20.6 (CH_3, Me*), 37.1 (CH_2, C-3), 40.4 (CH_2, C-2'), 63.0 (CH_2, C-6'), 66.9 (CH, C-3a*), 67.5 (CH, C-3a), 69.0 (CH, C-11b*), 69.5 (CH, C-11b), 70.7 (CH, C-5*), 72.1 (CH, C-5), 71.9, 73.3, 73.5 (CH, C-3', C-4', C-5'), 81.6 (CH, C-1'), 119.3 (quat., C-8), 119.4 (CH, C-10), 113.7 (quat., C-10a), 134.3 (CH, C-9), 138.9 (quat., C-5a), 149.9, 151.5 (quat., C-2, C-7); *m/z* (CI) 449 (MH_3^+, 100%), 447 (MH^+, 77), 431 (37), 413 (21), 403 (46), 385 (45), 371 (29).



257a



257b

Appendix 1: Supplemetary Crystal Structure Data for Acetate 351.

X-ray diffraction analysis was performed by Dr. Peter Turner and Assoc. Prof. Trevor Hambley, Division of Inorganic Chemistry, The University of Sydney.

A pale brown acicular crystal having approximate dimensions of 0.55 x 0.12 x 0.08 mm was attached to a thin glass fibre, and mounted on a Rigaku AFC7R diffractometer employing graphite monochromated Cu-Kα radiation from a rotating anode generator. Primitive orthorhombic cell constants were obtained from a least-squares refinement using the setting angles of 25 reflections in the range $53.19 < 2\theta < 60.42°$. Diffraction data were collected at a temperature of 21 ± 1 ℃ using ω-2θ scans to a maximum 2θ value of 130.0°. Omega scans of several intense reflections made prior to data collection, had an average width at half-height of 0.21° , and scans of (1.52 + 0.35 tan θ)° were made at a speed of 32.0°/min (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned up to 10 times. Stationary background counts were recorded on each side of the reflection, with a 2:1 ratio of peak to background counting time. The intensities of three representative reflections measured every 150 reflections, did not change significantly during the data collection. An empirical absorption correction based on azimuthal scans of three reflections was applied and the data were also corrected for Lorentz and polarization effects.

All calculations were undertaken with the teXsan[1] crystallographic software package. Neutral atom scattering factors were taken from Cromer and Waber.[2] Anomalous dispersion effects were included in Fcalc[3] and the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[4] The values for the mass attenuation coefficients were those of Creagh and Hubbell.[5] The structure was solved in the space group $P2_12_12_1$ (#19) by direct methods[6] and expanded using Fourier techniques.[7] Non-hydrogen atoms were modelled with anisotropic thermal parameters. Hydrogen atoms were included included in the model at calculated positions with group thermal parameters. Anomalous scattering from the bromine determined the absolute configuration of the molecule and ORTEP projection of the molecule is provided in Fig. X.[8]

References

(1) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

(2) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(3) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(4) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(5) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(6) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(7) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(8) ORTEP: Johnson,C.K.; ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee (1976).

Experimental Details.

A. Crystal Data

Empirical Formula	$C_{34}H_{33}BrO_7$
Formula Weight	633.53
Crystal Colour, Habit	brown, acicular
Crystal Dimensions	0.55 X 0.12 X 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (53.2 - 60.4°)
Omega Scan Peak Width at Half-height	0.21°
Lattice Parameters	a = 19.515(1) Å b = 23.667(2) Å c = 6.541(2) Å V = 3021.0(7) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.393 g/cm^3
F_{000}	1312.00
μ(CuKα)	22.54 cm^{-1}

B. Intensity Measurements.

Diffractometer	Rigaku AFC7R
Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Attenuator	Ni foil (factor = 9.29)
Detector Aperture	3.0 mm horizontal 3.0 mm vertical
Voltage, Current	50kV, 150mA
Temperature	21.0°C
Scan Type	ω-2θ
Scan Rate	32.0°/min (in ω) (up to 10 scans)
Scan Width	(1.52 + 0.35 tan θ)°

$2\theta_{max}$	130.0°
HKL Range:	0 22, 0 27, 0 7
No. of Reflections Measured	Total: 3140 Unique: 2990 (R_{int} = 0.358)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.8535 - 0.9979)
	Secondary Extinction
	(coefficient: $5.5310^{-0.7}$)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fol - |Fcl)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0020
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2010
No. Variables	380
Reflection/Parameter Ratio	5.29
Residuals: R; Rw	0.035; 0.033
Goodness of Fit Indicator	1.91
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.24 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.29 $e^-/Å^3$

Table 1. Non hydrogen atom coordinates and parameters.

atom	x	y	z	Beq
Br(1)	0.96744(3)	0.09680(2)	-0.0526(1)	7.40(1)
O(1)	0.5638(1)	0.2080(1)	0.4268(5)	5.06(7)
O(2)	0.5603(1)	0.3424(1)	0.5697(6)	5.80(7)
O(3)	0.5447(2)	0.1856(1)	0.8650(6)	6.71(8)
O(4)	0.7470(1)	0.2329(1)	0.1457(4)	4.66(6)
O(5)	0.8308(1)	0.2637(1)	0.3496(6)	6.20(8)
O(6)	0.8586(1)	0.1856(1)	-0.0133(4)	5.12(7)
O(7)	0.8079(2)	0.0017(1)	0.4891(6)	6.74(9)
C(1)	0.6315(2)	0.2297(2)	0.3925(6)	4.28(8)
C(2)	0.6533(2)	0.2719(1)	0.5577(7)	4.06(7)
C(3)	0.6298(2)	0.2517(2)	0.7665(7)	4.41(8)
C(4)	0.5528(2)	0.2403(2)	0.7740(7)	4.83(8)
C(5)	0.5236(2)	0.2427(2)	0.5631(7)	4.91(8)
C(6)	0.5129(2)	0.3027(2)	0.4866(9)	6.1(1)
C(7)	0.6297(2)	0.3332(2)	0.5136(8)	5.23(10)
C(8)	0.6721(2)	0.3751(2)	0.6326(8)	5.5(1)
C(9)	0.6502(2)	0.3985(2)	0.8143(9)	6.5(1)
C(10)	0.6913(3)	0.4355(2)	0.925(1)	7.9(2)
C(11)	0.7559(3)	0.4486(2)	0.852(1)	8.4(2)
C(12)	0.7783(3)	0.4256(2)	0.675(1)	8.0(2)
C(13)	0.7365(2)	0.3899(2)	0.5657(10)	6.6(1)
C(14)	0.6804(2)	0.1801(2)	0.3788(6)	4.20(8)
C(15)	0.6689(2)	0.1306(2)	0.4889(7)	4.81(10)
C(16)	0.7158(2)	0.0876(2)	0.4902(8)	5.13(10)
C(17)	0.7756(2)	0.0908(2)	0.3669(7)	4.57(9)
C(18)	0.8242(2)	0.0455(2)	0.3651(8)	5.22(10)
C(19)	0.8818(2)	0.0486(2)	0.2479(8)	5.7(1)
C(20)	0.8900(2)	0.0955(2)	0.1223(7)	5.08(9)
C(21)	0.8462(2)	0.1403(2)	0.1142(6)	4.31(8)
C(22)	0.7870(2)	0.1393(1)	0.2461(7)	3.98(8)
C(23)	0.7388(2)	0.1839(2)	0.2626(6)	4.08(8)
C(24)	0.7977(2)	0.2689(2)	0.2000(8)	5.4(1)
C(25)	0.8024(2)	0.3153(2)	0.043(1)	8.1(2)
C(26)	0.8294(3)	0.1788(3)	-0.2135(8)	8.1(2)
C(27)	0.8569(3)	-0.0428(2)	0.508(1)	7.8(2)
C(28)	0.4852(2)	0.1784(2)	0.9723(9)	6.9(1)
C(29)	0.4724(2)	0.1167(2)	1.0076(8)	5.44(9)
C(30)	0.4778(3)	0.0946(2)	1.2018(8)	6.1(1)
C(31)	0.4632(3)	0.0378(2)	1.2346(9)	7.3(1)
C(32)	0.4455(3)	0.0041(2)	1.074(1)	7.3(1)
C(33)	0.4418(3)	0.0252(2)	0.884(1)	7.7(1)
C(34)	0.4564(3)	0.0818(2)	0.8469(8)	6.9(1)

Table 2. Hydrogen atom coordinates and parameters.

atom	x	y	z	Beq
H(1)	0.6317	0.2491	0.2619	5.1360
H(2)	0.7030	0.2723	0.5598	4.8754
H(3a)	0.6540	0.2171	0.7998	5.2974
H(3b)	0.6408	0.2805	0.8669	5.2974
H(4)	0.5307	0.2684	0.8591	5.7985
H(5)	0.4785	0.2255	0.5703	5.8925
H(6a)	0.4669	0.3146	0.5230	7.3374
H(6b)	0.5177	0.3028	0.3390	7.3374
H(7)	0.6349	0.3408	0.3687	6.2813
H(9)	0.6051	0.3889	0.8662	7.8365
H(10)	0.6747	0.4520	1.0512	9.4531
H(11)	0.7852	0.4741	0.9286	10.0679
H(12)	0.8239	0.4343	0.6245	9.6137
H(13)	0.7530	0.3746	0.4372	7.9757
H(15)	0.6267	0.1265	0.5662	5.7709
H(16)	0.7082	0.0547	0.5759	6.1542
H(19)	0.9160	0.0189	0.2520	6.8075
H(25a)	0.7566	0.3275	0.0055	9.7512
H(25b)	0.8276	0.3469	0.0994	9.7512
H(25c)	0.8259	0.3013	-0.0776	9.7512
H(26a)	0.8470	0.1445	-0.2754	9.7433
H(26b)	0.8415	0.2110	-0.2978	9.7433
H(26c)	0.7799	0.1763	-0.2023	9.7433
H(27a)	0.8985	-0.0281	0.5694	9.3502
H(27b)	0.8383	-0.0724	0.5946	9.3502
H(27c)	0.8671	-0.0581	0.3742	9.3502
H(28a)	0.4889	0.1975	1.1030	8.2666
H(28b)	0.4474	0.1943	0.8953	8.2666
H(30)	0.4916	0.1185	1.3149	7.2665
H(31)	0.4656	0.0221	1.3714	8.7238
H(32)	0.4354	-0.0355	1.0970	8.7095
H(33)	0.4288	0.0008	0.7709	9.2338
H(34)	0.4552	0.0966	0.7086	8.2813

$$B_{eq} = 8/3\ PI^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

Table 3. Anisotropic Displacement Parameters.

atom	U11	U22	U33	U12	U13	U23
Br(1)	0.0723(3)	0.0959(4)	0.1131(5)	0.0179(3)	0.0306(3)	0.0167(4)
O(1)	0.050(1)	0.068(2)	0.074(2)	-0.004(1)	0.002(1)	-0.010(2)
O(2)	0.062(1)	0.053(1)	0.106(3)	0.011(1)	-0.015(2)	0.008(2)
O(3)	0.075(2)	0.058(2)	0.122(3)	0.008(2)	0.029(2)	0.024(2)
O(4)	0.053(1)	0.063(2)	0.061(2)	0.004(1)	-0.003(1)	0.021(1)
O(5)	0.071(2)	0.068(2)	0.096(3)	-0.015(2)	-0.018(2)	0.008(2)
O(6)	0.058(2)	0.077(2)	0.059(2)	0.007(1)	0.006(1)	0.017(1)
O(7)	0.085(2)	0.057(2)	0.114(3)	0.011(1)	0.027(2)	0.024(2)
C(1)	0.053(2)	0.056(2)	0.053(2)	0.001(1)	0.000(2)	0.006(2)
C(2)	0.045(2)	0.047(2)	0.062(2)	0.003(2)	-0.002(2)	0.003(2)
C(3)	0.064(2)	0.042(2)	0.062(2)	0.004(2)	-0.005(2)	0.003(2)
C(4)	0.063(2)	0.052(2)	0.069(2)	0.005(2)	0.012(2)	0.002(2)
C(5)	0.041(2)	0.066(2)	0.079(2)	0.000(2)	-0.002(2)	-0.002(2)
C(6)	0.060(3)	0.071(2)	0.101(4)	0.006(2)	-0.019(3)	0.008(3)
C(7)	0.064(2)	0.047(2)	0.088(4)	-0.001(2)	-0.006(2)	0.015(2)
C(8)	0.073(2)	0.038(2)	0.099(3)	0.003(2)	-0.014(2)	0.016(2)
C(9)	0.081(3)	0.053(3)	0.114(4)	0.011(2)	0.000(3)	-0.007(3)
C(10)	0.108(3)	0.053(3)	0.138(6)	0.011(2)	-0.021(4)	-0.029(3)
C(11)	0.106(3)	0.048(3)	0.164(6)	-0.002(3)	-0.033(4)	-0.003(3)
C(12)	0.085(4)	0.055(3)	0.164(6)	-0.014(2)	-0.011(4)	0.012(3)
C(13)	0.086(3)	0.055(3)	0.112(4)	-0.011(2)	0.012(3)	0.021(3)
C(14)	0.055(2)	0.049(2)	0.056(3)	-0.004(2)	-0.003(2)	-0.003(2)
C(15)	0.062(2)	0.054(2)	0.066(3)	-0.005(2)	0.011(2)	0.004(2)
C(16)	0.071(2)	0.047(2)	0.077(3)	-0.005(2)	0.014(2)	0.005(2)
C(17)	0.059(2)	0.046(2)	0.069(3)	-0.005(1)	-0.004(2)	0.001(2)
C(18)	0.065(2)	0.048(2)	0.085(3)	0.001(2)	0.002(2)	0.002(2)
C(19)	0.065(3)	0.064(3)	0.087(4)	0.013(2)	0.004(2)	0.012(2)
C(20)	0.064(2)	0.058(2)	0.071(3)	0.003(2)	0.000(2)	-0.005(2)
C(21)	0.051(2)	0.064(2)	0.049(2)	0.000(2)	-0.006(2)	-0.003(2)
C(22)	0.048(2)	0.048(2)	0.055(2)	-0.005(1)	-0.005(2)	-0.004(2)
C(23)	0.051(2)	0.055(2)	0.049(2)	0.001(2)	-0.011(2)	0.003(2)
C(24)	0.052(2)	0.063(2)	0.092(3)	0.000(2)	0.003(2)	0.011(2)
C(25)	0.086(3)	0.083(3)	0.139(6)	-0.003(3)	0.015(4)	0.066(4)
C(26)	0.091(4)	0.166(6)	0.051(3)	0.035(4)	0.002(2)	0.018(4)
C(27)	0.095(3)	0.071(3)	0.129(5)	0.024(2)	0.016(4)	0.034(4)
C(28)	0.093(3)	0.069(2)	0.100(4)	-0.017(3)	0.033(3)	0.000(3)
C(29)	0.067(2)	0.065(2)	0.074(2)	-0.008(2)	0.017(3)	-0.002(2)
C(30)	0.088(3)	0.069(2)	0.073(3)	0.006(3)	0.010(3)	-0.003(3)
C(31)	0.105(4)	0.071(2)	0.100(4)	0.002(3)	0.025(4)	0.015(3)
C(32)	0.085(3)	0.062(3)	0.128(4)	-0.013(3)	0.009(4)	0.006(3)
C(33)	0.097(4)	0.078(3)	0.117(4)	-0.020(3)	-0.003(4)	-0.018(3)
C(34)	0.108(4)	0.080(3)	0.075(3)	-0.017(3)	-0.005(3)	-0.005(2)

The general temperature factor expression:

$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 4. Least Squares Planes

Plane number 1

Atoms defining plane	Distance
C(8)	0.002(5)
C(9)	0.004(7)
C(10)	-0.007(7)
C(11)	0.001(8)
C(12)	0.007(8)
C(13)	-0.008(7)

Additional Atoms	Distance
C(7)	0.062

Plane number 2

Atoms defining plane	Distance
C(14)	0.011(5)
C(15)	-0.052(6)
C(16)	-0.009(6)
C(17)	0.005(6)
C(18)	0.027(7)
C(19)	0.049(7)
C(20)	-0.022(6)
C(21)	-0.051(5)
C(22)	0.005(5)
C(23)	0.054(5)

Additional Atoms	Distance
O(4)	0.046
O(6)	-0.106
O(7)	0.042
C(1)	0.088

Plane number 3

Atoms defining plane	Distance
C(29)	-0.017(6)
C(30)	0.011(7)
C(31)	-0.002(8)
C(32)	-0.007(8)
C(33)	-0.002(8)
C(34)	0.016(8)

Additional Atoms	Distance
C(28)	-0.059

Plane number 4

Atoms defining plane	Distance
O(4)	-0.001(4)
O(5)	-0.002(5)
C(24)	0.007(6)
C(25)	-0.004(8)

Additional Atoms	Distance
C(23)	0.132

Summary

plane	mean	deviation
1	0.0046	3.2
2	0.0286	394.4
3	0.0090	13.2
4	0.0035	1.6

Dihedral angles between planes (°)

plane	1	2	3
2	75.76		
3	62.29	73.41	
4	65.21	106.33	33.54

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