THE SYNTHESIS OF 3-ALLYL-4-ETHYL-2-(1′-HYDROXYETHYL)-1-METHOXYNAPHTHALENE AND ITS BEHAVIOUR TOWARDS BASE- AND PALLADIUM-PROMOTED CYCLISATION UNDER AEROBIC AND ANAEROBIC CONDITIONS

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A thesis submitted in partial fulfillment of the requirements for the degree of Magister Scientiae in the Department of Chemistry, University of the Western Cape

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I declare that this thesis is my own account of my research and contains as its main content work, which has not previously been submitted for a degree at any tertiary educational institution.

Wendell Peter Swigelaar

2005

ABSTRACT

Over the years, Giles and co-workers have established that, upon treatment with potassium *tert*-butoxide, tetra-substituted naphthalenes undergo cyclisations to afford naphthopyrans. It was suggested that these base-induced cyclisations was as a result of the reacting centers being forced into close proximity as a consequence of steric crowding.

This thesis describes the synthesis of 3-allyl-4-ethyl-2-(1′-hydroxyethyl)-1-methoxy-naphthalene **177** and its behaviour towards Pd(0) and potassium *tert*-butoxide under aerobic and anaerobic conditions, to verify whether the base-promoted cyclisations are indeed caused by the steric influences of the substituents.

Two synthetic routes were attempted in the synthesis of the target naphthalene **177**. The first of these attempted routes involved the conversion of 2-acetyl-4-hydroxy-1-methoxynaphthalene **182** into 2-acetyl-1-methoxy-4-trifluoromethanesulphonyloxy-naphthalene **191** and subsequently into 2-acetyl-4-ethyl-1-methoxynaphthalene **192** via Stille coupling. However, the subsequent Snieckus *ortho*-directed metalation reactions on the reduced 4-ethyl-2-(1′-hydroxyethyl)-1-methoxynaphthalene **193**, and analogues of it, to afford naphthalene **177** were unsuccessful. The second route entailed a Claisen rearrangement of the tri-substituted 2-acetyl-4-allyloxy-1-methoxynaphthalene **209** to afford the unstable tetra-substituted 2-acetyl-3-allyl-4-hydroxy-1-methoxynaphthalene **210**, which was immediately converted into the corresponding 2-acetyl-3-allyl-1-methoxy-4-trifluoromethanesulpholnyloxynaphthalene **211**. Stille coupling of the triflate **211** gave the 2-acetyl-3-allyl-4-ethyl-1-methoxy-naphthalene **212**, which was subsequently reduced to the target naphthalene alcohol **177**.

The base-induced cyclisation studies performed on naphthalene **177**, confirmed the hypothesis that these cyclisations of terta-substituted naphthalenes are indeed as a result of steric crowding.

ABBREVIATIONS

$BF_3.OEt_2$ - boron trifluoride diethyl etherate

BuLi - butyl lithium

CAN - cerium (IV) ammonium nitrate

DCM - dichloromethane

DHP - dihydropyran

DMF - dimethylformamide

DMG - directing metalation group

DoM - directed *ortho* metalation

EtOAc - ethyl acetate

HCl - hydrochloric acid

PPTS - pyridinium-*p*-toluene sulfonate

TFA - trifluoroacetic acid

TMEDA - tetramethylethylenediamine

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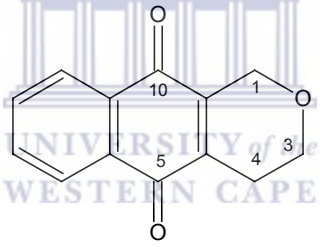
CHAPTER 1

INTRODUCTION

Various naturally occurring quinones containing the naphtho[2,3-*c*]pyran ring systems have been isolated from a variety of microorganisms, fungi, higher plants and animals. Over the years numerous research groups have been involved in the development of new methods for synthesis of the above mentioned ring systems as a result of their wide range of biological activities. This significant class of compounds acts as powerful antibiotics, anticancer, anti-coccidal, anti-fungal, and anti-microbial agents.

These naphthoquinones contain a basic structural skeleton of the naphtho[2,3-*c*]pyran ring system and occur commonly as the 5,10-quinones **1** with carbon substituents at C-1 and C-3. [1]



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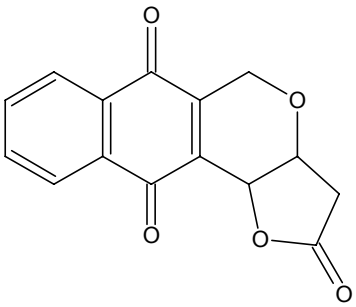
Some members of this group have an additional γ-lactone ring fused to the dihydropyran moiety **2** as the basic subunit. [1] Others possess a carboxylic acid side chain **3** caused by ring opening of the γ-lactone. [2]



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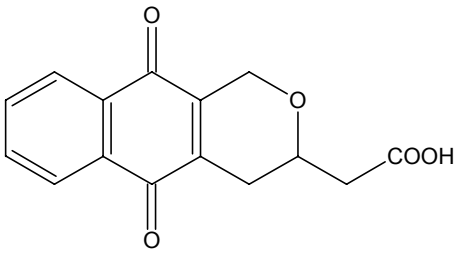

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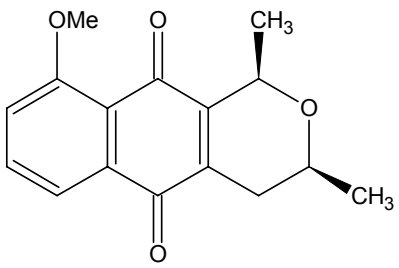
1.1 Natural occurrence and biological activity of naphthopyranquinones

Three major groups of naphtho[2,3-*c*]pyrans can be identified from these naphtho-quinones, based on the degree of oxidation of analogous polyketide precursors. [3] The first class, and the most common, is the 5,10-quinones. Eleutherin **4** and isoeleutherin **5** are the simplest examples of the naturally occurring naphtho[2,3-*c*]pyran-5,10-quinones and are found in *Eleutherin bulbosa*. [4]



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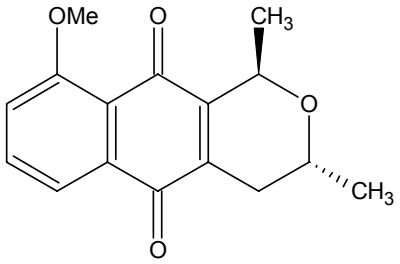

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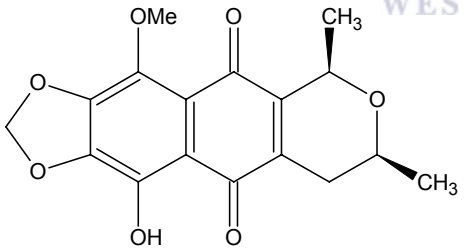
Other examples include ventiloquinone A **6** and B **7** isolated from the roots of *Ventilago maderaspatana*. [5]



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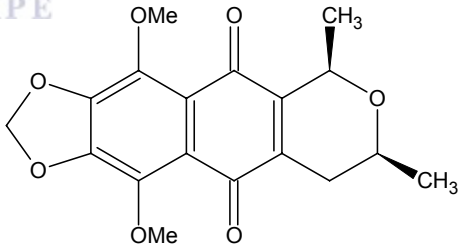

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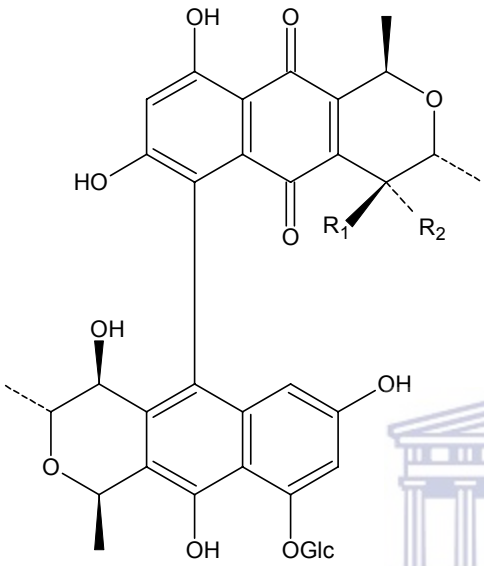
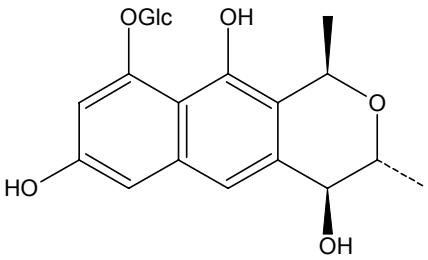
In 1950 protoaphins were isolated from the haemolymph of a dark species of *Aphididae*. [6] Two isomeric protoaphins have been studied and are respectively, the parent substances of the *fb* and *sl* series of aphid pigments i.e. protoaphin-*fb* **8** and protoaphin-*sl* **9**. Another aphid pigment is deoxyprotoaphin **10**.





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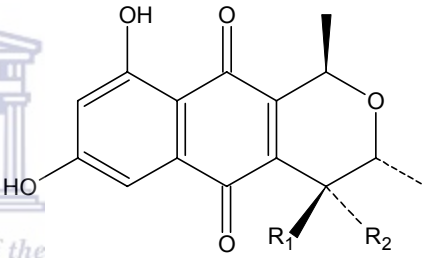
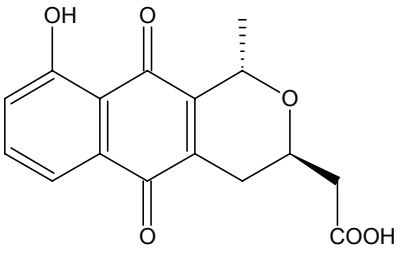


8	R_1 = OH, R_2 = H	**12**
9	R_1 = H, R_2 = OH	**13**
10	R_1 = R_2 = H	**14**

Glucoside B **11** is the β-glycosidic naphthopyran obtained by reductive cleavage of each of the aphid pigments. [7] A second naphthopyran is also isolated as the 5, 10-quinone upon aerial reoxidation of each reaction mixture. Thus, in addition to **11**, this process also yields quinone A **12** from protoaphin-*fb* **8**, quinone A' **13** from protoaphin-*sl* **9** and deoxyquinone A **14** from deoxyprotoaphin **10**. [7]

In 1974 Omura and co-workers [8] isolated nanaomycin A **15** and C **16** from *Streptomyces rosa var. notoenses*.



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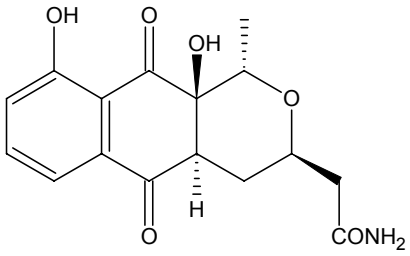

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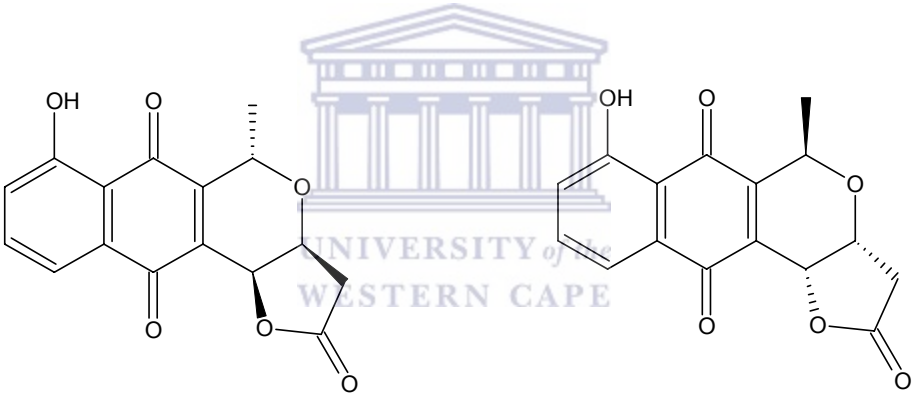
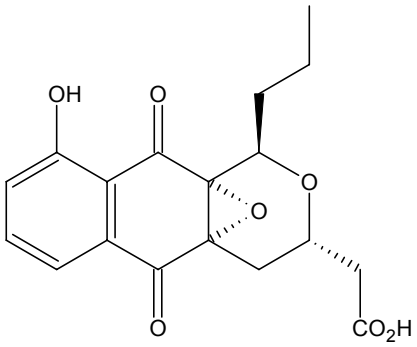
Enantiomers nanaomycin D **17** and kalafungin **18** were isolated from *Streptomyces tanashiensis* and both display antimicrobial, anti-tumor, anti-fungal and antineoplastic activity.[9]



17 **18**

Other 5,10-quinones of the family of naphthopyranquinone antibiotics include frenolicin **19** [10], granaticin **20** [11], and griseusin A and B, **21** and **22** [12], which have been isolated from the cultures of *Streptomyces roseofulvus* [13], *Streptomyces olivaceus* [14], and *Streptomyces griseus* [15] respectively.



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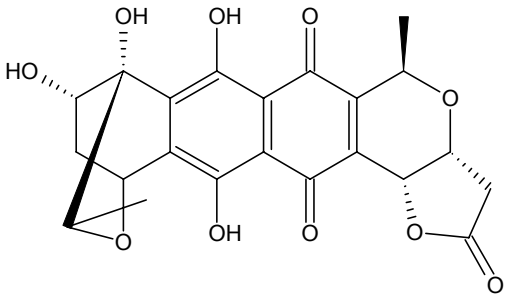

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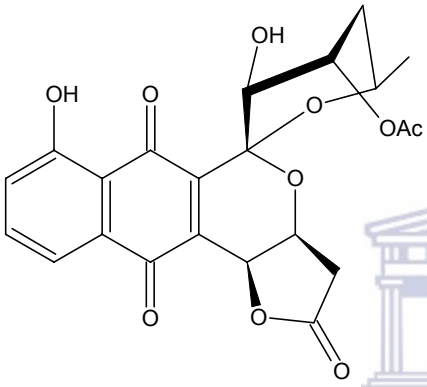

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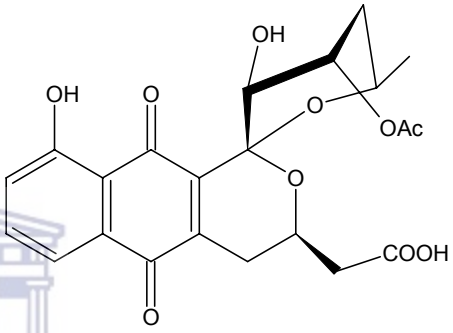

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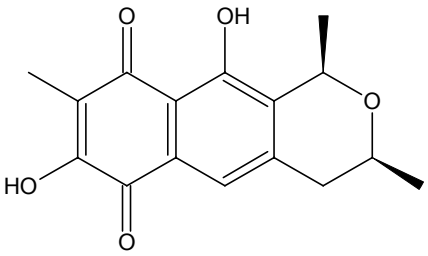
The second class of naphtho[2,3-*c*]pyrans includes the isomeric 6,9-quinones, which are not as widely found in nature. Examples of this class of compounds are ventilagone **23** [16] and ventiloquinone G **24** [5].



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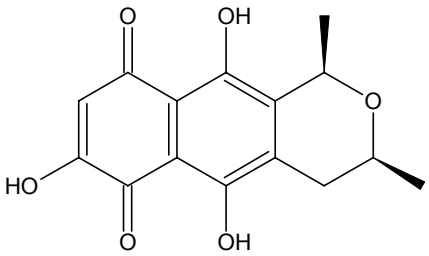

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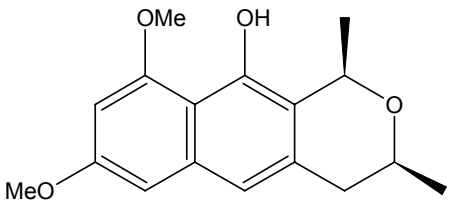
The third class is represented by non-quinonoid systems such as the naphthopyran karwinaphthol B **25** [3].



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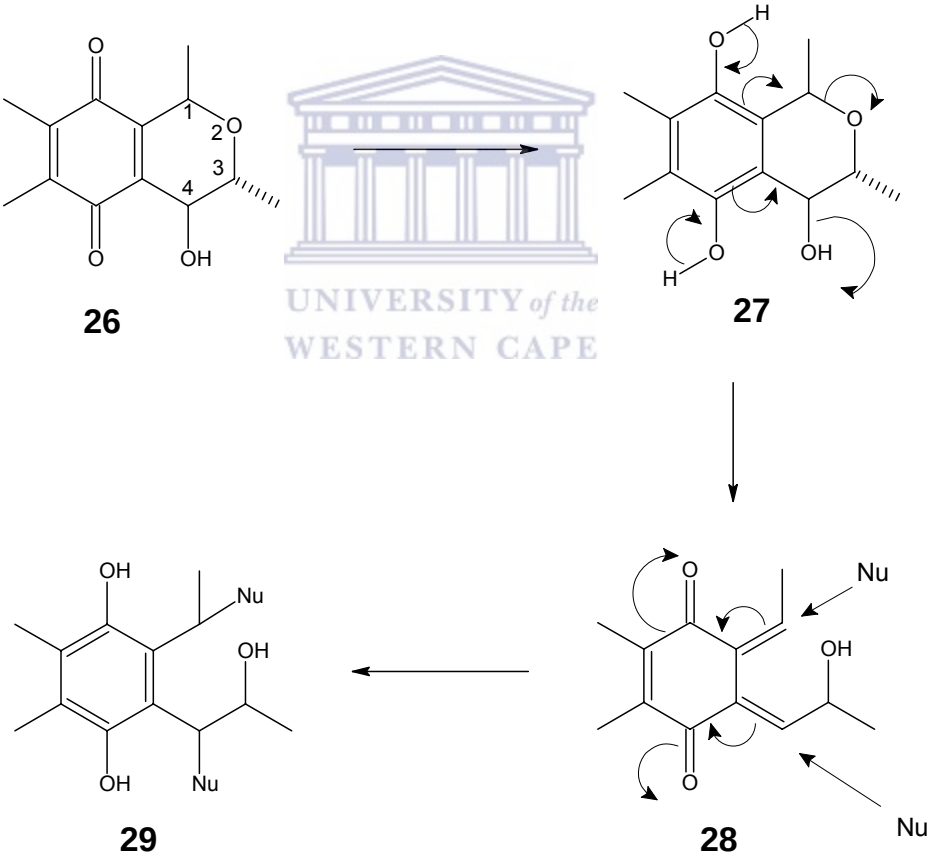
1.2 Bioreductive Alkylation

The term bioreductive alkylating agents refers to those types of compounds that become potent alkylating agents after they undergo reduction *in vivo*. Such reactive species may then alkylate DNA/RNA and/or other biomolecules resulting in potentially effective cancer-inhibitory drugs. From the work done by Sartorelli *et al*. [17, 18], Moore [19] proposed a mechanism for the biological activity of several natural products as depicted by **Scheme 1**. According to Moore the quinone **26** undergoes initial *in vivo* reduction to the quinol **27**.



Scheme 1

In order for ring opening of the pyran-ring to occur, the C-1-O and C-4-O bonds must undergo cleavage. This results in the formation of the highly active bisquinone-methide system **28** that in turn is able to react with biological nucleophiles such as DNA, proteins and carbohydrates to yield **29** effectively altering the activities of the nucleophilic species that reacted with intermediate **28**. Further oxidation of the product **29** will result in a biologically inactive quinone.

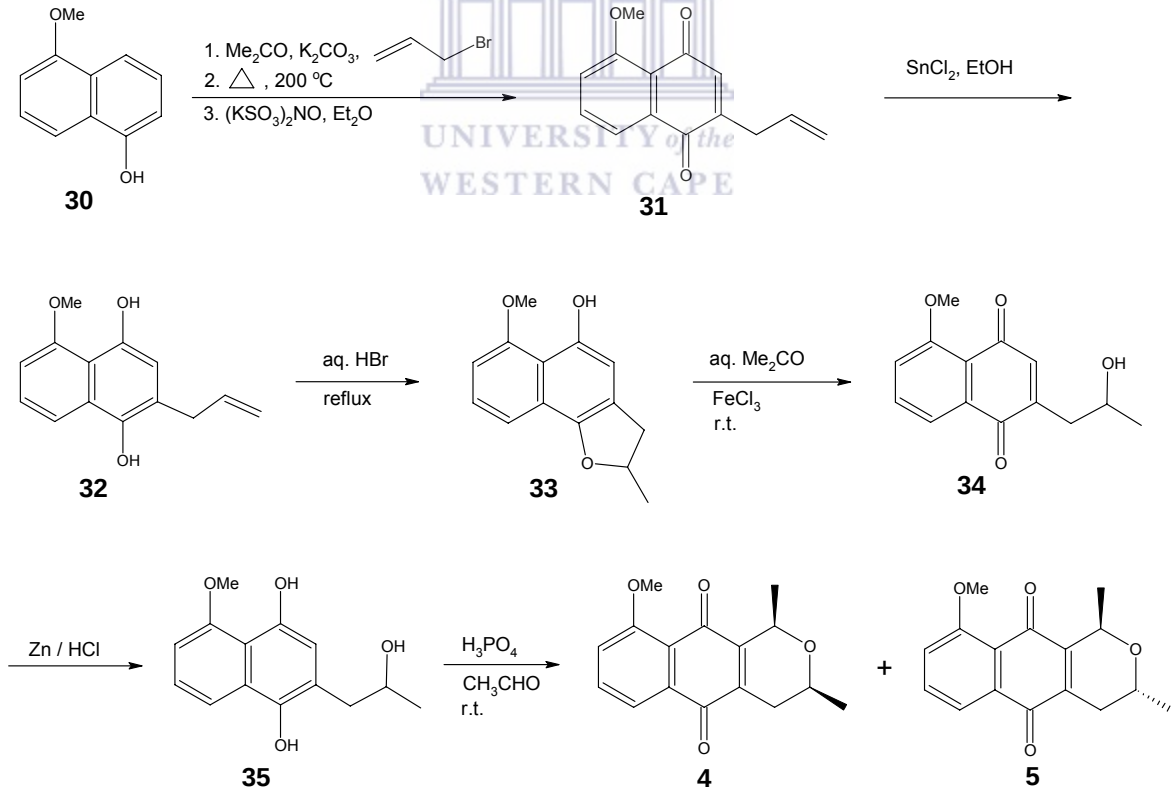
Moore [19] includes the eleutherins, γ-actinorhodin, granaticin, kalafungin, the nanaomycins D, A and C, γ-naphthocyclinone and the protoaphins in a list of examples of possible bioreductive alkylating agents. Work done by Brimble and colleagues [20, 21] supports the argument that the aforementioned naturally occurring pyranonaphthoquinones may undergo similar reductive thioalkylations, however the precise mechanism of thioalkylation still remains open for discussion.

CHAPTER 2

SYNTHESIS OF NATURALLY OCCURRING NAPHTHOPYRAN-QUINONE ANALOGUES

2.1 The Eleutherins

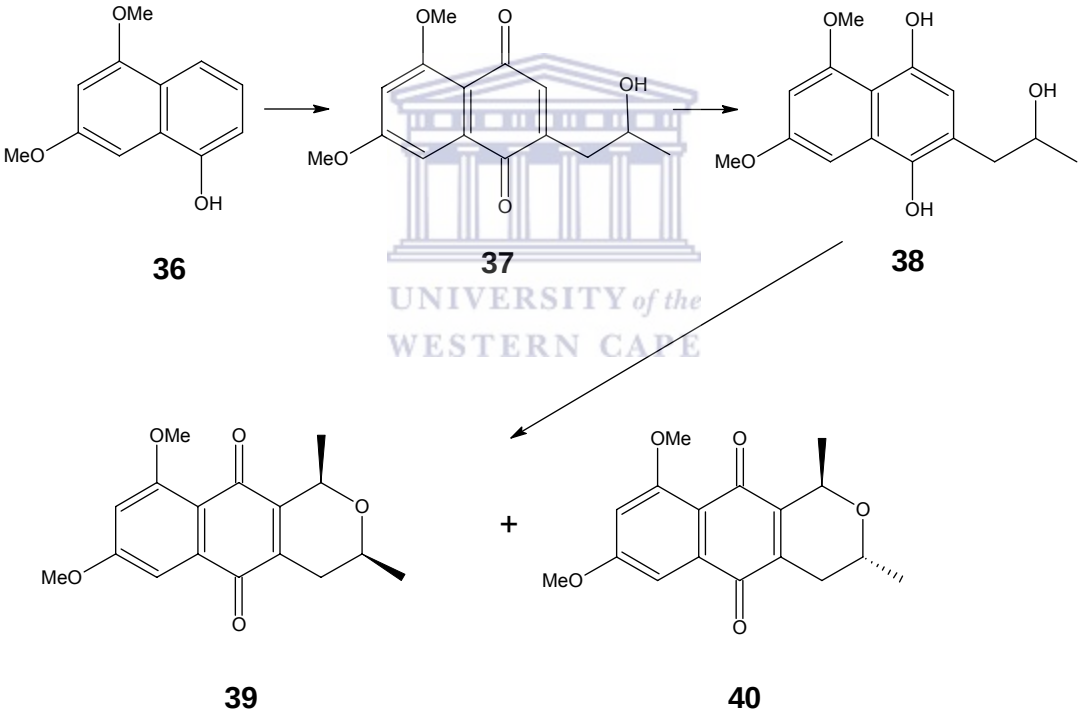
The pyran ring of a number of naphthopyranquinones has been formed by the condensation between 3-(2-hydroxyalkyl)naphthoquinones and aldehydes under acidic conditions. The synthesis of eleutherin **4** and isoeleutherin **5** were first reported by Eisenhuth and Schmid [22] and started with the allylation of 5-methoxy-1-naphthol **30** and Claisen rearrangement followed by oxidation of the derived phenol into the allylquinone **31 (Scheme 2)**.



Scheme 2

Reduction of the quinone **31** with stannous chloride to the corresponding hydroquinone **32** and subsequent cyclisation with HBr gave the hydrofuran **33**. Reoxidation of the furan **33** with Fe (III) chloride produced the hydroxypropylquinone **34**. The key step in the synthesis involved the reduction of the quinone **34** to the quinol **35** followed by a condensation reaction with acetaldehyde under acidic conditions to afford a separable racemic mixture of the epimeric eleutherin **4** and isoeleutherin **5** as their racemates.

Using a similar approach Cameron *et al*. [23] reported the synthesis of (±)-7-methoxy eleutherin **39** and (±)-deoxyquinone A dimethyl ether **40 (Scheme 3)**. Conversion of the naphthol **36** to the hydroxypropylquinone **37** proceeded in the same manner as previously described [22] **(Scheme 2)**.

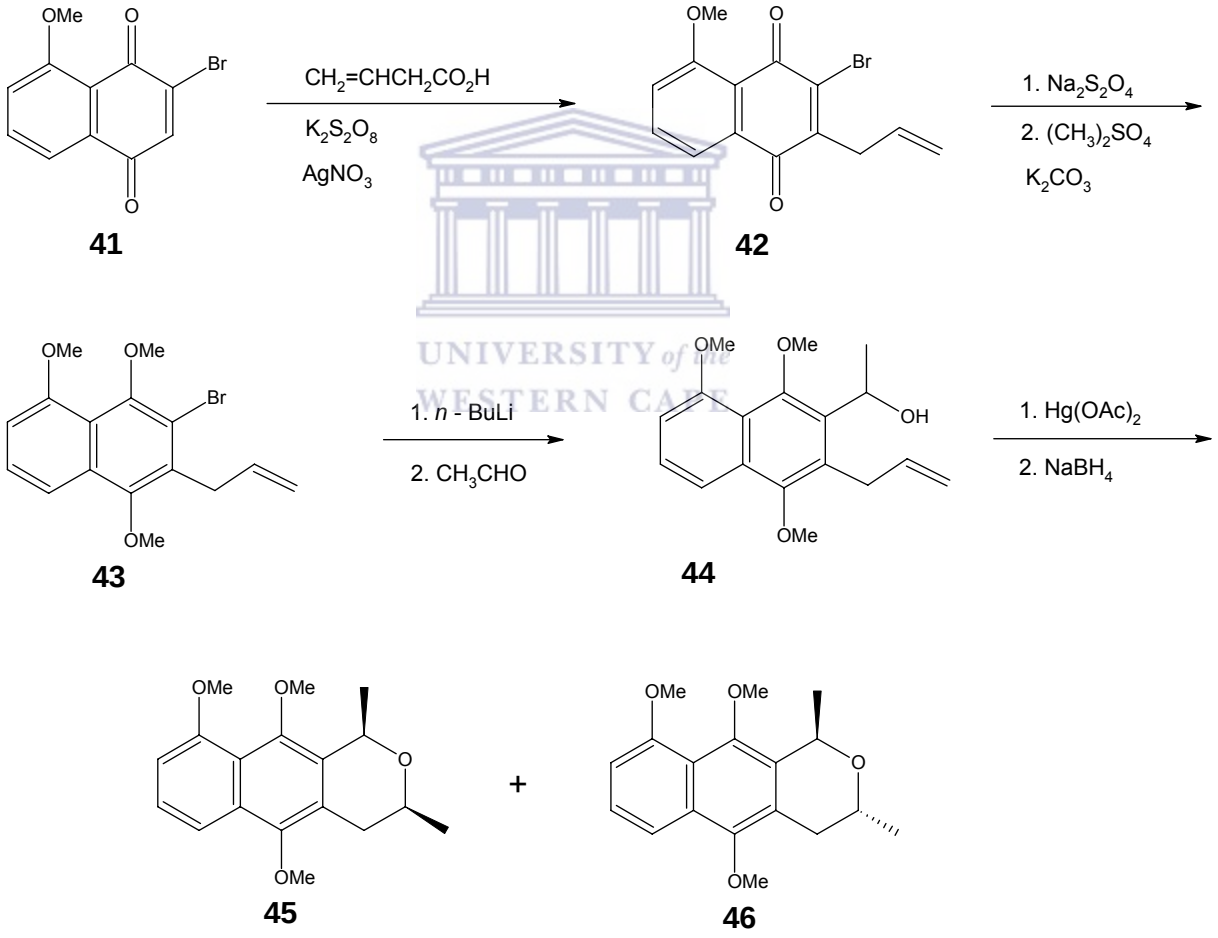


Scheme 3

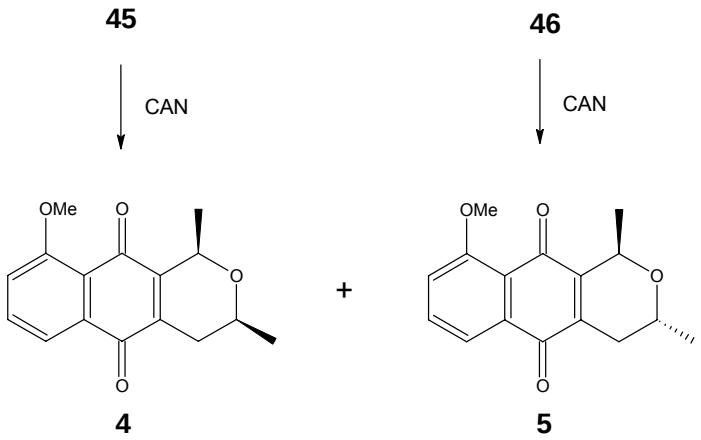
Reduction of the quinone **37** to form the quinol **38**, by using an excess of zinc and HCl in tetrahydrofuran followed by condensation with acetaldehyde and atmospheric reoxidation afforded a 3:1 mixture of the *cis* and *trans* pyranquinones **39** and **40** respectively.

In 1981, Yoshii and co-workers [24] described a shorter route to racemic eleutherin **4** and isoeleutherin **5**. Oxidative alkylation of 2-bromo-8-methoxy-1,4-naphthoquinone **41** [25] with vinylacetic acid in the presence of persulphate and silver nitrate gave the 3-allyl derivative **42** which was then reduced and methylated to afford 3-allyl-2-bromo-1,4,8-trimethoxynaphthalene **43 (Scheme 4)**.

Treatment of the trimethoxynaphthalene **43** with *n*-butyl lithium and the subsequent addition of acetaldehyde resulted in the formation of the naphthylcarbinol **44**. Acetoxy-mercuration-demercuration of **44** afforded the cyclisation product, a *ca*. 1: 0.9 mixture of stereoisomers **45** and **46**.



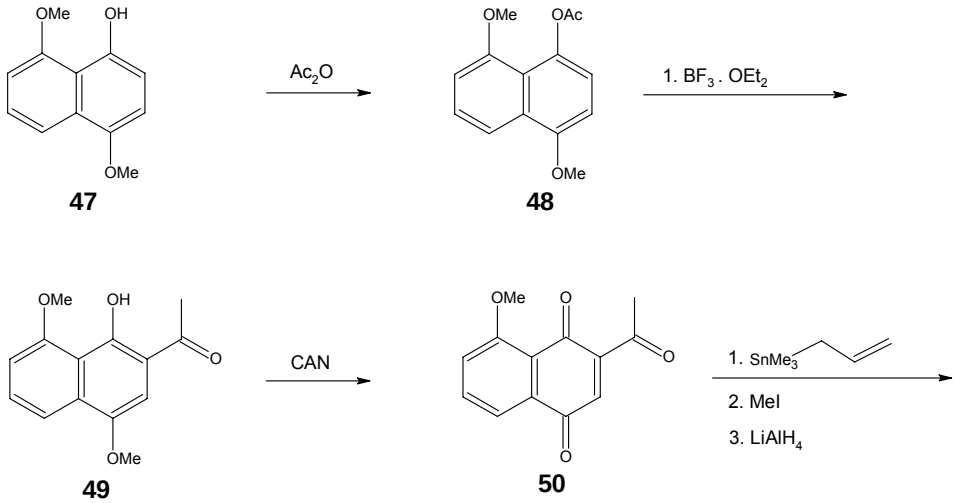
Scheme 4(contd. over)



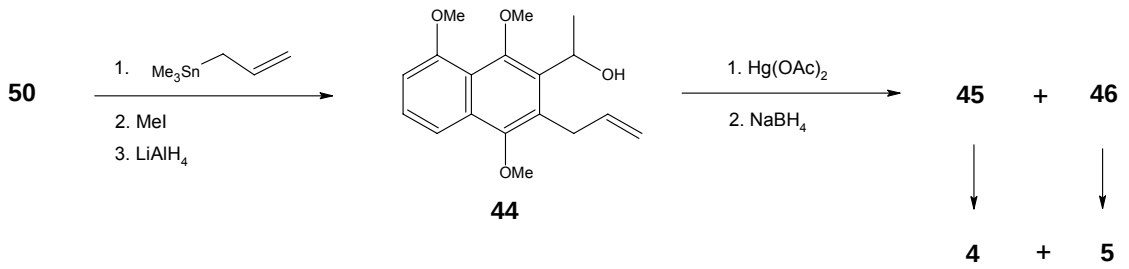
Scheme 4 (contd.)

The isomers **45** and **46** were separated chromatographically and oxidized with cerium (IV) ammonium nitrate to afford (±)-eleutherin **4** and (±)-isoeleutherin **5** in 87 and 82% yield respectively.

Naruta *et al*. [26] reported a different route to the naphthylcarbinol **44**. 4,8-Dimethoxy-1-naphthol **47** was acetylated to give the acetate **48 (Scheme 5)**. Fries rearrangement of **48** on treatment with boron trifluoride diethyl etherate afforded the 2-acetyl derivative **49**, which then underwent oxidative demethylation with cerium (IV) ammonium nitrate to yield the naphthoquinone **50**.



Scheme 5 (contd. over)

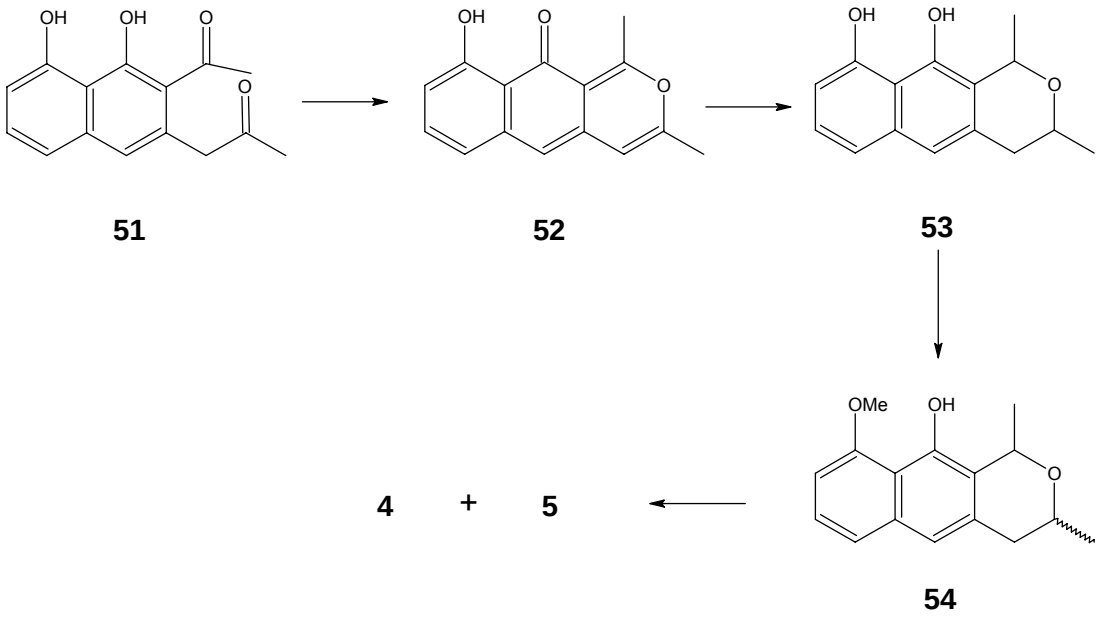


Scheme 5 (contd.)

Nucleophilic addition of allyltrimethylstannane [27] to **50** in the presence of boron trifluoride diethyl etherate followed by methylation and reduction resulted in the formation of the key benzylic alcohol **44**. Cyclisation of **44** then followed as previously described **(Scheme 4)**.

In an alternative method by Giles *et al.* [28], it was reported that potassium *t*-butoxide in dimethylformamide under nitrogen caused cyclisation of the naphthylcarbinol **44** to afford the *trans*-isomer **46** in 88% yield, uncontaminated by the *cis*-isomer. It is suggested that base-catalysed conjugation of the isolated double bond precedes cyclisation [28]. Oxidation of **46** with cerium (IV) ammonium nitrate then gave (±)-iso-eleutherin **5**.

Harris and Webb [29] reported a biogenetically modeled synthesis of the racemic eleutherin **4** and isoeleutherin **5**. In this synthesis, cyclisation was achieved by the treatment of the naphthyl diketone **51** with a catalytic amount of trifluoroacetic acid to form the pyrene **52**. Catalytic reduction of the pyrene **52** afforded the air-sensitive naphthopyran **53**. Immediate treatment of **53** with an excess of ethereal CH_2N_2 gave a 9:1 *cis* : *trans* isomeric mixture **54** in the absence of light. Fremy salt oxidation of the isomeric mixture **54** gave the corresponding quinones **4** and **5** in a combined yield of 56% **(Scheme 6)**.

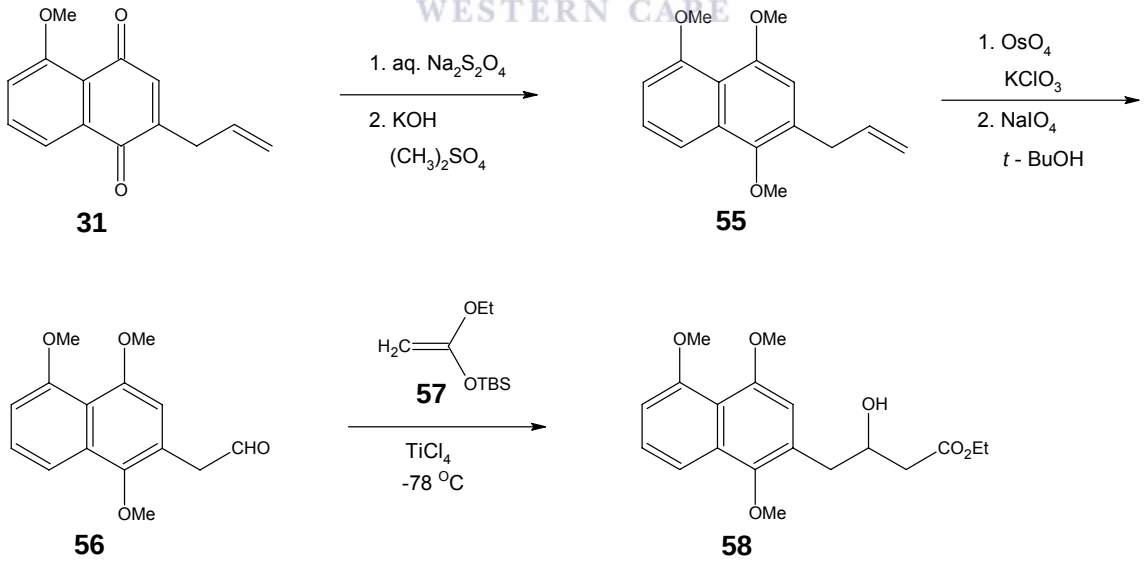


Scheme 6

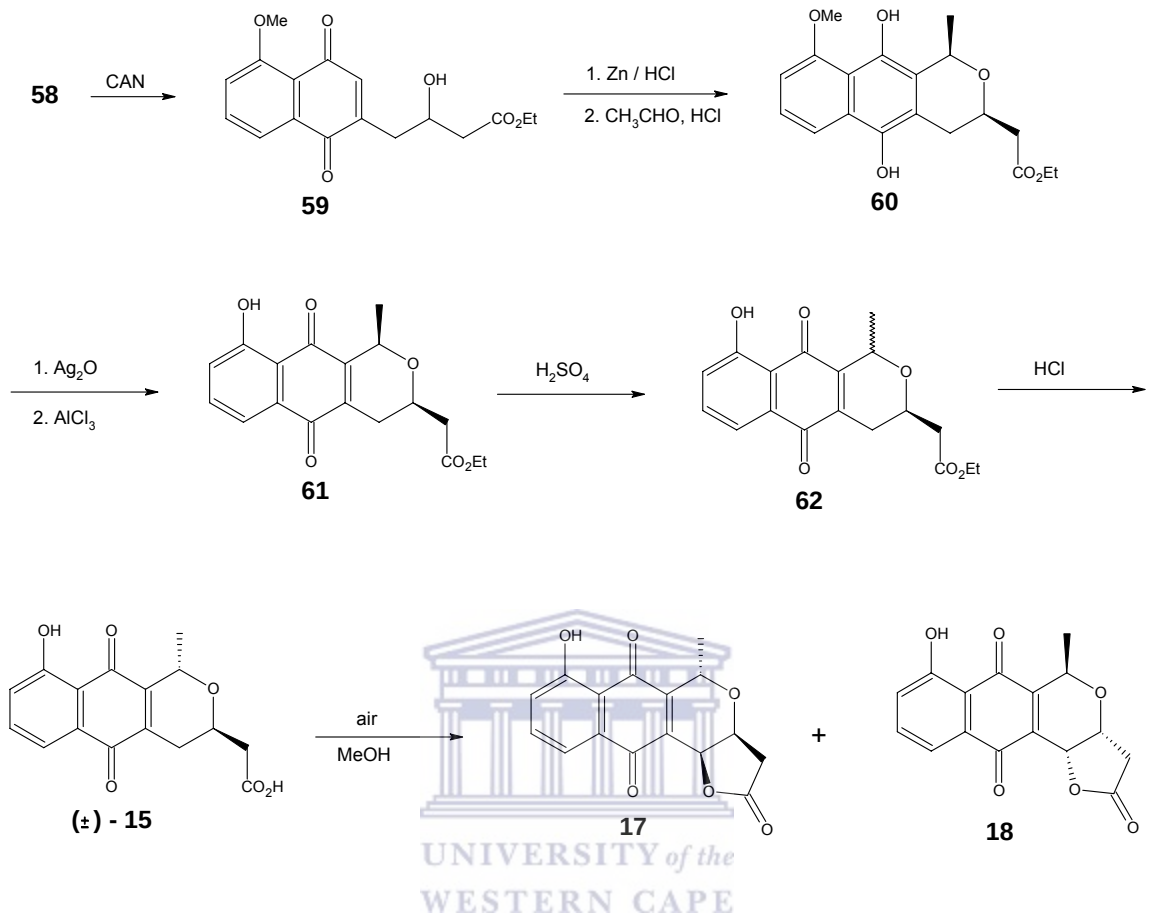
2.2 Nanaomycins and Kalafungin

There have been many interesting synthetic routes to kalafungin, the nanomycins and their derivatives since these compounds were first isolated and identified as having significant anti-microbial properties.

The first synthesis of the racemate of kalafungin **18** and nanaomycin A **15** and D **17** were reported by Li and Ellison in 1978 [30] **(Scheme 7)**. They used the same methodology reported by Schmid [22] for the synthesis of the eleutherins, and started with the same quinone **31**, which was reduced with aqueous sodium dithionate to form the corresponding hydroquinone, and subsequent methylation with dimethyl sulphate afforded the allylnaphthalene **55**. Vicinal dihydroxylation of the propenyl side chain and oxidative cleavage of the resultant diol by using osmium tetroxide and potassium chlorate afforded the aldehyde **56**. Chain extension to the hydroxy ester **58** was achieved by adding a catalytic amount of titanium tetrachloride to a mixture of **56** and ketene ethyl *tert*-butyldimethylsilyl acetal **57**. Oxidative demethylation of **58** with cerium (IV) ammonium nitrate gave the quinone **59**.



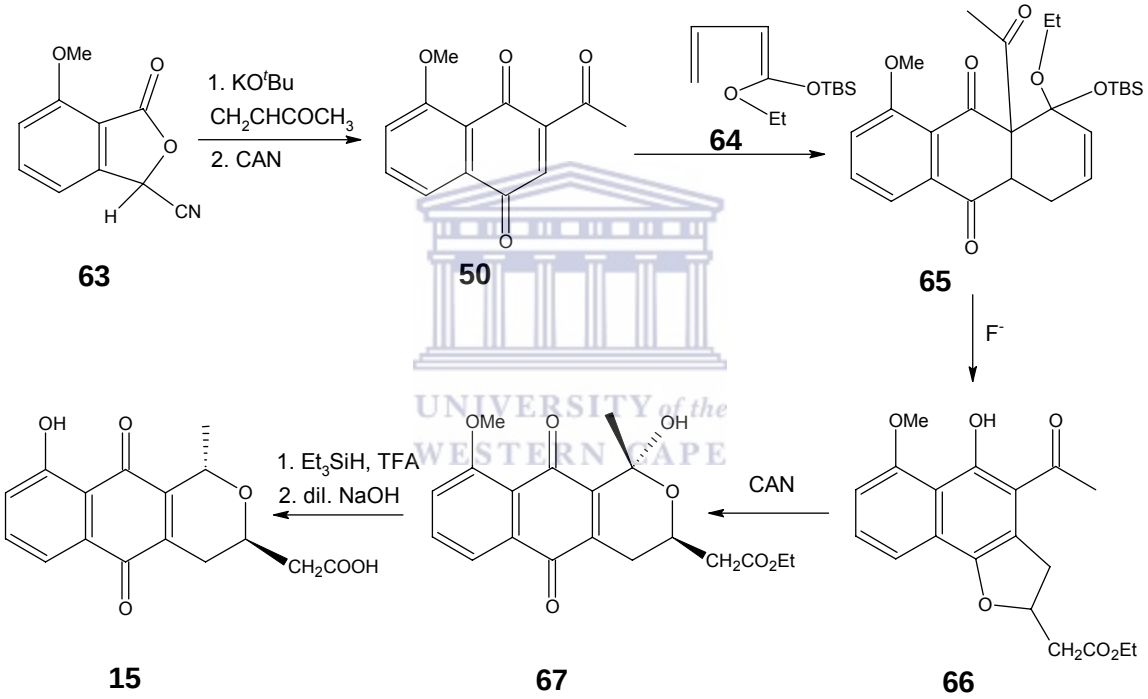
Scheme 7 (contd. over)



Scheme 7 (contd.)

Reduction of **59** with zinc and hydrochloric acid in tetahydrofuran and subsequent reaction with acetaldehyde produced the naphthopyran **60**. Oxidation with silver (I) oxide and *O*-demethylation with aluminium chloride afforded the *cis* naphthopyranquinone **61**. Treatment of **61** with concentrated sulfuric acid induced epimerisation at C-1 to form a 2:1 ratio of the *cis* and *trans* isomers **62**. The individual diastereomers were separated by fractional distillation. Hydrolysis of the *trans* isomer of **62** with concentrated hydrochloric acid gave the racemic nanaomycin A **15**. Treatment of nanaomycin A **15** with aerated methanol gave a mixture of racemic nanaomycin D **17** and kalafungin **18** respectively.

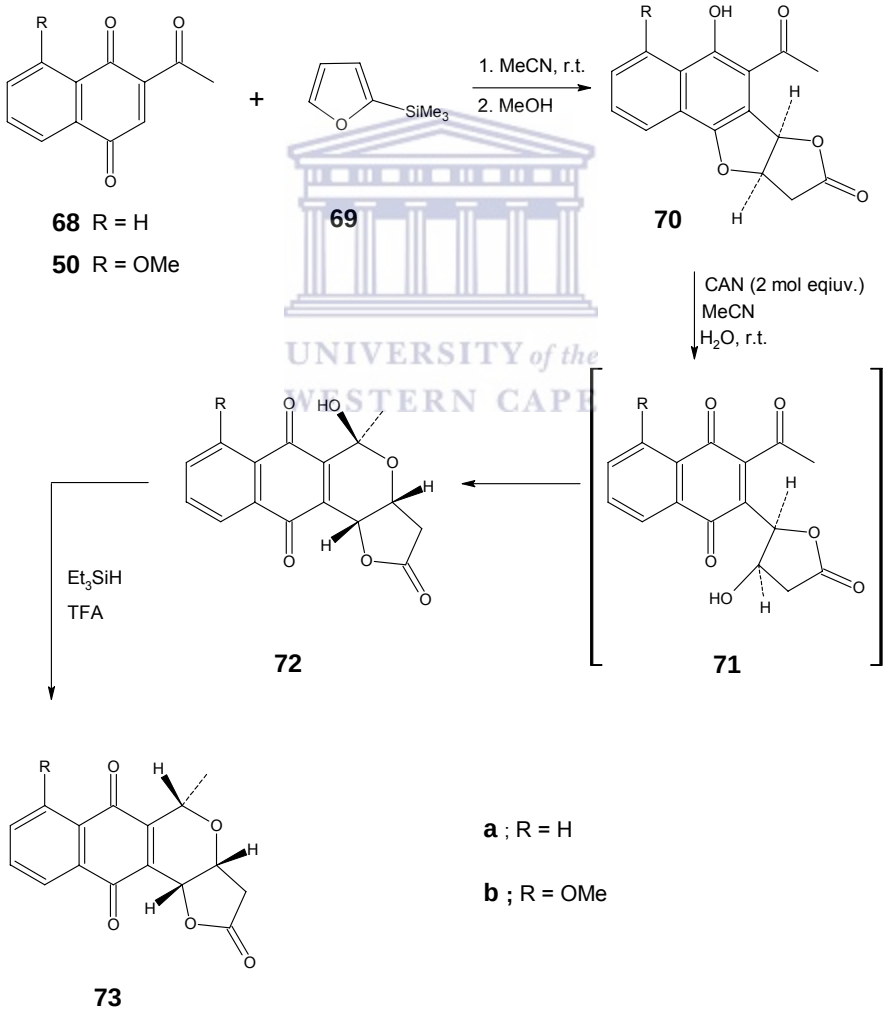
In 1987, Kraus *et al*. [31] reported that nanaomycin A **15** can be synthesized using the Diels-Alder/retro Claisen (DARC) reaction **(Scheme 8)**. Deprotonation of the cyanophthalide **63**, followed by Michael addition with methyl vinyl ketone and an intra molecular Claisen reaction, afforded a hydroquinone that was then oxidized with cerium (IV) ammonium nitrate to quinone **50**. The Diels-Alder reaction of **50** with the diene **64** afforded the naphthalene **65**. The *cis* crotonate subunit that was liberated by the retro-Claisen reaction of **65**, with tetrabutyl-ammonium fluoride in tetrahydrofuran, rapidly reacted with the neighbouring phenol to produce the angular naphthofuran **66**.



Scheme 8

Oxidation of **66** with cerium (IV) ammonium nitrate produced the key hemiketal **67** in 71% yield. Both the proton and carbon NMR spectra of **67** indicated that only one hemiketal was present. Treatment of **67** with triethylsilane and trifluoroacetic acid and subsequent hydrolysis with dilute sodium hydroxide produced nanaomycin A **15**.

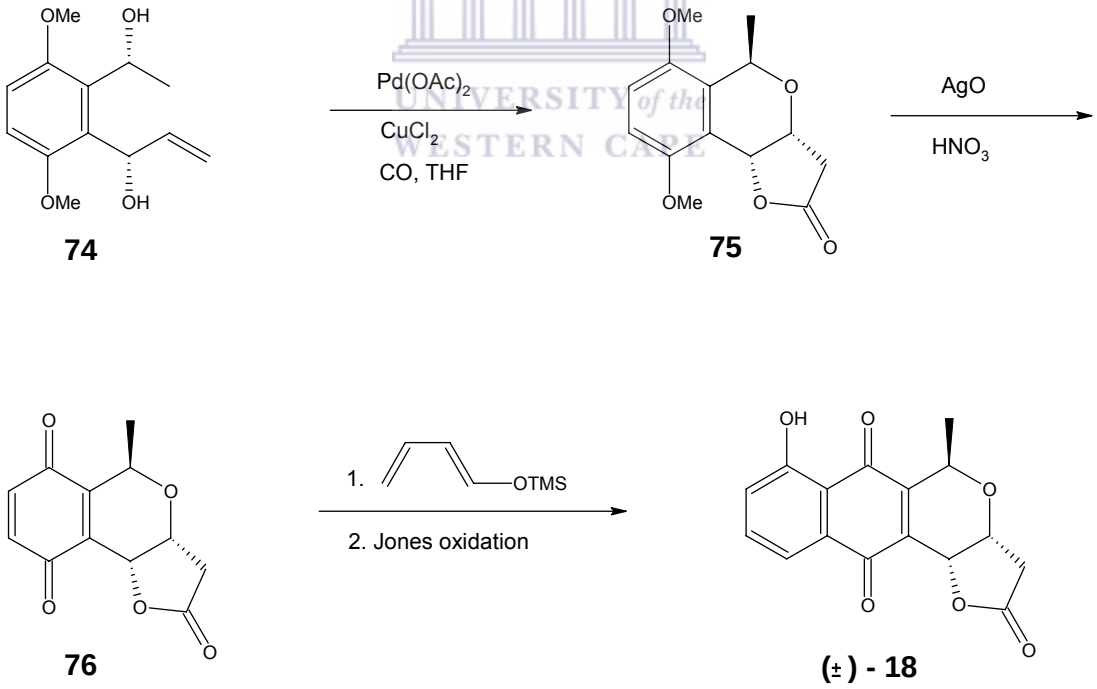
In 1990, Brimble *et al*. [32, 33] reported the synthesis of 5-*epi*-7-deoxykalafungin **73a** and 5-*epi*-7-O-methylkalafungin **73b**, making use of a rearrangement of a furo[3,2-*b*] naphtho[2,1-*d*]furan to a pyranonaphthoquinone . Addition of 2-trimethylsilyloxyfuran **69** to the naphthoquinones **68** and **50** gave the desired furo[3,2-*b*]naphtho[2,1-*d*]furans **70** **(Scheme 9)**. Castagnoli, Jr. *et al*. [34] had reported that cerium (IV) ammonium nitrate in aqueous acetonitrile can be used to oxidize a variety of hydroquinone methyl ethers to the corresponding quinones. In a similar reaction reported by Kraus [31] **(Scheme 8)** cerium (IV) ammonium nitrate was added to a solution of the furans **70** in acetonitrile to afford the desired pyranonaphthoquinones **72**.



Scheme 9

It was proposed that the 6-acetyl-5-hydroxylactones **70**, as cyclic ethers of a hydroquinone, might undergo an analogous oxidative dealkylation reaction to give the β-hydroxylactones **71**. Subsequent nucleophilic attack of the hydroxyl group on the methyl ketone would then give rise to the hemiacetals **72**. Using the method of Kraus [31] the hemiacetals **72** were reduced to the ethers **73** with a *cis*-relationship between the groups at C-5 and C-3a. This was consistent with axial delivery of hydride from triethylsilane as reported by Kraus [31].

In 1995 Kraus *et al*. [36] reported a shorter and more direct route to racemic kalafungin **18**, which is outlined in **Scheme 10**. The starting diol **74** was treated with palladium acetate and cupric chloride under an atmosphere of carbon monoxide to give lactone **75** in 61% yield. Oxidation using silver (II) oxide generated the benzoquinone **76** which was treated with 1-trimethylsilyloxy-1,3-butadiene in dichloromethane followed by Jones oxidation to provide racemic **18** in moderate yield from **76**.

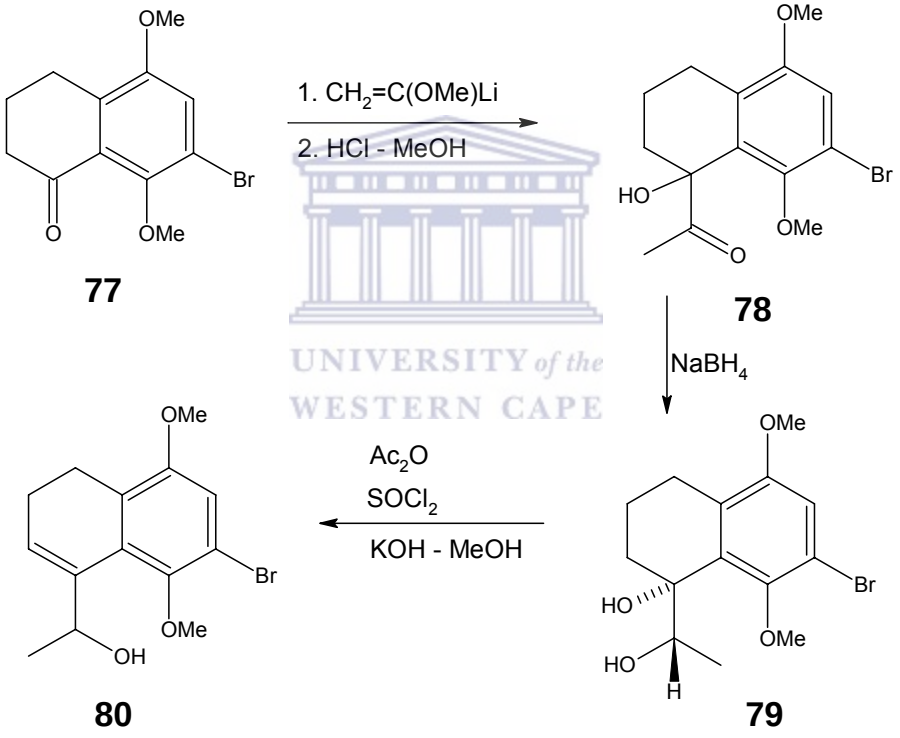


Scheme 10

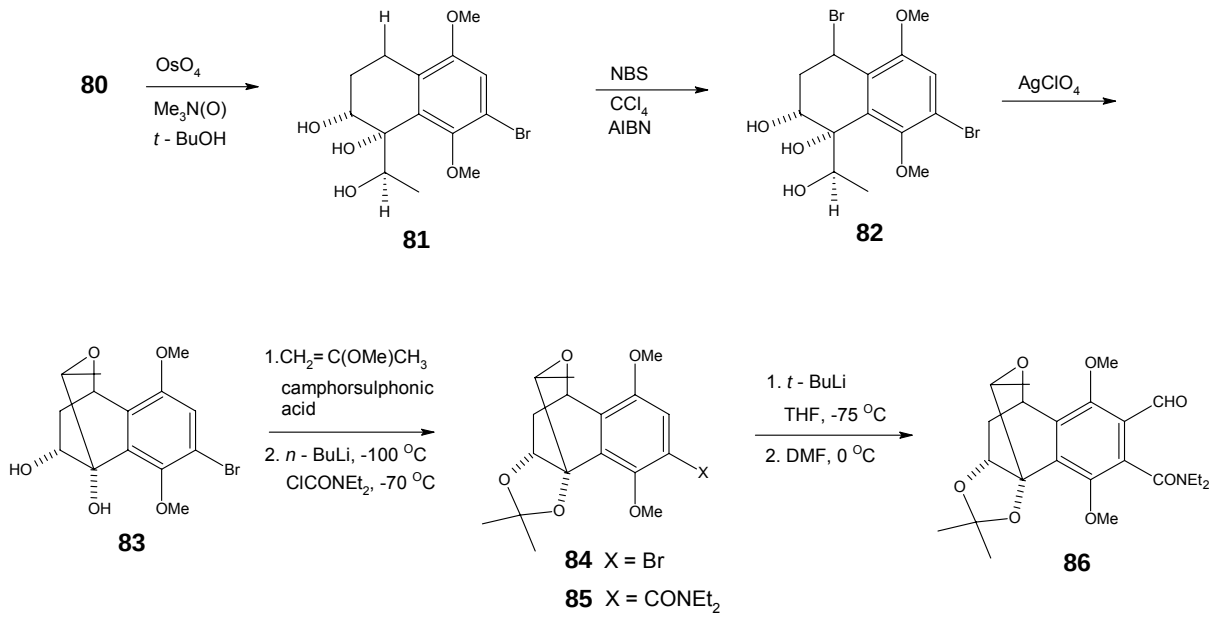
2.3 The Granaticins

Yoshii and co-workers [36] were the first to achieve the challenging total synthesis of granaticin **20** with its unique structural feature, the 2-oxabicyclo[2,2,2]oct-5-ene moiety. In 1987, they reported the synthesis of racemic granaticin **20 (Scheme 11)**.

Reaction of the tetralone **77** with lithiated methyl vinyl ether followed by brief acid-treatment of the reaction product afforded α-ketol **78**. This material was then reduced with sodium borohydride to afford **79** as a 1:9 mixture of diastereomers. Regioselective dehydration of **79** afforded the allylic alcohol **80**.

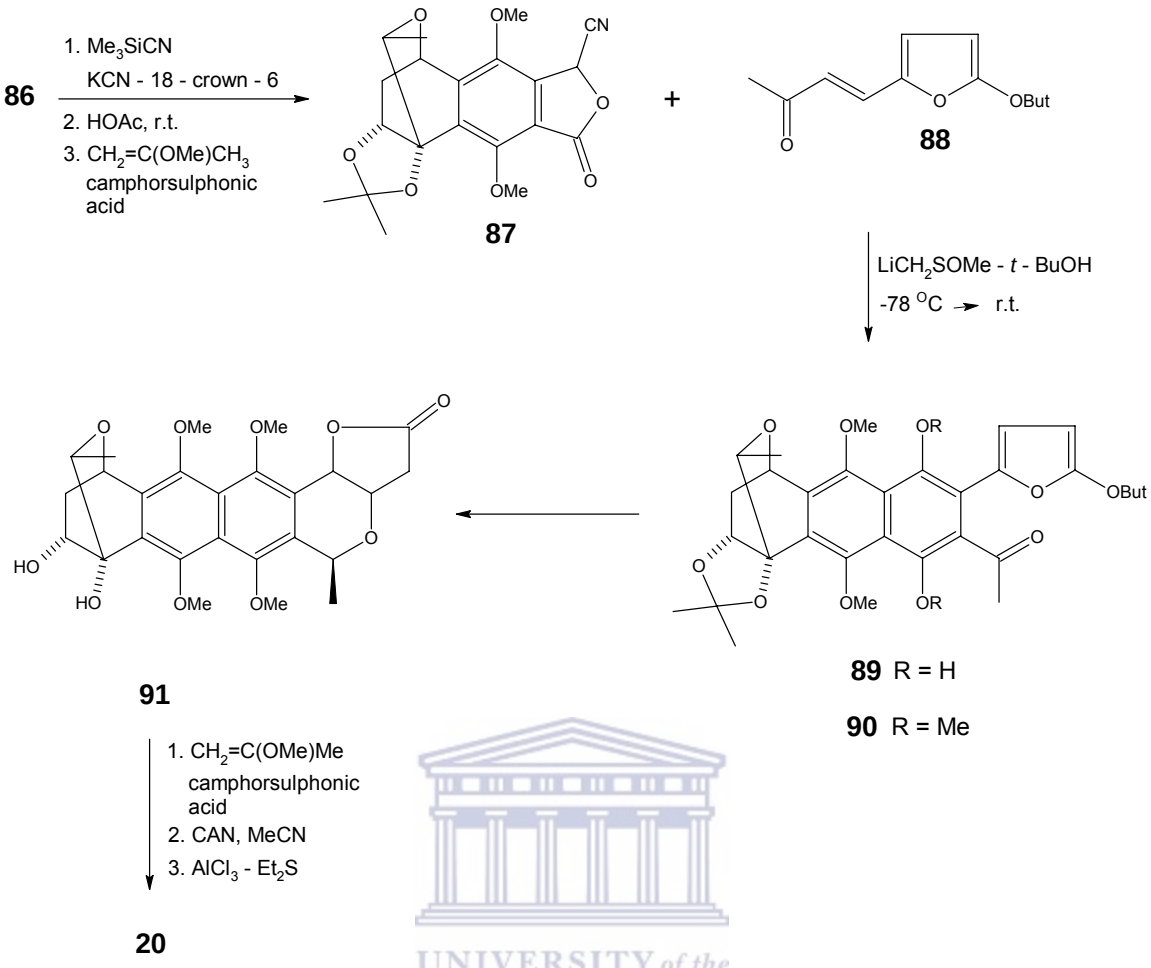


Scheme 11 (contd. over)



Scheme 11 (contd. over)

Catalytic osmylation of **80**, using trimethylamine *N*-oxide as cooxidant, in aqueous *tert*-butyl alcohol produced a 25:1 mixture of the triol **81** and its 1` epimer. The pure diastereomer **81** was readily obtained by recrystallization of the miture from *i*-Pr_2O-AcOEt in 65% from **80**. Treatment of **81** with *N*-bromosuccinimide in the presence of azobisisobutyronitrile afforded the benzylic bromination product **82**, which on treatment with silver perchlorate gave the oxabicycle **83**. The stereochemistry of **83** was determined by ^{1}H NMR spectroscopy [37]. Replacement of the aryl bromine atom in **83** with the *N*,*N*-diethylcarbamoyl group was carried out on its acetonide **84** by sequential treatment with *n*-butyllithium and diethylcarbamoyl chloride to afford **85**. Introduction of a formyl group onto the free position of the aromatic ring was achieved by treating compound **85** with *tert*-butyllithium and then with *N*,*N*-dimethylformamide to afford aldehyde **86**. Compound **86** was then transformed into the cyanophthalide **87** *via* a different method developed by the group [36].



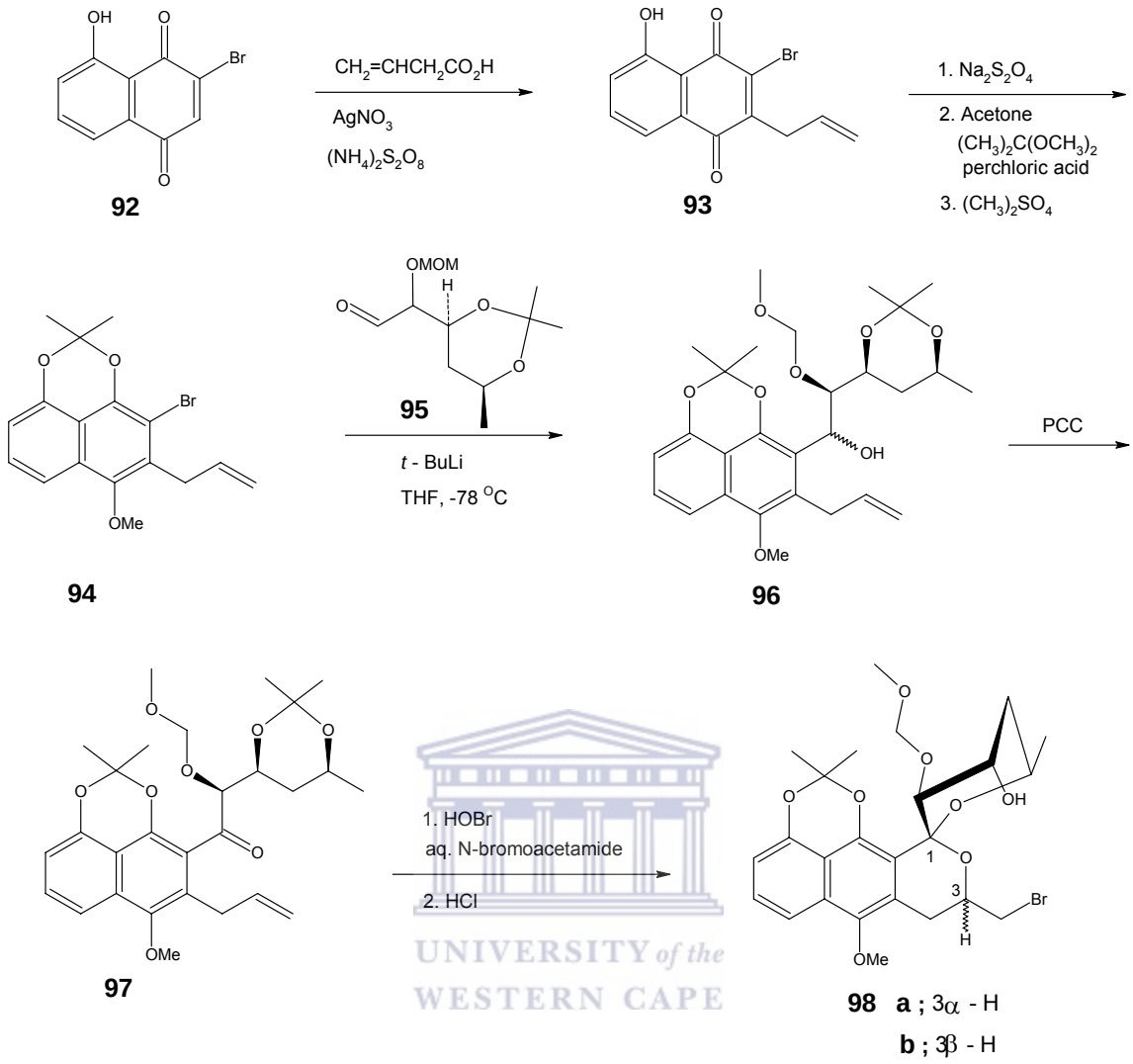
Scheme 11 (contd.)

Through Kraus' benzannulation [38] the naphthyl ketone **89** was obtained by using 5-*tert*-butoxy-2-furfurylidene-acetone **88** as a Michael acceptor. *O*-Methylation of **89** with dimethyl sulfate and potassium carbonate afforded **90**. Using a modified method [39] of the Kraus protocol [40], the pyrano-γ-lactone annulation on **90** afforded four pyrano-γ-lactones bearing the granaticin skeleton with compound **91** being isolated in 32% yield [36]. Protection of the 1, 2-diol group followed by oxidative demethylation with cerium (IV) ammonium nitrate and subsequent treatment of the crude product with aluminium chloride-diethyl sulfide complex afforded the racemic mixture of granaticin **20**. The synthetic (±)-**20** was identical with a sample of natural granaticin in terms of the ^{1}H NMR and UV spectra and R_f values (TLC).

2.4 The Griseusins

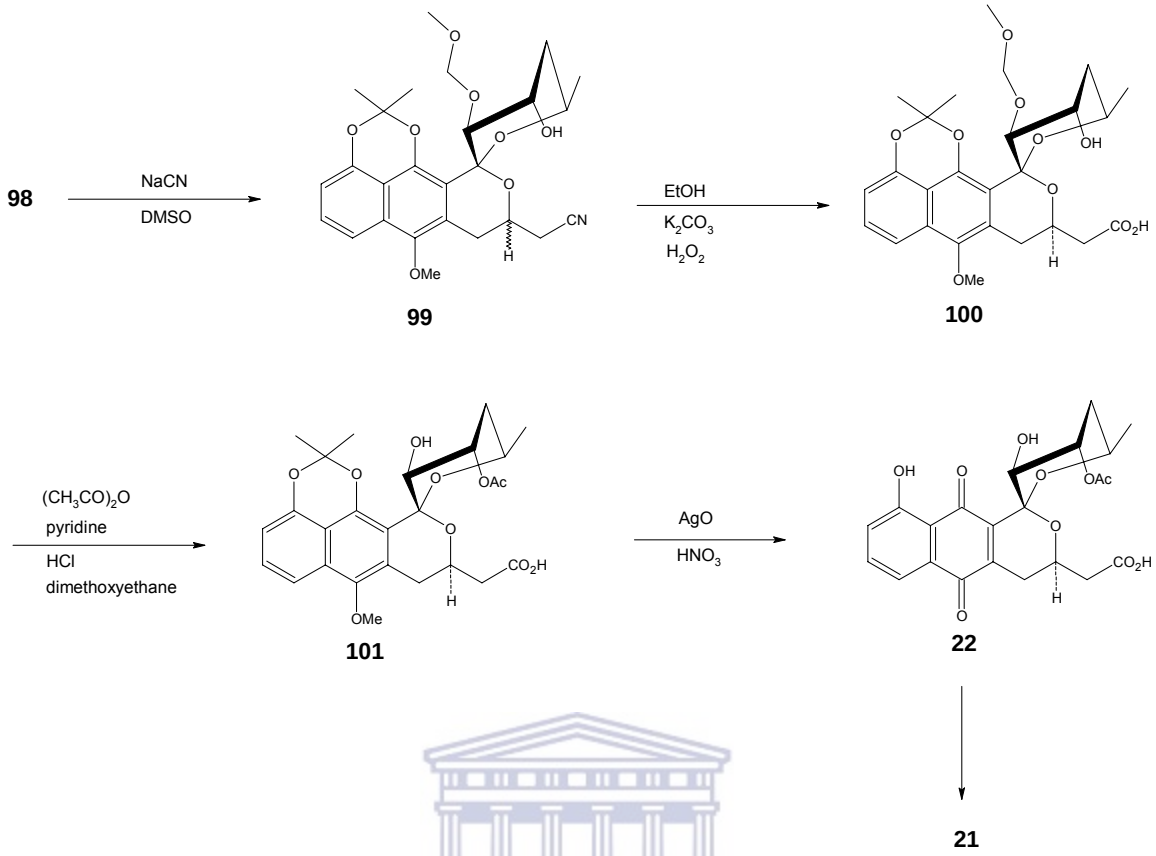
Griseusin A and B, **21** and **22**, isolated from a strain of *Sterptomyces griseus* [15], are members of the pyranonaphthoquinone family of antibiotics and are distinguished from the simpler members of the family, kalafungin and nanaomycin A and D by the presence of the 1,7-dioxaspiro[5,5]undecane ring system. The first total synthesis of the compounds of (+)-griseusin A **21** and (+)-B **22**, the enantiomers of the naturally occurring materials, has been reported by Yoshii *et al*. in 1983 [41, 42]. The key step involved an assembly of the spiroacetal moiety of the griseusins *via* intramolecular ketalization of a δ,δ'-dihydroxyketone derived from a bromohydrin **(Scheme 12)**.

2-Bromo-8-hydroxy-1,4-naphthoquinone **92** [25] was used as starting material since it could serve as the basis for the pyranojuglone moiety. Reaction of **92** with 3-butenoic acid in the presence of silver nitrate and ammonium persulphate afforded the 3-allyl-2-bromojuglone **93**. Reduction of **93** with an excess of sodium hydrosulphite gave the unstable hydroquinone, which was then immediately treated with acetone and 2,2-dimethoxypropane in the presence of perchloric acid and subsequent *O*-methylation with dimethyl sulphate afforded the acetonide **94** in a 63% overall yield. Compound **94** was treated with *tert*-butyllithium in tetrahydrofuran at low temperature after which addition of the *L*-glucose derivative **95** gave the epimeric carbinols **96**. Subsequent slow oxidation with PCC gave a 51% yield of **97** with 28% recovery of **96**. Addition of HOBr to the olefinic bond of **97**, followed by selective removal of the acetonide-protecting group on the sugar moiety with hydrochloric acid, produced a mixture of **98a** and **98b** in a ratio of 1:2 respectively.



Scheme 12 (contd. over)

These diastereomers were separated by preparative TLC and their structures confirmed by ^{1}H NMR spectroscopy. Reaction of the diastereomeric mixture of **98a** and **98b** with excess sodium cyanide in dimethyl sulphoxide gave the diastereomeric nitriles **99** in a combined yield of 83%. Hydrolysis of the nitriles with ethanolic potassium hydroxide in the presence of hydrogen peroxide afforded the carboxylic acid **100** as a single stereoisomer in 61% yield. This epimerization at the C-3 centre from a 3*S* to a more stable 3*R* configuration under basic conditions has been reported previously [41].



Scheme 12(contd.)

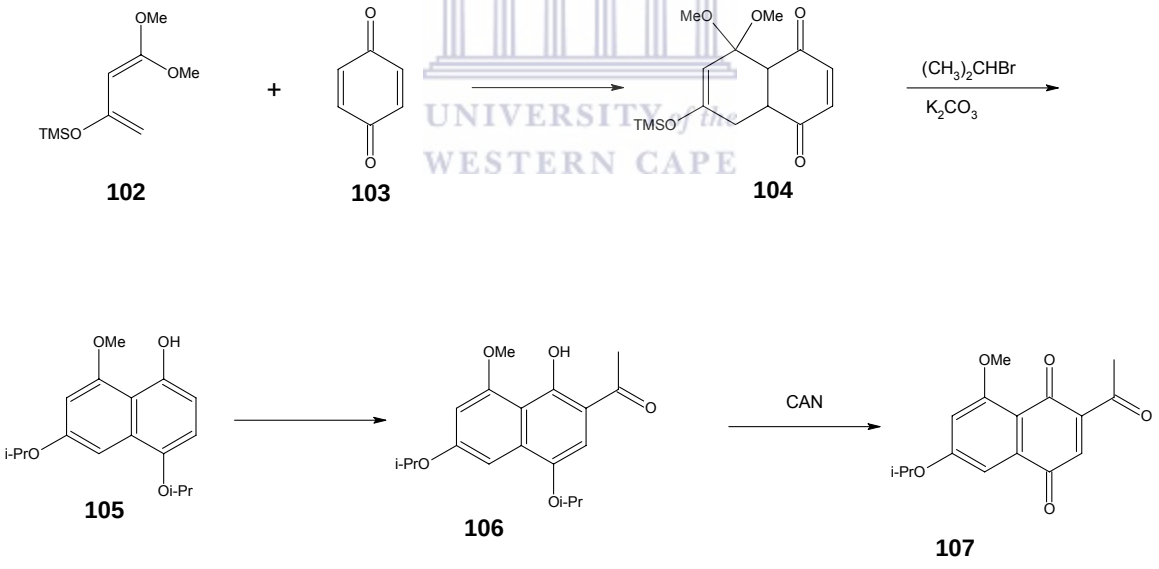
Acetylation of **100** followed by selective removal of the methoxymethyl group with hydrochloric acid in dimethoxy ethane gave product **101** possessing the correct functional groups on the sugar moiety in 58% yield. Oxidation of the latter with silver (II) oxide in nitric acid [43] afforded (+)-griseusin B **22**. Aerial oxidation of **22** produced the γ-lactone thereby producing (+)-griseusin A **21** in 63% yield. The spectral data (IR, ^{1}H NMR, and MS) and the TLC behaviour of the synthetic (+)-griseusin A were identical to the naturally occurring (-)-griseusin A and their CD spectra were mirror images of each other.

In an alternative method, Brimble *et al*. [44] reported an efficient synthesis of the pentacyclic framework of Griseusin A **21** in which the furo[3,2-*b*]naphtho[2,3-*d*]pyran ring system is assembled *via* a ceric (IV) ammonium nitrate oxidative rearrangement of a furo[3,2-*b*]naphtho[2,1-*d*]furan. This strategy was employed by the same group in the synthesis of kalafungin [33].

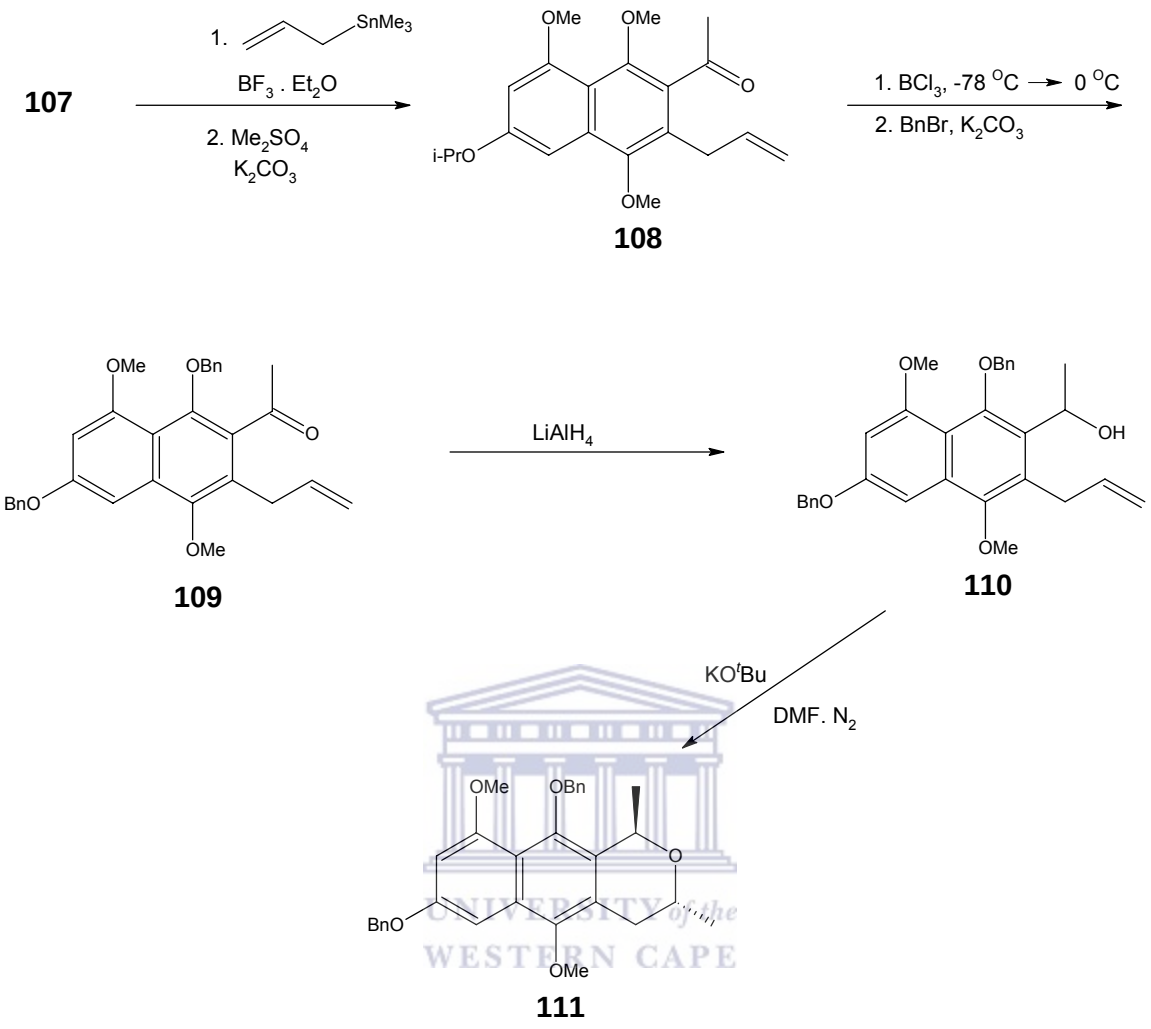
2.5 The Protoaphins

In 1988 Giles and co-workers published two papers [45, 46] describing the successful racemic synthesis of quinone A **12**, quinone A` **13** and deoxyquinone A **14 (Scheme 13)**.

The sequence started with a Diels-Alder condensation between Brassard's diene **102** and 1,4-benzoquinone **103**, and the intermediate adduct **104** was alkylated directly with isopropyl bromide and potassium carbonate in dimethylformamide to afford the naphthol **105** in 71% yield. The naphthol **105** was then acylated to produce the desired 2-acetyl-1-naphthol **106** in 48% yield from the original starting benzoquinone. Oxidation of **106** afforded the quinone **107** which was then allylated with allyltrimethylstannane in the presence of boron trifluoride, and the derived crude adduct was subsequently methylated directly with dimethyl sulphate and potassium carbonate in boiling acetone to afford the allylnaphthalene **108** in a yield of 61% from the starting naphthol **106**.



Scheme 13 (contd. over)

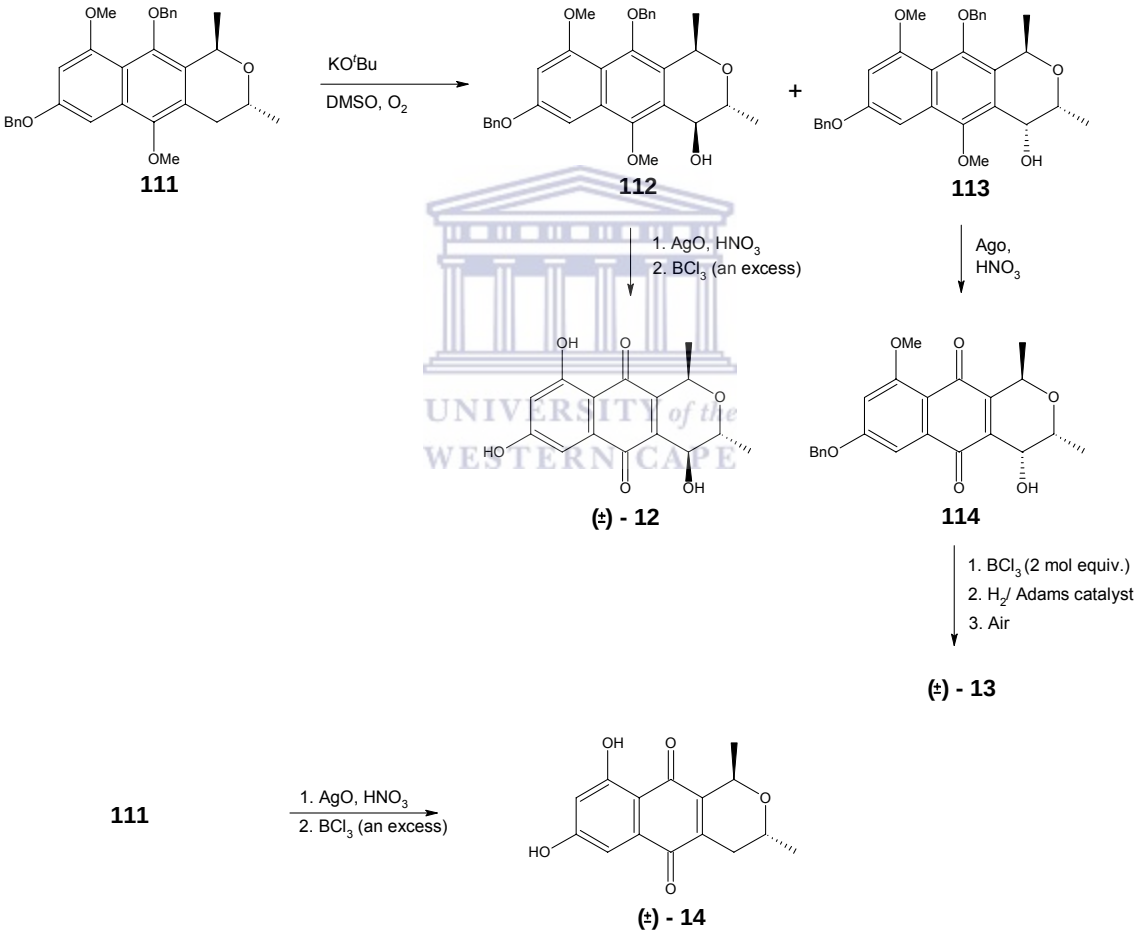


Scheme 13 (contd.)

The next step was to remove the methyl from the oxygen *ortho* to the acyl group with an excess of boron trichloride at -78 ^{0}C, while the isopropyl group was removed with this reagent at 0 ^{0}C [47], and this was followed by benzylation of the resulting naphthalenediol to give the dibenzyl ether **109**. This change of the protecting group at C-7 from isopropyl to benzyl was necessary in order to facilitate its removal in the concluding steps of the synthesis, since this was shown not to occur with the isopropyl group. [45] On the other hand, lower yields arose through initial benzylation, to give the dibenzyl analogue of naphthol **106**. Compound **109** was reduced with lithium aluminium hydride in high yield

to give the alcohol **110**. This alcohol was then readily and stereospecifically cyclised in 97% yield to the *trans*-1,3-dimethylnaphtho[2,3-*c*]pyran **111** with potassium t-butoxide in dry dimethylformamide. [28]

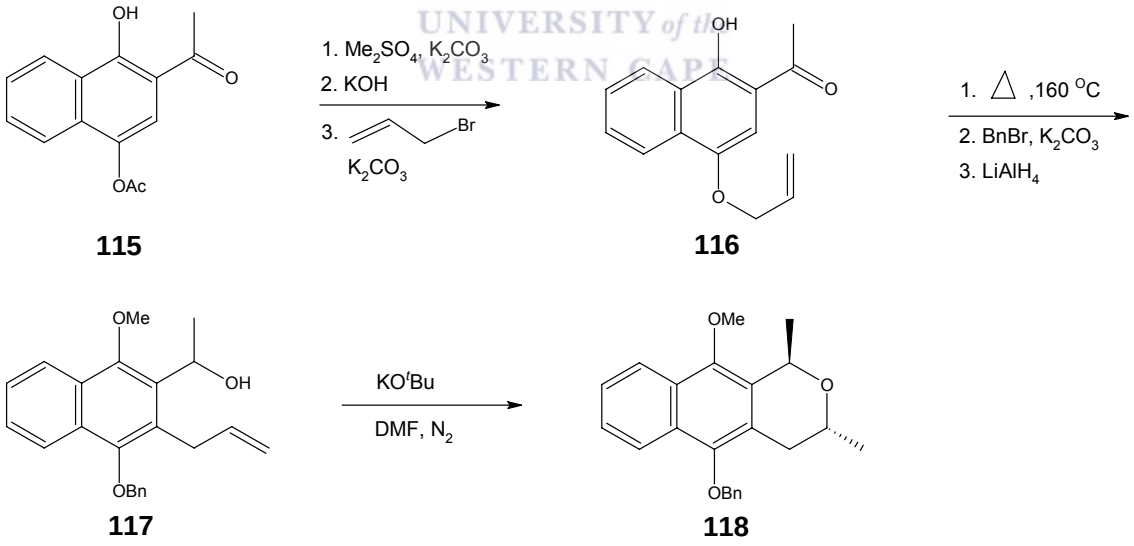
Oxygenation of the naphthopyran **111** by stirring with potassium t-butoxide in dry dimethyl sulphoxide in the presence of dry oxygen produced the favoured C-4 pseudoequatorial hydroxyl derivative **112** together with the pseudoaxial epimer **113** in yields of 60% and 24% respectively **(Scheme 14)**.



Scheme 14

Oxidation of the naphthopyran **112** with silver(II)oxide followed by deprotection with an excess of boron trichloride afforded the racemic quinone A **12**. The epimeric alcohol **113** was similarly oxidized to the quinone **114**, however similar deprotection using an excess of boron trichloride led to decomposition. A possible explanation is that in quinone A` **13** the axial and pseudoaxial configurations of the adjacent hydrogen and hydroxyl at C-3 and C-4, respectively, may enable more ready elimination of water. [46] The *O*-methyl group was removed using a limited amount of boron trichloride (2 mol equiv.), followed by debenzylation through hydrogenolysis, after which racemic quinone A` **13** was formed. Similarly to pyran **112** the naphthopyran **111** was oxidized and deprotected to give (±)-deoxyquinone A **14**.

Having successfully synthesized the racemates of quinone **12**, **13**, and **14** Giles and co-workers turned their attention to the synthesis of glucoside B **11**, in order to achieve the total synthesis of the naturally occurring aphid pigments, protoaphin-*fb* **8**, protoaphin-*sl* **9** and deoxyprotoaphin **10**. In 1994 Giles *et al.* [48] reported the synthesis of a 7,9-dideoxy derivative of glucoside B **(Scheme 15)**.

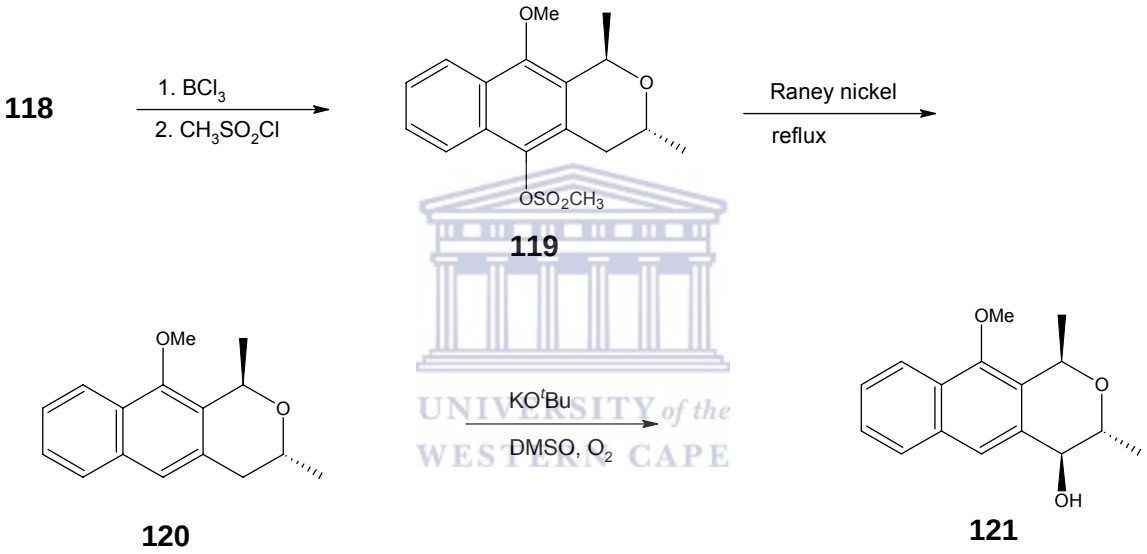


115 **116**

117 **118**

Scheme 15 (contd. over)

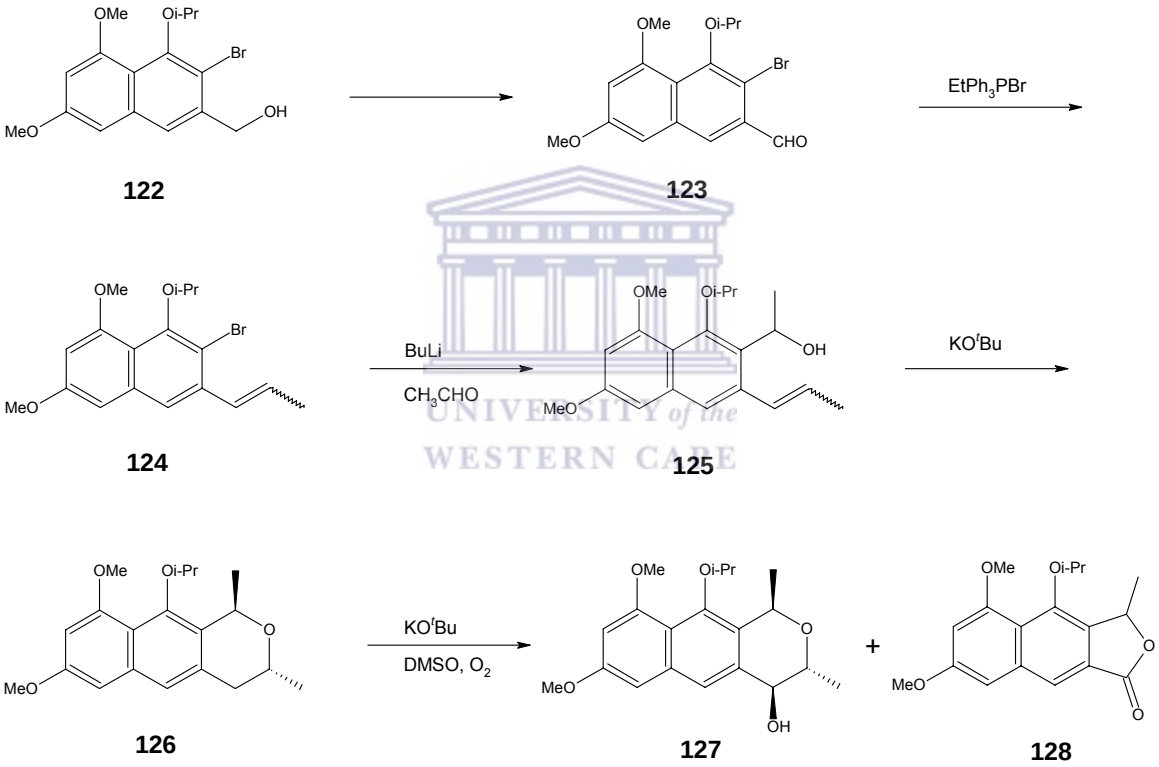
The chosen target naphthalene **117**, for the latter process of base-induced cyclisation, was synthesized over six steps from starting material **115** in an overall yield of 42%. The starting material **115** was methylated, and the resulting intermediate adduct was hydrolysed, followed by allylation to produce allyl ether **116**, which underwent a Claisen rearrangement at 160 ^{0}C to afford an unstable oil, which was immediately benzylated and the subsequent reduction with lithium aluminium hydride gave rise to the alcohol **117**. Stereoselective base-induced cyclisation of the alcohol **117** was obtained by treating it with potassium t-butoxide in dry dimethylformamide to give solely the *trans*-naphthopyran **118** in 72% yield.



Scheme 15 (contd.)

Subsequent treatment of **118** with boron trichloride (2 mol equiv.) afforded an unstable intermediate naphthol through selective debenzylation, which was converted directly into the methanesulphonate ester **119**. Selective cleavage of the aryl-oxygen bond at C-5 of compound **119** was achieved with Raney nickel catalyst to afford the *trans*-1,3-dimethylnaphthopyran **120**. Treatment of **120** with potassium *tert*-butoxide in oxygenated dry dimethyl sulfoxide [46] afforded the target molecule **121**, with the correct relative stereochemistry, in a 61% yield.

In the previous examples **(Scheme 14)** oxygenations on substrates with 5-methoxy substituents, the products produced were both the corresponding pseudoequatorial and pseudoaxial C-4 epimeric alcohols present in quinones A **12** and A` **13** respectively. However, none of the pseudoaxial C-4 epimer is produced in the absence of an oxygen substituent at C-5 of the naphthopyran ring. This methodology would thus be useful for the synthesis of glucoside B that only possesses the pseudoequatorial alcohol. Giles and co-workers [48] then set out to use the same methodology to construct a glucoside B derivative starting off with a naphthalene without the oxygen at the C-5 position **(Scheme 16)**.



Scheme 16

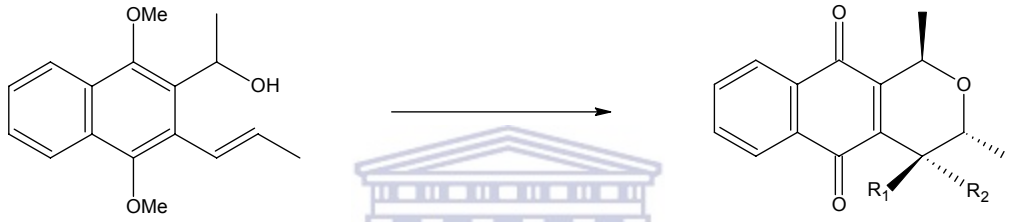
After oxidizing the starting material **122** [48] to the aldehyde **123**, it was subsequently subjected to a Wittig reaction by treatment with ethyltriphenylphosphonium bromide. The resulting mixture of *cis*- and *trans*-olefins **124** was treated with butyl lithium and acetaldehyde to give the corresponding mixture of olefinic cis- and trans-alcohols **125**,

which was then treated with base to induce stereoselective cyclisation to give only the trans-naphthopyran **126** in 83% yield. This proved that the stereochemistry of the product pyran was not determined by that of the olefinic double bond of the starting material. Hydroxylation [46] of **126** produced the target compound **127** in a poor yield of 33%. Difficulty in controlling the reaction led to over-oxidation and the formation of lactone **128** as a by-product. Optimum results were obtained by using potassium *tert*-butoxide in oxygenated dimethylformamide instead of dimethyl sulfoxide as used before. The pseudoequatorial alcohol **127** was obtained in a yield of 46% based on recovered starting material.

CHAPTER 3

The synthesis of precursors and an investigation into their base-induced cyclisation reactions.

In 1981, Giles *et al*. [49] reported the oxidative cyclisation of the naphthalene dimethyl ether **129**, in which the *trans*-prop-1-enyl substituent was derived from propyl by bromination-dehydrobromination, with cerium(IV)ammonium nitrate to give a mixture of the isomeric quinones **130** and **131**.



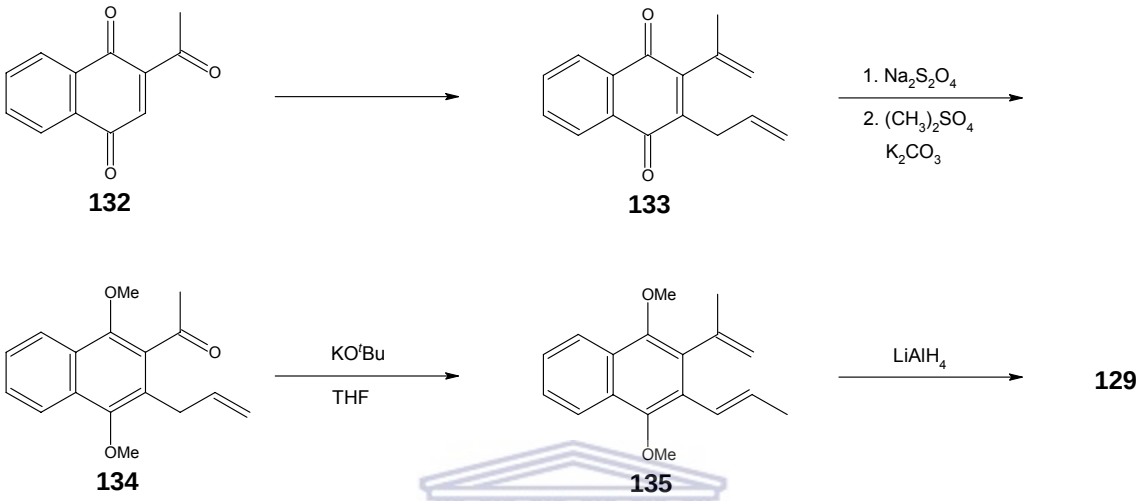
129

130 R_1 = OH , R_2 = H

131 R_1 = H , R_2 = OH

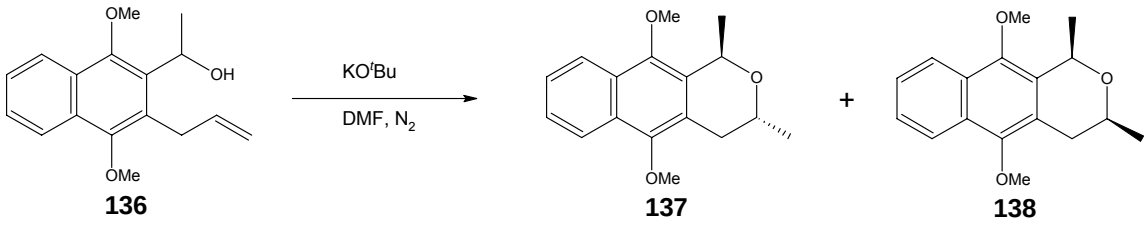
However, they were forced to seek an alternative route, since certain difficulties were encountered in the synthesis of compound **129**. A convenient synthesis of naphthalene **129** was achieved starting with the allylation of 2-acetyl-1,4-naphthoquinone **132 (Scheme 17)** by treating it with vinylacetic acid in the presence of silver nitrate and potassium peroxodisulphate to give the quinone **133**, which was then reductively methylated to the naphthalene dimethyl ether **134** with sodium dithionate followed by dimethyl sulphate and potassium carbonate in boiling acetone. [50] The key step now was to conjugate the allylic double bond. This was done by treating ketone **134** with potassium *tert*-butoxide in tetrahydrofuran to give the naphthalene **135** in which the stereochemistry of the resulting double bond was solely *trans*.

Reduction of this ketone with lithium aluminium hydride gave the alcohol **129**. The possibility of conjugation of the allylic double bond of the alcohol **136**, obtained by lithium aluminium hydride reduction of **134**, to give the isomer **129** was also investigated.

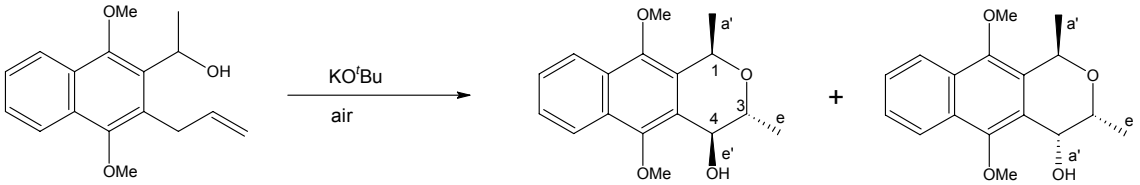


Scheme 17

In actual fact, when treated at 60 ^{0}C in dimethylformamide under nitrogen with potassium *tert*-butoxide (4 mol equiv.), the alcohol **136** was rapidly consumed with the initial formation of the *trans*-dimethylnaphthopyran **137** almost exclusively. [50, 28] However, an increase in reaction time resulted in the formation of both *cis*- and *trans*-dimethylnaphthopyran, **138** and **137** respectively, with the latter predominating. In a similar treatment compound **129** gave identical results.



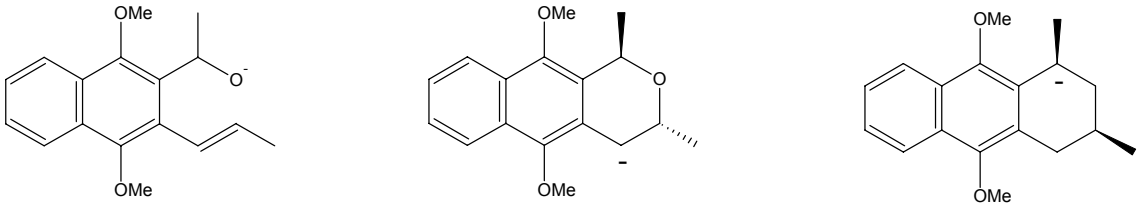
Treatment of the alcohol **136** with potassium *tert*-butoxide without the exclusion of air afforded the isomeric naphthopyrans **139** and **140** in a moderate combined yield of 35%.



136 **139** **140**

These compounds had been isolated earlier as intermediates in the cerium(IV)ammonium nitrate oxidative cyclisation of the naphthalene **129** to the isomeric quinones **130** and **131**.[51] What was interesting is that, in the cerium reaction, the product with the pseudoaxial (a') hydroxyl group predominated, the reverse being true for the base-induced reaction, where the compound with the hydroxyl group pseudoequatorial (e') was more abundant.

A possible explanation for the base-induced cyclisation of alcohols **136** and **129** under anaerobic and aerobic conditions is as follows. An alkoxide anion **141** is produced under the strongly basic conditions generated by butoxide in the dipolar aprotic solvent, which undergoes cyclisation to the *trans*-dimethylpyran anion **142**, favoured kinetically because the methyl group at C-3 prefers the less crowded equatorial position, while that at C-1 adapts a pseudoaxial position in order to reduce *peri* interactions. [51]

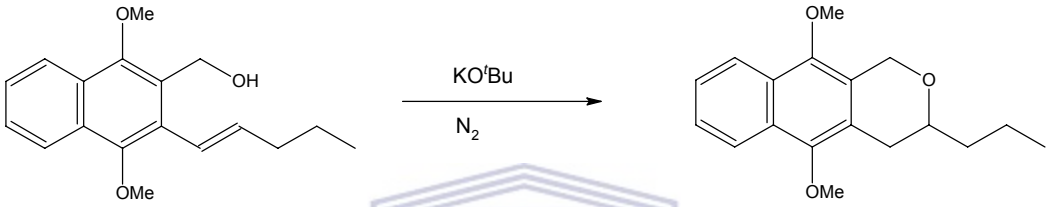


141 **142** **143**

Anion **142** then undergoes protonation to form the product. Longer treatment with base converts **137** into **138**, and this may occur by one one of several routes. Compound **137** may be deprotonated at C-4 to afford the anion **142** again, which reverts to **141** before

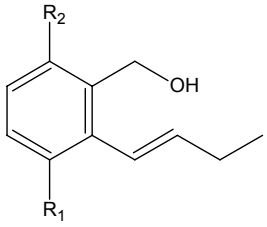
reclosing to form the *cis* compound **138**. Alternatively the initial protonation of anion **142** to form **137** may not occur, since **142**, as soon as it is formed, may ring-open again to **141**, which then recyclises to form the thermodynamically more stable product **138**. Another possibility is that deprotonation of **137** takes place at C-1 rather than at C-4, to give the anion **143**, thermodynamically preferred under the reaction conditions.

It was also shown that the naphthalene **144** cyclises rapidly and in high yield to give the naphthopyran **145**, using potassium *tert*-butoxide in dimethylformamide under anaerobic conditions. [50]



144 **145**

In order to determine which structural features are required in compounds **129** and **144** for the base-induced cyclisation, Giles and co-workers [52] made the benzyl-analogues **146** - **149** of compound **144**, each of which lacks one or more of the functionalities present in **144**.

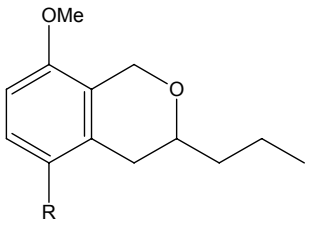


146 R_1 = R_2 = H

147 R_1 = OMe ; R_2 = H

148 R_1 = R_2 = OMe

149 R_1 = H ; R_2 = OMe



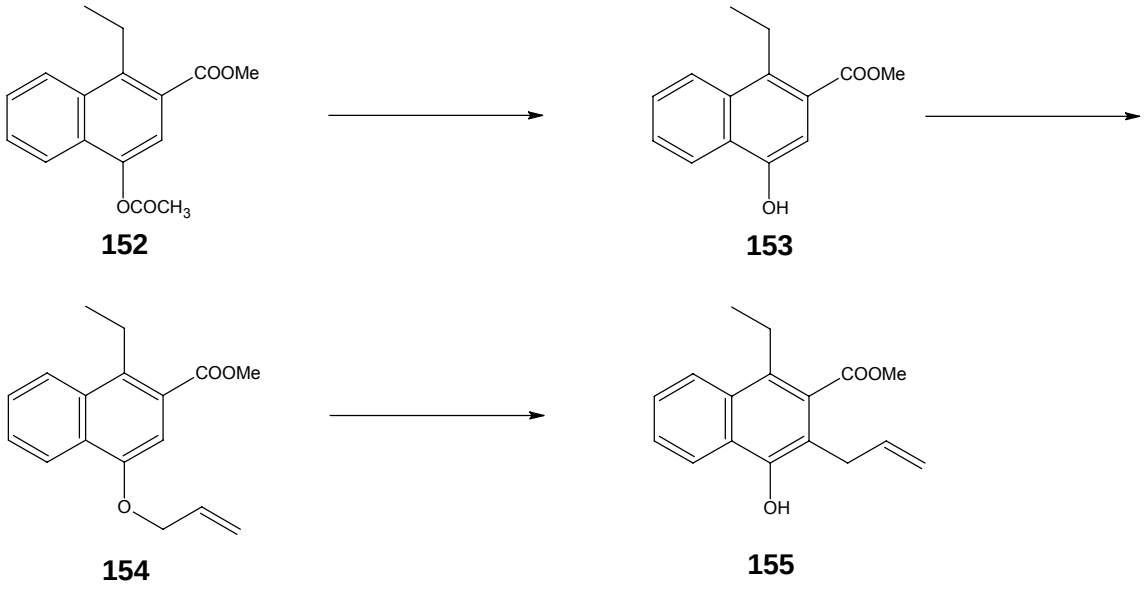
150 R = OMe

151 R = H

Treatment of the benzyl alcohols **146** and **147** with potassium *tert*-butoxide in dimethylformamide afforded the starting material, even after extending the reaction time. In stark contrast, the alcohol **148** with the two methoxy groups cyclised readily to compound **150** in a yield of 85%. The alcohol **149** with the methoxy group *ortho* to the hydroxymethyl gave a number of products, but the cyclic ether **151** was the predominant one in a yield of 25%.

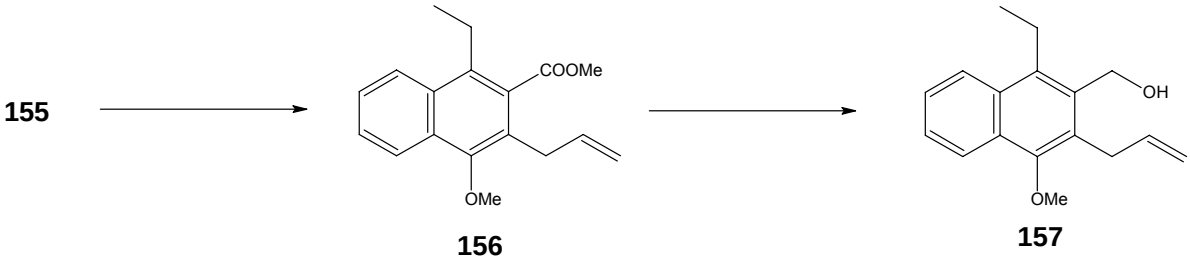
It was suggested that these base-induced cyclisations arose through the close proximity of the reacting centers as a consequence of steric crowding effects, for which there was precedent [53], since it is those alcohols in which both the hydroxymethyl and alkenyl substituents are flanked by methoxy groups that cyclise readily and in high yield. [52] However, the involvement of electronic factors could not be excluded. In an independent study by Kirby and co-workers [54], they investigated in some depth alternative examples involving the intramolecular addition of phenolate to isolated unactivated double bonds. They suggested that the π-system of even an entirely unactivated double bond could act as an acceptor for a nucleophile brought up to it in appropriate juxtaposition.

In order to exclude the electronic effects, Giles and co-workers [55] investigated the influence of the two methoxy oxygen atoms by replacing one of the methoxy groups by an ethyl substituent. They synthesized the analogue **157** of naphthalene **136**, where the methoxy group *ortho* to the hydroxymethyl was replaced by an ethyl group. A convenient synthesis of naphthalene **157 (Scheme 18)** was achieved starting with the naphthalene **152** [56] obtained from propiophenone using a Stobbe reaction. Selective hydrolysis of the acetate ester of compound **152** with dilute methanolic sodium hydroxide afforded the naphthol **153**, which was in turn O-allylated to yield the ether **154**.



Scheme 18 (contd. over)

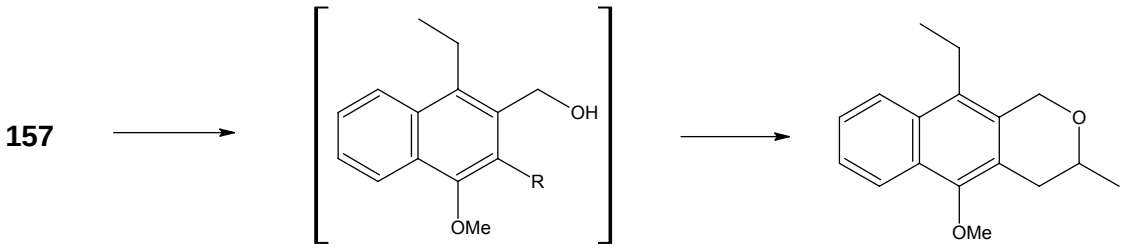
Claisen rearrangement of **154** afforded the unstable tetrasubstituted naphthol **155** in high yield, which was immediately methylated to give the ether **156**. The ester function of compound **156** was reduced slowly with lithium aluminium hydride to the corresponding alcohol **157**.



Scheme 18 (contd.)

When treated for two hours at 60 ^{0}C with potassium *tert*-butoxide in dimethylformamide under nitrogen, the naphthalene **157** underwent cyclisation to afford the naphthopyran **158** in a yield of 69%. [55] When the cyclisation reaction of naphthalene **157** was quenched

before completion, intermediate compounds were observed by thin layer chromatography that had R_F values close to that of the starting material **157**. From their ^{1}H NMR spectra they were identified as being the (*E*)/(*Z*)-mixtures of the conjugated dienes **159** and **160** isolated from their unconjugated precursor. This showed that the initial step in the cyclisation of **157** involved the conjugation of the isolated double bond and that cyclisation occurs irrespective of the stereochemistry of the double bond [55, 48].

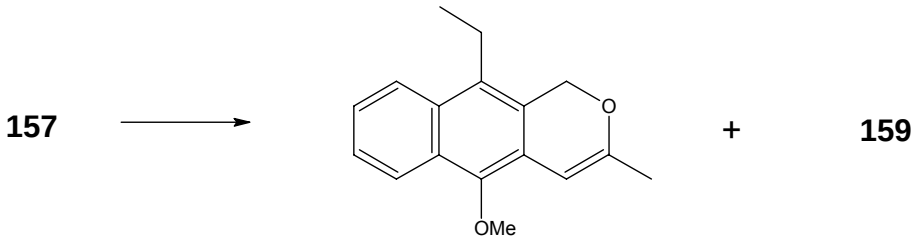


159 R = (*E*)-CH=CHCH$_3$

160 R = (*Z*)-CH=CHCH$_3$

158

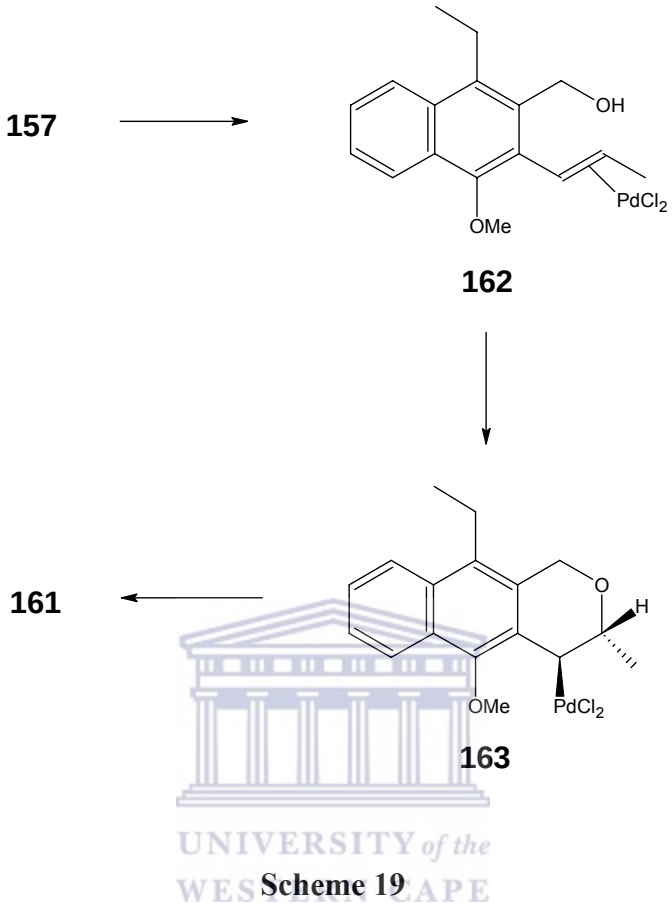
Treatment of the naphthalene **157** with bis(acetonitrile)dichloropalladium(II) also induced cyclisation . Thus, when naphthalene **157** was boiled in dichloromethane containing the metal complex (1 mol equiv.), the naphthopyren **161** was isolated in a yield of 50%, together with the (*E*)-alkene **159** in a yield of 21%. [55]



161

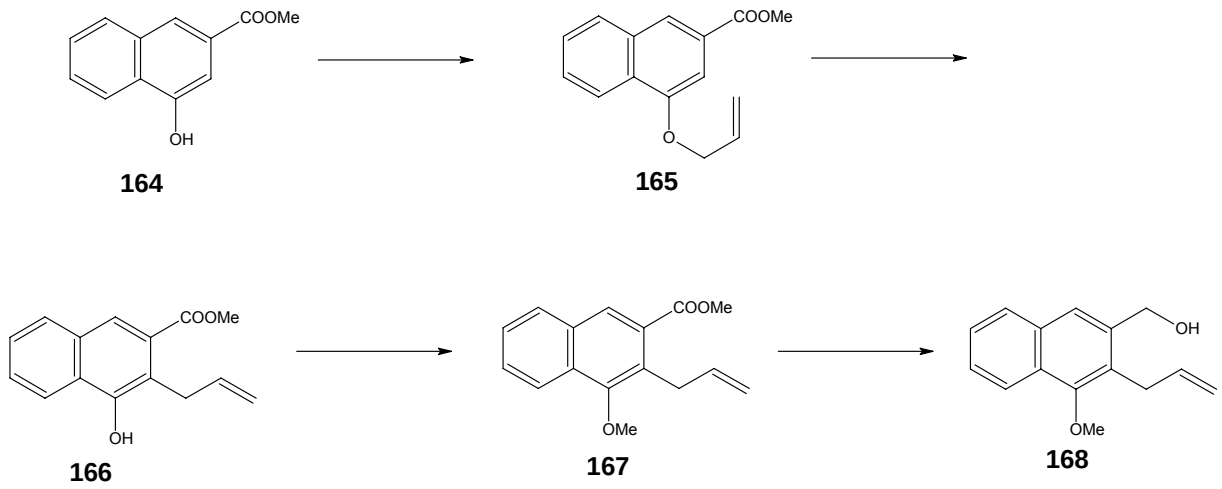
It is speculated that the palladium-mediated cyclisation involves the conversion by the palladium complex of the allylnaphthalene **157** into the (*E*)-styrene derivative **162 (Scheme 19)**. [55, 57] Intramolecular nucleophilic attack by the adjacent hydroxyl group

leads to the formation of the σ-palladium species **163**, which can undergo *cis* β-elimination to yield the product pyren **161**.



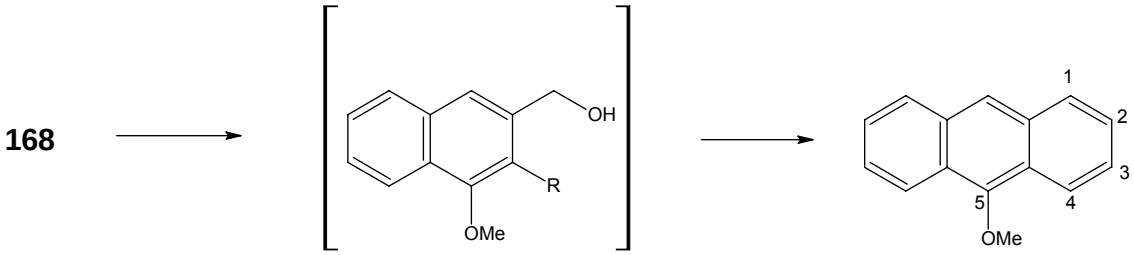
Scheme 19

For comparison purposes the group also synthesized the less crowded analogue **168** of naphthalene **157**, but without the ethyl substituent **(Scheme 20)**. [55] The Stobbe-derived starting material **164** was allylated with allylbromide in the presence of potassium carbonate to yield the allyl ether **165**, and this was in turn subjected to a Claisen rearrangement, giving rise to the naphthol **166** in high yield. This naphthol **166** was methylated to afford the ether **167**, which was subsequently reduced rapidly with lithium aluminium hydride to afford the alcohol **168**.



Scheme 20

When alcohol **168** was subjected to the same reaction conditions used for ring-closure of compound **157**, the less crowded analogue **168** did not undergo cyclisation. However, when air was not excluded from the reaction mixture, naphthalene **168** was converted very slowly and in a yield of 25% into 5-methoxyanthracene **169 (Scheme 21)**. The (*E*)/(*Z*)-mixtures of the conjugated dienes **170** and **171** were also isolated from the reaction mixture by quenching the reaction before completion, supporting the fact that the initial step in the cyclisation also involved the conjugation of the isolated double bond.



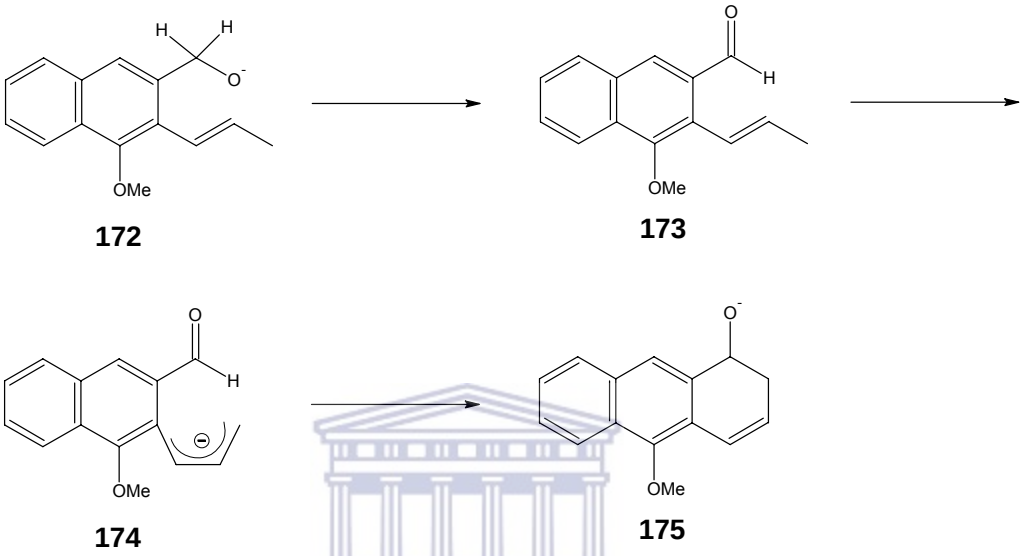
170 R = (*E*)-CH=CHCH$_3$

171 R = (*Z*)-CH=CHCH$_3$

169

Scheme 21

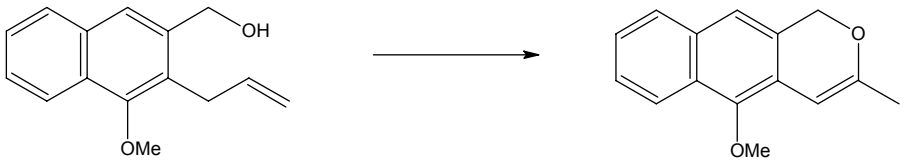
The proposed mechanism for the formation of compound **169** from naphthalene **168** involves slow oxidation of the hydroxymethyl group to formyl **173** in the presence of both base and oxygen **(Scheme 22)**. Subsequent proton abstraction from the allyl substituent of **173** would afford the carbanion **174** and this would then cyclise to give **175**.[55]



172 **173** **174** **175**

Scheme 22

The naphthalene **168** also cyclised to the naphthopyran **176** when reacted similarly with bis(acetonitrile)dichloropalladium(II), which shows that steric crowding is not a requirement under these conditions.



168 **176**

On the basis of these results the group concluded that ring-closures under basic conditions requires the reacting centers to be held in close proximity through steric crowding, since it is only the sterically crowded naphthalene **157** that cyclises to afford the naphthopyran **158**, whereas the less crowded analogue **168** does not form a naphthopyran under the same conditions. This also showed that by replacing the methoxy substituent *ortho* to the hydroxyalkyl in naphthalene **136** by ethyl in analogue **157** still underwent cyclisation to form the naphthopyran **158**, and that this methoxy group is exerting a steric rather than an electronic influence on the ring-closure.

CHAPTER 4

AIM

The goal of my research project was to synthesize 3-allyl-4-ethyl-2-hydroxyethyl-1-methoxynaphthalene **177**, an analogue of **157** in which the ethyl and methoxy substituents are transposed, and to compare its behaviour, towards Pd (0) and potassium *tert*-butoxide catalysed ring closure protocols under aerobic and anaerobic conditions, to that of naphthalene **157** in order to confirm what features are indeed required to promote cyclisation.

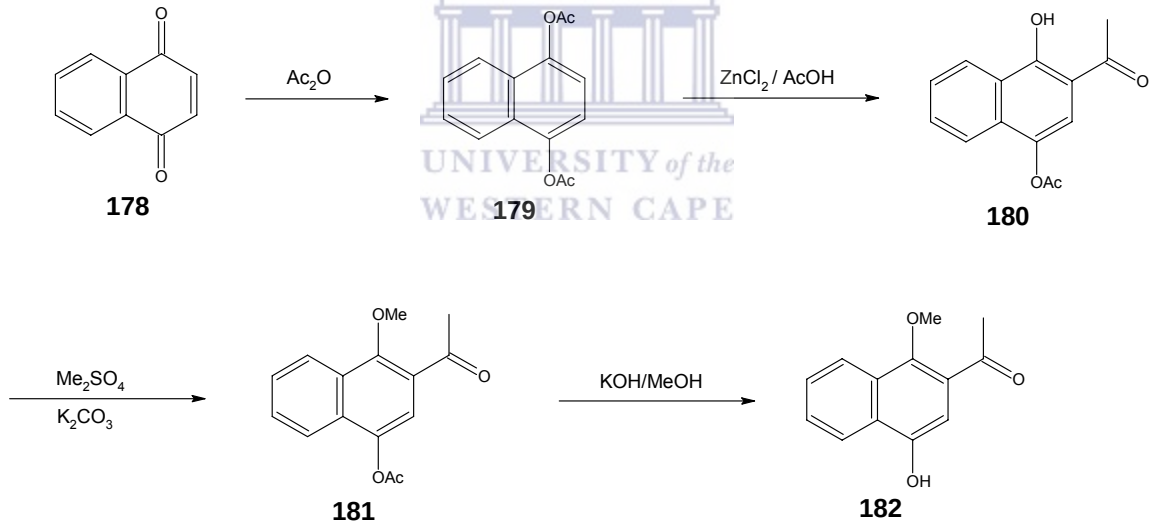
177 **157**

CHAPTER 5

RESULTS AND DISCUSSION

5.1 Synthesis of 3-allyl-4-ethyl-2-hydroxyethyl-1-methoxynaphthalene 177

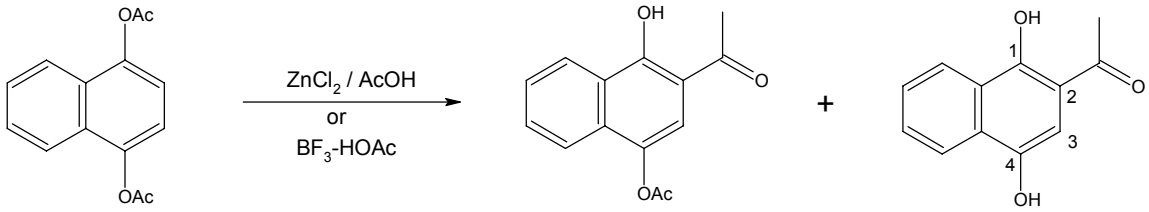
Two synthetic routes were attempted in the synthesis of compound **177**. For both sequences the pivotal naphthalene chosen was naphthol **182** [48] **(Scheme 23)**. The starting material chosen for the target naphthalene **177** was the commercially available 1,4-naphthoquinone **178**, which was reductively acetylated with sodium acetate and zinc dust in boiling acetic anhydride to afford the diacetoxynaphthalene **179**. The ^{1}H NMR spectrum confirmed the structure of this symmetrical naphthalene with a singlet at δ 2.47, integrating for the six protons for the two acetoxy groups.



Scheme 23

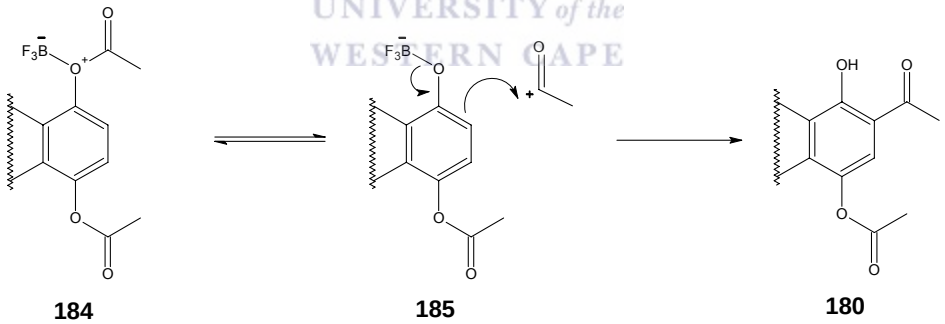
Treatment of the diacetoxynaphthalene **179** with zinc chloride in boiling acetic acid according to the Fries rearrangement method of Read and Ruiz [58] afforded after chromatography the expected product **180** but in a low yield of 35%. A second highly

fluorescent fraction isolated from the column was identified as the quinol **183** (20%) representing deacetylation of the naphthalene **180**. The structure of compound **183** was confirmed by the absence of the methyl signal for the C-4 acetoxy group at δ 2.46 in its ^{1}H NMR spectrum and at δ 21.0 in its ^{13}C NMR spectrum, respectively. In a D_2O exchange experiment the 4-OH singlet at δ 8.70 in its ^{1}H NMR spectrum was confirmed.

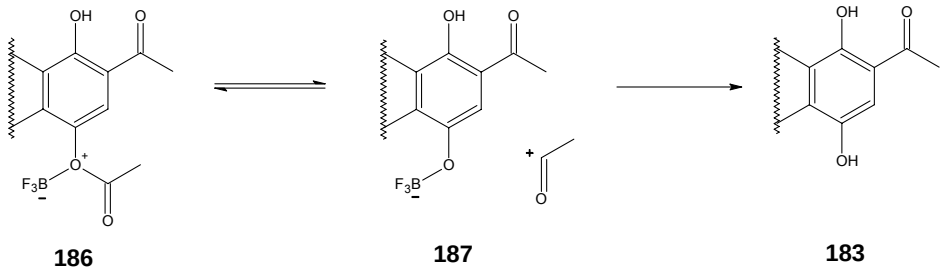


179 **180** **183**

In an alternative protocol a solution of boron triflouride in acetic acid was used according to the method of Kurosawa [59]. There appeared to be very little difference in the yields obtained in this method viz., naphthol **180** (40%) and quinol **183**(25%), after chromatography. A proposed mechanism for the latter reaction is depicted in **Scheme 24**. [60]



184 **185** **180**

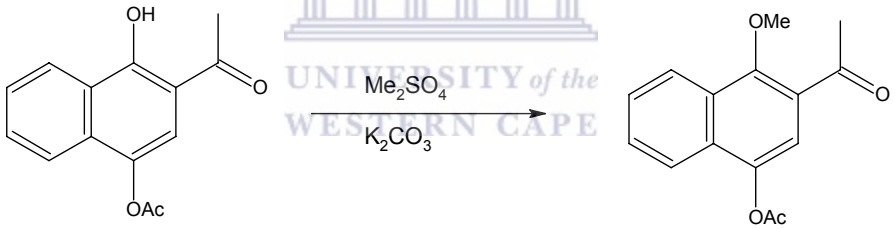


186 **187** **183**

Scheme 24

The reaction of the diester **179** with boron trifluoride gives the Lewis adduct **184**. Dissociation of **184** results in the formation of an acylium ion and an aromatic anion **185**. Electrophilic aromatic substitution by the acylium ion on **185** results in the naphthol **180**. Reaction of **180** with boron trifluoride gives the second Lewis adduct **186** which also dissociates into an acylium ion and an aromatic anion. The electron-withdrawing effect of the acetyl group on **187** deactivates the ring, disfavouring acyl alkylation. Protonation of **187** results in the formation **183**.

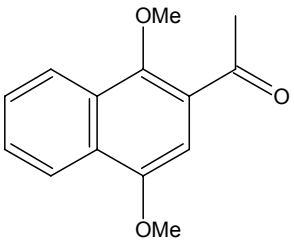
Methylation of **180** using potassium carbonate and dimethyl sulphate in boiling acetone afforded the methyl ether **181** [48] in a yield of 81% and an overall yield of 29% from the starting naphthoquinone **178**. The structure of compound **181** was supported by the appearence a new 3-proton singlet in its ^{1}H NMR spectrum at δ 4.01, characteristic of a methoxy group.



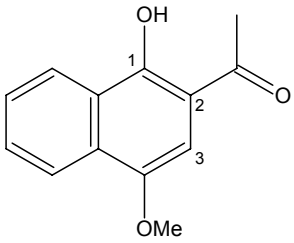
180 **181**

In an attempt to improve the formation of the methyl ether **181**, the crude mixture obtained from a new Fries rearrangement procedure was without prior chromatography subjected to methylation as described before. However, in this case, in addition to the desired methyl ether **181** (15%), the dimethoxyacetylnaphthalene **188** (10%) and the naphthol **189** (50%) was obtained after chromatography.

The ^{1}H NMR spectrum of **188** displayed the two methoxy groups as two singlets at δ 3.96 and δ 4.01. The structure of compound **189** was confirmed by the replacement of the δ 2.46 signal of the acetoxy group with that of a singlet at δ 3.99 due to the methoxy group, and the upfield shift of the 3-H proton from δ 7.42 to δ 6.83.

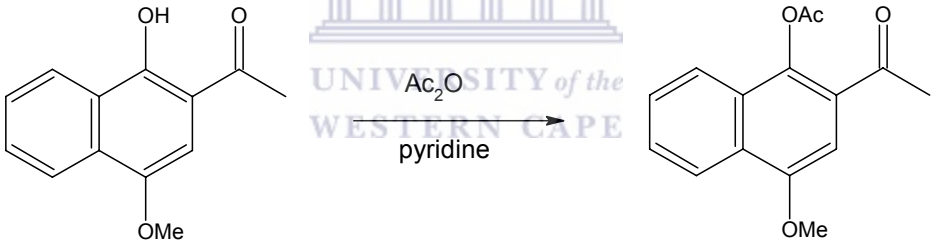


188



189

Acetylation of naphthol **189** into the regioisomeric acetate **190** of naphthalene **181** was effected quantitatively by employing acetic anhydride and pyridine.

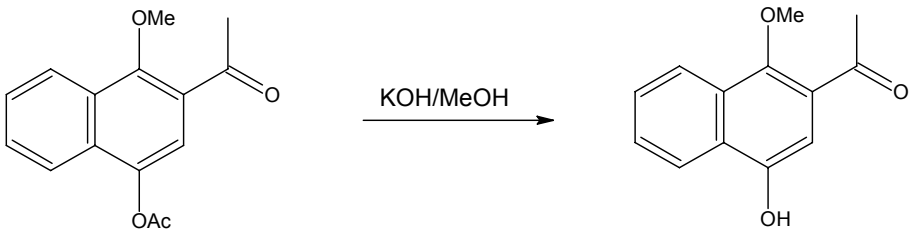


189 **190**

The appearance of a 3-proton singlet at δ 2.51, due to the C-1 acetate group supported the structure of naphthalene **190.**

In the end we eventually managed to improve the yield of naphthol **180** (89%) using the Kurosawa [59] protocol and freshly distilled BF_3-acetic acid complex, resulting in an improvement in the overall yield of 65% from the starting naphthoquinone **178**.

The next step in our reaction sequence was the hydrolysis of the acetate group of compound **181**. Thus treatment of **181** with a 1% (w/v) methanolic solution of potassium hydroxide afforded the naphthol **182** [48] in 96% yield.



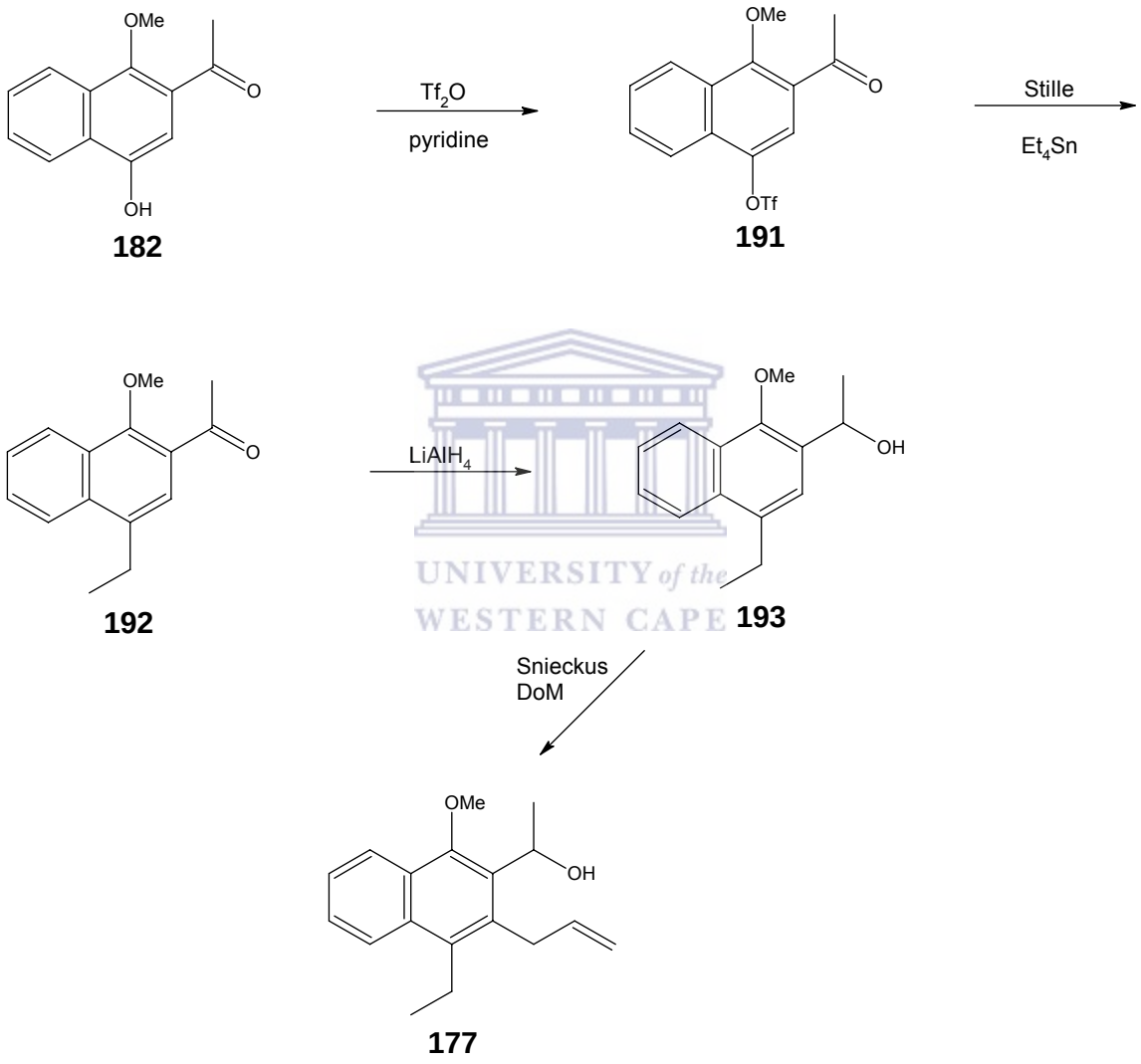
181 **182**

The IR spectrum of compound **182** showed a broad absorption peak at 3423 cm^{-1} confirming the presence of a phenolic group.

Thus with the important and pivotal naphthol **182** in hand, the next stages of the synthesis could be investigated. In this instance the routes diverged and will be dealt with separately.

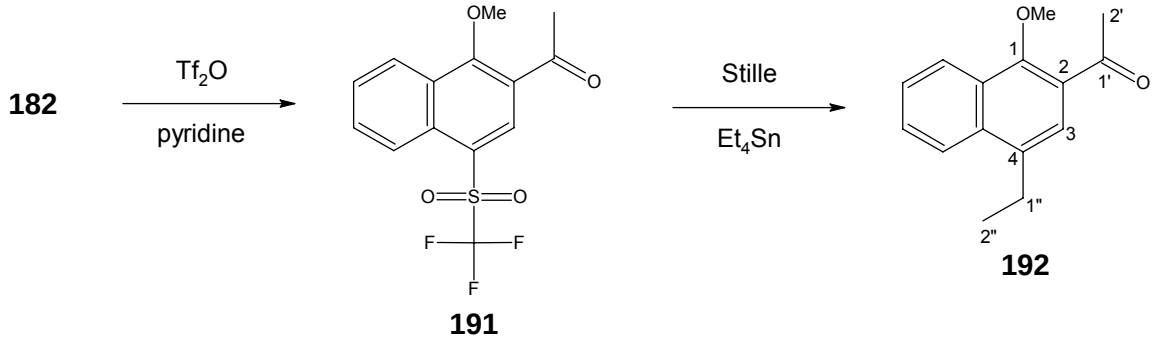
5.1.1 Route A : Synthesis of 177 via Stille Coupling followed by the Snieckus ortho metalation

The first of the routes attempted involved a Stille Coupling protocol towards the target naphthalene **177** and is outlined in **Scheme 25.**



Scheme 25

Thus, in order to transform the naphthol **182** into a suitable precursor for the Stille Coupling procedure, it was converted into the corresponding triflate **191 (Scheme 26)**, by treating it with trifluoromethanesulphonic anhydride in dry pyridine.

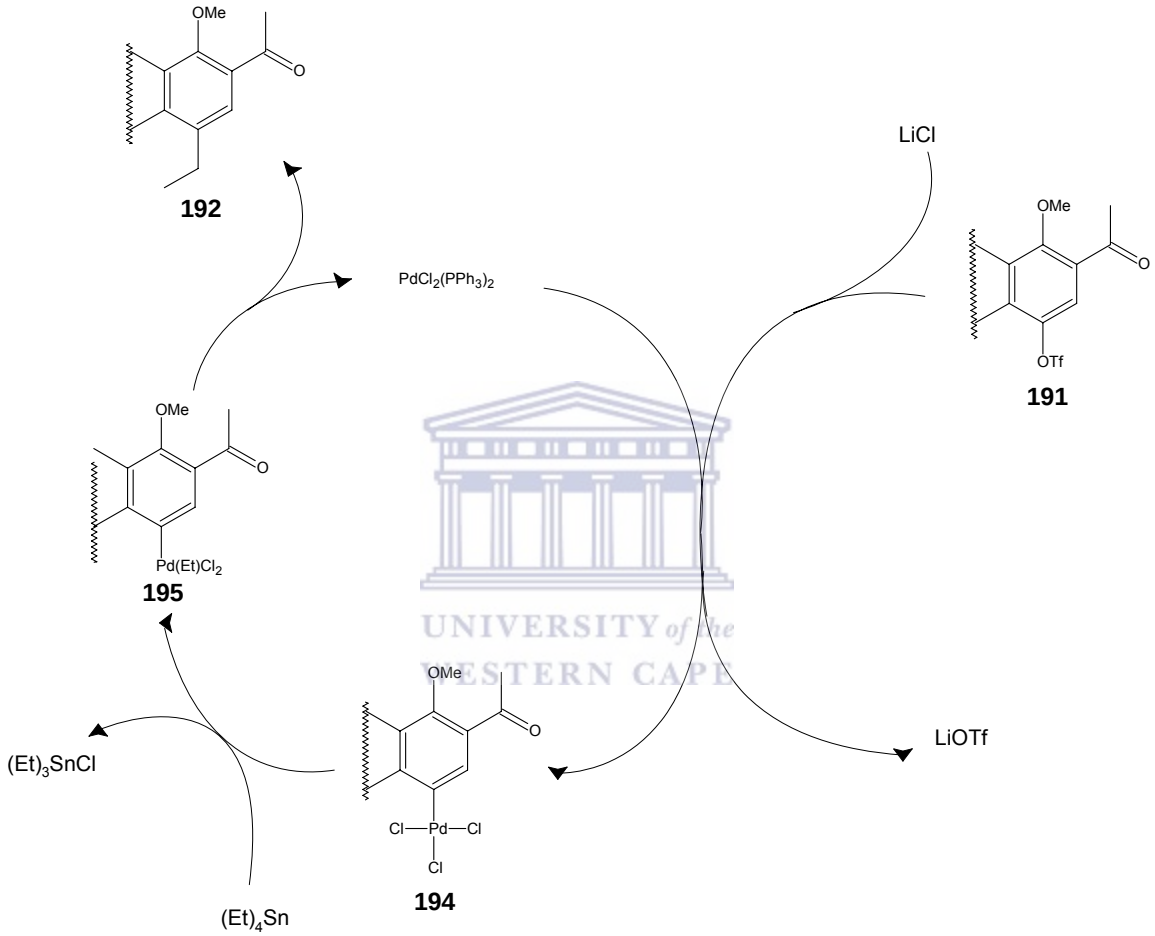


Scheme 26

A significant change could be noticed between the aromatic regions of compounds **182** and **191** in their respective ^{1}H NMR spectra. The deshielding effect of the triflate substituent caused a downfield shift for the 3-H proton from δ 7.33 to δ 7.78. In the ^{1}H NMR spectrum of compound **182** the 8-H and 5-H appear as a multiplet at δ 8.15 - 8.29, whilst in the ^{1}H NMR spectrum of compound **191** 1-proton doublet of doublets at δ 8.08 and δ 8.28 (J 7.8 and J 1.6) are assigned to 8-H and 5-H, respectively. The broad quartet at δ 118.8 (J 318.5) in the ^{13}C NMR spectrum, due to the coupling between the 3 F-atoms and the C-atom of the triflate group, confirmed the structure of compound **191.** The IR spectrum showed a strong signal at 1685 cm^{-1} due to the C=O stretch of the acetate group. The mass spectrum had the expected M^{+} signal at *m/z* 348 and the base peak of *m/z* 215 is ascribed to the loss of the triflate group i.e. (-133).

Stille coupling [61] between triflate **191** and tetraethyltin and bistriphenylphosphine-dichloropalladium(II) in the presence of lithium chloride afforded the desired ethyl naphthalene **192** in 51% yield **(Scheme 26)**. The structural assignment of **192** was confirmed by its ^{1}H NMR spectrum, which had the following characteristics *inter alia*; a 3-proton triplet at δ 1.37 (J 7.6) assigned to 2′′-CH_3 whilst the 1′′-methene group

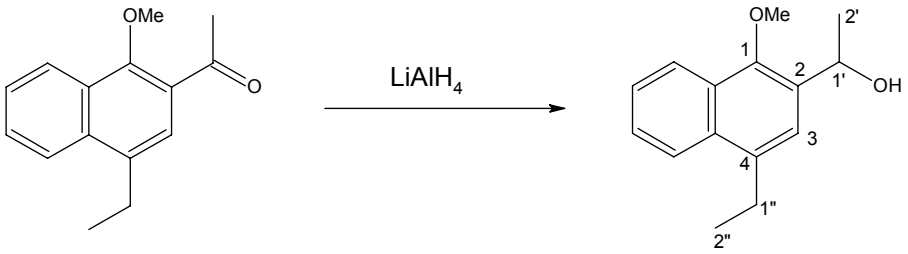
appeared as a quartet at δ 3.05 (J 7.6). C-2″ and C-1″ resonated at δ 14.9 and δ 30.9, respectively in the ^{13}C NMR spectrum, with the C=O appearing at δ 200.4. The molecular ion peak at *m/z* 228 in the mass spectrum supported the molecular formula corresponding to compound **192**. The proposed catalytic cycle for the Stille reaction are depicted in **Scheme 27**. [61]



Scheme 27

Oxidative addition of the naphthalene triflate **191** to the palladium (II) complex in the presence of lithium chloride yields **194** and lithium triflate. Transmetalation of **194** with tetraethyltin yields triethyltin chloride and the bis(organo)palladium(IV) complex **195**, which rapidly undergoes reductive elimination to give compound **192**, regenerating the palladium (II) catalyst.

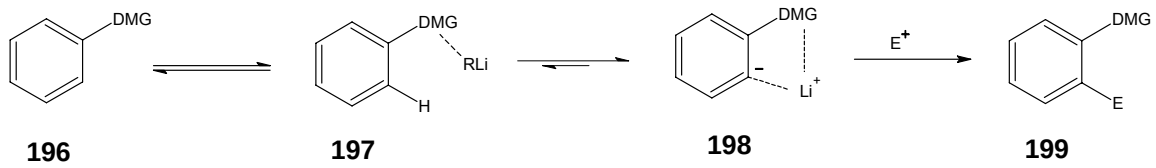
The reduction of naphthalene **192** with lithium aluminium hydride afforded the alcohol **193** in an excellent yield of 94% yield.



192 **193**

The structure of alcohol **193** was supported by its ^{1}H NMR spectrum, which had the following signals *inter alia*; a 3-proton triplet at δ 1.38 (J 7.8) for 2″-CH_3; a 3-proton doublet at δ 1.58 (J 6.6) for 2′-CH_3; a broad 1-proton singlet at δ 2.37 assigned to 1′-OH; a 2-proton quartet at δ 3.08 (J 7.8) for 1″-CH_2 and a 1-proton quartet at δ 5.44 (J 6.6) assigned to 1′-CH. The ^{13}C NMR spectrum also revealed the absence of the C=O signal, whilst the C-1′ signal appeared at δ 64.9.

The key step now was to introduce the allyl group at C-3 of naphthalene **193** via a Snieckus directed *ortho* lithiation (DoM) reaction to afford the target naphthalene **177**. The utility of this general methodology derives from the regiospecific deprotonation of an aryl H *ortho* to a directing metalation group (DMG) by a strong base, normally an alkyllithium reagent. For a successful deprotonation to occur, the DMG must be a good coordinating site for alkyllithium and a poor electrophilic site for attack by this base, hence a heteroatom-containing DMG is a requirement. The general mechanism of the DoM process is outlined in **Scheme 28**. [62]

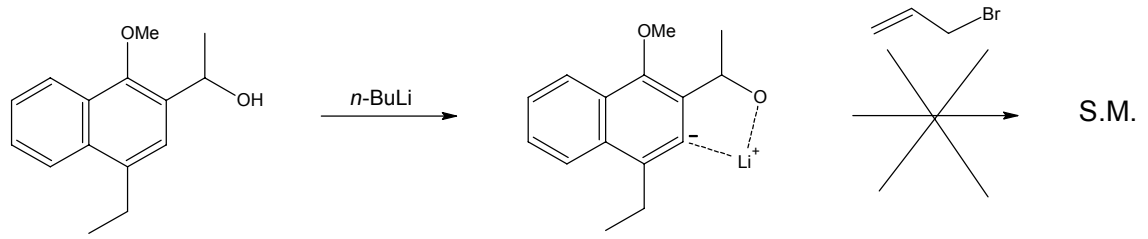


196 **197** **198** **199**

Scheme 28

The first step involves the coordination of the alkyllithium base to the heteroatom of the DMG of compound **196** to give the coordinated species **197**. Deprotonation of **197** results in the formation of the *ortho*-lithiated intermediate **198**. Studies have shown that the *ortho*-lithiated species **198** is stabilized by coordination between the DMG and Li. [62] Treatment of **198** with an electrophilic reagent then yields the 1,2-disubstituted product **199**.

Using the general Snieckus DoM protocol, naphthol **193** was dissolved in THF and cooled down to *ca*. -78 ^{O}C under nitrogen. Upon treatment with *n*-BuLi, the colour changed from almost colourless to blue, suggesting the formation of the 3-lithiated naphthylcarbanion **200**. The reaction mixture was kept at -78 ^{O}C and on addition of allyl bromide the colour changed back to light yellow. Upon work-up, only starting material **193** was recovered.

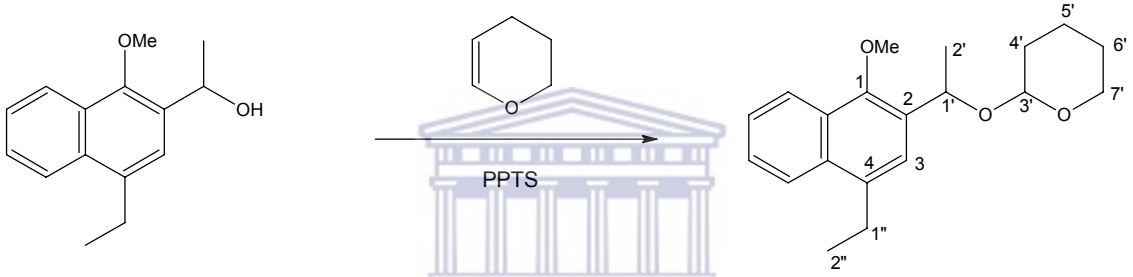


193 **200**

The experiment was repeated using a stronger base, *sec*-BuLi, and this time the reaction mixture was allowed to reach ± -20 ^{O}C, before being cooled down to -78 ^{O}C again. The reason for this was to give the anion ample opportunity to form. Allyl bromide was added and again only starting material was obtained after work-up.

Assuming that the anion formed is not stabilized enough by the interaction between the Li- and O-atom, we then converted the 2-(1′-hydroxyethyl) side chain of **193** into the dihydropyran (DHP) derivative **201**, in the hope that the two oxygen atoms in the side chain would stabilize the C-3 naphthyl carbanion upon treatment with alkyllithiums.

DHP analogues are highly effective protecting groups for alcohols and the DHP reagent is commercially available, inexpensive, and easy to handle. The corresponding ethers are also stable to, *inter alia*, hydrides, redox reagents, organometallics, strong bases, alkylating/acylating agents, and catalytic reduction. [63]



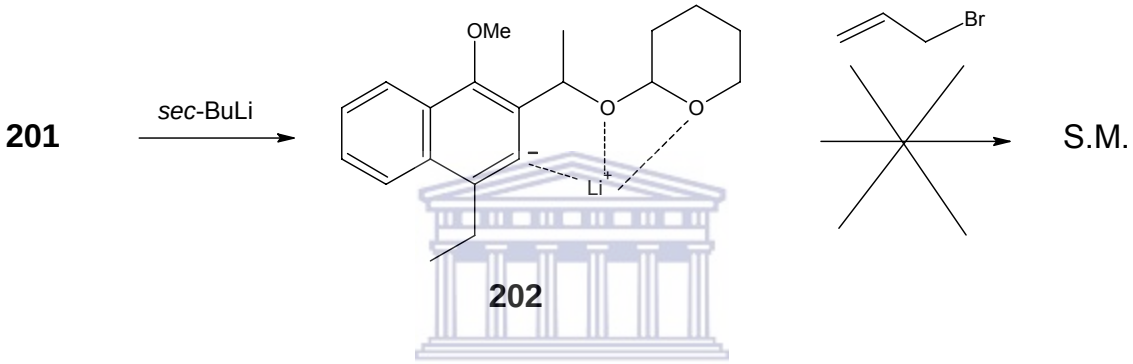
193 **201**

Thus alcohol **193** was treated with dihydropyran and pyridinium-*p*-toluene sulfonate as catalyst in dichloromethane to afford the DHP derivative **201** in 74% yield.

The total integration in the ^{1}H NMR spectrum for compound **201** confirmed the presence of the DHP group. What was interesting to note in both the ^{1}H NMR- and ^{13}C NMR spectra was that all the H-signals as well as the C-signals were duplicated by slightly parallel shifts, *inter alia*, the quartet of the 1′-CH appeared at two different chemical shifts in the ^{1}H NMR spectrum, *i.e.*, at δ 5.37 and δ 5.53, as does the 3′-CH which appeared as two triplets at δ 4.38 and δ 4.95. However, the GC-MS showed a single peak and the M^{+} signal was at the expected *m/z* 314.

The reason for the duplication of the signals is due to the molecule having two chiral centers at C1′ and C3′, which result in the formation of a pair of diastereoisomers, *i.e.*, the (1′R, 3′R)-isomer and the (1′R, 3′S)-isomer or the (1′S, 3′R)-isomer or the (1′S, 3′S)-isomer.

When compound **201** was treated with *sec*-BuLi at -78 ^{O}C under nitrogen the solution turned yellow then blue, again implying the formation of the 3-lithiated anion **202**. After adding the allyl bromide the solution turned light brown. However, only starting material was recovered after work-up.

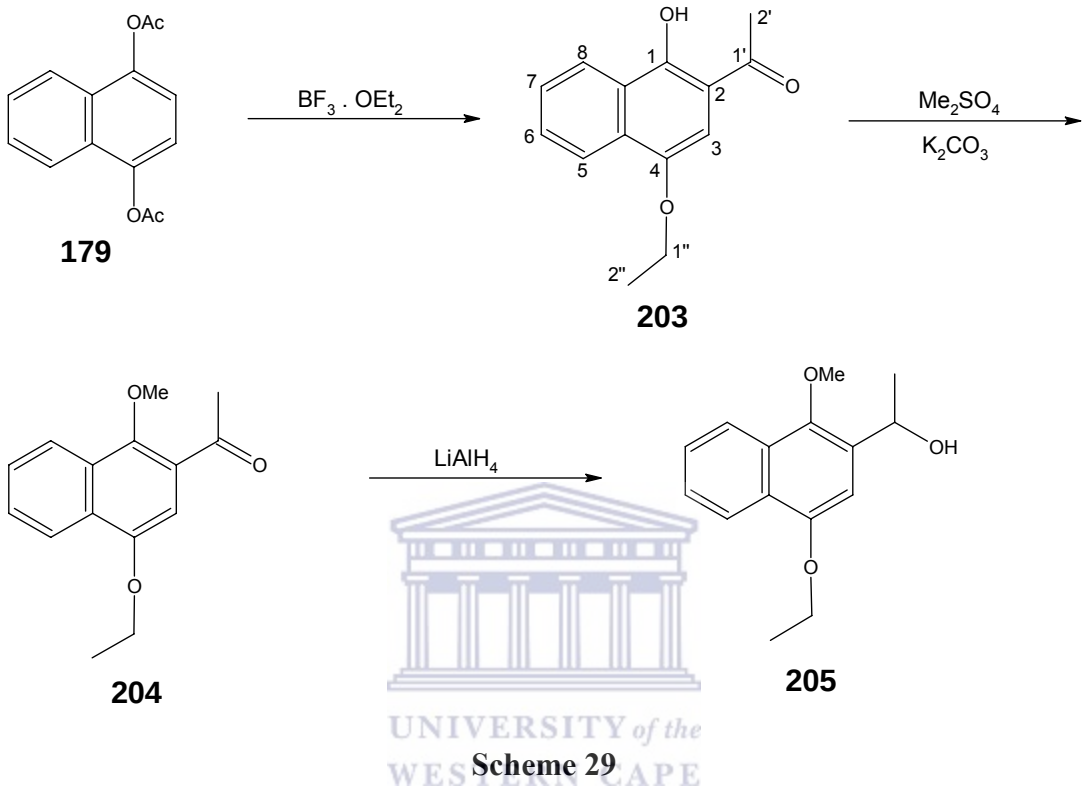


It has been shown that bidentate ligands, in particular tetramethylethylenediamine (TMEDA), increase the basicity of the alkyllithium being used and that the *sec*-BuLi-TMEDA combination appears to be the most potent metalating agent. [62]

Thus upon repeating the above experiment, TMEDA was introduced prior to the addition of the base after which the solution took on a light yellow colour that gradually turned dark brown. However, after adding allyl bromide and subsequent work-up, only starting material was recovered.

We inferred that this could be the result of either insufficient *O*-complexation, or that the reaction site might be too sterically crowded for the delivery of the allyl group.

While the work on the DHP derivative **201** was being undertaken, a parallel sequence of experiments was investigated to synthesize naphthalene **205**, an analogue of naphthol **193** in which, the ethyl group was replaced by an ethoxy group **(Scheme 29).**



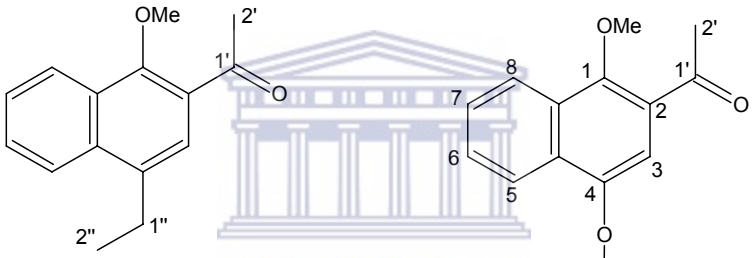
Scheme 29

1,4-Diacetoxynaphthalene **179** was treated with a boron trifluoride-diethyl etherate complex, according to the method of Wigal [60], and afforded the ethoxy-substituted naphthalene **203** in a yield of 92 %.

This unique Fries rearrangement of **179** into **203** was confirmed by the ^{1}H NMR spectrum of compound **203**, which had the following signals: *inter alia*; a 3-proton triplet at δ 1.55 (J 7.0) assigned to 2′′-CH_3 while the 1′′-CH_2 appeared as a quartet at δ 4.17 (J 7.0). The 3-H proton appeared as a singlet at δ 6.84, upfield from where it resonated at δ 7.27 in the ^{1}H NMR spectrum of compound **179**. This could be ascribed to the replacement of the slightly electron-withdrawing acetyl group with the electron-donating ethoxy group.

The 8-H and 5-H protons appeared as two doublets of doublets at δ 8.44 and δ 8.22 (J 8.0 and J 1.6) whilst the 6- and 7-H protons resonated as a doublet of triplets at δ 7.20 – 7.70. The mass spectrum showed both the molecular ion and base peak at *m/z* 230, which corresponds to the molecular weight of compound **203** and a peak at *m/z* 201 relating to the loss of the ethyl group i.e. (-29).

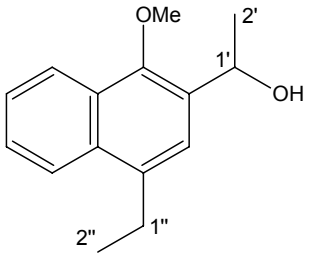
Methylation of **203**, using the method described earlier [48], afforded the naphthalene **204** in 76%.



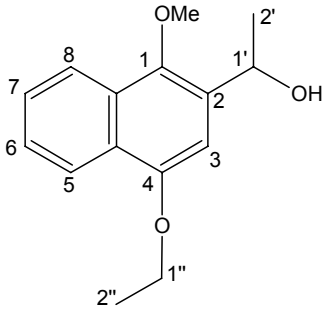
192 **204**

The appearance of a new 3-proton singlet in the ^{1}H NMR spectrum at δ 4.01, characteristic of a methoxy group, supported the structure of compound **204**. Comparison of the ^{1}H NMR spectrum of naphthalene **192** to that of naphthalene **204**, revealed the downfield shift of the ethyl signals, especially that of 1′′-CH_2 from δ 3.06 to 4.22, due to the deshielding effect of the O-atom. The mass spectrum of naphthalene **204** had a M^+ peak at *m/z* 244, confirming the structure of compound **204**.

The reduction of the ethyl ether **204** with lithium aluminium anhydride in dry ether gave rise to the alcohol **205** in 90% yield.



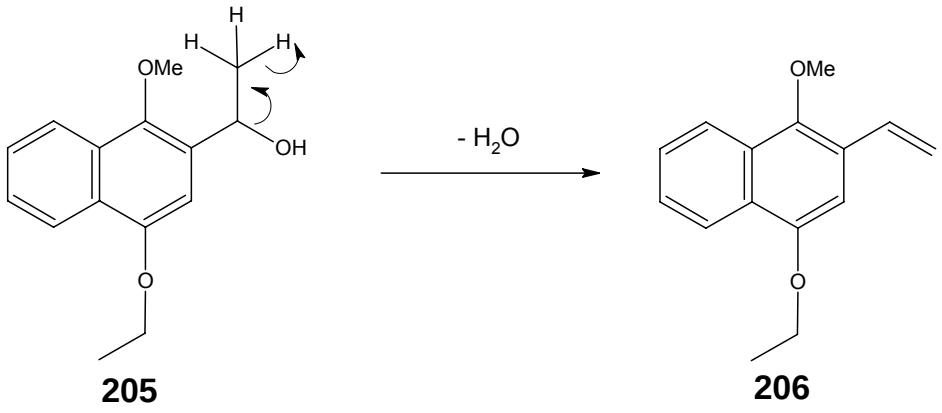
193



205

The ^{1}H NMR spectrum confirmed the structure of alcohol **205**, which showed the following signals: *inter alia*; a broad singlet at δ 2.93 assigned to 1′-OH, a 2-proton quartet at δ 4.15 (J 7.2) for 1′′-CH_2 and a 1-proton quartet at δ 5.43 (J 6.4) assigned to 1′-CH. The upfield shift of the 3-H aromatic proton from δ 7.06 to δ 6.86 in the ^{1}H NMR spectra of compound **204** and **205** respectively, was also observed in the ^{1}H NMR spectra of **192** (3-H, δ 7.60) and **193** (3-H, δ 7.43). This chemical shift of the aforementioned signals could be the result of the subdued deshielding effect of the C-O bond, caused by the reduction of the carbonyl to an alcohol group.

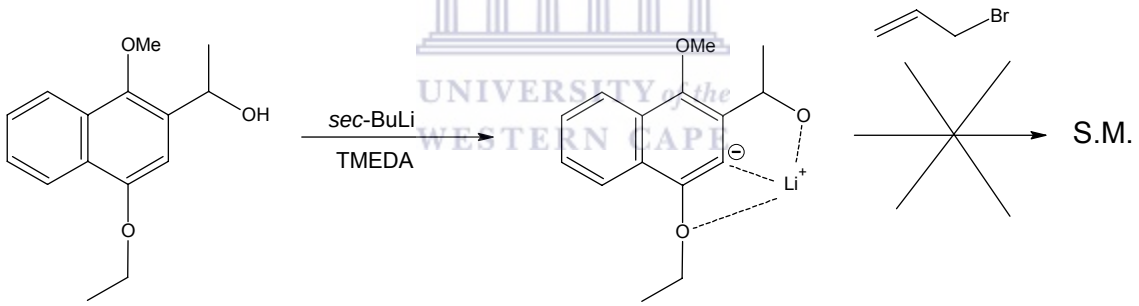
In the GC-MS of compound **205** two peaks were observed. The major peak was the first to elute and had both its molecular ion and base peak at *m/z* 228, corresponding to the vinyl derivative **206** of alcohol **205**, due to the loss of water under the conditions of heat **(Scheme 30)**. The compound with the higher retention time, as a result of hydrogen bonding was that of the expected alcohol **205**, which gave the correct M^{+} peak at *m/z* 246 in the mass spectrum.



205 **206**

Scheme 30

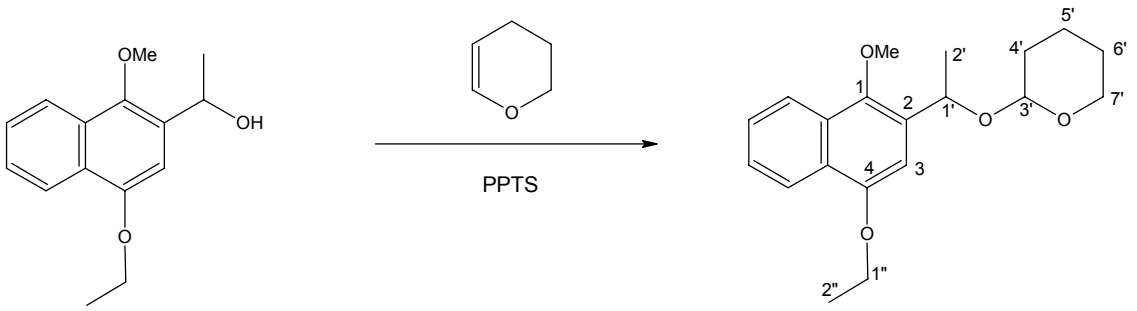
The next challenge was to introduce the allyl group at C-3 of alcohol **205** making use of the Snieckus DoM protocol as previously described. However, only starting material was recovered upon work-up in spite of several attempts at achieving the desired reaction.



205 **207**

The formation of the 3-lithiated naphthyl carbanion **207** was again evident due to the colour changes observed.

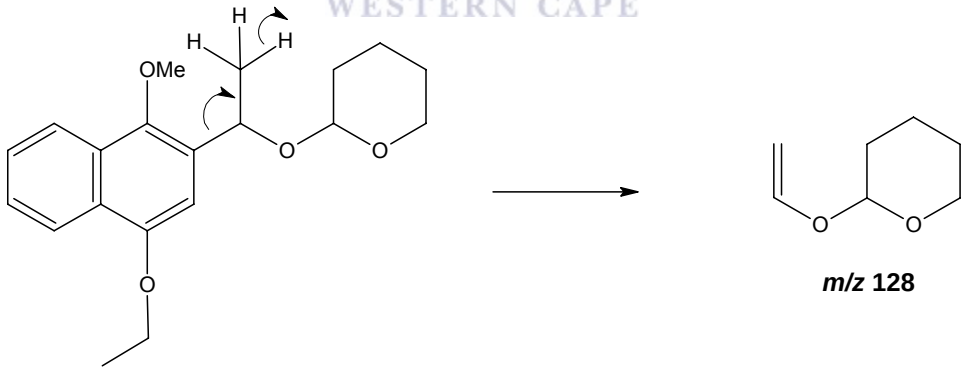
In a final attempt to allylate the C-3 position, the 2-(1′-hydroxyethyl) side chain of alcohol **205** was converted into the DHP derivative **208** in 67% yield based on recovered starting material **(Scheme 31)**.



205 **208**

Scheme 31

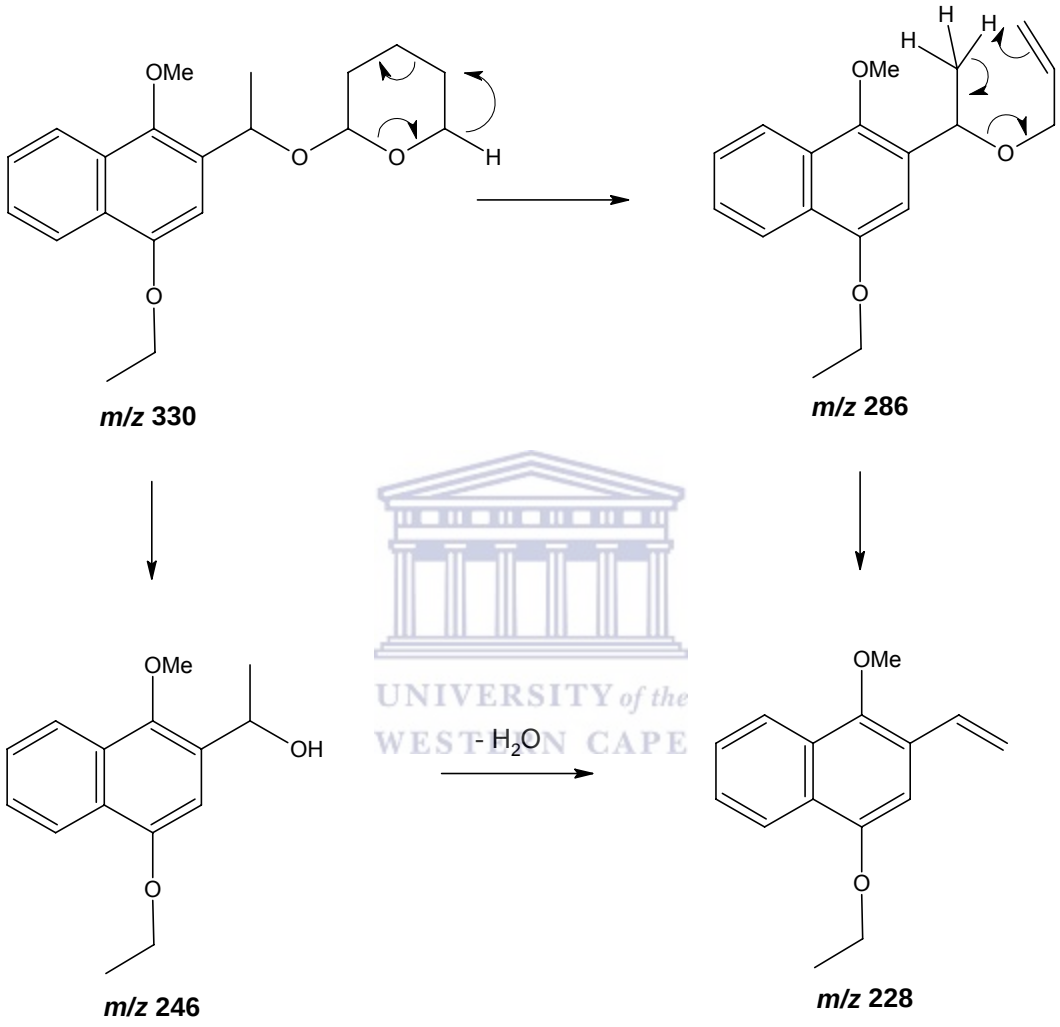
Analysis of both the ^{1}H – and ^{13}C NMR spectra of compound **208** revealed the duplication of the signals as we found in the case of compound **201**, again implying the presence of a pair of diastereoisomers due to the asymmetric carbons at C′1 and C′3. Three peaks were observed in the GC-MS of compound **208**. The first compound to elute was that of a degradation product. The mass spectrum of the second compound gave no molecular ion peak but showed a fragment ion at *m/z* 128 as a result of the loss of the DHP side chain **(Scheme 32)**.



208 ***m/z* 128**

Scheme 32

In addition to the correct combustion data of the last compound to elute, the molecular formula of the DHP derivative 208 was confirmed by an accurate mass measurement (*m/z* 330) through high resolution mass spectrometry. A suggested fragmentation pattern for the DHP derivative 208 in the mass spectrometer is outlined in **Scheme 33**.



Scheme 33

Upon repeating the Snieckus DoM reaction on the DHP derivative **208** the same results were obtained as we found for the other compounds.

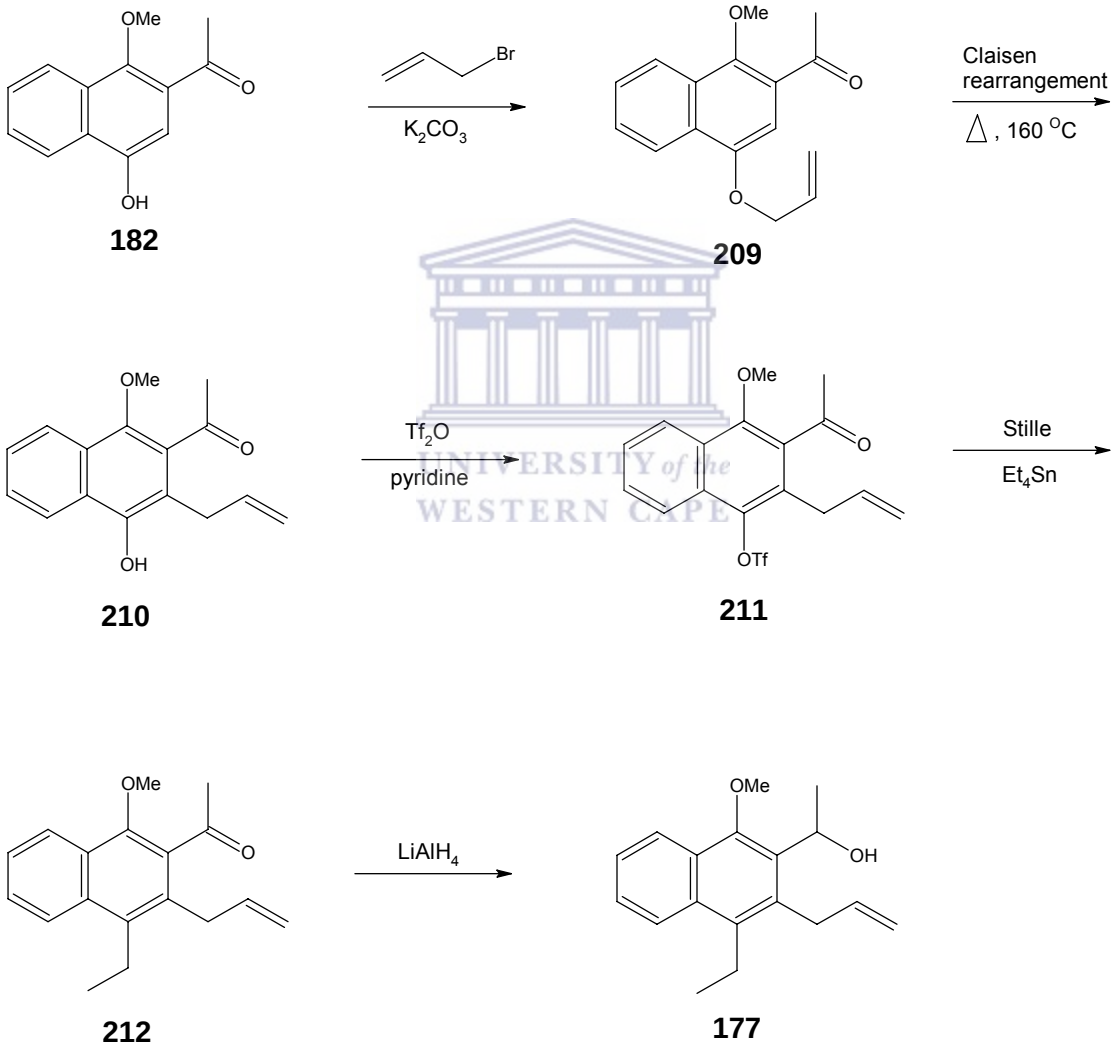
5.1.1.1 Concluding Remarks

Thus, from all the results on the attempted Snieckus DoM reaction, it was concluded that in each case, because of the colour changes that were observed, due to the extended conjugation, that the naphthyl carbanion was formed and that the C-3 reaction site was too sterically crowded for the delivery of the allyl group.

In view of this, an alternative synthetic route to the target naphthalene **177** was sought.

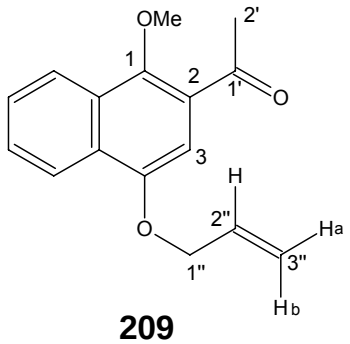
5.1.2 Route B : Synthesis of naphthalene 177 via a Claisen rearrangement followed by Stille Coupling

Due to the failure of the Snieckus directed *ortho* metalation (DoM) reaction as a result of steric crowding a different approach to naphthalene **177** was envisaged, involving the *O*-allylation of the pivotal ketonaphthalene **182** to afford the allyloxynaphthalene **209**. Subsequent Claisen rearrangement of naphthalene **209** followed by a Stille coupling reaction and reduction would then afford the target naphthalene **177 (Scheme 33)**.



Scheme 33

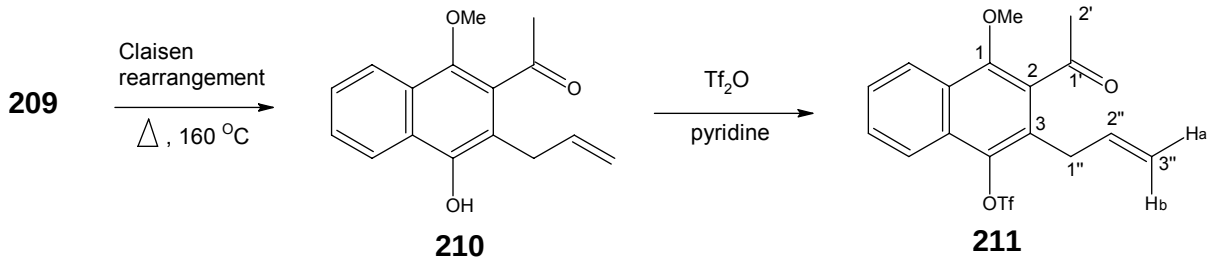
Having successfully synthesized the phenol **182 (Scheme 23)**, it was treated with allyl bromide in the presence of potassium carbonate in boiling acetone to afford the allyloxynaphthalene **209** [62] in 86% yield.



209

The ^{1}H NMR spectrum showed the 1″-CH_2 as a doublet of triplets at δ 4.73 (J 5.2 and 1.4). The two doublets of a quartet at δ 5.34 (J 10.2 and 1.4) and 5.52 (J 17.2 and 1.4) were assigned to 3″-Ha and 3″-Hb, respectively because the *trans* interaction characteristically has a larger coupling constant. Although the expected multiplicities of the Ha and Hb of the allylic group should be a doublet of a doublet of a triplet (ddt), the observed multiplicities were that of a doublet of a quartet (dq). The multiplet further downfield at δ 5.34 was assigned to the 2″-CH. The aromatic 3-H proton resonated as a singlet at δ 7.09 and in the infrared spectrum the C=O stretching frequency was observed at 1670 cm^{-1}. The molecular ion peak at *m/z* 256 in the mass spectrum supported the molecular formula corresponding to compound **209**.

The allyloxynaphthalene **209** underwent a Claisen rearrangement at 160 ^{O}C to afford the unstable *C*-allylnaphthol **210** [62] which was immediately converted into the corresponding triflate **211**, in an overall yield of 92% from naphthalene **209**, by treating it with trifluoromethanesulphonic anhydride in pyridine **(Scheme 34)**.



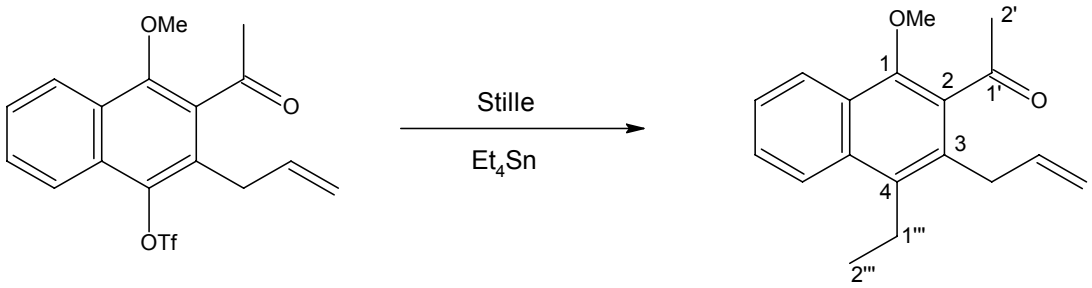
Scheme 34

A significant change could be noticed in the ^{1}H NMR of the naphthalene **211** which lacked the 3-H aromatic singlet present in the starting material **209**. All the protons of the allylic group appeared more upfield, especially that of 1′′-C which was shielded by more than 1ppm, from δ 4.73 in **209** to δ 3.66 in **211**. However, the doublet of a quartet at δ 4.99 (J 17.2 and 1.8) due to the *trans* 3′′-Hb, appeared more upfield than the *cis* proton at 5.11 (J 10.2 and 1.8); the reverse to what was being observed in the ^{1}H NMR spectrum of compound **209**. This might be due to the deshielding effect of the carbonyl group being in close proximity to the olefinic region of the allylic side chain.

The broad quartet at δ 118.8 (J 318.1) in the ^{13}C NMR spectrum, due to the coupling between the 3 F-atoms and the C-atom of the triflate group, confirmed the structure of compound **211**.

In the infrared spectrum of the tetra-substituted naphthalene **211** the carbonyl stretch appeared at 1704 cm^{-1}, which was at a significantly higher value than that of the less substituted naphthalene **209** (C=O stretch at 1670 cm^{-1}). This is ascribed to the C-2 acetyl group being twisted out of the plane of the naphthalene ring as a result of the increased steric demand in the tetra-substituted analogue. [65]

Palladium-catalyzed Stille coupling [61] of triflate **211** with tetraethyltin in the presence of lithium chloride afforded the ethyl naphthalene **212** in 75% yield.

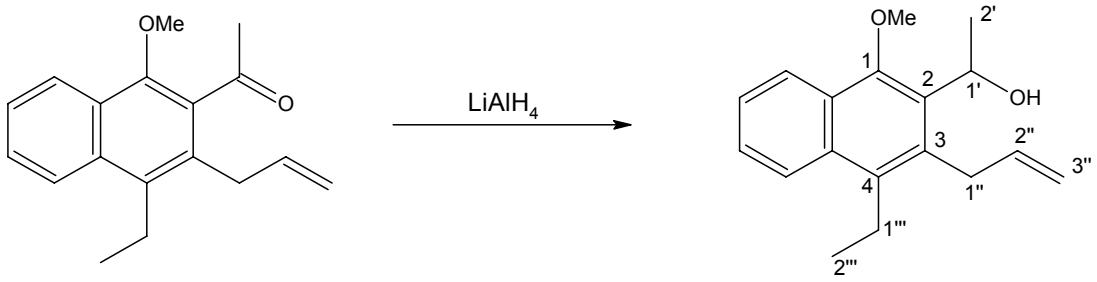


211 **212**

Analysis of the ^{1}H NMR spectrum of **212** showed no significant changes to that of naphthalene **211**, except for the presence of the ethyl substituent *i.e.*, a 3-proton triplet at δ 1.28 (J 7.4) assigned to 2′′′-CH_3 and a 2-proton quartet at δ 3.07 (J 7.4) assigned to 1′′′-CH_2.

Again the carbonyl stretching frequency was observed at 1703 cm^{-1} in the infrared spectrum of naphthalene **212**, as it was in the case of its precursor, implying the loss of coplanarity between the C-2 acetyl group and the naphthalene ring. The mass spectrum had the expected M^{+} at *m/z* 268, confirming the molecular formula of naphthalene **212**.

The reduction of naphthalene **212** with lithium aluminium anhydride in diethyl ether afforded the desired 3-allyl-4-ethyl-2-hydroxyethyl-1-methoxynaphthalene **177** almost quantitatively (96 % yield).



212 **177**

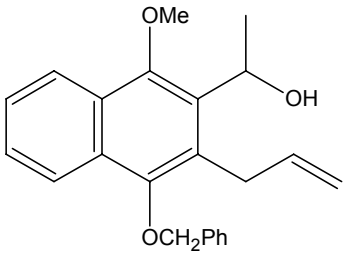
Assignment of structure **177** is based on the following ^{1}H NMR evidence. A 3-proton triplet at δ 1.28 (J 7.6) was assigned to 2‴-CH_3, whilst a 3-proton doublet at δ 1.6 (J 6.8) was assigned to the 2′-CH_3. At δ 3.04 a 2-proton doublet of a quartet (J 7.6 and 2.2) was assigned to1‴-CH_2 and the 2-proton multiplet at δ 3.63 was assigned to 1″-CH_2. The methoxy signal resonated characteristically as a singlet at δ 3.89 and 1′-OH was confirmed as a broad doublet (J 7.8) at δ 4.22 in a D_2O exchange experiment.

The *trans* 3″-H and *cis* 3″-H appeared as two doublets of quartets at δ 4.84 (J 17.2 and 2.2) and at δ 5.10 (J 10.2 and 2.2), respectively. The broad 1-proton quartet at δ 5.27 (J 6.8) was assigned to 1′-CH, the 1-proton multiplet at δ 6.10 to the 2″-CH, whilst the 2-proton multiplets at δ 7.54 and δ 8.10 was assigned to 6- and 7-H and 5- and 8-H, respectively.

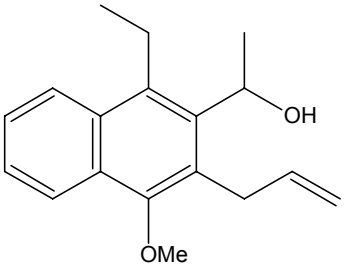
In the ^{13}C NMR spectrum the C=O signal was replaced by the C-1′ signal at δ 67.5. The molecular formula of naphthalene **177** was supported by its mass spectrum, which had a molecular ion peak at *m/z* 270 and a peak at *m/z* 252 due to the loss of water.

5.1.2.1 Concluding Remarks

The tetra-substituted naphthalene **177** was successfully synthesized via a Stille coupling reaction. It was noted that the IR carbonyl stretch of the tetra-substituted naphthalene **212** at 1703 cm^{-1} appears at a significantly higher value than those for the less crowded precursors **209** and **182** where the C=O stretching frequency appears at 1670 cm^{-1} and 1653 cm^{-1}, respectively. This is ascribed to a sterically-induced loss of coplanarity between the acetyl and naphthyl moieties in naphthalene **212**, which was observed in other systems.[48, 64] This observation is not inconsistent with the tentative suggestion [52] that the base-induced cyclisation of related alcohols, such as **213** [48] and **157** [55] arise, at least in part, through steric compression of the reacting centers.



213



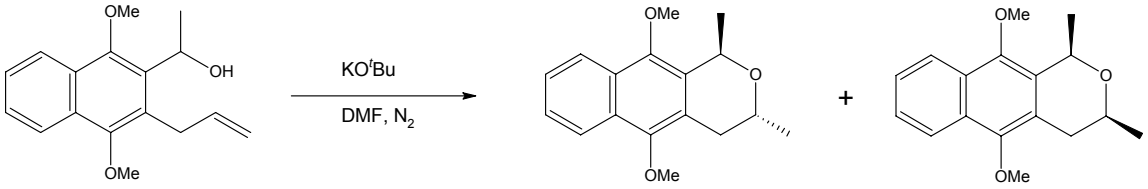
157

In view of this, the smaller coupling constant of J 2.2 observed for 1‴-CH_2 in the ^1H NMR spectrum of naphthalene **177** might be due to the coupling between the protons of 1‴-CH_2 and that of 1″-CH_2 as a result of the substituents being forced into such close proximity due to the increase in steric demand. A more plausible explanation would be that the side chains at C-2, C-3 and C-4 would have preferred conformations and this is clearly reflected by the fact that the signals of the hydrogens at the α-C's are not pure but duplicated due to the different conformations adopted.

CHAPTER 6

CYCLISATION REACTIONS

As mentioned before, it has been shown that on treatment with potassium *tert*-butoxide in DMF under nitrogen, tetra-substituted 2-hydroxyalkyl-3-alkenylnaphthalenes undergo cyclisation to afford naphthopyrans, e.g. naphthalene **136** cyclises to form both the *cis* and *trans* naphthopyrans **138** and **137**, with the latter predominating. [50]



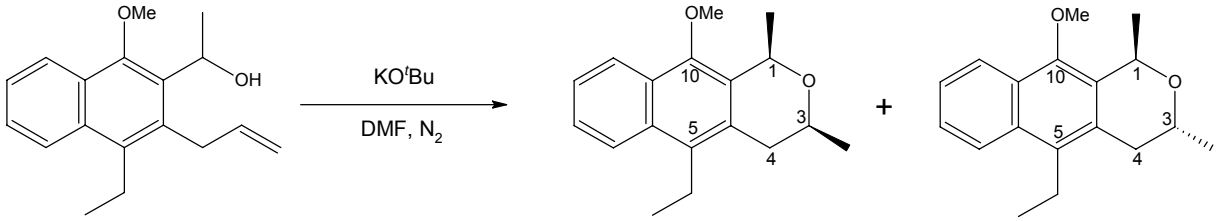
136 **137** **138**

However, it was not clear whether this potassium *tert*-butoxide catalysed ring closure reaction was as a result of electronic or steric factors. Since then, various analogues [48, 52, 55], related to naphthalene **136,** have been synthesized in an attempt to determine which structural features cause this base-induced cyclisation to occur. Subsequently it was tentatively suggested that this reaction arose through the close proximity of the reacting centers as a consequence of steric crowding.

In order to confirm what features are indeed required to promote cyclisation, naphthalene **177** was subjected to similar cyclisation conditions.

6.1 Base-induced cyclisation of naphthalene 177 under anaerobic conditions

Naphthalene **177** was treated with potassium *tert*-butoxide in dimethylformamide under nitrogen for two hours and the subsequent analysis of the residue obtained upon work-up, by TLC (10% ethyl acetate-hexane), revealed the presence of two products.

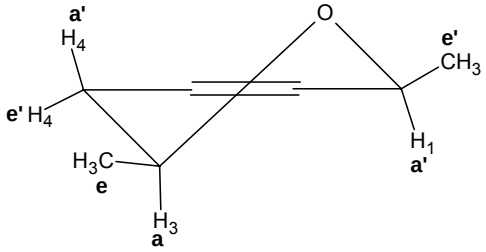


177 **214** **215**

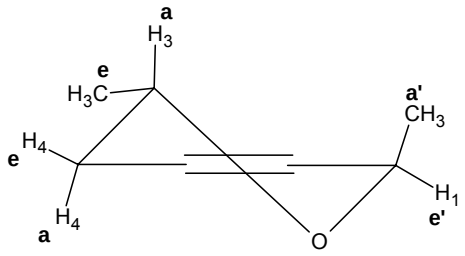
It has been found empirically that the 3-H multiplets for the *cis* and *trans* isomers of 1,3-dimethylnaphthopyrans differ substantially in chemical shift *i.e.,* those for the *cis* isomers appear more upfield at δ 3.5-3.8, while those of the *trans* isomers fall in the range of δ 3.9-4.3. [50] Hence, the ^{1}H NMR spectrum, of the first product to elute, showed it to be the *cis*-dimethylnaphthopyran **214** (16% yield), due to the 1-proton multiplet at δ 3.74 assigned to 3-H.

The ^{1}H NMR spectrum of **214** also had the following signals *inter alia*; a 3-proton triplet at δ 1.24 (J 7.8) assigned to the methyl group of the ethyl substituent, whilst the two doublets at δ 1.43 (J 6.0) and δ 1.66 (J 6.2) were assigned to the methyl groups of C-3 and C-1, respectively. The doublet of a doublet at δ 2.72 (J 15.8 and 10.6) was assigned to 4-Ha′, whilst the 4-He′ resonated as a doublet of a doublet at 2.90 (J 15.8 and 2.8). The large coupling constant of 15.8 Hz is as a result of the geminal coupling between the 2 H's of C-4. The 2-proton doublet of a quartet at δ 3.04 (J 7.8 and 2.8) was assigned to the methylene group of the ethyl substituent at C-4 and H-1 appeared as a quartet at δ 5.29 (J 6.2).

The final product to elute was that of the *trans*-dimethylnaphthopyran **215** (58% yield), confirmed by the characteristic multiplet of the 3-H at δ 4.20 in the ^{1}H NMR spectrum of **215** and the downfield appearance of the 1-H quartet at δ 5.36 (J 6.4), compared to where it appeared in the ^{1}H NMR spectrum of **214**. [50] The likely conformations of the *cis*-naphthopyran **214** and the *trans*-naphthopyran **215** are drawn in **Scheme 35**.



214



215

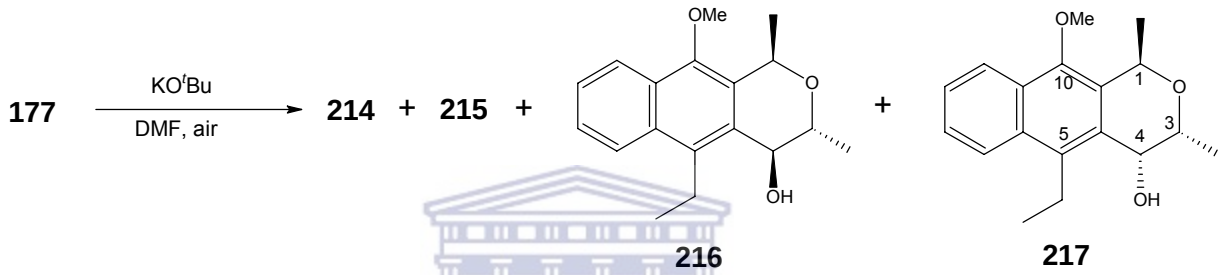
Scheme 35

In the case of chair conformation **214**, the C-3 methyl group is equatorial and the C-1 methyl group pseudoequatorial. On the hand chair conformation **215** is the more likely conformation, for the *trans*-isomer, since the methyl group at C-3 is equatorial and the methyl group at C-1 is pseudoaxial to minimize its *peri*-interaction with the C-10 methoxy group.

The mass spectrum of both isomers had a molecular ion peak at *m/z* 270 supporting the molecular formulae of these isomers.

6.2 Base-induced cyclisation of naphthalene 177 under aerobic conditions

Repeating the base-induced cyclisation of naphthalene **177** but without the exclusion of air as described earlier produced three products. The first two naphthopyrans to elute from the column were shown to be the *cis*-dimethylnaphthopyran **214** (17%) followed by the *trans*-dimethylnaphthopyran **215** (23%). The third fraction to elute was shown by ^{1}H NMR to be a diastereomeric mixture of the 4-hydroxynaphthopyrans **216** and **217** (31%) in a ratio of 1:3 respectively **(Scheme 36)**. Chromatographically, it was not possible to separate this latter mixture, which was unexpected.

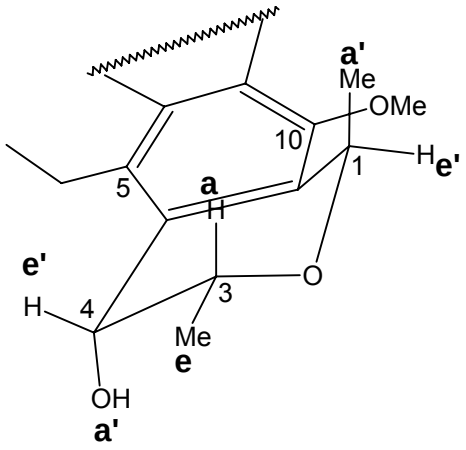


216 **217**

Scheme 36

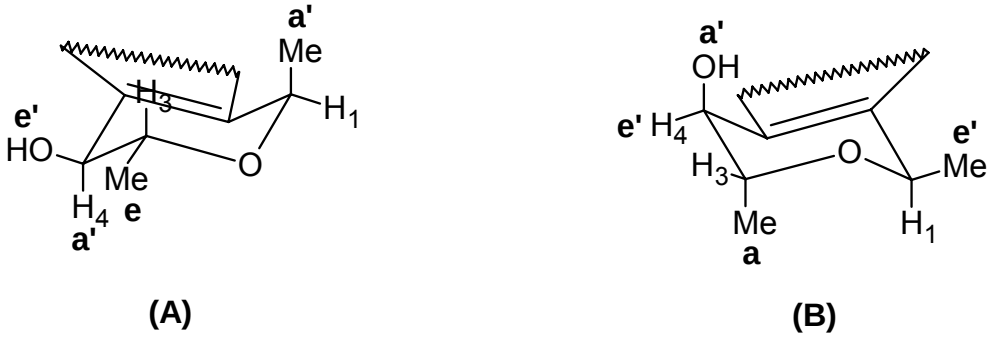
Signals at δ 4.19 and δ 4.34 for the 3-H of compounds **216** and **217** respectively, appeared as doublets of quartets (J 6.6 and 1.3) and (J 6.6 and 2.6), which is consistent with values reported for similar compounds having a *trans*-1,3-dimethylpyran substitution pattern. [50, 51] Confirmation of the relative stereochemistries of the three stereogenic centers viz., C-1, C-3 and C-4 was derived in the following way.

The major diastereomer **217** would have the pyran ring in the chair conformation as shown in **Scheme 37**. In this instance the C-1 methyl group is pseudoaxial to minimize *peri*-interaction with the C-10 methoxy group and the C-3 methyl group is in the thermodynamically more stable equatorial position. The C-4 hydroxyl group is pseudoaxial to reduce *peri*-interaction with the C-5 ethyl group. The smaller coupling constant of 2.6 Hz between 3-H and 4-H would thus be expected, because of a smaller dihedral angle which, with 3-H axial, required 4-H to be pseudo-equatorial.



Scheme 37

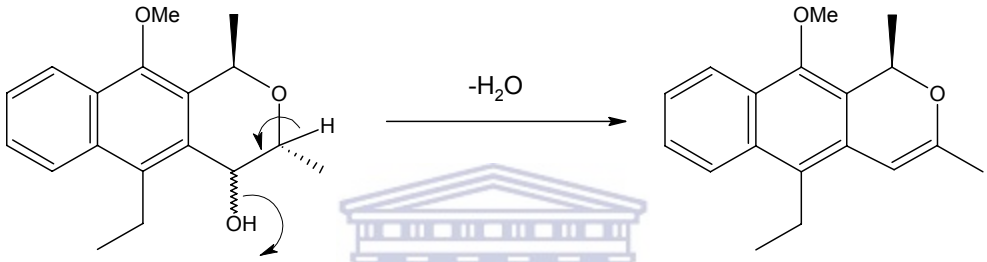
On the other hand the alternative diastereoisomer, also has the *trans*-1,3-dimethyl arrangement due to the position of the 3-H signal viz., δ 4.19 also as a doublet of a quartet but in this instance the *J* values are 6.6 and 1.3 Hz. Assuming that the initial 4-hydroxypyran **216** had formed (**A**), the C-4 hydroxy group would be pseudo-equatorial and thus experience a large *peri*-interaction with the C-5 ethyl group. For this initial conformation to be adopted, the ^{3}J between 3- and 4-H would be in the region of 7-8 Hz. [65] However the ^{3}J of 1.3 Hz suggests that the conformer **(A)** undergoes a conformational inversion to the alternative chair conformer **(B)**, shown in **Scheme 38**.



Scheme 38 (216)

In conformer **(B)**, which is less stable than **(A)** since the C-1 methyl group is pseudo-equatorial, the C-3 methyl group is axial and the C-4 hydroxy group is pseudoaxial to relieve the *peri*-strain with the C-5 ethyl group, the dihedral angle between H-3 and H-4 is vastly reduced and thus this accounts for the reason as to why the *J* value is so small.

In the GC-MS of the diastereomeric mixture of **216** and **217**, three peaks were observed. The first product to elute was that of the naphthopyrene **218** (M^+ 268) formed as a result of the loss of water due to heat **(Scheme 39)**. The last two products to elute were the 4-hydroxynaphthopyrans **216** and **217**, respectively.



216 + 217 **218**

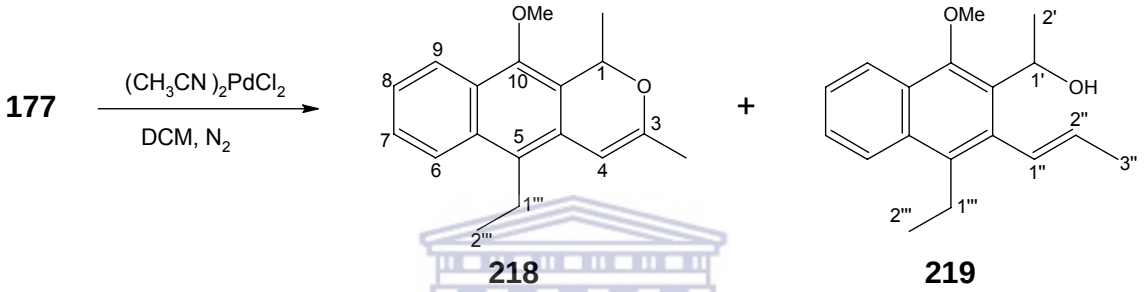
***m/z* 268**

Scheme 39

6.3 Palladium-promoted cyclisation of naphthalene 177

In a previous study by Giles *et al.* [55] it was shown that cyclisation of naphthalenes to give naphthopyrenes can also be achieved using bis(acetonitrile)dichloropalladium(II).

Thus, when naphthalene **177** was boiled in dichloromethane containing one mole equivalent of the metal complex, the naphthopyrene **218** was isolated in a yield of 67%, together with the (*E*)-alkene **219** in a yield of 4%.



218 **219**

The structure of pyrene **218** was confirmed by the mass spectrum, which showed a molecular ion at *m/z* 268. The ^{1}H NMR spectrum showed the presence of the double bond between C-3 and C-4, with the 3-CH_3 resonating as a singlet at δ 2.03 and a 1-proton olefinic signal at δ 5.94 due to 4-H. The ^{1}H NMR spectrum of **218** also had the following signals *inter alia*; a 3-proton triplet at δ 1.27 (J 7.6) assigned to 2′′′-CH_3, while a 3-proton doublet at δ 1.50 (J 6.6) is assigned to 1-CH_3. A 2-proton quartet at δ 3.06 (J 7.6) was assigned to the methylene protons of 1′′′-CH_2, whilst a downfield 1-proton quartet at δ 5.82 (J 6.6) is due to 1-H of the pyrene ring.

The product with the higher R_F value showed the OH stretch at 3520 cm^{-1} in the infrared spectrum and was assigned the structure of the conjugated (*E*)-alkene **219** based on the ^{1}H NMR spectrum which indicated that the coupling constant between the vicinal protons H-1′′ and H-2′′ is relatively large (J 13.0), confirming their *trans* relationship.

The ^{1}H NMR spectrum also showed the following signals *inter alia*; a 3-proton triplet at δ 1.25 (J 8.0) assigned to 2‴-CH_3; a 3-proton doublet at δ 1.41 (J 7.0) assigned to 2′-CH_3; a 3-proton doublet of a doublet at δ 2.08 (J 5.8 and 1.4) assigned to 3″-CH_3; a 2-proton quartet at δ 3.02 (J 8.0) assigned to 1‴-CH_2; a 1-proton quartet at δ 4.52 (J 7. 0) assigned to 1′-CH; a 1-proton multiplet at δ 5.18 assigned to 2″-CH and a 1-proton doublet of a doublet at δ 6.47 (J 13.0 and 1.4) assigned to 1″-CH.

No molecular ion peak was observed at the expected *m/z* 270, but the base peak at *m/z* 252 due to the loss of water, supported the structure of the (*E*)-alkene **219 (Scheme 40)**. Interestingly enough, two peaks, each with M^+ 252 were observed in the GC-MS and have been assigned to the *cis* and *trans* geometric isomers of naphthalene **220**.

219
m/z 270

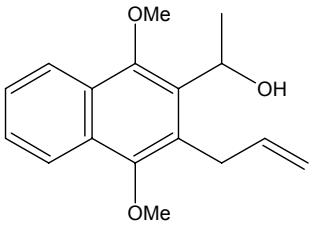
220
m/z 252

Scheme 40

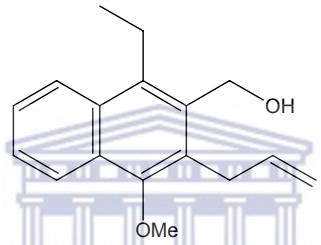
6.4 Concluding remarks

The results described in this chapter corresponds to what has been found in earlier studies [50, 55] and supports the view that these base-induced cyclisations are as a result of the reacting centers being held in close proximity through steric crowding.

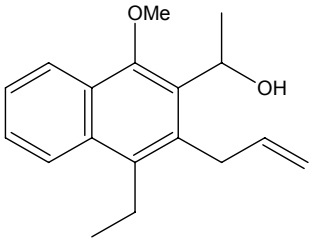
Furthermore, the replacement of the methoxy groups *ortho*- to the hydroxyalkyl and allyl group in naphthalene **136** [50], by an ethyl group in analogue **157** [55] and **177** respectively, shows that these methoxy groups exert a steric rather than an electronic influence on the ring-closure, which occurs with all three naphthalenes.



136

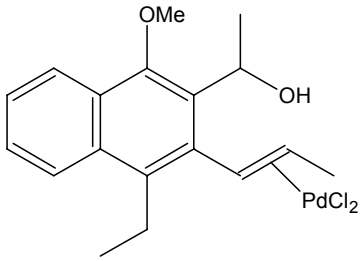


157



177

In the palladium-catalyzed cyclisation of naphthalene **177**, similar results were obtained as reported by Giles [55] viz., the isolation of both the naphthopyrene **218** and the conjugated (*E*)-naphthalene **219**. The presence of the of the (*E*)-naphthalene supports the proposed mechanism **(Scheme 19)**, which suggests that the palladium-mediated cyclisation involves the conversion of the allylnaphthalene **177** into the (*E*)-styrene intermediate **221**, which then undergoes ring closure to form naphthopyrene **218**.



221

CHAPTER 7

EXPERIMENTAL – GENERAL PROCEDURES

Purification of solvents

All solvents used for reactions and preparative chromatography, were distilled prior to use. Tetrahydrofuran and dietyl ether were dried using sodium wire and the sodium benzophenone ketyl radical as indicator. Dimethylformamide, tetrahydrofuran, acetone and diethyl ether were stored over molecular sieves (4A). Other reagents obtained from commercial sources were used without further purification.

Chromatographic Separations

Preparative column chromatography was carried out on dry-packed columns using Merck silica gel (particle size 0.2 - 0.5 mm) as adsorbent and Merck silica gel 60 (0.063 - 0.2 mm) as the stationary phase. Mixtures of ethyl acetate and hexane were used as eluent.

Physical and Spectroscopic Data

All melting points were obtained on a FISCHER-JOHNS melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded using a VARIAN 200 spectrometer (^{1}H, 200MHz; ^{13}C, 50MHz). The spectra were run at ambient temperature in deuterated chloroform ($CDCl_3$) solution, with $CHCl_3$ at δ 7.26 for ^{1}H NMR spectra and chloroform (δ 77.00) for ^{13}C-NMR spectra as internal standards. In the NMR spectra, assignments of signals with the same superscripts are interchangeable. Splitting patterns are designated as “s”, “d”, “t”, “q”, “m” and “bs”. These symbols indicate “singlet”, “doublet”, “triplet”, “quartet”, “multiplet” and “broad singlet”.

Infrared (IR) spectra were recorded as a nujol mull for solids and as thin films between sodium chloride plates for oils on a PERKIN ELMER FT-IR spectrometer PARAGON 2000. Mass spectra were performed on a Finnigan-MAT GCQ, gas chromatography-mass

spectrometer. Mass spectrometry is reported as follows: *m/z* (% relative abundance). Elemental analyses were performed on both oil and solid samples where possible on CARLO ERBA 1500 NA analyzer.

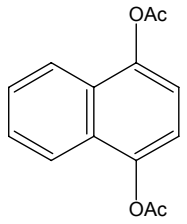
Other General Procedures

The term "residue obtained upon work-up" refers to the residue obtained when the organic layer was separated, dried over magnesium sulphate ($MgSO_4$) followed by filtration and the removal of solvent by evaporation.

CHAPTER 8

EXPERIMENTAL PROCEDURES

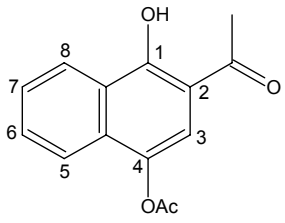
1,4-Diacetoxynaphthalene 179



179

A mixture of 1,4-naphthoquinone (5.50 g; 35.0 mmol), zinc dust (4.50 g; 69.0 mmol), and sodium acetate (1.00g; 12.0 mmol) in acetic anhydride was stirred vigorously and heated to 90 ^{O}C for 1 hr. The hot solution was treated with glacial acetic acid (20 ml), heated again and then filtered. The filtrate was poured into water (500 ml) and stirred until the oil solidified. The crystalline material was filtered to yield the diacetoxynaphthalene **179** (7.86 g; 92%) as white crystals, m.p. 161-163 ^{O}C (from 90% ethanol). Lit.[58] m.p. 164-166 ^{O}C.

4-Acetoxy-2-acetyl-1-hydroxynaphthalene 180



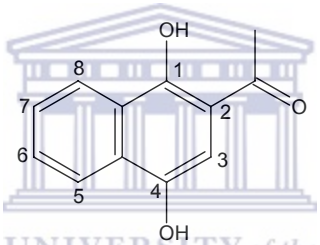
180

Method A

A solution of 1,4-diacetoxynaphthalene **179** (10.0 g; 41.0 mmol), zinc chloride (10.0 g; 73.0 mmol) and acetic acid (20 ml) was stirred and heated under reflux under nitrogen for

30 min. The reaction mixture was cooled and then thrown into ice water (500 ml) and extracted into dichloromethane (3 x 150 ml), and then backwashed with saturated sodium hydrogen carbonate, and water. The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (3:7) as eluent to afford two products.

1. **4-Acetoxy-2-acetyl-1-hydroxynaphthalene 180** (3.50 g; 35%) as light yellow crystals, m.p. 106-107 ^{O}C (from 70% ethanol) (Lit.[58] m.p. 106-107 ^{O}C). ν_{max}/cm^{-1} 3174 (O-H) and 1772 (C=O); δ_H 2.46 (3H, s, 4-OAc), 2.66 (3H, s, 2-$COCH_3$), 7.42 (1H, s, 3-H), 7.57-7.74 (3H, m, 6-, 7- and 8-H) and 8.50 (1H, dd, *J* 8.0 and 1.6, 5-H); δ_C 21.0 (CH_3CO_2), 27.0 ($COCH_3$), 116.5 (3-C), 121.2 (6-C)[a], 125.1 (7-C)[a], 126.2 (4a-C)[b], 126.7 (5-C)[c], 130.7 (8-C)[c], 131.1 (8a-C)[b], 138.0 (2-C), 160.7 (1- and 4-C), 169.9 (C=O ester), and 203.8 (C=O).



183

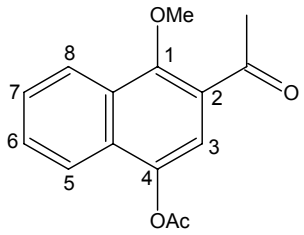
2. **2-Acetyl-1,4-dihydroxynaphthalene 183** (3.50 g; 35%) as bright orange cubes, m.p. 193-195 ^{O}C (from ethyl acetate); δ_H (Acetone-D6) 2.64 (3H, s, CH_3CO), 7.16 (1H, s, 3-H), 7.56-7.76 (2H, m, 6- and 7-H), 8.22 (1H, dd, *J* 8.4 and 2.0, 5-H), 8.38 (1H, dd, *J* 8.4 and 2.0, 8-H) and 8.70 (1H, s, D_2O exchangeable, 4-OH); δ_C 27.2 (CH_3CO), 106.2 (3-C), 113.5 (2-C), 123.1 (6-C)[a], 124.8 (7-C)[a], 126.7 (4a-C)[b], 127.2 (5-C)[c], 130.2 (8-C)[c], 130.8 (8a-C)[b], 145.5 (4-C)[d], 156.7 (1-C)[d], and 205.3 (C=O). (Found: HRMS 202.0625. Calc. For $C_{12}H_{10}O_3$: 202.0630).

Method B

A solution of the diacetate **179** (1.0 g; 4.10 mmol) in freshly distilled boron trifluoride-acetic acid complex (4 ml) was stirred and heated under reflux for 1hr, cooled and poured into water and extracted into DCM (3 x 50 ml). The organic phase was washed with

saturated sodium hydrogen carbonate (50 ml), water (50 ml) and the residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:4) as eluent to yield **180** in 89% yield.

4-Acetoxy-2-acetyl-1-methoxynaphthalene 181

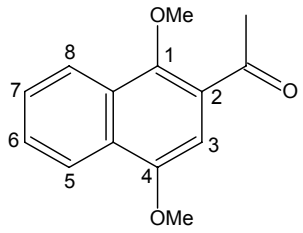


181

Naphthol **180** (3.87 g; 15.84 mmol) was dissolved in dry acetone (60 ml) and potassium carbonate (5.47 g; 39.61 mmol) was added to it. Dimethyl sulphate (3.75 ml; 39.61 mmol) was added and the reaction mixture was then stirred vigorously and heated under reflux for 1.5 hrs. It was then cooled, filtered, and the solvent evaporated. The residue was taken up in ether (50 ml) and washed with water (50 ml) followed sequentially by 25% ammonia (50 ml), water (50 ml), then 0.1M HCl (50 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:4) as eluent, to afford the acetoxynaphthalene **181** (3.33 g; 81%) as white needles), m.p. 91-93 ^{O}C, (from hexane). Lit.[48] m.p. 92-93 ^{O}C. ν_{max}/cm^{-1} 1752 (OAc) 1668 (C=O); δ_H 2.46 (3H, s, 4-OAc), 2.78 (3H, s, 2-$COCH_3$), 4.01 (3H, s, CH_3O), 7.54 (1H, s, 3-H), 7.58-7.68 (2H, m, 6- and 7-H), 7.80-7.90 (1H, m, 8-H), and 8.20-8.28 (1H, m, 5-H); δ_C 21.0 (CH_3CO_2), 30.8 ($COCH_3$), 64.1 (CH_3O), 117.7 (3-C), 121.9 (6-C)[a], 124.0 (7-C)[a], 127.2 (5-C)[b], 127.5 (4a-C)[c], 128.9 (8-C)[b], 129.3 (8a-C)[c], 130.3 (2-C), 143.0 (1-C)[d], 155.7 (4-C)[d], 169.4 (C=O ester), and 198.7 (C=O). (Found: C, 69.7; H, 5.50; M^+ 256. Calc. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.40%; M 256).

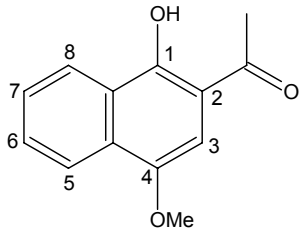
In an attempt to improve the formation of the methyl ether **181**, a solution of the diacetate **179** (10.0 g; 41.0 mmol) in boron trifluoride-acetic acid complex (45 ml) was stirred and heated under reflux for 1hr, cooled and poured into water and extracted into DCM (3 x

200 ml). The organic phase was washed with saturated sodium hydrogen carbonate (100 ml), water (200 ml) and the residue obtained upon work-up was without prior chromatography subjected to methylation as described above. The residue obtained upon work-up as described earlier was chromatographed using ethyl acetate-hexane (1:4) as eluent to afford three products.



188

1. **2-Acetyl-1,4-dimethoxynaphthalene 188** (0.94 g; 10%) as white needles, m.p. 59-60 ^{O}C (from methanol-water). Lit.[66] m.p. 61-62 ^{O}C. ν_{max}/cm^{-1} 1670 (C=O); δ_H 2.81 (3H, s, CH_3CO), 3.96 and 4.01 (each 3H, s, OCH_3), 7.08 (1H, s, 3-H), 7.56-7.64 (2H, m, 6- and 7-H), 8.12-8.30 (2H, m, 5- and 8-H); δ_C 31.0 (CH_3CO), 55.9 (OCH_3), 63.9 (OCH_3), 102.3 (3-C), 122.7 (6-C)[a], 123.3 (7-C)[a], 127.2 (5-C)[b], 127.4 (4a-C)[c], 127.9 (8-C)[b], 128.9 (2-C)[b], 129.2 (8a-C)[c], 151.9 (1-C)[d], 151.9 (4-C)[d] and 200.0 (C=O).



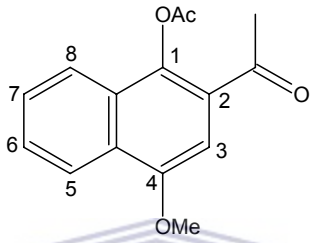
189

2. **2-Acetyl-1-hydroxy-4-methoxynaphthalene 189** (4.43 g; 50%) as olive needles, m.p. 120-121 ^{O}C (from methanol). ν_{max}/cm^{-1} 3450 (O-H) and 1700 (C=O); δ_H 2.69 (3H, s, CH_3CO), 3.99 (3H, s, CH_3O), 6.83 (1H, s, 3-H), 7.54-7.72 (2H, m, 6- and 7-H), 8.16-8.22 (1H, dm, *J* 8.0, 5-H), and 8.42-8.48 (1H, dm, *J* 8.0, 8-H); δ_C 27.1 ($COCH_3$), 55.9 (CH_3O), 101.1 (3-C), 112.1 (2-C), 122.0 (6-C)[a], 124.5 (7-C)[a],

126.1 (4a-C)[b], 126.7 (5-C)[c], 129.8 (8-C)[c], 130.5 (8a-C), 147.6 (1-C)[d], 157.6 (4-C)[d], and 203.7 (C=O). (Found: C, 72.0; H, 5.70; M^+ 216. Calc. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.60%; M 216).

3. Further elution afforded the desired acetylnaphthalene **181** (1.59 g; 15%) identical in all aspects to the material synthesized before.

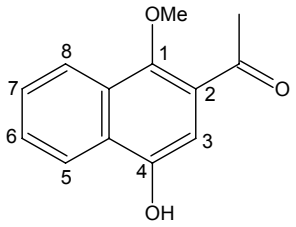
1-Acetoxy-2-acetyl-4-methoxynaphthalene 190



190

A solution of naphthol **189** (0.22 g; 1.0 mmol) in acetic anhydride (10 ml) and pyridine (3.5 ml) was stirred for 8 hrs and the mixture was then poured into water (60 ml). The crystalline material was filtered off to yield the 1-acetoxynaphthalene **190** (0.230 g; 89%) as white cubes, m.p. 111-112 ^{O}C (from methanol). ν_{max}/cm^{-1} 1720 (OAc) and 1695 (C=O); δ_H 2.51 (3H, s, 4-OAc), 2.65 (3H, s, $COCH_3$), 4.05 (3H, s, CH_3O), 7.13 (1H, s, 3-H), 7.54-7.64 (2H, m, 6- and 7-H), 7.82-7.90 (1H, m, 5-H), and 8.24-8.32 (1H, m, 8-H); δ_C 21.1 (CH_3CO_2), 30.1 ($COCH_3$), 55.8 (CH_3O), 102.1 (3-C), 122.6 (6-C)[a], 122.7 (7-C)[a], 126.7 (4a-C)[b], 127.9 (5-C)[c], 128.0 (8a-C)[b], 128.1(8-C)[c], 128.5 (2-C), 140.4 (1-C)[d], 153.4 (4-C)[d], 169.8 (C=O ester), and 197.5 (C=O). (Found: C, 69.6; H, 5.30; M^+ 258. Calc. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.50%; M 258).

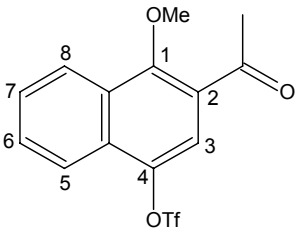
2-Acetyl-4-hydroxy-1-methoxynaphthalene 182



182

Methyl ether **181** (3.33 g; 12.89 mmol) was dissolved in 110 ml of a 1% (w/v) methanolic solution of potassium hydroxide (1.09 g; 19.34 mmol) and the solution was stirred at room temperature for 30 min. before being quenched by addition of 0.1M HCl (100 ml). The organic material was extracted into DCM (3 x 50 ml) and the extract was washed with water (100 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:4) as eluent, to afford the naphthol **182** (2.40 g; 86%) as pale yellow plates, m.p. 138-139 ^{O}C (EtOAc:Hexane). Lit.[48] m.p. 137-138 ^{O}C. ν_{max}/cm^{-1} 3420 (O-H) and 1655 (C=O); δ_H 2.83 (3H, s, $COCH_3$), 3.97 (3H, s, CH_3O), 7.33 (1H, s, 3-H), 7.42 (1H, s, D_2O exchangeable, 4-OH, 7.58-7.63 (2H, m, 6- and 7-H), and 8.15-8.29 (2H, m, 5- and 8-H); δ_C 31.0 ($COCH_3$), 64.0 (CH_3O), 106.7 (3-C), 122.8 (6-C)[a], 123.5 (7-C)[a], 127.1 (5-C)[b], 127.3 (4a-C)[c], 127.9 (8-C)[b], 128.5(8a-C)[c], 129.1 (2-C), 148.6 (1-C)[d], 152.1 (4-C)[d], and 200.8 (C=O). (Found: C, 72.3; H, 5.65%; M^+ 216. Calc. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.60%; M 216).

2-Acetyl-1-methoxy-4-trifluoromethanesulphonyloxynaphthalene 191

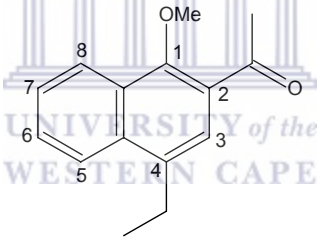


191

Trifluoromethanesulphonic anhydride (7.05 g; 4.40 ml; 25.0 mmol) was added to a solution of naphthol **182** (4.40 g; 20.35 mmol) in dry pyridine (15.0 ml) at 0 ^{O}C. The

mixture was stirred for 10 min., allowed to warm to room temperature and stirred for 24 hrs. The reaction mixture was quenched with water (200 ml) and the resulting mixture extracted with ether (3 x 50 ml). The organic extract was washed consecutively with water (100 ml), 0.1M HCl (3 x 50 ml) and water (100 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:9) as eluent, to afford the triflate **191**. (6.50 g; 92%) as an orange oil. ν_{max}/cm^{-1} 1685 (C=O); δ_H 2.79 (3H, s, $COCH_3$), 4.04 (3H, s, CH_3O), 7.78 (1H, s, 3-H), 7.60-7.81 (2H, m, 6- and 7-H), 8.08 (1H, dd, *J* 7.8 and 1.6, 8-H), and 8.28 (1H, dd, *J* 7.8 and 1.6, 5-H); δ_C 30.6 ($COCH_3$), 64.4 (CH_3O), 117.9 (3-C), 118.8 (q, *J* 318.5, CF_3), 121.6 (6-C)[a], 124.1 (7-C)[a], 127.3 (2-C), 128.2 (5-C)[b], 129.7 (4a-C)[c], 129.8 (8a-C)[c], 130.2 (8-C)[b], 141.8 (4-C), 157.5 (1-C), and 197.5 (C=O); *m/z* 349 ($M+1^+$), 348 (M^+, 22%), 215 (100), 155, and 129. (Found: C, 48.40; H, 3.40%. Calc. for $C_{14}H_{11}F_3O_5S$: C, 48.27; H, 3.19%).

2-Acetyl-4-ethyl-1-methoxynaphthalene 192

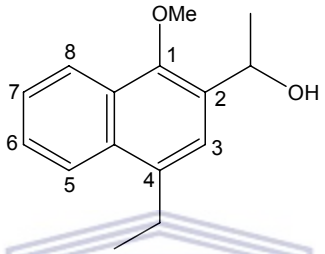


192

Tetraethyltin (0.30 g; 1.28 mmol) was added to a solution of triflate **191** (0.45 g; 1.29 mmol), bis(triphenylphosphine)dichloropalladium(II) (8.0 mg; 0.012 mmol), lithium chloride (0.15g; 3.56 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (~ 0.01 g) in dry DMF (10 ml). The solution was stirred at 85 ^{O}C under nitrogen for 24 hrs. The dark red reaction mixture was cooled, dissolved in dry ether (100 ml) and washed with a 10% aqueous ammonium fluoride solution (100 ml). The organic layer was filtered and then washed with water (100 ml), 25% aqueous ammonia (100), water (100 ml), 0.1M HCl (100 ml) and water (100 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:9) as eluent, to afford the naphthalene **192** (0.15 g; 51%) as an oil. ν_{max}/cm^{-1} 1678 (C=O); δ_H 1.37 (3H, t, *J* 7.6, $-CH_2CH_3$), 2.78 (3H, s, $COCH_3$), 3.06

(2H, q, *J* 7.6, -C*H*$_2$CH$_3$), 3.98 (3H, s, CH$_3$O), 7.56-7.63 (2H, m, 6- and 7-H), 7.60 (1H, s, 3-H), 8.03 (1H, dd, *J* 6.8 and 1.6, 8-H), and 8.27 (1H, dd, *J* 6.8 and 1.6, 5-H); δ_C 14.9 (CH$_2$*C*H$_3$), 25.6 (CO*C*H$_3$), 30.9 (*C*H$_2$CH$_3$), 63.9 (*C*H$_3$O), 124.1 (3-C)[a], 124.1 (6-C)[a], 124.3 (7-C)[a], 126.2 (5-C)[b], 127.5 (2-C), 128.2 (8-C)[b], 128.5 (4-C), 135.3 (4a-C)[c], 136.6 (8a-C)[c], 156.1 (1-C), and 200.4 (C=O); *m/z* 229 (M+1$^+$), 228 (M$^+$, 100%), 213, 181, 157, and 43. (Found: C, 78.91; H, 7.07%. Calc. For $C_{15}H_{16}O_2$: C, 78.90; H, 7.05%).

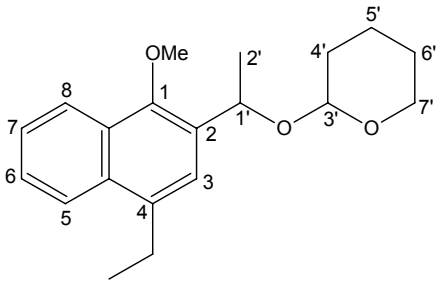
4-Ethyl-2-(1′-hydroxyethyl)-1-methoxynaphthalene 193



193

The ketone **192** (0.54 g; 2.37 mmol) was dissolved in dry ether (30 ml) and added dropwise, using a dropping funnel to a stirred suspension of $LiAlH_4$ (0.36 g; 9.46 mmol) in dry ether (30 ml) over 5 min. at room temperature under nitrogen. After allowing the mixture to stir for a further 10 min., sufficient saturated aqueous ammonium chloride was added to destroy the excess of reagent. DCM (50 ml) was added to the mixture and the residue obtained upon work-up was then chromatographed using ethyl acetate-hexane (3:7) as eluent, to give product **193** (0.51 g; 94%) as an oil. ν_{max}/cm^{-1} 3321 (O-H); δ_H 1.38 (3H, t, *J* 7.8, -CH$_2$C*H*$_3$), 1.58 (3H, d, *J* 6.6, -CH(OH)C*H*$_3$), 2.37 (1H, bs, D$_2$O exchangeable, OH), 3.08 (2H, q, *J* 7.8, -C*H*$_2$CH$_3$), 3.95 (3H, s, CH$_3$O), 5.44 (1H, q, *J* 6.6, -C*H*(OH)CH$_3$, 7.43 (1H, s, 3-H), 7.50-7.54 (2H, m, 6- and 7-H), 8.03 (1H, dd, *J* 6.6 and 3.2, 8-H), and 8.10 (1H, dd, *J* 6.6 and 3.2, 5-H); δ_C 15.1 (CH$_2$*C*H$_3$), 24.3 (CH(OH)*C*H$_3$), 25.9 (*C*H$_2$CH$_3$), 62.8 (*C*H$_3$O), 64.9 (*C*H(OH)CH$_3$), 122.7 (6-C)[a], 122.9 (7-C)[a], 124.2 (3-C), 125.7 (5-C)[b], 125.9 (8-C)[b], 128.1 (2-C)[c], 132.6 (4-C)[c], 132.9 (4a-C)[d], 137.1 (8a-C)[d], and 150.8 (1-C); *m/z* 230 (M$^+$), 212 (100%), 185, 159, 128 and 43. (Found: C, 78.21; H, 7.87. Calc. for $C_{15}H_{16}O_2$: C, 78.23; H, 7.88%).

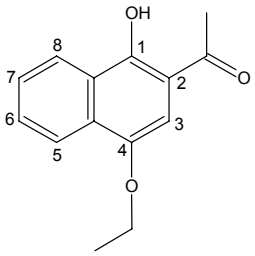
4-Ethyl-1-methoxy-2-(1′-oxadihydropyranoethyl)naphthalene 201



201

The alcohol **192** (0.12 g; 0.52 mmol) was dissolved in dry DCM (10 ml), and DHP (55 mg; 0.65 mmol) followed by PPTS (12 mg, 0.052mmol), was added. The reaction mixture was then allowed to stir at room temperature for 24 hrs, under nitrogen. The residue obtained upon work-up was then chromatographed using ethyl acetate-hexane (1:4) as eluent, to give product **201** (0.12 g; 74%) as an oil. ν_{max}/cm^{-1} 1601 (C=C); δ_H **(mixture of diastereomers)** 1.38 and 1.39 (each 3H, t, *J* 7.6, -CH_2CH_3 for each isomer), 1.49 and 1.55 (each 3H, d, *J* 6.6, 2′-CH_3 for each isomer), 1.52-1.98 (12H, m, 4′-, 5′-, and 6′-CH_2 for both isomers) 3.09 and 3.11 (each 2H, q, *J* 7.6, -CH_2CH_3 for each isomer), 3.24-3.67 (4H, m, 7′-CH_2 for both isomers), 3.94 and 3.96 (each 3H, s, CH_3O for each isomer), 4.38 and 4.95 (each 1H, t, *J* 4.4, 3′-CH for each isomer), 5.37 and 5.53 (each 1H, q, *J* 6.6, 1′-CH for each isomer), 7.40 and 7.49 (each 1H, s, 3-H for each isomer), 7.51-7.56 (4H, m, 6- and 7-H for both isomers), 7.98-8.10 (2H, m, 8-H for both isomers), and 8.11-8.16 (2H, m, 5-H for both isomers); δ_C **(mixture of diastereomers)** 15.1 and 15.2 (CH_2CH_3), 19.4 and 20.0 (2′CH_3), 22.5 and 23.6 (CH_2CH_3), 25.56 and 25.59 (4′-CH_2)[a], 25.64 and 25.76 (5′-CH_2)[a], 25.86 and 25.89 (6′-CH_2)[a], 30.4 and 31.0 (7′-CH_2), 62.6 and 62.9 (CH_3O), 67.1 and 68.3 (1′-CH), 96.2 and 97.1 (3′-CH), 122.7 and 122.90 (6-C)[b], 122.98 and 123.03 (7-C)[b], 123.8 and 124.1 (3-C)[b], 125.4 and 125.6 (5-C)[b], 125.7 and 125.9 (8-C)[b], 128.1 and 131.0 (2-C)[b], 132.44 and 132.57 (4-C)[c], 132.64 and 132.96 (4a-C)[c], 136.5 and 136.9 (8a-C)[c], and 150.1 and 152.0 (1-C); *m/z* 314 (M^+, 27%), 229 (5), 213 (90) and 185 (100). (Found: C, 76.20; H, 8.10%; HRMS 314.1886. Calc. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33%; HRMS 314.1882).

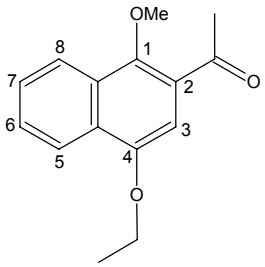
2-Acetyl-4-ethoxy-1-hydroxynaphthalene 203



203

A mixture of naphthalene **172** (2.00 g; 8.19 mmol) and $BF_3.OEt_2$ was heated under reflux for 1hr. The reaction mixture was allowed to cool to room temperature and then poured into water (100 ml) and extracted with DCM (3 x 50 ml). The residue obtained upon work-up was then chromatographed using ethyl acetate-hexane (3:7) as eluent, to give product **203** (1.77 g; 94%) as white crystals, m.p. 100-101 ^{O}C (from EtOAc-hexane). ν_{max}/cm^{-1} 3440 (O-H) and 1700 (C=O); δ_H 1.55 (3H, t, *J* 7.0, -CH_2CH_3), 2.67 (3H, s, -$COCH_3$), 4.17 (2H, q, *J* 7.0, -CH_2CH_3), 6.84 (1H, s, 3-H), 7.61 (2H, m, 6- and 7-H), 8.22 (1H, dd, *J* 8.0 and 1.6, 8-H)[a], and 8.44 (1H, dd, *J* 8.0 and 1.6, 5-H)[a]; δ_C 14.9 (CH_2CH_3), 27.1 ($COCH_3$), 64.3 (CH_2CH_3), 102.2 (2-C)[a], 112.2 (3-C)[a], 122.1 (6-C)[b], 124.4 (7-C)[b], 126.0 (4a-C)[c], 126.6 (5-C)[d], 129.7 (8-C)[d], 130.6 (8a-C)[c], 146.8 (1-C)[e], 157.4 (4-C)[e], 203.8 (C=O). (Found: C, 73.2; H, 6.20; HRMS 230.0941. Calc. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.10%; HRMS 230.0943).

2-Acetyl-4-ethoxy-1-methoxynaphthalene 204

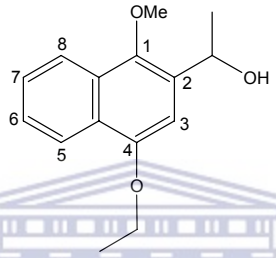


204

Under a similar protocol described earlier, the methylation of naphthol **203** (0.97 g; 4.21 mmol) afforded the naphthalene **204** (0.78 g; 76%) as an oil. ν_{max}/cm^{-1} 1666 (C=O); δ_H

1.54 (3H, t, *J* 7.0, -CH_2CH_3), 2.80 (3H, s, -$COCH_3$), 3.96 (3H, s, -OCH_3), 4.22 (2H, q, *J* 7.0, -CH_2CH_3), 7.06 (1H, s, 3-H), 7.60 (2H, m, 6- and 7-H), 8.16 (1H, dd, *J* 6.2 and 3.6, 8-H)[a], and 8.30 (1H, dd, *J* 6.2 and 3.6, 5-H)[a]; δ_C 14.9 (CH_2CH_3), 31.0 ($COCH_3$), 63.9 (CH_2CH_3)[a], 64.1 (OCH_3)[a], 103.0 (3-C), 122.8 (6-C)[b], 123.3 (7-C)[b], 127.1 (5-C)[c], 127.4 (2-C), 127.8 (8-C)[c], 128.9 (4a-C)[d], 129.3(8a-C)[d], 151.2 (1-C)[e], 151.7 (4-C)[e], 200.0 (C=O). (Found: C, 73.6; H, 6.50; HRMS 244.10990. Calc. for $C_{15}H_{16}O_3$: C, 73.8; H, 6.60%; HRMS 244.10994).

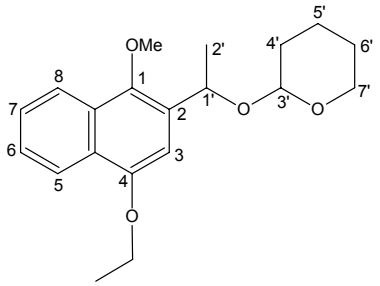
2-Acetyl-4-ethoxy-1-methoxynaphthalene 205



205

Using a similar method described earlier, the reduction of naphtalene **204** (0.33 g; 1.35 mmol) afforded the alcohol **205** (0.30 g; 90%) as an oil. ν_{max}/cm^{-1} 3421 (O-H); δ_H 1.52 (3H, t, *J* 7.2, -CH_2CH_3), 1.53 (3H, d, *J* 6.4, -$CH(OH)CH_3$), 2.93 (1H, bs, D_2O exchangeable, OH), 3.85 (3H, s, -OCH_3), 4.15 (2H, dq, *J* 7.2 and 0.8, -CH_2CH_3), 5.43 (1H, q, *J* 6.4, -$CH(OH)CH_3$, 6.86 (1H, s, 3-H), 7.48 (2H, m, 6- and 7-H), 7.97 (1H, dd, *J* 7.4 and 2.2, 8-H), and 8.26 (1H, dd, *J* 7.4 and 2.2, 5-H); δ_C 14.8 (CH_2CH_3), 24.4 ($CH(OH)CH_3$), 62.6 (OCH_3), 63.9 (CH_2CH_3), 64.5 ($CH(OH)CH_3$), 102.0 (3-C), 121.8 (6-C)[a], 122.5 (7-C)[a], 125.2 (5-C)[b], 126.3 (2-C), 126.5 (8-C)[b], 128.3 (4a-C)[c], 133.3(8a-C)[c], 145.2 (1-C)[d], 151.7 (4-C)[d]. (Found: C, 73.4; H, 7.60; M^+ 246. Calc. for $C_{15}H_{18}O_3$: C, 73.2; H, 7.40%; M 246).

4-Ethoxy-1-methoxy-2-(1′-oxadihydropyranoethyl)naphthalene 208



208

Under the same reaction conditions described earlier the alcohol **205** (0.25 g; 1.02 mmol) was converted into the DHP derivative **208** (0.18 g; 54%, 67% based on recovered starting material). ν_{max}/cm^{-1} 1606 (C=C); δ_H **(mixture of diastereomers)** 1.39-1.60 (12H, m, $-CH_2CH_3$ and 2′-CH_3 for both isomer), 1.61-1.98 (12H, m, 4′-, 5′-, and 6′-CH_2 for both isomers), 3.26-3.68 (4H, m, 7′-CH_2 for both isomers), 3.92 and 3.94, (each 3H, s, CH_3O for each isomer), 4.21 and 4.26 (4H, q, *J* 7.0, $-CH_2CH_3$ for each isomer), 4.41 and 4.95 (each 1H, t, *J* 4.0, 3′-CH for each isomer), 5.39 and 5.55 (1H, q, *J* 6.6, 1′-CH for each isomer), 6.84 and 7.01 (each 1H, s, 3-H for each isomer), 7.45-7.55 (4H, m, 6- and 7-H for both isomers), 8.05 (2H, dd, *J* 7.2 and 1.8, 8-H for both isomers), and 8.29 (2H, dd, *J* 7.2 and 1.8, 5-H for both isomers); δ_C **(mixture of diastereomers)** 14.90 and 14.93 (CH_2CH_3), 19.4 and 20.1 (2′CH_3), 22.6 and 23.5 (4′-CH_2)[a], 25.55 and 25.60 (5′-CH_2)[a] , 31.0 and 31.1 (6′-CH_2)[a], 62.0 and 62.2 (CH_2CH_3)[b], 62.5 and 63.0 (7′-CH_2)[b], 64.0 (CH_3O for both isomers), 67.1 and 68.3 (1′-CH), 96.2 and 97.1 (3′-CH), 102.2 and 103.2 (3-C), 122.03 and 122.05 (6-C)[c], 122.5 and 122.6 (7-C)[c], 125.0 and 125.3 (5-C)[d], 126.3 and 126.4 (8-C)[d], 126.5 and 126.6 (2-C), 128.4 and 128.5 (4a-C)[e], 131.2 and 132.9 (8a-C)[e], 145.0 and 147.0 (1-C)[f] and 151.3 and 151.8 (4-C)[f]. (Found: C, 72.5; H, 7.7%; M^+ 330. Calc. for $C_{20}H_{26}O_4$: C, 72.7; H, 7.9%; M 330).

Attempted Snieckus directed *ortho* metalation reactions on naphthalenes 193, 201, 205 and 208.

1st Method

Using the general Snieckus DoM protocol, the respective naphthalene (0.828 mmol) was dissolved in THF (10 ml) and cooled down to *ca*. -78 ^{O}C under nitrogen. The reaction mixture was then treated with the alkyl lithium base, *n*- or *sec*-BuLi (1.3M; 0.64 ml), after which a colour change was observed. Upon addition of allyl bromide (157 mg; 0.83 mmol), at -78 ^{O}C, the colour lightened up to give a light yellow colour. The reaction mixture was left to stir at -78 ^{O}C for 2 hrs, before being allowed to come to room temperature. The reaction mixture was allowed to reach room temperature and then poured into water (100 ml) and extracted with DCM (3 x 50 ml). Upon work-up only starting material was recovered.

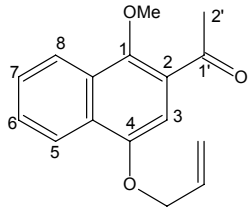
2nd Method

Upon repeating the experiment the reaction mixture was allowed to reach ± -20 ^{O}C, before being cooled down to -78 ^{O}C, prior to the addition of the allyl bromide. However, only starting material was obtained upon work-up.

3rd Method

Using the method described above, TMEDA (1 mol equiv.) was introduced prior to the addition of the base. Again, only starting material was obtained upon work-up.

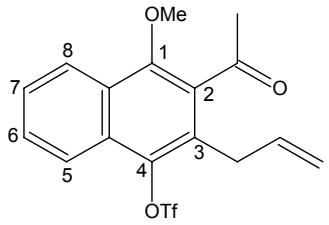
2-Acetyl-4-allyloxy-1-methoxynaphthalene 209



209

The naphthol **182** (4.38 g; 20.26 mmol) was dissolved in dry acetone (200 ml) and treated with potassium carbonate (7.00 g; 50.64 mmol) and allylbromide (6.13 g; 50.64 mmol). The mixture was heated under reflux with vigorous stirring under nitrogen for 24hrs after which it was cooled, filtered, and evaporated to give a residue which was dissolved in DCM (200ml) and the solution washed with water (3 x 50 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:9) as eluent, to afford the naphthalene **209** (4.68 g; 86%) as a pale yellow oil. ν_{max}/cm^{-1} 1670 (C=O) and1619 (C=C); δ_H 2.80 (3H, s, $COCH_3$), 3.96 (3H, s, CH_3O), 4.73 (2H, dt, *J* 5.2 and 1.4, -CH_2CH=CH_2), 5.34 (1H, dq, *J* 10.2 and 1.4, *cis*-CH_2CH=CH_2), 5.52 (1H, dq, *J* 17.2 and 1.4, *trans*-CH_2CH=CH_2), 6.16 (1H, m, -CH_2C*H*=CH_2), 7.09 (1H, s, 3-H), 7.60 (2H, m, 6- and 7-H), and 8.17 (1H, m, 8-H)[a], 8.32 (1H, m, 5-H)[a] ; δ_C 31.0 ($COCH_3$), 64.0 (-CH_2CH=CH_2), 69.3 (CH_3O), 103.6 (3-C), 117.7 (-CH_2CH=CH_2), 122.8 (6-C)[a], 123.3 (7-C)[a], 127.2 (5-C)[b], 127.4 (2-C), 127.9 (8-C)[b], 129.0 (4a-C)[c], 129.4 (8a-C)[c], 133.2 (-CH_2CH=CH_2), 150.8 (1-C)[d], 152.0 (4-C)[d], and 199.8 (C=O). (Found: C, 75.1; H, 6.30; M^+ 256. Calc. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.25%; M 256).

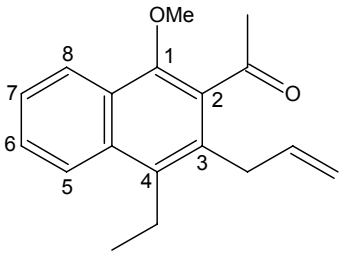
2-Acetyl-3-allyl-1-methoxy-4-trifluoromethanesulpholnyloxynaphthalene 211



211

The naphthalene **209** (4.11 g; 16.04 mmol) was heated in an oil bath at 160 ^{O}C for 5 hrs. The cooled residue was dissolved in dry pyridine (25 ml) and cooled to 0 ^{O}C. Trifluoro-methanesulphonic anhydride (5.64 g; 3.40 ml; 20.0 mmol) was added dropwise to the cooled solution. The resulting mixture was stirred under nitrogen at 0 ^{O}C for 10 min., and then at room temperature for 24 hrs. The reaction mixture was then quenched with water (100 ml) and the mixture extracted with ether (3 x 50 ml). The organic extract was washed consecutively with water (100 ml), 0.1M HCl (3 x 50 ml) and water (100 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:9) as eluent, to afford the triflate **211** (5.73 g; 92%) as a thick light yellow oil. ν_{max}/cm^{-1} 1704 (C=O); δ_H 2.62 (3H, s, $COCH_3$), 3.66 (2H, dt, *J* 6.2 and 1.8, -CH_2CH=CH_2) 3.92 (3H, s, CH_3O), 4.99 (1H, dq, *J* 17.2 and 1.8, *trans*-CH_2CH=CH_2), 5.11 (1H, dq, *J* 10.2 and 1.8, *cis*-CH_2CH=CH_2), 5.87 (1H, ddt, *J* 17.2, 10.2 and 1.8, -CH_2CH=CH_2), 7.66 (2H, m, 6- and 7-H), and 8.12 (2H, m, 5- and 8-H); δ_C 31.2 ($COCH_3$), 33.0 (-CH_2CH=CH_2), 64.0 (CH_3O), 117.8 (-CH_2CH=CH_2), 118.8 (q, *J* 318.1, CF_3), 122.2 (6-C)[a], 122.7 (7-C)[a], 127.5 (5-C)[b], 127.9 (2-C)[c], 128.1 (3-C)[c], 128.6 (4a-C)[d], 129.0 (8-C)[b], 132.9 (8a-C)[d], 134.4 (-CH_2CH=CH_2), 139.2 (4-C), 153.2 (1-C), and 203.6 (C=O). (Found: C, 52.7; H, 3.8%; M^+ 388. Calc. for $C_{17}H_{15}F_3O_5S$: C, 52.6; H, 3.9%; M 388).

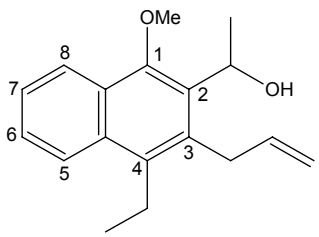
2-Acetyl-3-allyl-4-ethyl-1-methoxynaphthalene 212



212

Tetraethyltin (2.60 g; 11.07 mmol) was added to a solution of triflate **211** (1.04 g; 2.68 mmol), bis(triphenylphosphine)dichloropalladium(II) (~20 mg), lithium chloride (0.34g; 8.02 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (~ 0.03 g) in dry DMF (20 ml). The solution was stirred at 85 ^{O}C under nitrogen for 4 days. The reaction mixture was cooled, dissolved in dry ether (150 ml) and washed with a 10% aqueous ammonium fluoride solution (100 ml). The organic layer was filtered and then washed with water (100 ml), 25% aqueous ammonia (100), water (100 ml), 0.1M HCl (100 ml) and water (100 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:9) as eluent, to give the ketonaphthalene **212** (0.54 g; 75%) as a yellow oil. ν_{max}/cm^{-1} 1703 (C=O); δ_H 1.28 (3H, t, *J* 7.4, -CH_2CH_3), 2.61 (3H, s, $COCH_3$), 3.07 (2H, q, *J* 7.4, -CH_2CH_3), 3.53 (2H, dt, *J* 5.4 and 1.8, -$CH_2CH{=}CH_2$), 3.89 (3H, s, CH_3O), 4.90 (1H, dq, *J* 17.2 and 1.8, *trans*-$CH_2CH{=}CH_2$), 5.07 (1H, dq, *J* 10.2 and 1.8, *cis*-$CH_2CH{=}CH_2$), 5.98 (1H, m, -$CH_2CH{=}CH_2$), 7.54 (2H, m, 6- and 7-H), and 8.10 (2H, m, 5- and 8-H); δ_C 15.2 (-CH_2CH_3), 21.4 ($COCH_3$), 33.1 (-$CH_2CH{=}CH_2$)[a], 33.6 (-CH_2CH_3)[a], 63.6 (CH_3O), 116.2 (-$CH_2CH{=}CH_2$), 122.7 (6-C)[b], 124.6 (7-C)[b], 125.6 (5-C)[c], 126.9 (2-C)[d], 127.1 (8-C)[c], 129.9 (3-C)[d], 133.4 (4a-C)[e], 133.6 (8a-C)[e], 135.6 (4-C)[d], 136.8 (-$CH_2CH{=}CH_2$), 151.1 (1-C), and 206.8 (C=O). (Found: C, 80.4; H, 7.6%; M^+ 268. Calc. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5%; M 268).

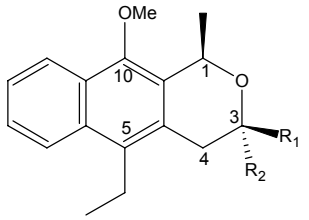
3-Allyl-4-ethyl-2-(1′-hydroxyethyl)-1-methoxynaphthalene 177



177

Using a similar method described earlier, the reduction of naphtalene **212** (0.58 g; 2.16 mmol) afforded the alcohol **205** (0.56 g; 96%) as an oil. ν_{max}/cm^{-1} 3412 (O-H) and 1634 (C=C); δ_H 1.28 (3H, t, *J* 7.6, -CH_2CH_3), 1.66 (3H, d, *J* 6.8, -$CH(OH)CH_3$), 3.04 (2H, dq, *J* 7.6 and 2.2, -CH_2CH_3), 3.63 (2H, m, $CH_2CH{=}CH_2$), 4.06 (3H, s, -OCH_3), 4.22 (1H, d, *J* 7.8), D_2O exchangeable, OH), 4.84 (1H, dq, *J* 17.2 and 2.2, *trans*-$CH_2CH{=}CH_2$), 5.10 (1H, dq, *J* 10.2 and 2.2, *cis*-$CH_2CH{=}CH_2$), 5.27 (1H, q, *J* 6.8, -$CH(OH)CH_3$, 6.10 (1H, m, $CH_2CH{=}CH_2$), 7.50 (2H, m, 6- and 7-H), and 8.05 (2H, m, 5- and 8-H); δ_C 15.3 (CH_2CH_3), 21.8 ($CH(OH)CH_3$), 25.1 (CH_2CH_3), 33.1 (-$CH_2CH{=}CH_2$), 63.5 (OCH_3), 67.5 ($CH(OH)CH_3$), 116.1 (-$CH_2CH{=}CH_2$) , 122.5 (6-C)[a], 124.6 (7-C)[a], 125.1 (5-C)[b], 126.0 (8-C)[b], 127.2 (3-C)[c], 132.0 (4a-C)[d], 132.6(8a-C)[d], 133.2 (4-C)[c], 135.4 (2-C)[c], 136.9 (-$CH_2CH{=}CH_2$), 152.8 (1-C). (Found: C, 79.9; H, 8.4; M^+ 270. Calc. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2%; M 270).

***Rac* (1*R*, 3*S*) and (1*R*, 3*R*)-5-Ethyl-10-methoxy-1,3-dimethylnaphtho[2,3-*c*]pyrans 214 and 215.**



214 $R_1 = CH_3$; $R_2 = H$

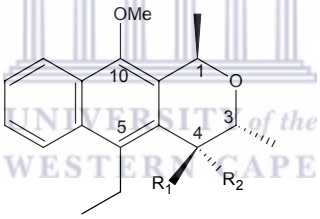
215 $R_1 = H$; $R_2 = CH_3$

The naphthalene alcohol **177** (80 mg; 0.30 mmol) in dry DMF (10 ml) at an oil bath temperature of 60 ^{O}C was degassed and stabilized under nitrogen for 10 min after which potassium *tert*-butoxide (134 mg; 1.20 mmol) was added at once. After 2 hrs of stirring the reaction mixture was poured into water (100 ml) and extracted with ether (3x 50 ml). The residue obtained upon work-up was plated and eluted with ethyl acetate-hexane (1:9) to afford two products.

1. **(1*R*, 3*S*)-5-Ethyl-10-methoxy-1,3-dimethylnaphtho[2,3-*c*]pyran 214** (13 mg; 16%) as colourless cubes, m.p. 108-110 ^{O}C (from hexane). ν_{max}/cm^{-1} 1260; δ_H 1.24 (3H, t, *J* 7.8, CH_2CH_3), 1.43 (3H, d, *J* 6.0, 3-CH_3), 1.66 (3H, d, *J* 6.2, 1-CH_3), 2.72 (1H, dd, *J* 15.8 and 10.6, 4-Ha′), 2.90 (1H, dd, *J* 15.8 and 2.8, 4-He′), 3.04 (2H, dq, *J* 7.8 and 2.8, CH_2CH_3), 3.74 (1H, m, 3-H), 3.88 (3H, s, OCH_3), 5.29 (1H, q, *J* 6.2, 1-H), 7.47 (2H, m, 7- and 8-H), 8.10 (2H, m, 6- and 9-H); δ_C 14.5 (-CH_2CH_3), 21.0 (3-CH_3)[a], 22.1 (1-CH_3)[a], 22.8 (-CH_2CH_3)[a], 35.2 (4-C), 61.1 (OCH_3), 69.9 (1-C)[b], 71.6 (3-C)[b], 122.5 (7-C)[c], 124.0 (8-C)[c], 124.9 (6-C)[d], 125.8 (9-C)[d], 127.0 (4a-C)[e], 128.8 (5-C)[e], 131.4 (9a-C)[e], 131.7 (5a-C)[e], 133.0 (10a-C)[e], 150.7 (10-C). (Found: C, 79.8; H, 8.1%; HRMS 270.1622. Calc. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2%; HRMS 270.16198).

2. **(1*R*, 3*R*)-5-Ethyl-10-methoxy-1,3-dimethylnaphtho[2,3-*c*]pyran 215** (46 mg; 58%) as colourless plates, m.p. 113-114 ^{O}C (from hexane). ν_{max}/cm^{-1} 1258; δ_H 1.24 (3H, t, *J* 7.8, CH_2CH_3), 1.41 (3H, d, *J* 6.2, 3-CH_3), 1.65 (3H, d, *J* 6.4, 1-CH_3), 2.65 (1H, dd, *J* 16.8 and 10.8, 4-Ha′), 2.95 (1H, dd, *J* 16.8 and 3.6, 4-He′), 3.03 (2H, dq, *J* 7.4 and 1.4, CH_2CH_3), 3.90 (3H, s, OCH_3), 4.20 (1H, m, 3-H), 5.36 (1H, q, *J* 6.4, 1-H), 7.49 (2H, m, 7- and 8-H), 8.05 (2H, m, 6- and 9-H); δ_C 14.3 (-CH_2CH_3), 20.78 (3-CH_3)[a], 20.80 (1-CH_3)[a], 22.3 (-CH_2CH_3), 34.0 (4-C), 61.4 (OCH_3), 62.9 (1-C)[b], 69.1 (3-C)[b], 122.5 (7-C)[c], 124.1 (8-C)[c], 124.9 (6-C)[d], 125.7 (9-C)[d], 126.4 (4a-C)[e], 128.5 (5a-C)[e], 129.4 (9a-C)[e], 132.0 (10a-C)[e], 133.5 (5-C)[e], 149.7 (10-C). (Found: C, 80.1; H, 8.0%; HRMS 270.1623. Calc. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2%; HRMS 270.16198).

***Rac* (1*R*, 3*S*, 4*S*) and (1*R*, 3*R*, 4*R*)-5-Ethyl-4-hydroxy-10-methoxy-1,3-dimethyl-naphtho[2,3-*c*]pyrans 216 and 217.**



216 R_1 = OH ; R_2 = H

217 R_1 = H ; R_2 = OH

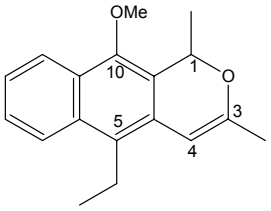
The naphthalene alcohol **177** (70 mg; 0.26 mmol) in dry DMF (6 ml) in an oil bath at 60 ^{O}C was treated at once with potassium *tert*-butoxide (116 mg; 1.04 mmol). After 2 hrs of stirring, the reaction mixture was worked up as described above to afford three products.

1. The first product to elute was that of the *cis*-dimethylnaphthopyran **214** (12 mg; 17%), identical in all aspects to the material synthesized before.

2. The second band to elute was the *trans*-dimethylnaphthopyran **215** (16 mg; 23%), identical to the material synthesized before.

3. **A diastereomeric mixture of (1*R*, 3*R*, 4*S*) and (1R, 3R, 4R)-5-Ethyl-4-hydroxy-10-methoxy-1,3-dimethylnaphtho[2,3-*c*]-pyran 216 and 217** (25 mg; 34%) as a thick oil. ν_{max}/cm^{-1} 3450; δ_H **(mixture of diastereomers)** 1.18 and 1.46 (each 3H, d, *J* 6.6, 3-C*H*$_3$ for each isomer), 1.28 and 1.32 (each 3H, t, *J* 6.2 and *J* 7.4, -CH_2CH_3 for each isomer), 1.63 and 1.68 (each 3H, d, *J* 6.6 and *J* 6.4, 1-CH_3 for each isomer), 3.20 and 3.25 (each 2H, q, *J* 6.2 and *J* 7.4, -C*H*$_2$CH$_3$ for each isomer), 3.87 and 3.89 (each 3H, s, CH_3O for each isomer), 4.19 and 4.34 (each 1H, dq, *J* 6.6 and 1.3 and *J* 6.6 and 2.6, 3-H for each isomer), 4.60 and 4.68 (each 1H, bs, 4-H for each isomers), 5.22 and 5.35 (each 1H, q, *J* 6.4 and *J* 6.6, 1-H for each isomer), 7.49-7.54 (4H, m, 7- and 8-H for both isomers), 8.01-8.15 (4H, m, 6- and 9-H for both isomers). (Found: C, 75.4; H, 7.8%; HRMS 286.1566. Calc. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7%; HRMS 286.1569).

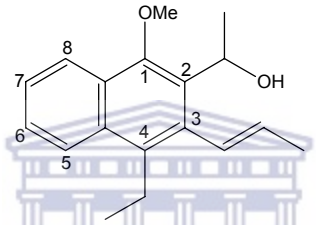
Rac **(1*R*)-5-Ethyl-10-methoxy-1,3-dimethyl-3,4-dehydronaphtho[2,3-*c*]pyran 218 and *E* 4-ethyl-2-(1′-hydroxyethyl)-1-methoxy-3-prop-1″-enylnaphthalene 219.**



218

The naphthalene alcohol **177** (248 mg; 0.92 mmol) in dry DCM (20 ml) was treated with bis(acetonitrile)dichloropalladium(II) (239 mg; .92 mmol) and the mixture was stirred under reflux, under nitrogen, for 30 min. The reaction mixture was then filtered and the filtrate evaporated to a residue, which was chromatographed using ethyl acetate-hexane (1:9), as eluent, to afford two products.

1. **(1*R*)-5-Ethyl-10-methoxy-1,3-dimethyl-3,4-dehydronaphtho[2,3-*c*]pyran 218** (165 mg; 67%) as a thick colourless oil. ν_{max}/cm^{-1} 1258; δ_H 1.27 (3H, t, *J* 7.6, CH_2CH_3), 1.50 (3H, d, *J* 6.6, 1-CH_3), 2.03 (3H, s, 3-CH_3), 3.06 (2H, q, *J* 7.6, -CH_2CH_3), 3.97 (3H, s, OCH_3), 5.82 (1H, q, *J* 6.6, 1-H), 5.94 (1H, s, 4-H), 7.45 (2H, m, 7- and 8-H), 8.02 (2H, m, 6- and 9-H); δ_C 14.9 (-CH_2CH_3), 20.4 (1-CH_3)[a], 20.5 (3-CH_3)[a], 21.0 (-CH_2CH_3)[a], 62.2 (OCH_3), 70.2 (1-C), 97.4 (4-C), 122.56 (7-C)[b], 122.63 (4a-C)[c], 124.19 (8-C)[b], 124.21 (6-C)[b], 125.98 (5a-C)[c], 126.05 (9-C)[b], 126.9 (9a-C)[c], 127.0 (10a-C)[c], 133.0 (5-C)[c], 148.6 (3-C), 152.6 (10-C). (Found: C, 80.4; H, 7.3%; HRMS 268.1464. Calc. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5%; HRMS 268.1463).



219

2. **4-Ethyl-2-(1′-hydroxyethyl)-1-methoxy-3-prop-1″-enylnaphthalene 219** (10 mg; 4%) as a thick oil. ν_{max}/cm^{-1} 3520; δ_H 1.25 (3H, t, *J* 8.0, -CH_2CH_3), 1.41 (3H, d, *J* 7.0, CH(OH)CH_3), 2.08 (3H, dd, *J* 5.8 and 1.4, -CH=CHCH_3), 3.02 (2H, q, *J* 8.0, -CH_2CH_3), 3.83 (3H, s, OCH_3), 4.52 (1H, q, *J* 7.0, -CH(OH)CH_3), 5.18 (1H, m, CH=CHCH$_3$), 6.47 (1H, dd, *J* 13.0 and 1.4, -CH=CHCH$_3$), 7.44 (2H, m, 6- and 7-H), 7.98 (2H, m, 5- and 8-H). (Found: (M^+ - H_2O) HRMS 252.1512. Calc. for $C_{18}H_{20}O$: HRMS 252.1514).

CHAPTER 9

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