Pergamon

Tetrahedron 56 (2000) 1937–1992

TETRAHEDRON

Tetrahedron Report Number 521

Synthetic Strategies Towards Pyranonaphthoquinone Antibiotics

Margaret A. Brimble,* Michael R. Nairn and Hishani Prabaharan

Department of Chemistry, University of Auckland, Pte Bag 92019, Auckland, New Zealand

Received 18 November 1999

Contents

1. Introduction

The class of compounds known as the pyranonaphthoquinone antibiotics are isolated from various strains of bacteria and fungi, the majority being microbial in origin.[1]

The basic skeleton of these antibiotics is the naphtho[2,3-*c*]pyran-5,10-dione ring system (Fig. 1), with some members of the family containing an additional γ-lactone ring fused to the dihydropyran moiety as the basic subunit. This substituted benzoisochromane skeleton represents a biosynthetic product common to all members of this class and is built up from acetate/malonate units via a polyketide pathway.[2–5]

* Corresponding author. Tel.: +64-9-3737599; fax: +64-9-3737422; e-mail: m.brimble@auckland.ac.nz

PII: S0040-4020(99)01021-2

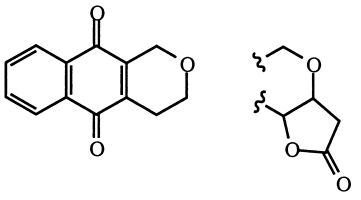


Figure 1.

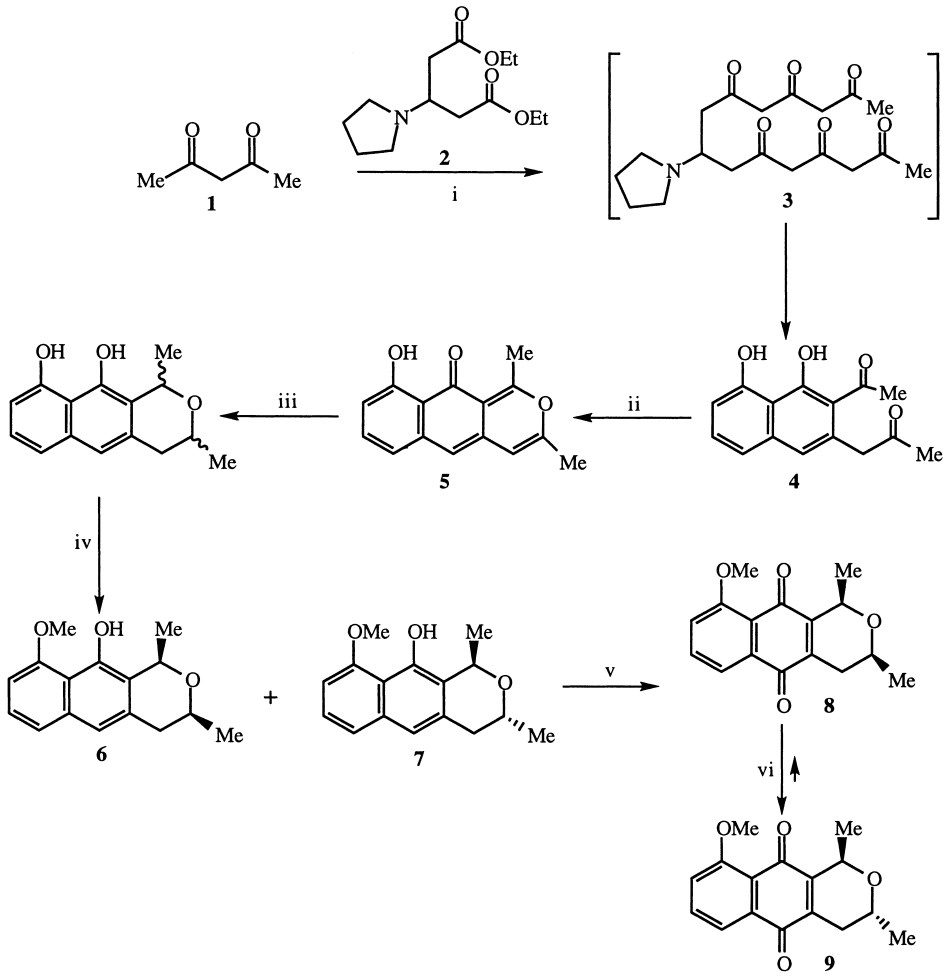
This family of antibiotics has been shown to exhibit activity against a variety of Gram-positive bacteria, pathogenic fungi and yeasts, as well as antiviral activity. In addition, they have been proposed to act as bioreductive alkylating agents.[6,7] Such properties have made the pyranonaphthoquinone class of antibiotics interesting and worthwhile synthetic targets, and with some of the more recently discovered examples being structurally quite complex, they provide significant synthetic challenges. The diversity of chemical structures found within the pyranonaphthoquinone family of antibiotics has prompted a number of syntheses of this class of compound and these have been reviewed earlier.[1,8–10] This report aims to compile an account of the various strategies involved in the construction of the pyranonaphthoquinone nucleus and provide a summary of more recent (1992–1998) syntheses.

2. Synthetic Strategies

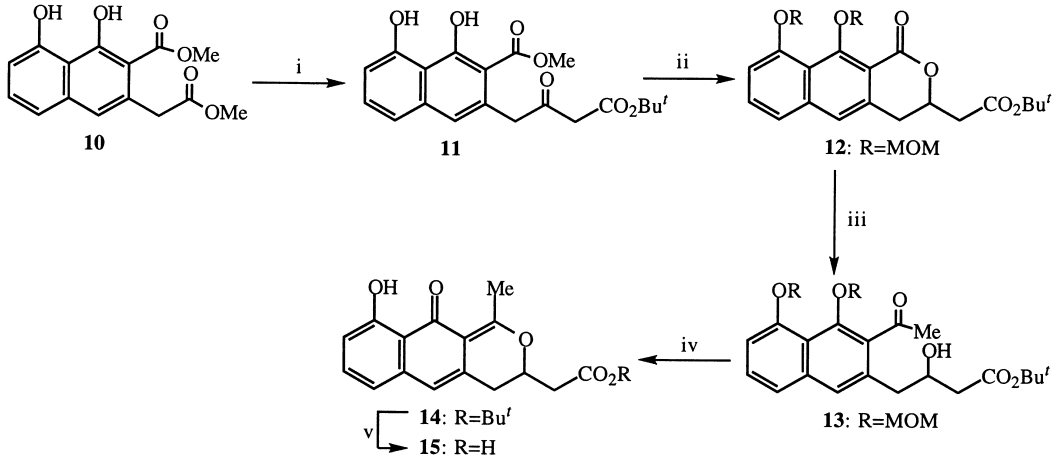
2.1. Biomimetic approaches

Much chemical effort has been devoted to the study of polyketide chains as a means of synthesising certain natural products, thus mimicking the strategy adopted by nature.[11] A biomimetic synthesis of (±)-eleutherin **8** and isoeleutherin **9** was devised[12] starting from 2-pyrrolidinyl glutarate diester **2** (Scheme 1). Tandem attack of 2 equiv. of the dianion of acetylacetone **1** on ester **2** gave the linear heptaketide **3**, which underwent spontaneous cyclisation to form the naphthyl diketone **4**. Cyclisation to form the third ring was accomplished by treatment with trifluoroacetic acid, affording the pyran **5**. Catalytic hydrogenation followed by monomethylation in the absence of light afforded a 9:1 mixture of *cis* and *trans* pyrans **6** and **7**. Oxidation of the mixture of isomers with Fremys salt resulted in the corresponding quinones **8** and **9**. The major *cis* isomer was assigned as (±)-eleutherin **8** while the minor component was established as the *trans* isomer. Isomerisation of *cis* isomer **8** in phosphoric acid afforded an equilibrium mixture containing mainly *trans* isomer **9**.

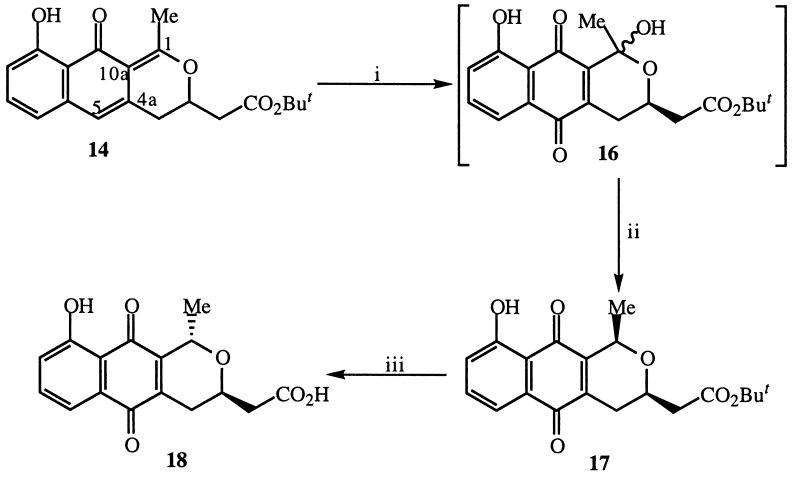
Using an analogous biomimetic strategy, (±)-nanaomycin A **18**[13] was synthesised from a biosynthetic intermediate of



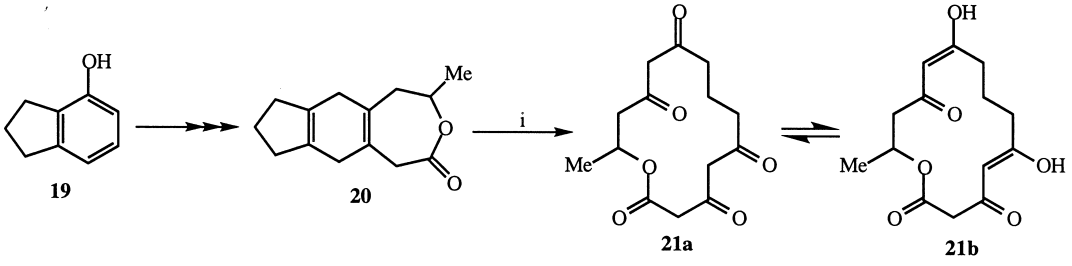
Scheme 1. Reagents and conditions: (i) **1**, LDA, THF, −78°C, then **2**, −35°C; (ii) EtOH, CF_3CO_2H cat., reflux; (iii) 5% Pd/C, EtOH, H_2, RT; (iv) CH_2N_2, Et_2O; (v) $(KSO_3)_2NO$; (vi) H_3PO_4.



Scheme 2. Reagents and conditions: (i) $MeCO_2Bu^t$, LDA, THF, −78°C to RT; (ii) a: $NaBH_4$, EtOH, −45°C; b: Et_3N (12 equiv.), CH_2Cl_2, 0°C; c: MOMCl, Pr^i_2NEt, CH_2Cl_2, RT; (iii) a: $MeCO_2CMe_2CH{=}CH_2$ (6 equiv.), LDA, THF, −78°C; b: $Pd(OAc)_2$, Ph_3P, Et_3N, HCO_2H, THF, reflux; (iv) HCl, MeOH, 0°C; (v) CF_3CO_2H, CH_2Cl_2, RT.

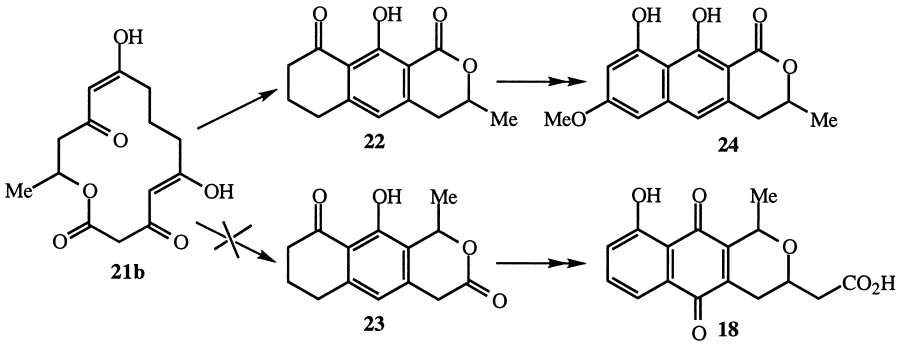


Scheme 3. Reagents and conditions: (i) 3,3-dimethyldioxirane (15 equiv.), C_6H_6, pH 8 buffer, 18-C-6, 6°C; (ii) CF_3CO_2H (8.5 equiv.), Et_3SiH (8.5 equiv.), CH_2Cl_2, −78°C to RT; (iii) cat. conc. H_2SO_4, C_6H_6, RT.

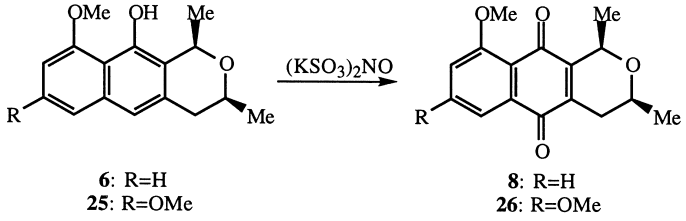


Scheme 4. Reagents and conditions: (i) CH_2Cl_2, −85°C, O_3, then Me_2S, RT.

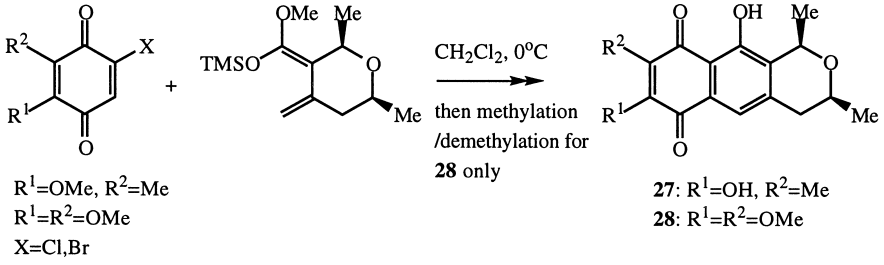
several isochromane antibiotics (Scheme 2). This synthesis was based on the differentiation of two ester groups of the naphthalenediol **10** such that a methyl group could be added to the aromatic carboxylate and an acetate to the aliphatic carboxylate. The acetate group was introduced by Claisen condensation of lithiated *tert*-butyl acetate and the naphthalenediol **10** to afford the keto ester **11**. Reduction, lactonisation and protection then converted the ketoester **11** to lactone **12**. A second Claisen condensation followed by palladium catalysed removal of the alkoxycarbonyl group furnished the methyl ketone **13**, deprotection and dehydration of which gave the pyran **14** and finally pyran **15** after removal of the *tert*-butyl group. The pyran **15**, commonly referred to as 'yellow pigment' is an intermediate



Scheme 5.



Scheme 6.



Scheme 7.

in the biosynthesis of several pyranonaphthoquinone antibiotics.

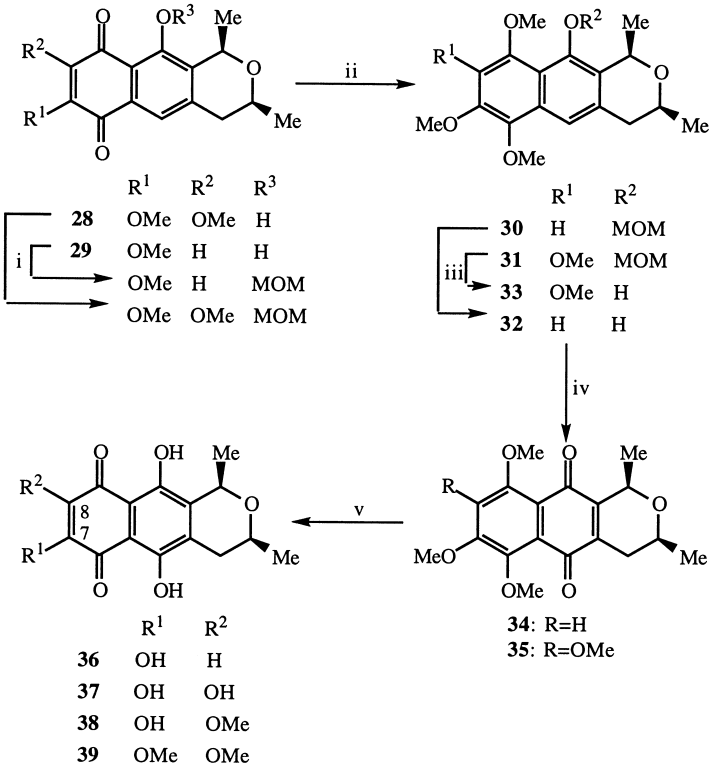
Oxidation of the pyran **14** to generate an epoxide at the 4a,5 position resulted in the lactol **16**, which after in situ reduction to the *cis*-pyran **17** using Kraus's methodology was finally converted to nanaomycin A **18** (Scheme 3).[14]

Although naphthopyrans such as nanaomycin A **18** are widely accepted to be biologically derived from polyketide chains, exploratory work has also been carried out with polyketide lactones.[15] Lactone **20** was synthesised in several steps from 4-indanol **19**, and after extensive ozonolysis furnished polyketide **21a** (Scheme 4).[16] This cyclic lactone was found to exist in the bis-enol form **21b** both in solution and in the solid state. It was hoped that intramolecular aldolisation of polyketide lactone **21b** would result in lactones **22** and **23** which correspond to synthetic precursors of semivioxanthin **24** and nanaomycin A **18**, respectively (Scheme 5). After extensive investigation, however, only lactone **22** was isolated in 36% yield.[15] Aromatisation of lactone **22** and methylation followed by acetylation then afforded semivioxanthin **24**.

Semivioxanthin **24** has additionally been synthesised[17] via a polyketide, in a manner similar to those noted previously.[12,13] Several intermediates similar to bioprecursors of naphthopyran antibiotics[13,15] were formed in the synthesis of a tetracycline precursor,[18] from *O-tert*-butyl analogues of **3**.

2.2. Synthesis from other natural products

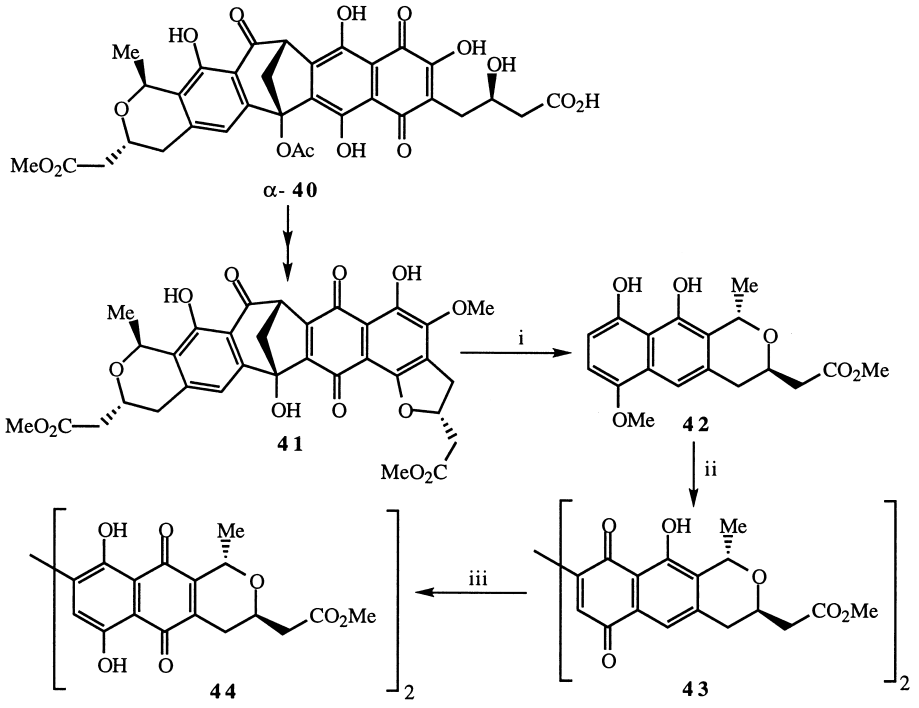
Many of the pyranonaphthoquinone antibiotics have been synthesised from closely related naturally occurring metabolites. This approach has been particularly useful for the synthesis of dimeric pyranonaphthoquinone antibiotics. Facile syntheses of eleutherin **8** and 7-methoxyeleutherin **26** have been achieved by treatment of karwinaphthols A **6** and B **25** (Scheme 6) which occur in *Karwinskia humboldtiana*[19] with Fremys salt.



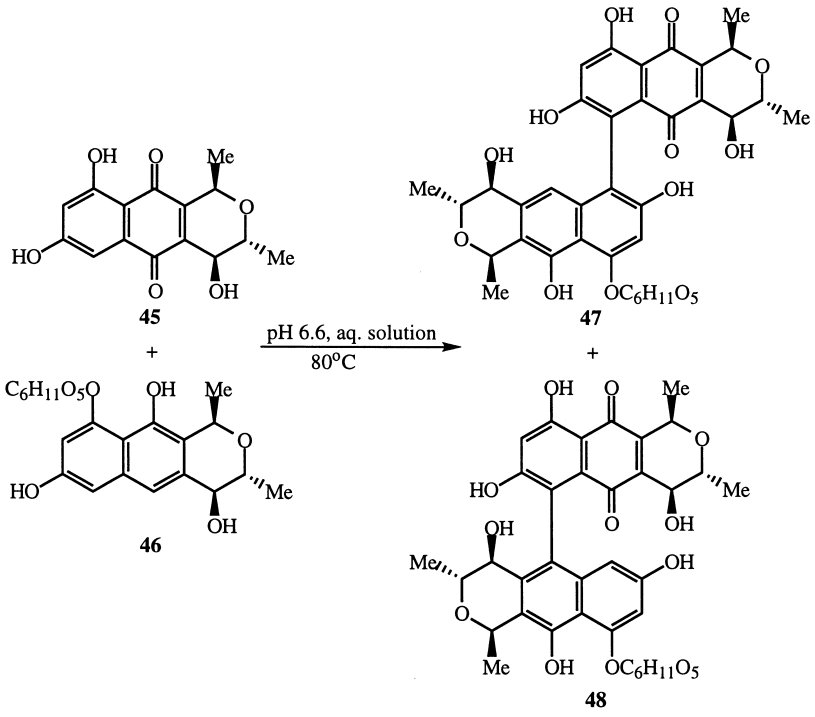
Scheme 8. Reagents and conditions: (i) NaH, THF, N_2, 50°C, then MOMCl; (ii) $Me(CH_2)_{15}N(Me)_3^+Br^-$, THF, H_2O, N_2, aq. $Na_2S_2O_4$, then aq. KOH, Me_2SO_4, RT; (iii) MeOH, conc. H_2SO_4, RT; (iv) aq. CAN, MeCN, RT or $(CF_3CO_2)_2IPh$, aq. MeCN, 0°C to RT; (v) $AlCl_3$, CH_2Cl_2, RT or LiI, $(Me)_3CCOMe$, reflux.

Syntheses[20] of naturally occurring juglones such as ventilagone **27** and ventiloquinone H **28** (Scheme 7) provided convenient substrates for the elaboration of related naphthazarins.

Selective protection of naphthols **29** and **28** by conversion to MOM ethers followed by reductive methylation gave ethers **30** and **31**, respectively[21] (Scheme 8). Cleavage of the MOM protecting groups to phenols **32** and **33** and subsequent



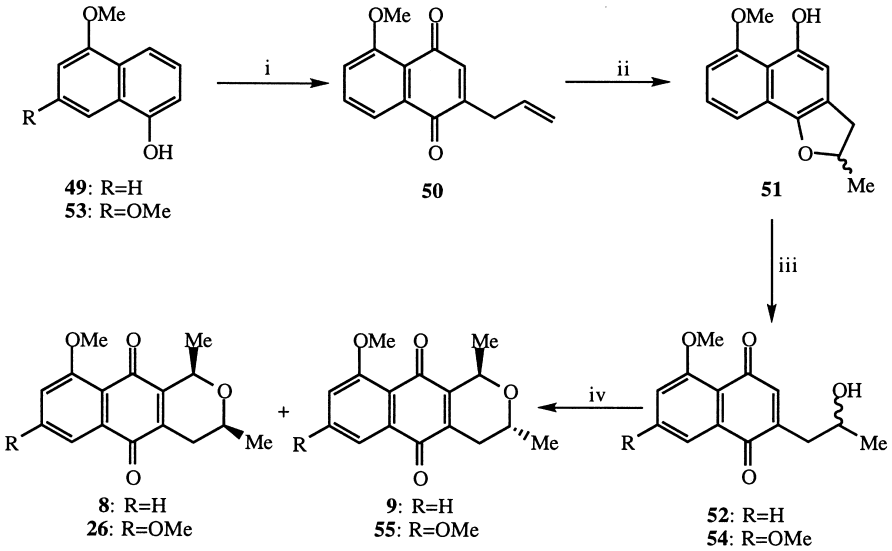
Scheme 9. Reagents and conditions: (i) CH_2N_2, CH_2Cl_2, 0°C; (ii) Ag_2O, Et_3N, $CHCl_3$; (iii) aq. CAN, MeCN.



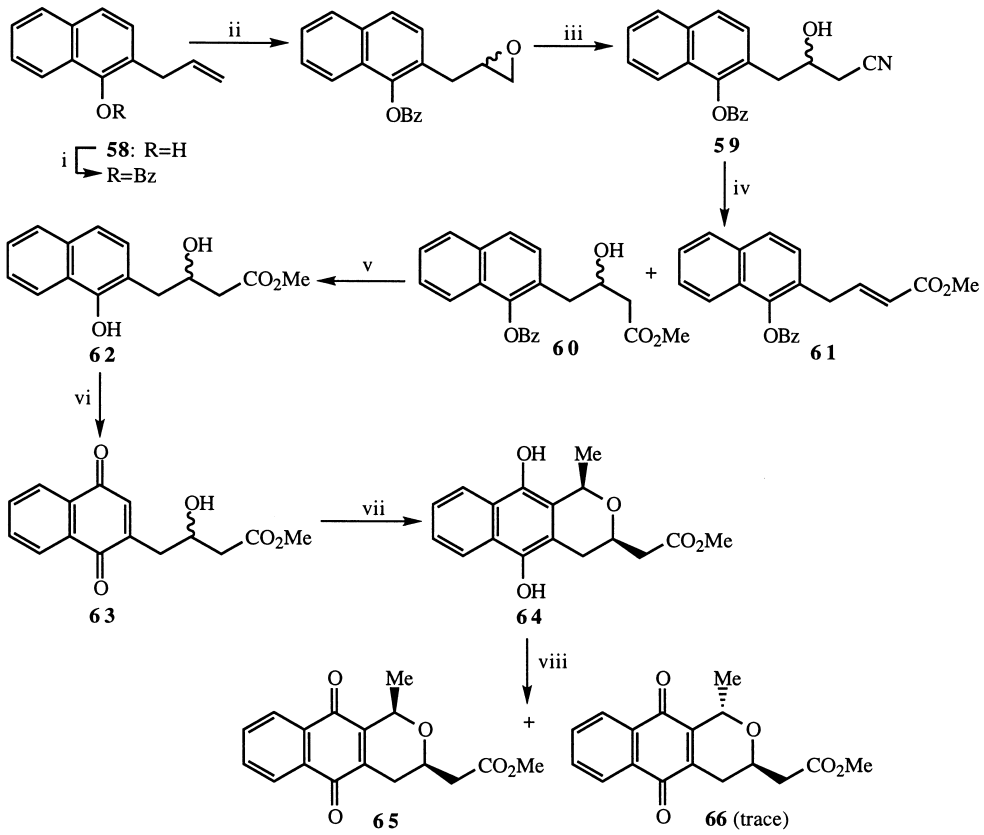
Scheme 10.

oxidation afforded pyranonaphthoquinones **34** (ventiloquinone E) and **35**. Oxidative demethylation of pyranonaphthoquinone **34** gave ventiloquinone G **36**; demethylation of pyranonaphthoquinone **35**, however, gave mainly the 7,8-demethylated product **37**. Monodemethylation was also possible by treatment of pyranonaphthoquinone **35** with lithium iodide in refluxing pinacolone to afford quinone **38**, whilst holding the reaction temperature at 50°C produced the 7,8-dimethoxyquinone **39**.

Monomer units of dimeric compounds can be synthesised although the penultimate coupling step is sometimes not achieved. Consequently these compounds are often made from pre-existing molecules that carry the required



Scheme 11. Reagents and conditions: (i) a: Me_2CO, K_2CO_3, allyl bromide; b: 200°C; c: $(KSO_3)_2NO$, Et_2O; (ii) a: $SnCl_2$, EtOH; b: aq. HBr, reflux; (iii) aq. Me_2CO, $FeCl_3$, RT; (iv) H_3PO_4, CH_3CHO, RT.



Scheme 12. Reagents and conditions: (i) BzCl, K_2CO_3, Me_2CO, reflux; (ii) CF_3CO_2H, Na_2CO_3, CH_2Cl_2, reflux; (iii) aq. KCN, EtOH, RT; (iv) a: aq. NaOH, reflux; b: CH_2N_2, Et_2O; (v) 10% Pd/C, H_2, MeOH; (vi) $(KSO_3)_2NO$, Et_2O; (vii) Zn dust, conc. HCl, Et_2O then CH_3CHO; (viii) O_2, Et_2O.

functionality, or by mimicking the process by which they are formed naturally.

A synthesis[22] of the enantiomer of actinorhodin **44** was achieved beginning from α-naphthocyclinone **40** (Scheme 9). Cyclisation, methylation and deacetylation produced deacetylanhydro-α-naphthocyclinone methyl ester **41** which was degraded by diazomethane to form naphthol **42** after monomethylation. Oxidative coupling of the monomer **42** using silver(I) oxide then provided the dimer **43** which after oxidation with cerium(IV) afforded the dimer **44**, the enantiomer of actinorhodin.

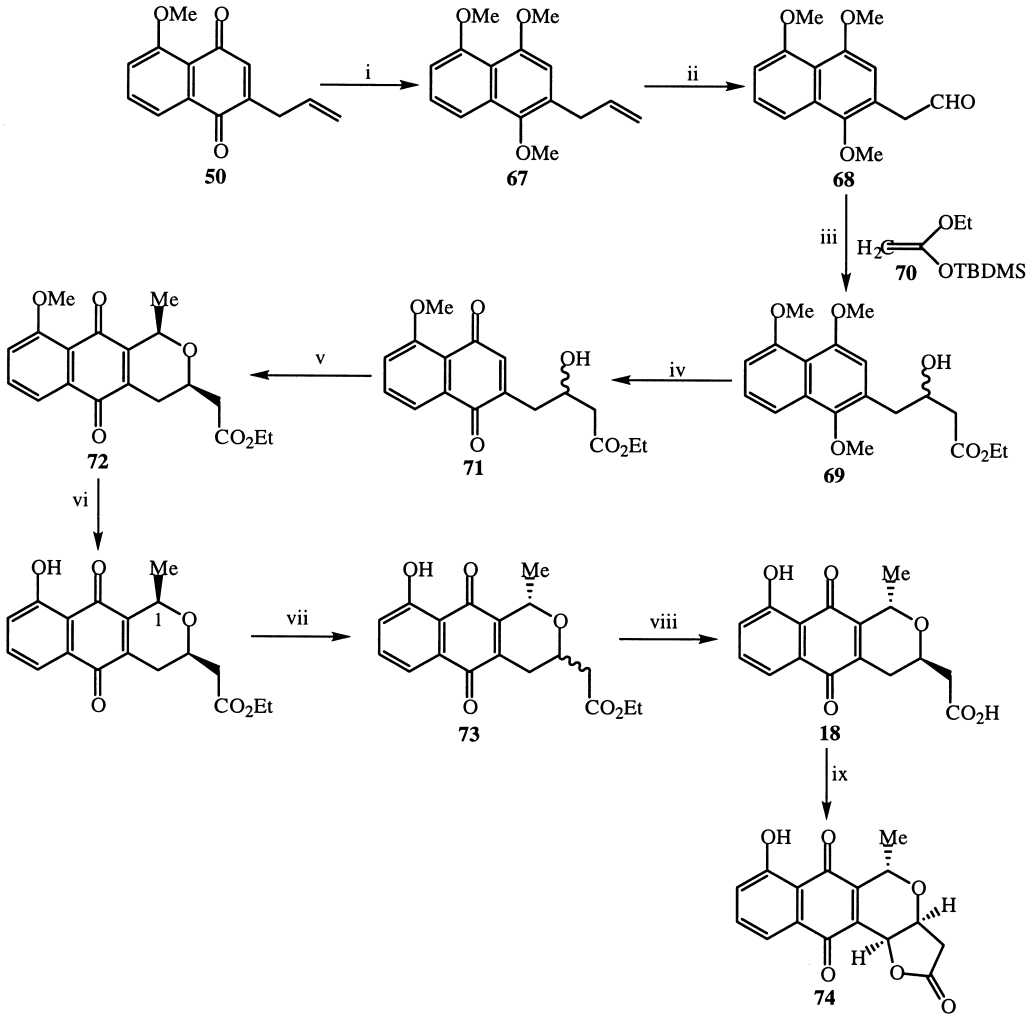
Formation of the protoaphins in vivo is highly likely to involve a coupling reaction between the two halves of the molecules. This has been achieved in vitro[23] by heating quinone A **45** and glucoside B **46** (Scheme 10) to afford **47** and 18% of protoaphin-*fb* **48**. In this instance the glucoside is thought to be utilised as an electron donor and the quinone as an acceptor. Self- rather than mixed-coupling has also been carried out with **45** and **46**.[24,25]

2.3. Electrophilic cyclisations

2.3.1. Condensation of 3-(2-hydroxyalkyl)naphthoquinones and hydroquinones with aldehydes and ketones. The pyran ring of a number of pyranonaphthoquinones has been generated by the condensation of 3-(2-hydroxyalkyl)naphthoquinones with an aldehyde under acidic, reducing conditions.

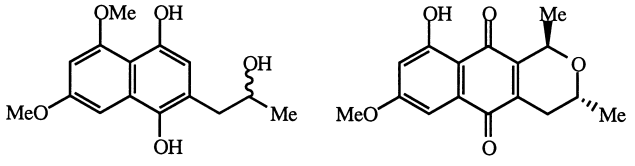
An example of this methodology was demonstrated in the first synthesis of eleutherins **8** and **9**[26,27] from 5-methoxy-1-naphthol **49** (Scheme 11). Allylation and Claisen rearrangement of **49** afforded the allyl quinone **50**. Reduction of **50** to the corresponding hydroquinone, cyclisation to the dihydrofuran **51** and reoxidation resulted in the hydroxypropylquinone **52**. Condensation with acetaldehyde under acidic conditions then afforded a separable mixture of (±)-eleutherin **8** and (±)-isoeleutherin **9**.

An adaptation of this route was used for the synthesis of (±)-7-methoxyeleutherin **26** and (±)-deoxyquinone A dimethyl ether **55**,[28] from 5,7-dimethoxy-1-naphthol **53** (prepared in seven steps from succinic acid) (Scheme 11). Conversion of naphthol **53** to hydroxypropylquinone **54** proceeded in essentially the same manner as previously described.[26] Reduction of the quinone **54** using zinc and hydrochloric acid gave the corresponding hydroquinone **56** which after condensation with acetaldehyde and atmospheric reoxidation afforded a 3:1 mixture of the *cis* and *trans* pyranquinones **26** and **55**, respectively.[29] The *cis* isomer was then equilibrated to the more thermodynamically stable *trans* isomer **55** by treatment with phosphoric acid.[28] Treatment of quinone **55** with boron trichloride at −78°C gave the monomethyl ether **57** while reaction of quinone **55** with



Scheme 13. Reagents and conditions: (i) a: aq. Na_2SO_4, Et_2O, RT; b: Me_2SO_4, aq. KOH, RT; (ii) a: OsO_4, $KClO_3$, THF, RT; b: $NaIO_4$, ^tBuOH, H_2O, RT; (iii) $TiCl_4$, CH_2Cl_2, −78°C; (iv) aq. CAN, CH_3CN, RT; (v) a: Zn, HCl, THF, RT; b: CH_3CHO, HCl, 60°C; c: Ag_2O, Et_2O, RT; (vi) $AlCl_3$, CH_2Cl_2, RT; (vii) conc. H_2SO_4, RT; (viii) a: separate; b: conc. HCl, RT; (ix) O_2, MeOH.

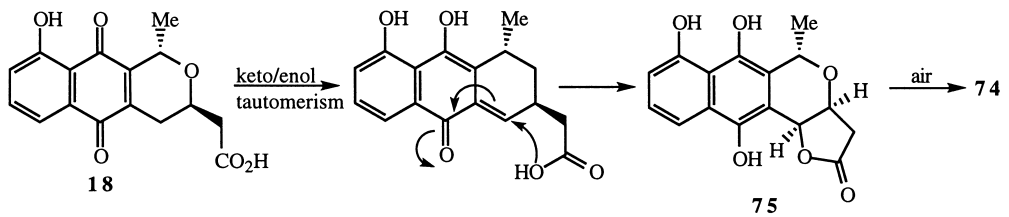
other Lewis acids resulted in the decomposition of starting material.



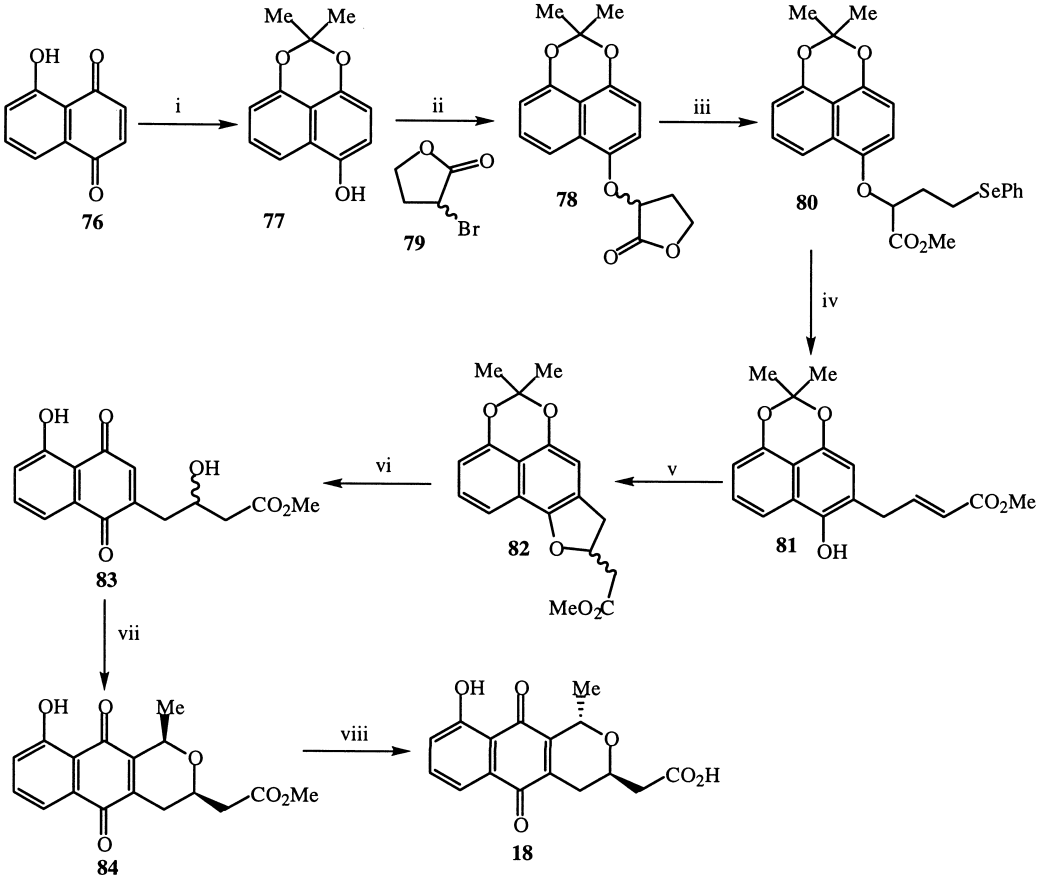
56 **57**

An approach to pyranonaphthoquinone systems bearing a two carbon methyl ester side chain required a four carbon side chain vs. three (vide supra), and began with 1-hydroxy-2-allyl naphthalene **58** protected as a benzyl ether (Scheme 12).[29] Epoxidation and nucleophilic ring opening furnished nitrile **59**. Hydrolysis of the nitrile moiety followed by methylation of the resultant crude acids afforded esters **60** and **61**, with ester **61** forming as a side product.

Hydrogenation of ester **60** produced naphthol **62** which was oxidised to quinone **63**. Attempts to directly combine quinone **63** with acetaldehyde as done previously[26] resulted in a complex mixture of products. Reduction of quinone **63** to the corresponding hydroquinone, however, and treatment in situ with acetaldehyde gave pyran **64**, which after aerial oxidation furnished *cis*-quinone **65** and a trace of *trans*-quinone **66**.

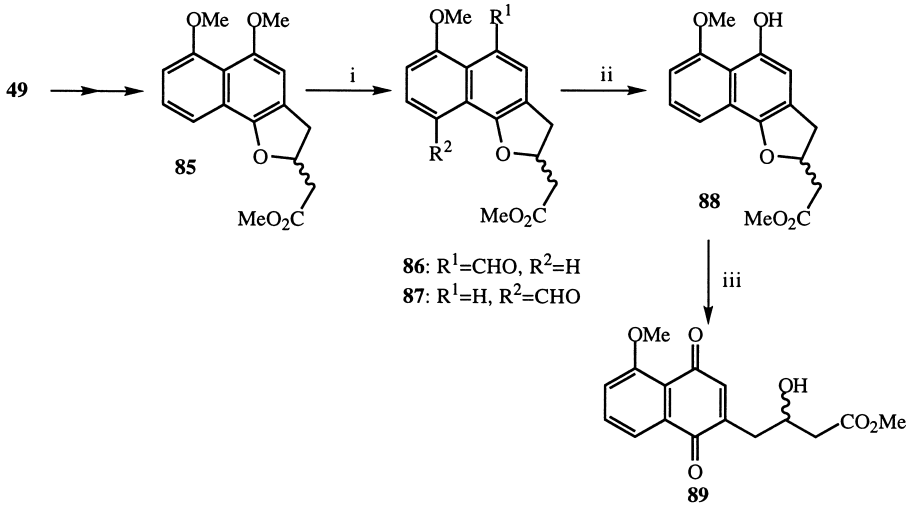


Scheme 14.

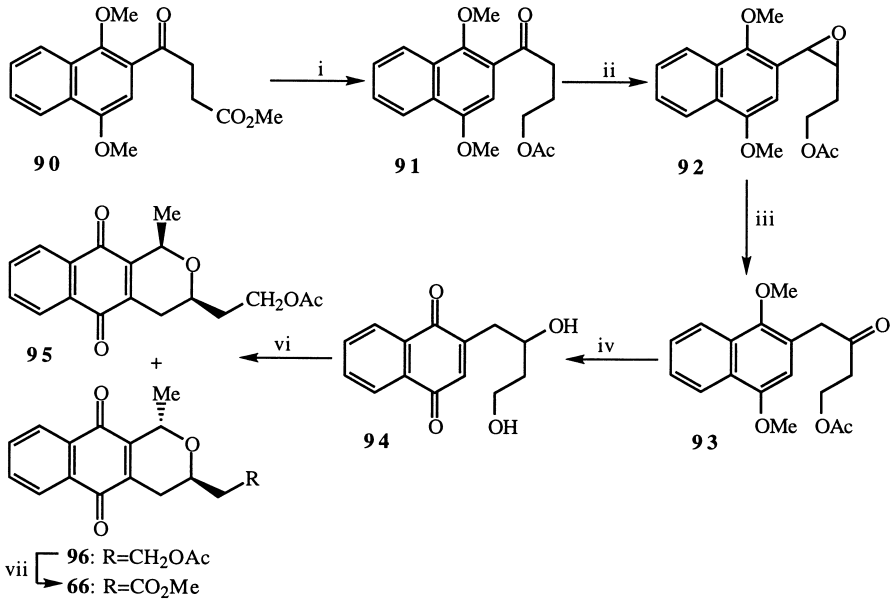


Scheme 15. Reagents and conditions: (i) a: Na_2SO_4, AcOEt, H_2O; b: $Me_2C(OMe)_2$, Me_2CO, $BF_3{\cdot}Et_2O$, RT; (ii) KF-Celite, MeCN, 60°C (iii) a: NaSePh, DMF, 120°C; b: CH_2N_2, Et_2O; (iv) a: H_2O_2, THF, RT; b: 90°C, 20 Torr; (v) Na_2CO_3, MeOH; (vi) Ag_2O, dioxane; (vii) a: Zn/HCl/THF, then MeCHO, 60°C; b: Ag_2O, dioxane; (viii) a: conc. H_2SO_4; b: KOH, MeOH.

The first synthesis[30] of (±)-nanaomycin A **18** used the same starting quinone **50** as Schmid[26] and involved assembly of the four carbon side chain via a ketene acetal. Reduction and methylation of quinone **50** (Scheme 13) gave allylnaphthalene **67** which after hydroxylation and oxidative cleavage of the resultant diol provided aldehyde **68**. Chain extension to hydroxyester **69** was achieved by reaction of aldehyde **68** with ketene silyl acetal **70**. Hydroxyester **69** was then oxidatively demethylated to furnish quinone **71** which was reduced to the corresponding hydroquinone before addition of acetaldehyde and reoxidation to *cis* ester **72**. Demethylation of ester **72** followed by epimerisation at C-1 afforded a 2:1, *trans*:*cis* mixture, from which the *trans* isomer of **73** was isolated and hydrolysed to give (±)-nanaomycin A **18**.



Scheme 16. Reagents and conditions: (i) $POCl_3$, DMF, PhMe, 0°C to reflux; (ii) a: MCPBA, CH_2Cl_2, RT; b: MeOH, THF, KOH, 0°C; (iii) aq. CAN, MeCN, RT.



Scheme 17. Reagents and conditions: (i) a: $LiAlH_4$, Et_2O; b: MeCOCl, py, MeCN; c: Jones reagent; (ii) a: Br_2, CH_2Cl_2, RT; b: $NaBH_4$, MeOH, 0°C; c: aq. NaOH; (iii) $BF_3{\cdot}Et_2O$, C_6H_6, RT; (iv) a: $NaBH_4$, aq. MeOH, 0°C; b: aq. CAN, MeCN; (vi) a: Zn, HCl, RT, MeCHO, 40°C; b: AgO, THF; c: Ac_2O, py; (vii) a: aq. KOH, MeOH, reflux; b: Jones reagent; c: CH_2N_2, Et_2O.

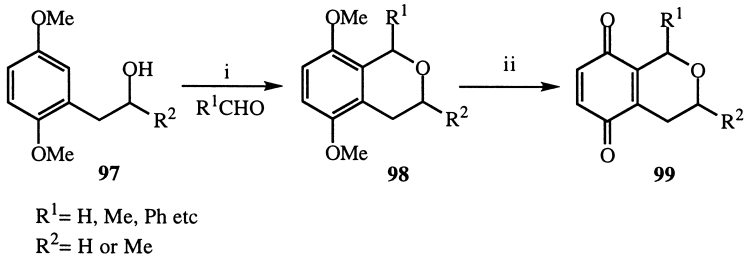
Oxidation of (±)-nanaomycin A **18** gave (±)-nanaomycin D **74**.

Conversion of (±)-nanaomycin A **18** to (±)-nanaomycin D **74** was suggested[30] to occur via a quinone methide[6] in an oxidative process (Scheme 14). Intramolecular conjugate addition of the carboxylic group onto the β position of the enone affords a quinol lactone **75**, which can then undergo oxidation to the corresponding naphthoquinone.

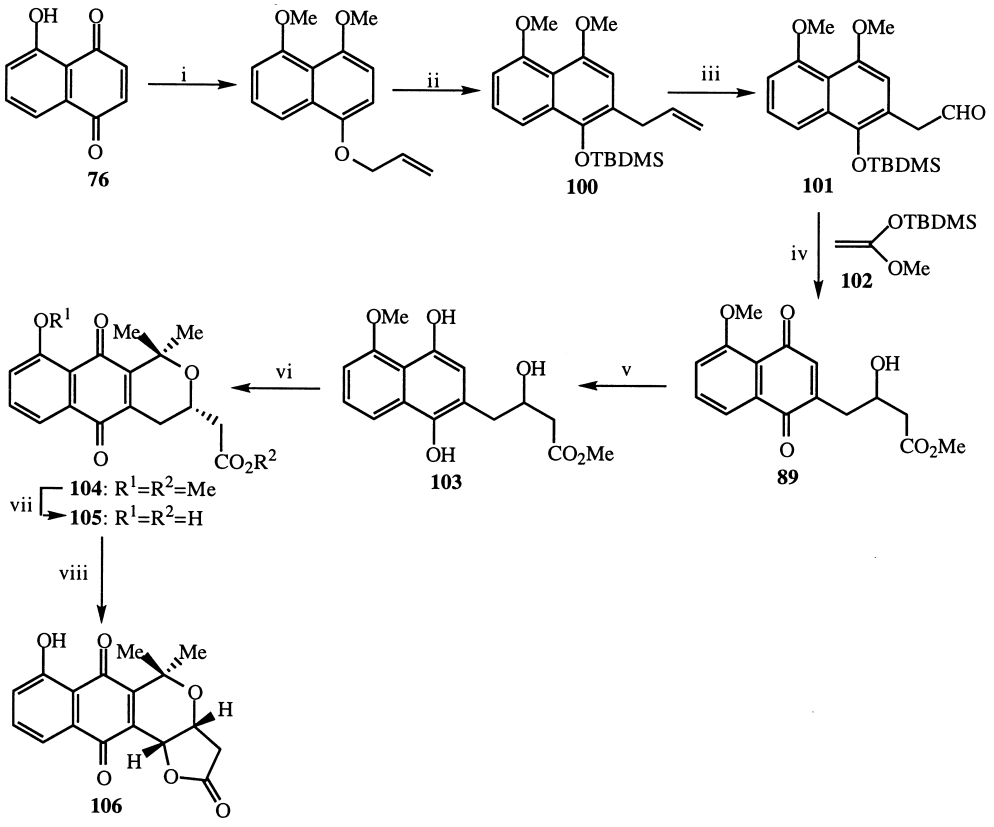
An analogue of quinone **71**[30] has been prepared by a variant of the Claisen rearrangement and used in the synthesis[31,32] of racemic nanaomycin A **18**. Juglone **76** was reduced to the corresponding hydroquinone and the 1,3-diol protected as acetal **77** before reaction of the remaining alcohol with α-bromo-γ-butyrolactone **79** to afford compound **78** (Scheme 15). Ring opening of the lactone with sodium phenylselenoate (or sodium selenophenolate) afforded ester **80** after methylation. Oxidative elimination and Claisen rearrangement of ester **80** afforded alkene **81**, which was cyclised to dihydrofuran **82**. In this procedure, sigmatropic rearrangement occurred at much lower temperatures compared to similar Claisen rearrangements of allyl 1-naphthyl ethers.[32] Oxidation of dihydrofuran **82** to quinone **83**, followed by reduction with zinc and acid, addition of acetaldehyde and oxidation by silver(II) oxide furnished *cis* methyl ester **84**. Isomerisation and saponification of ester **84** finally afforded (±)-nanaomycin A **18**.[30,33]

Two formal syntheses of (±)-nanaomycin A **18** relied on alternative approaches to hydroxybutyl quinone **83** and its methyl ether **89**. Ether **89**[32] (Scheme 16) was produced from 5-methoxy-1-naphthol **49**, using a strategy similar to the synthesis of dihydrofuran **82** {Scheme 15, (ii)±(v)}. Dihydrofuran **85** thus formed underwent a Vilsmeier reaction, giving isomeric aldehydes **86** and **87**. After isolation of aldehyde **86**, oxidation followed by hydrolysis of the resultant formate produced naphthol **88**. Finally, oxidation of naphthol **88** afforded ether **89** which was converted to (±)-nanaomycin A **18** using a similar procedure to that detailed for the conversion of ether **71**[30] to the natural product (Scheme 13).

A recent synthesis of (±)-9-deoxynanaomycin A methyl ester **66** made use of a diol precursor **94** for the construction of the pyranonaphthoquinone ring system. Diol **94** in turn, was synthesised starting from ketoester **90** which underwent reduction, selective acetylation and oxidation to afford ketoacetate **91**[34] (Scheme 17). 1,2-Ketone transposition of



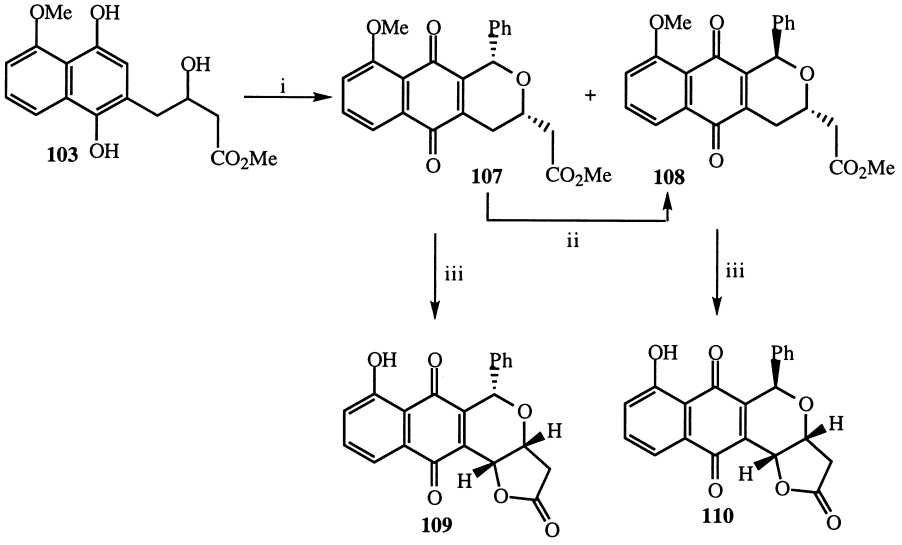
Scheme 18. Reagents and conditions: (i) dioxane, HCl, 0°C to RT; (ii) AgO, 6 M HNO_3, dioxane.



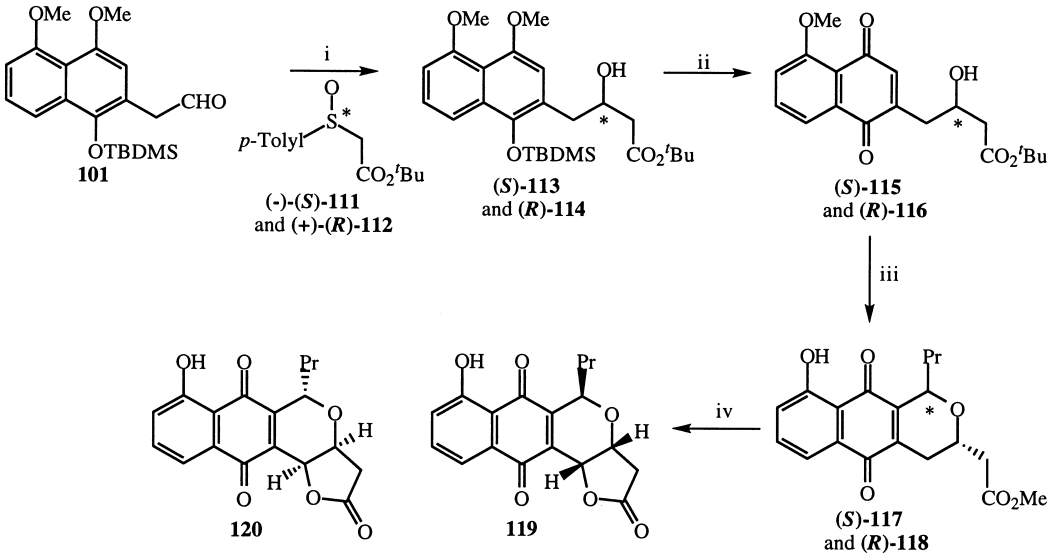
Scheme 19. Reagents and conditions: (i) a: MeI, Ag_2O, Ar, CH_2Cl_2, RT; b: aq. $Na_2S_2O_4$, EtOAc; c: Me_2CO, K_2CO_3, allyl bromide, reflux; d: Me_2SO_4, dioxane, RT, Ar, then 40% aq. NaOH; (ii) a: DMF, Ar, 140°C; b: imid, TBDMSCI, DMAP, RT; (iii) a: OsO_4, NMO, aq. Me_2CO, RT; b: MeOH, −5°C, Ar, $Pb(OAc)_4$; (iv) a: CH_2Cl_2, −78°C, Ar, $TiCl_4$; b: MeCN, 0°C, aq. CAN, RT; (v) Et_2O:dioxane (1:1), 0°C, aq. 18% HCl, Zn portionwise, RT; (vi) a: Et_2O, $HCl_{(g)}$, then **103**, then Me_2CO, RT; b: MeCN, aq. CAN, RT; (vii) a: CH_2Cl_2, −78°C, Ar, 1.0 M BCl_3 in CH_2Cl_2 dropwise, RT; b: MeOH, 0.16 M KOH, RT, then HCl; (viii) MeOH, py, O_2, reflux.

91 to ketone **93** was then accomplished via epoxide **92**. In turn, synthesis of epoxide **92** was accomplished by bromination of ketone **91**, reduction of the ketone moiety and displacement of the bromine by the corresponding hydroxyl group.

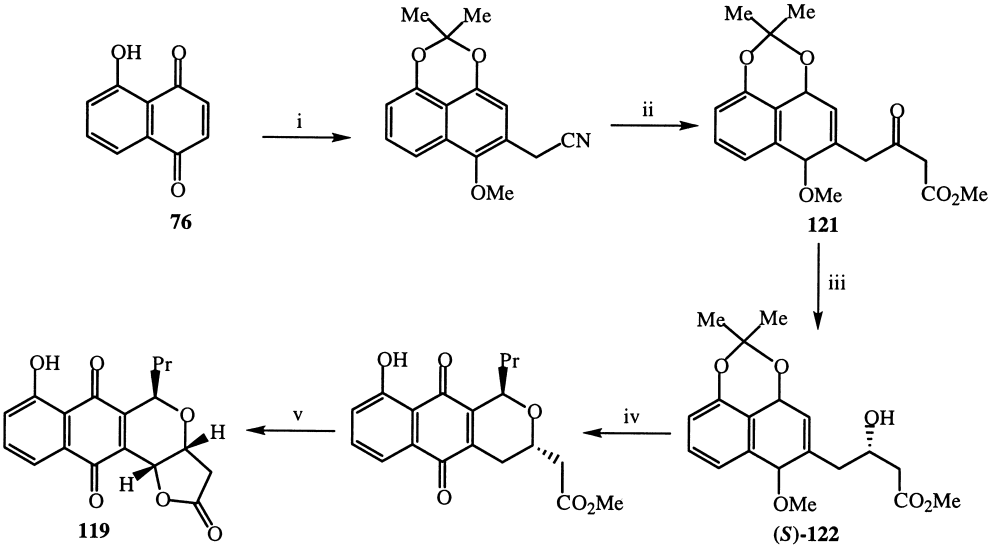
Lewis acid catalysed opening of the epoxide ring and concomitant pinacol type rearrangement furnished the transposed ketone **93**. Reduction of the carbonyl groups followed by oxidative demethylation then furnished the diol precursor **94**. Finally, addition of acetaldehyde under



Scheme 20. Reagents and conditions: (i) a: Et_2O, $HCl_{(g)}$, RT, then **103**, −5°C, PhCHO, 5 min, or **103**, −5°C, PhCHO, RT, 2 h; b: aq. CAN, MeCN, RT; c: fractional crystallisation; (ii) a: aq. $Na_2S_2O_4$, EtOAc; b: H^+; c: aq. CAN, MeCN, Rt; (iii) a: CH_2Cl_2, −78°C, Ar, 1.0 M BCl_3 in CH_2Cl_2 dropwise, RT; b: MeOH, 0.16 M KOH, RT, then HCl; c: MeOH, py, O_2, reflux.



Scheme 21. Reagents and conditions: (i) a: ^{t}BuMgBr, THF, −78°C; b: Al–Hg, THF/H_2O, RT; (ii) a: CAN, MeCN/H_2O, 0°C to RT; b: crystallisation; (iii) a: HCl_{aq}, Zn, dioxane/Et_2O, RT; b: PrCHO, $HCl_{(g)}$ in Et_2O; c: MeOH; d: CAN, MeCN/H_2O, 0°C to RT; e: BCl_3, −78°C, CH_2Cl_2; f: crystallisation; (iv) a: LiOH, THF/H_2O, RT; b: py, MeOH, MeCN, O_2, reflux.

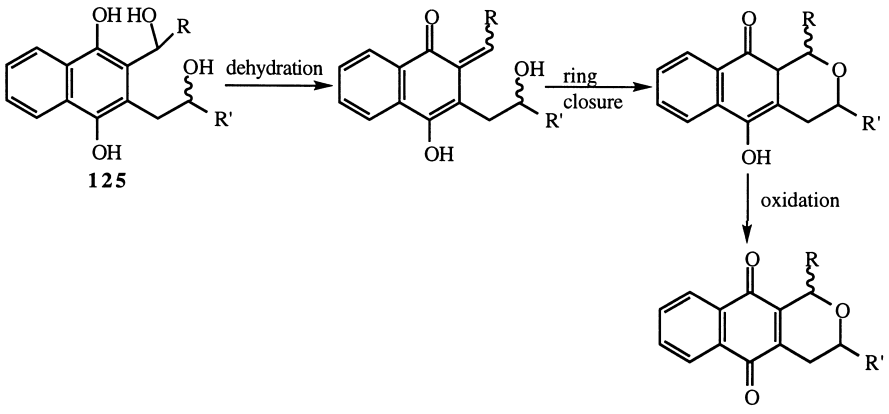


Scheme 22. Reagents and conditions: (i) a: $Na_2S_2O_4$; b: $(Me)_2C(OMe)_2$, $BF_3{\cdot}OEt_2$; c: Et_2NH, $(CH_2O)_n$, 70°C; d: KCN, 18-C-6, DMF, 70°C; e: MeI, K_2CO_3, 70°C; (ii) Br CH_2CO_2Me, Zn, THF, 60°C; (iii) H_2, [Ru{(*S*)-biphemp}]Cl_2, 60°C/60 bar; (iv) a: PrCHO, $HCl_{(g)}$ in Et_2O; b: AgO, HNO_3, dioxane; c: H_2SO_4, benzene, RT; d: crystallisation; (v) a: LiOH, THF/H_2O, RT; b: py, MeOH, O_2, reflux.

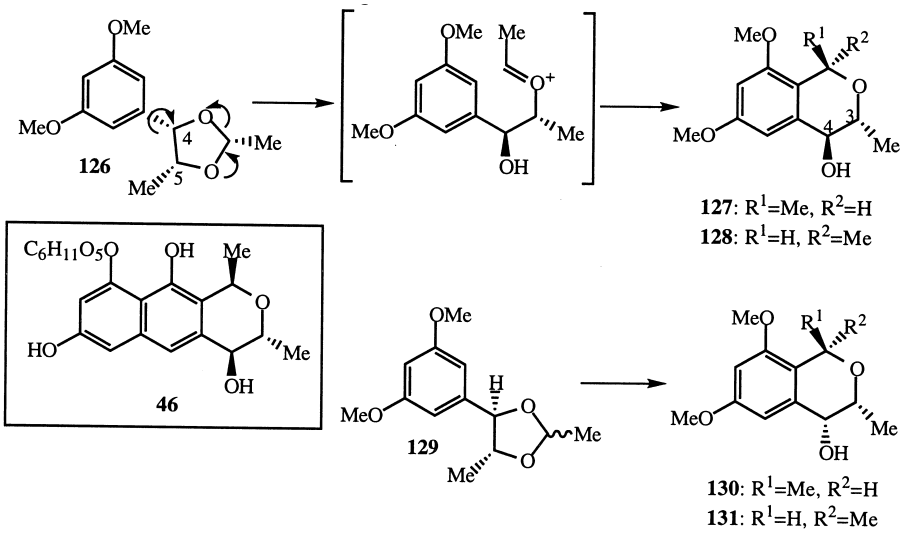
reducing conditions followed by oxidation provided a diastereomeric mixture of naphthopyrans **95** and **96**. Separation of the *trans*-isomer **96** and saponification followed by Jones oxidation to a carboxylic acid and esterification yielded (±)-9-deoxynanaomycin A methyl ester **66**.

Benzoisochroman-5,8-diones of general structure **99** were prepared[35] from condensation of 1,4-dimethoxyalcohols **97** with aldehydes followed by oxidative demethylation of the resultant pyrans **98** (Scheme 18). The formation of compounds represented by **98** involved the formation of two chiral centres, however, only one product was isolated in each case.

A range of racemic frenolicin B analogues were synthesised[36] by condensation of a key β-hydroxyester **103** with acetone and benzaldehyde (Schemes 19 and 20). The synthesis of ester **103** began with juglone **76**. Protection, allylation and Claisen rearrangement of juglone **76** afforded naphthylsilyl ether **100** (Scheme 19). Catalytic dihydroxylation of the exocyclic double bond and subsequent oxidative cleavage of the resulting diol afforded aldehyde **101**, which underwent a Mukaiyama aldol condensation with *tert*-butyl(1-methoxyvinyloxy)dimethylsilane **102** to give β-hydroxyester **89**. Reduction of ester **89** using zinc powder in a two phase system (Et_2O/HCl) yielded the corresponding hydroquinone **103**, which was isolable and purified by crystallisation. Treatment of hydroquinone **103** with



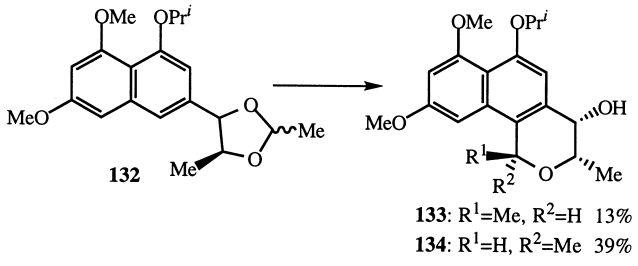
Scheme 23.



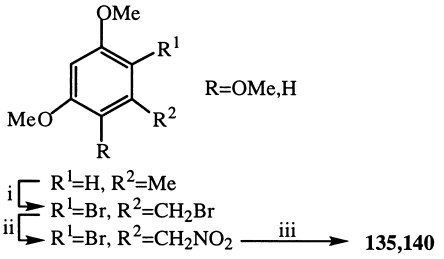
Scheme 24. Reagents and conditions: CH_2Cl_2, −78°C, $TiCl_4$ (2 equiv.).

acetone in a saturated gaseous HCl–diethyl ether solution gave a pyran ring derivative, which was oxidised to naphthoquinone **104**. Demethylation and saponification produced (±)-deoxyfrenolicin analogue **105**, and finally lactone **106** upon oxidative cyclisation.

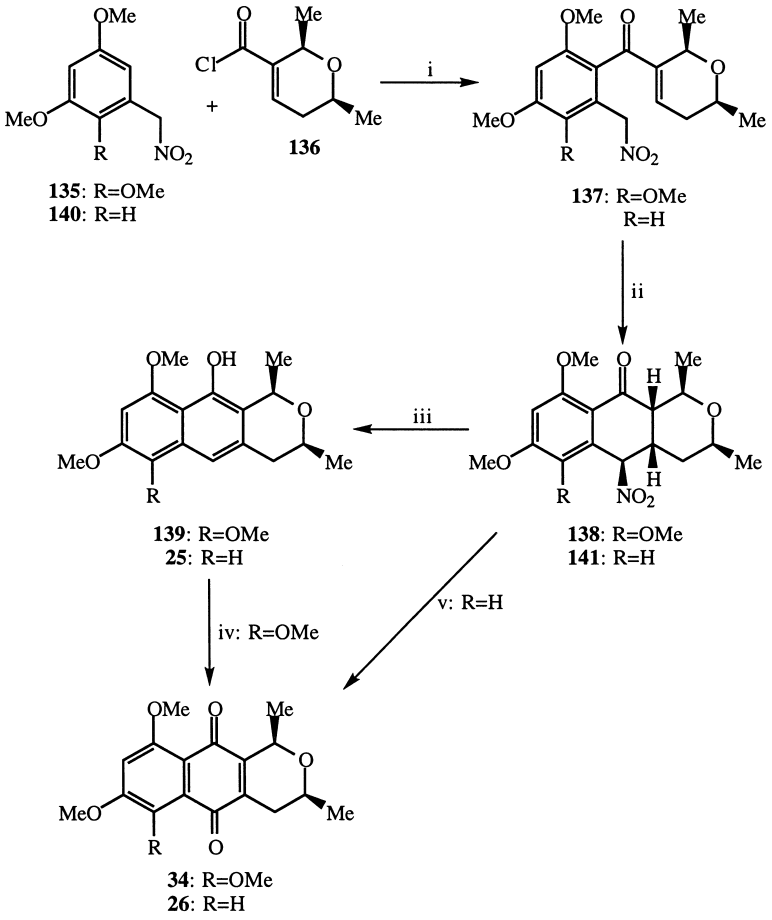
Treatment of hydroquinone **103** with benzaldehyde afforded racemic *cis* and *trans* hydroquinone stereoisomers, which were oxidised quantitatively to afford analogous quinones **107** and **108** and these were separated by fractional crystallisation in acetonitrile (Scheme 20). The ratio favoured the *cis* isomer **107** (94:6) if the condensation with benzaldehyde was carried out at −5°C for 5 min, and the *trans* isomer **108** (15:85) if conducted at room temperature over 2 h. Acid catalysed epimerisation of the kinetic product **107** (via reduction and reoxidation) afforded mainly the thermodynamic product **108**.



Scheme 25. Reagents and conditions: CH_2Cl_2, −78°C, $Ti(OPr^i)_4$ then $TiCl_4$, RT.



Scheme 26. Reagents and conditions: (i) NBS, $(PhCO_2)_2$ (cat.), CCl_4, reflux, hν; (ii) $NaNO_2$, NH_2CONH_2, C_6H_3-1,3,5-$(OH)_3$, DMF, 0°C, then bromide; (iii) THF, −78°C, Bu^nLi, then aq. AcOH, RT.



Scheme 27. Reagents and conditions: (i) $AlCl_3$, $CHCl_3$, 0°C; (ii) MeOH, $BzN(Me)_3^+OH^-$, RT; (iii) N_2, *p*-$MeC_6H_4CH(Me)_2$, reflux, no hν; (iv) aq. CAN, MeCN, RT; (v) a: $TiCl_3$, HCl, then **141** in THF, RT; b: H_2O, air.

Demethylation of quinones **107** and **108** with boron trichloride, hydrolysis of the methyl ester moiety and cyclisation afforded pyranonaphthoquinones **109** and **110**, respectively.

This strategy was later extended to two novel enantioselective syntheses of frenolicin B **119** and its enantiomer **120**.[37] The first route explored the possibility of using optically active sulfoxides in order to generate a stereoselective synthesis of (*S*)- and (*R*)-β-hydroxy esters **113** and **114** by condensation with aldehyde **101** in an aldol type fashion (Scheme 21). The (*S*)- and (*R*)-β-hydroxy esters **113** and **114** were both made using (−)-(*S*)- and (+)-(*R*)-sulfoxides **111** and **112**, respectively. Subsequent oxidative demethylation afforded quinones **115** and **116**. Condensation of the corresponding hydroquinones with propanal then provided pyranonaphthoquinones **46** and **118**. Finally, saponification of esters **46** and **118** followed by oxidative cyclisation afforded frenolicin B **119** and its enantiomer **120**.

A more efficient synthesis of optically pure frenolicin B **119** from prochiral β-keto ester **121** was also established (Scheme 22).[37] Ester **121** was conveniently made in six steps starting from juglone **76**. Asymmetric hydrogenation of ester **121** using a chiral ruthenium catalyst then afforded the desired (*S*)-alcohol **122** in >98% ee. Conversion of this optically pure alcohol **122** to frenolicin B **119** was then achieved using previously established methodology.

The mechanism of the key step {addition of an aldehyde or ketone to a 3-(2-hydroxyalkyl)naphthoquinone or hydroquinone} which is common to the above approaches, has been rationalised.[38] In the synthesis of the eleutherins **8** and **9**,[26] it was suggested that the last step probably proceeds via the cation **123** (Fig. 2) formed by an initial redox reaction generating the quinol of **52** which undergoes electrophilic substitution and subsequent reoxidation. The intermediate cation is therefore derived from the condensation of acetaldehyde with the side chain hydroxyl group and not directly with the quinone, as in **124**, which in comparison would be destabilised by the electron deficiency of the chromophore.

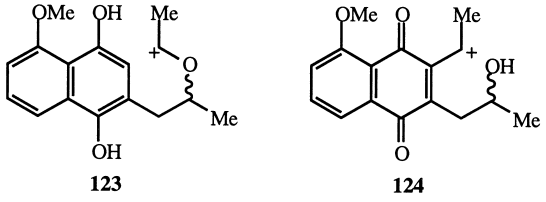
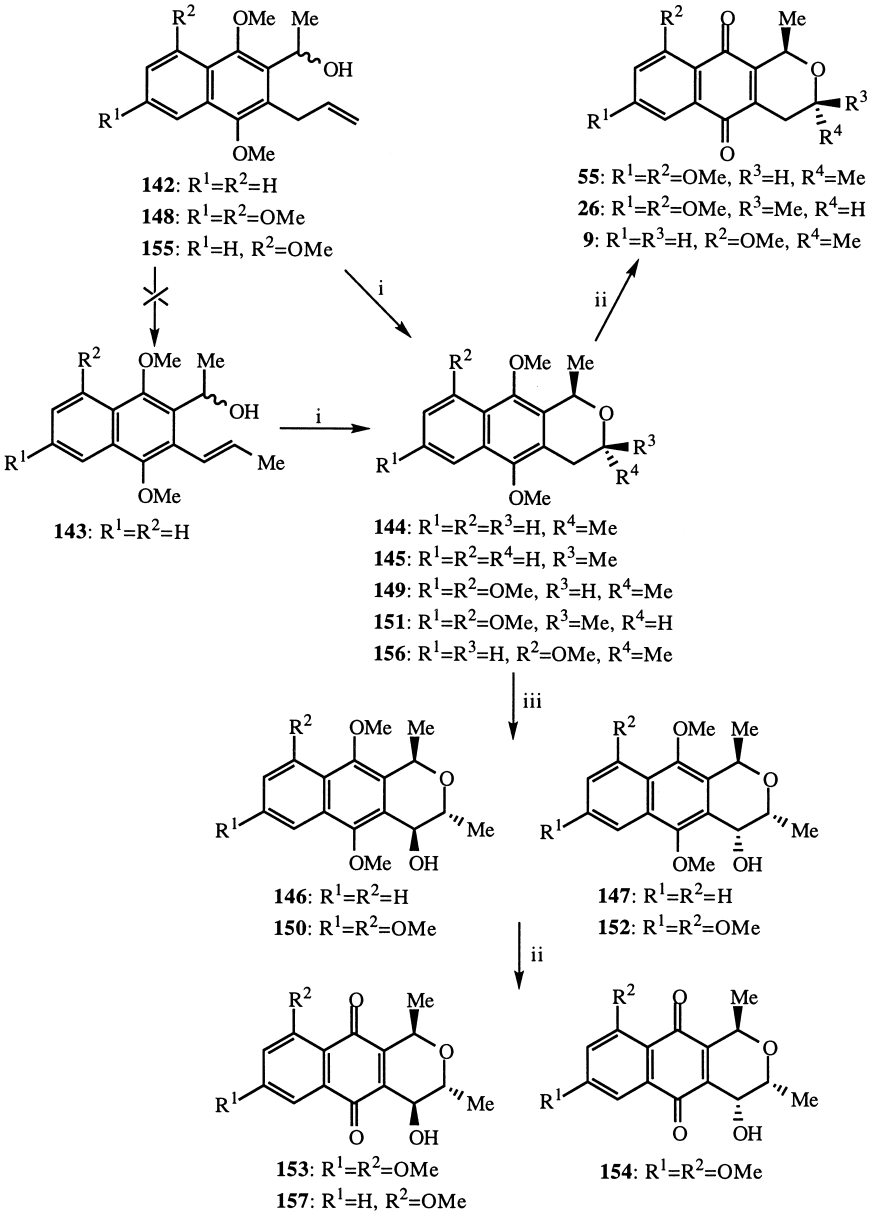


Figure 2.



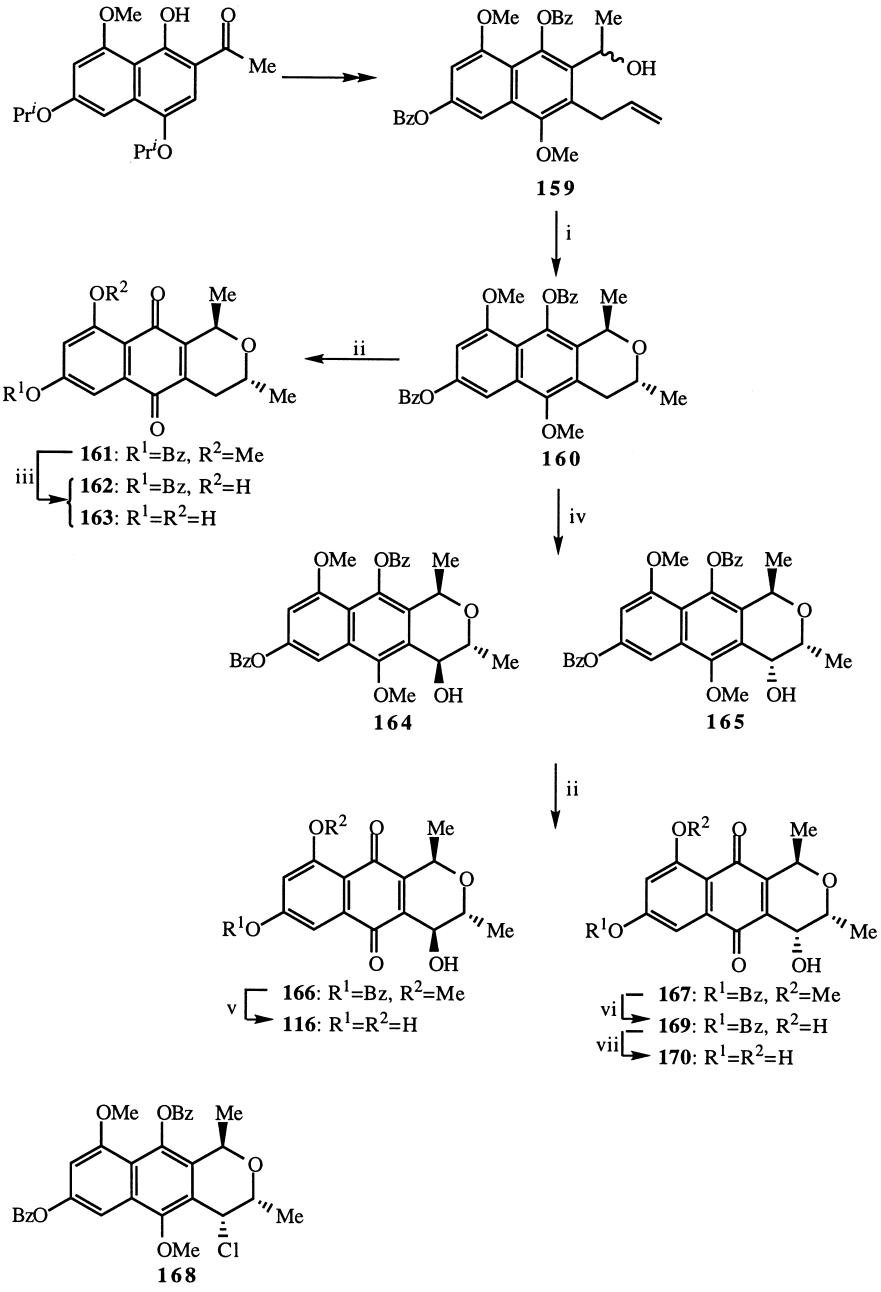
Scheme 28. Reagents and conditions: (i) DMF, KOBu^t, 60°C, N_2, 5–15 min; (ii) AgO, dioxane, 6 M HNO_3, RT; (iii) DMF, KOBu^t, 60°C, air, 2–3 h.

Liebeskind[39] also proposed that the starting quinone was rapidly reduced to the corresponding hydroquinone before the aldehyde condensed with the hydroquinone nucleus rather than the side chain (**125**, Scheme 23). Dehydration formed an *ortho*-quinone methide following which the pyran ring was constructed by an intramolecular Michael addition of the side chain hydroxyl group with the quinone methide tautomer. Evidence for this latter route has also been supported by others.[30,40]

2.3.2. Lewis acid cyclisation of dioxolanes. Closely related to the previously described syntheses is the electrophilic cyclisation of naphthyl and phenyl dioxolanes which have been stereoselectively isomerised using titanium tetrachloride to afford a pyran ring. Phenyldioxolane **126**, formed from the corresponding alkene by *cis*-hydroxylation and protection, when treated with $TiCl_4$ afforded a 4:1 ratio of benzopyrans **127** and **128** (Scheme 24).[41] These benzopyrans are structurally related to an aphid pigment monomer, namely glucoside B **46**.[42] Similarly a 1:9 ratio of benzopyrans **130** and **131** were formed starting from dioxolane **129**.

Attempts however to repeat the same experiments using 4-naphthyldioxolane **132** (Scheme 25) gave the angular naphthopyrans **133** and **134**.[43] Angular products resulted in this case due to the preference for electrophilic substitution of naphthalenes at the α- vs. β-position and crowding of the analogous naphthalene oxonium ion by the isopropoxy substituent. The synthesis of linear naphthopyrans by this method has therefore not yet been achieved.

2.3.3. Electrophilic aromatic substitution using acyl halides. A novel route to the pyranonaphthoquinone



Scheme 29. Reagents and conditions: (i) DMF, KOBu^t, 60°C, N_2, 7 min; (ii) AgO, dioxane, 6 M HNO_3, RT; (iii) BCl_3, CH_2Cl_2, 0°C, N_2; (iv) DMF, KOBu^t, 60°C, O_2, 15 min; (v) BCl_3, CH_2Cl_2, −5°C; (vi) BCl_3 (2 equiv.), CH_2Cl_2, 0°C; (vii) a: Adams catalyst, MeOH, H_2, then **169**, 30 min; b: aerial oxidation.

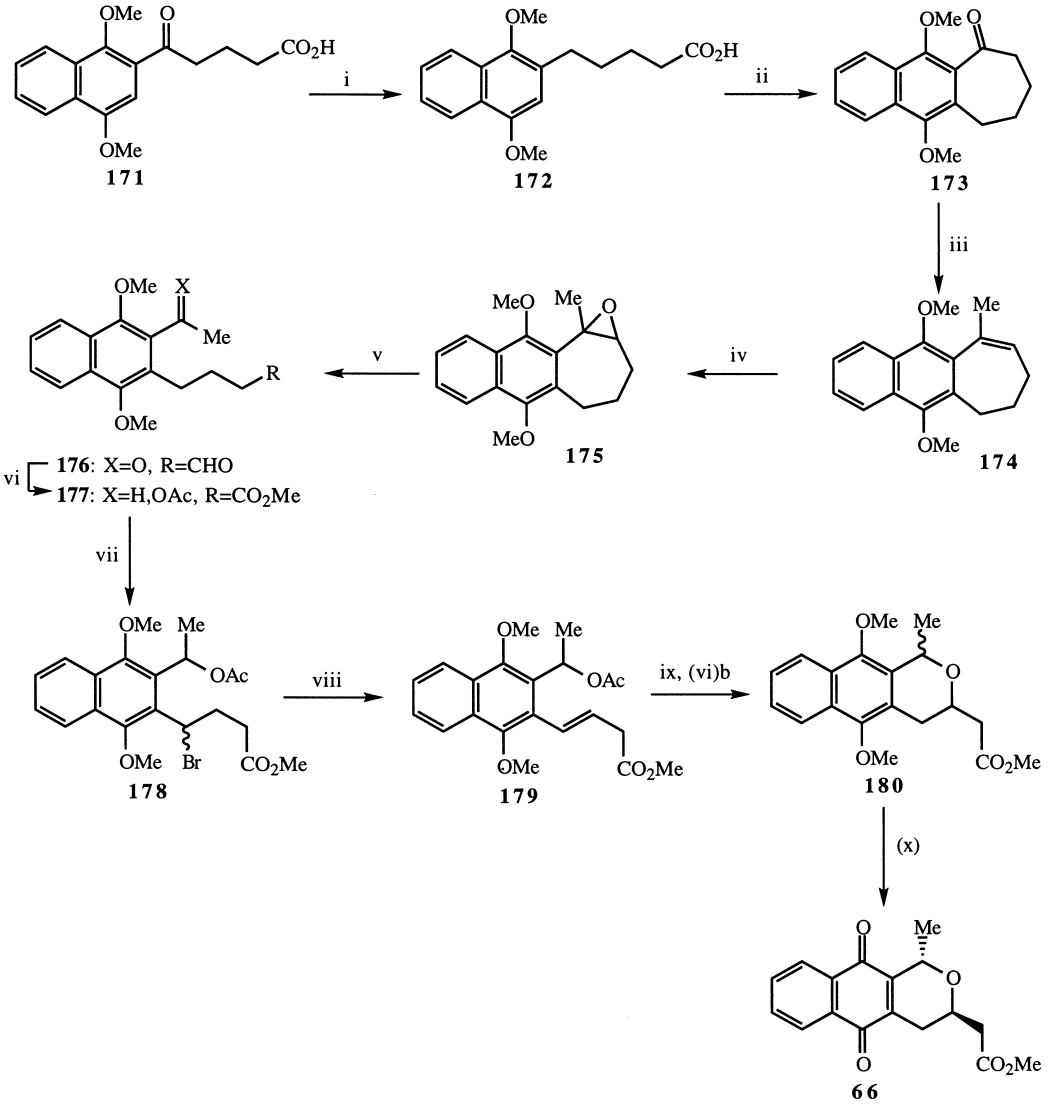
skeleton in which the quinone is generated at a later stage in the synthesis has been accomplished via convergent union of a substituted nitrobenzene and a pyran derivative bearing an acyl halide side chain.[44,45]

Acylation of nitro derivative **135** (made according to Scheme 26) with functionalised acid chloride **136** produced enone **137** (Scheme 27). Treatment of enone **137** with benzyltrimethylammonium hydroxide afforded ketone **141** with three new chiral centres being created and only one of eight possible diastereomers being favoured. Thermally induced nitrous acid elimination from ketone **141** gave naphthol **139** which upon oxidation with ceric ammonium nitrate produced ventiloquinone E **34**.

Analogous chemistry based on aryl nitromethane **140** yielded tricyclic ketone **138** and karwinaphthol B **25**. Subsequent application of the Nef reaction to ketone **138** and concomitant oxidation produced 7-methoxyeleutherin **26**.

2.4. Intramolecular cyclisations

2.4.1. Base induced cyclisation of naphthalenic alcohols. Several members of the aphid pigments and eleutherins have been synthesised in racemic form by Giles et al.[46,47] The key step in these syntheses has been the stereospecific base-induced cyclisation of naphthalenic alcohols to form naphtho[2,3-*c*]pyrans.



Scheme 30. Reagents and conditions: (i) Zn/Hg, HCl, PhMe; (ii) P_2O_5, H_3PO_4, 80°C; (iii) a: MeMgI, Et_2O/THF, reflux; b: HCl; (iv) MCPBA, CH_2Cl_2, 5°C; (v) H_5IO_6, THF/Et_2O; (vi) a: Jones reagent; b: CH_2N_2, Et_2O; c: $NaBH_4$, MeOH; d: Ac_2O, py; (vii) NBS, CCl_4, benzoyl peroxide, hν, reflux; (viii) DBU, C_6H_6, 70 to 25°C; (ix) aq. MeOH, KOH, reflux; (x) a: aq. CAN, MeCN, RT; b: separation.

Initial attempts to effect conjugation of the allylic double bond of dimethoxy alcohol **142** to alcohol **143** by treatment with potassium *tert*-butoxide in *N*,*N*-dimethylformamide under anaerobic conditions at 60°C for 5 min resulted in the formation of *trans* naphthopyran **144** (Scheme 28) while longer reaction times afforded a mixture of naphthopyrans **144** and **145**. Similar attempted conjugation of dimethoxy alcohol **142** *without* the exclusion of air, over longer reaction times produced a 4:1 mixture of C-4 hydroxylated products **146** and **147**.

Based on this methodology, four isochromanes were prepared from allylic alcohol **148**.[46,48] Cyclisation of alcohol **148** under anaerobic conditions afforded predominantly *trans*-naphthopyran **149** together with a minor quantity of pseudo-equatorial C-4 hydroxylated material **150**. Oxidation of *trans*-naphthopyran **149** with silver(II) oxide then provided (±)-deoxyquinone A dimethyl ether **55** (Scheme 28).

Base treatment of naphthopyran **149** under aerobic conditions afforded *cis* naphthopyran **151**, hydroxynaphthopyran **150** and its C-4 epimer **152** which, upon oxidation with silver oxide, provided (±)-7-methoxyeleutherin **26**, (±)-quinone A dimethyl ether **153** and (±)-quinone A′ dimethyl ether **154**, respectively. Similarly, base treatment of trimethoxy alcohol **155** produced *trans* naphthopyran **156** which, after oxidation produced (±)-isoeleutherin **9**. This

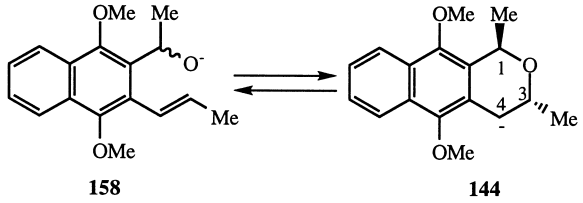
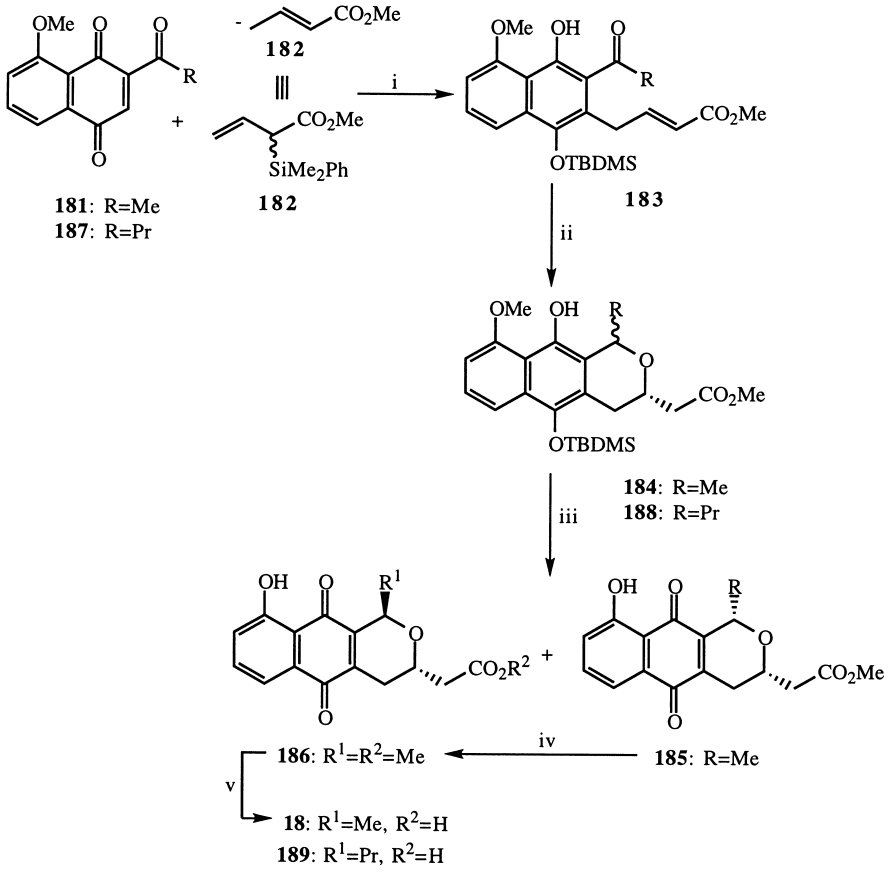


Figure 3.



Scheme 31. Reagents and conditions: (i) a: $SnCl_4$, CH_2Cl_2, −78 to −30°C; b: TBDMSCI, imid, DMF, RT; (ii) a: $NaBH_4$, MeOH (R=Me) or dioxane (R=Pr), RT; b: NaOMe, MeOH, RT; (iii) a: separate; b: aq. CAN, MeCN; c: $AlCl_3$, CH_2Cl_2, RT; (iv) conc. H_2SO_4, 0°C; (v) aq. KOH, EtOH, RT.

methodology has been further extended to the synthesis of quinone **157**.[48]

The mechanism of this reaction has been proposed[47] to involve anion **158** generated by treatment of alcohol **142** with butoxide anion in a dipolar aprotic solvent. Cyclisation of anion **158** results in the kinetically favoured *trans* naphthopyran anion **144** (Fig. 3) in which the methyl group at C-3 adopts a less crowded equatorial position, while the methyl group at C-1 is axial to avoid *peri* interactions with the adjacent alkoxy group. Protonation of anion **144** then results in *trans* naphthopyran **144** (Scheme 28).

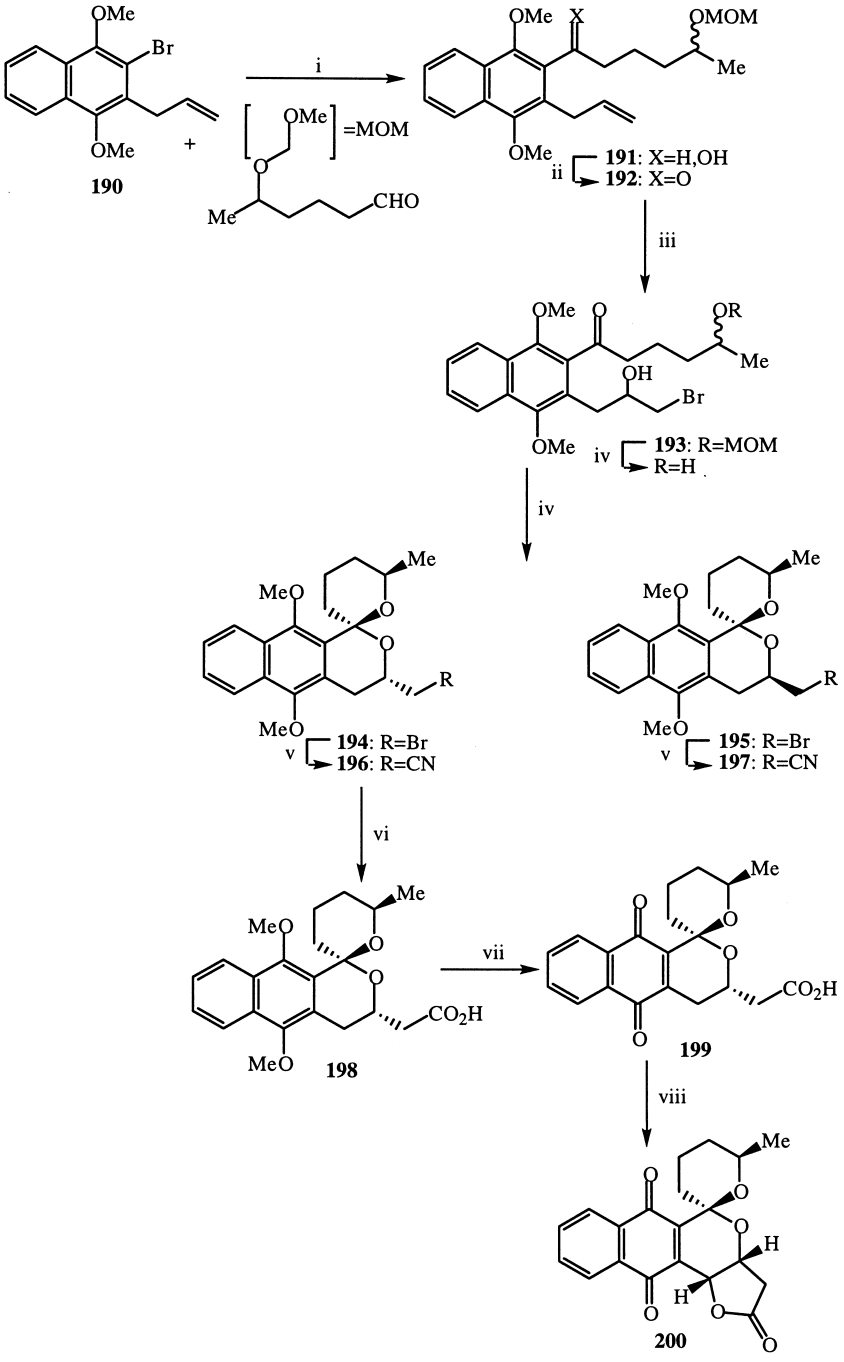
The conversion of *trans* naphthopyran **144** to *cis* naphthopyran **145** using longer reaction times has been attributed to the regeneration of anion **144** from *trans* naphthopyran **144**, which then reverts to anion **158** before ring closure to the thermodynamic product *cis* naphthopyran **145**. Later work[49] showed that both methoxy groups in the alkenyl alcohols were necessary for ready cyclisation and good yields, suggesting that this reaction may involve steric effects that force the reaction centres together by the proximity of the flanking methoxy groups.

In the case of the oxygenation reactions, anion **144** can undergo oxidation either to the corresponding carbonium ion followed by reaction with traces of adventitious water, or to the corresponding radical, which reacts with molecular oxygen to form products.

An improvement in the stereospecific base-induced cyclisation/oxygenation procedure has also been developed[50] and further aphid pigments and analogues were prepared by judicious use of protecting groups on the naphthalene nucleus and the use of a stronger oxidising agent. Alcohol **159** was cyclised under anaerobic conditions to naphthopyran **160** and then oxidised to pyranonaphthoquinone **161** (Scheme 29). Removal of both methoxy and benzyloxy groups was then effected using excess boron trichloride to afford racemic deoxyquinone A **163** (a small amount of benzyl quinone **162** was also obtained).

The attempted oxygenation reaction of naphthopyran **160** required modifications to the original procedure. Optimum yields were obtained by dissolving naphthopyran **160** in dry dimethylsulphoxide through which *oxygen* was bubbled to afford hydroxynaphthopyrans **164** and **165** in 60 and 24% yield, respectively. Related naphthopyrans, e.g. **149**[48] gave similar improvements. Finally, oxidation of naphthopyran **164** afforded pyranonaphthoquinone **166** which after deprotection resulted in (±)-quinone A **116**. A similar oxidation furnished pyranonaphthoquinone **167** from the pseudo-axial chloro derivative **168**. Treatment of pyranonaphthoquinone **167** with boron trichloride (strictly 2 equiv.) removed the *O*-methyl group to afford quinone **169**, which, upon hydrogenolysis and reoxidation resulted in (±)-quinone A′ **170**.

A novel route in which a terminal seven membered ring was



Scheme 32. Reagents and conditions: (i) Bu^{n}Li, −78°C; (ii) PCC, RT; (iii) aq. NBA, $HClO_4$, 0°C; (iv) 10% HCl, 50°C; (v) NaCN, DMF, 80°C; (vi) KOH, H_2O_2, 40°C; (vii) CAN, RT; (viii) O_2, py, RT.

manipulated to afford a pyran ring after base-induced cyclisation was introduced in the synthesis of racemic 9-deoxynanaomycin A methyl ester **66**[51] (Scheme 30). Friedel–Crafts acylation of 1,4-dimethoxynaphthalene with glutaric anhydride furnished keto-acid **171**. Clemmensen reduction and polyphosphoric acid catalysed cyclisation of the resulting acid **172** gave ketone **173**. Nucleophilic addition of methylmagnesium iodide followed by dehydration of the resulting alcohol produced alkene **174**, which was epoxidised to **175** and subsequently cleaved to keto-aldehyde **176**. Conversion of keto-aldehyde **176** to acetate **177** was achieved by Jones oxidation, esterification, reduction and acetylation. Bromination of acetate **177** gave bromide **178** as a mixture of diastereomers which, after elimination of hydrobromic acid provided alkene **179**. Base-induced cyclisation of alkene **179** afforded pyran **180** which, upon oxidation, gave (±)-9-deoxynanaomycin A methyl ester **66**.

The use of sodium methoxide for the cyclisation of naphthalenic alcohol **183**, precursor to (±)-nanaomycin A **18**[33,52] (Scheme 31), has also been accomplished. The formation of naphthalenic alcohol **183** in turn required allylation of quinone **181**. This was successfully accomplished by

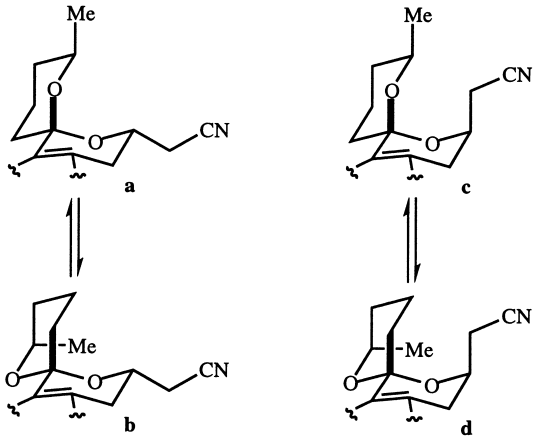


Figure 4.

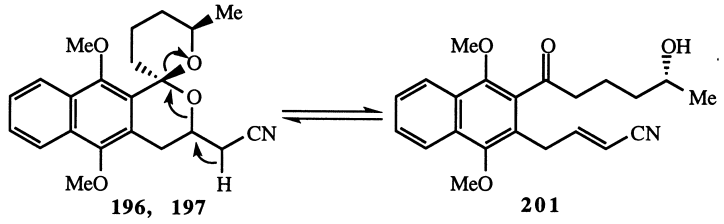
treatment with silylated butenoate **182** under Lewis acidic conditions followed by selective protection to prevent cyclisation onto the allylic side chain. Reduction of ketone **183** produced the corresponding alcohol, the anion of which cyclised onto the allyl side chain forming pyran isomers **184** in a 1:1, *cis*:*trans* ratio. Separation, oxidation and demethylation provided pyranonaphthoquinone epimers **185** and **186** of which the former was isomerised to quinone **186** in concentrated acid. Hydrolysis of quinone **186** afforded (±)-nanaomycin A **18**.

In the same manner, (±)-deoxyfrenolicin **189** was synthesised from quinone **187**. The two epimers of pyran **188**, obtained after reductive cyclisation had a *cis*:*trans* ratio of 2:5, and were converted to (±)-deoxyfrenolicin **189** as previously described.

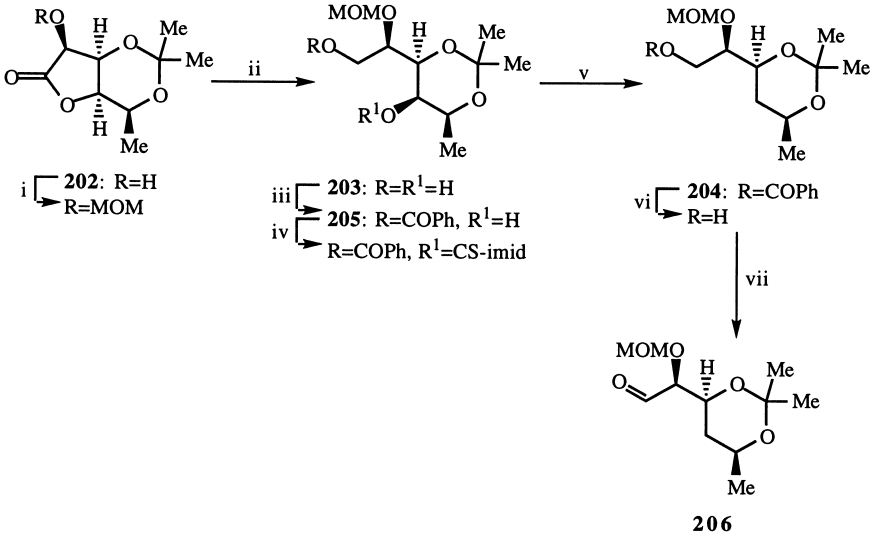
2.4.2. Acid catalysed acetalisation of a bromohydrin. Yoshii et al.[53–55] utilised an acid catalysed acetalisation of a bromohydrin in order to construct the pentacyclic ring system of griseusin A **222** (Scheme 36). Initially, 2-allyl-3-bromo-1,4-dimethoxynaphthoquinone **190** was alkylated with the methoxymethyl ether of 5-hydroxyhexanal to give carbinol **191** (Scheme 32).

Oxidation of carbinol **191** to the corresponding ketone **192**, followed by addition of hypobromous acid (generated in situ) to the allyl group then afforded bromohydrin **193** which underwent deprotection and concomitant intramolecular ketalisation when heated with acid to afford a 1:1 mixture of isomeric spiroketals **194** and **195**. Treatment of this mixture with sodium cyanide afforded a 3:2 mixture of nitriles **196** and **197**, respectively. The higher ratio of nitrile **196** observed in this reaction was attributed to the isomerisation of nitrile **197** to alkene **201** through β-elimination and subsequent addition of the cyanomethyl side chain (Eq. (1)). Finally, the target quinone (±)-**200** was achieved by hydrolysis of nitrile **196** to afford acid **198**, followed by oxidation to quinone **199** and cyclisation to construct the γ-lactone ring by aerial oxidation in pyridine.

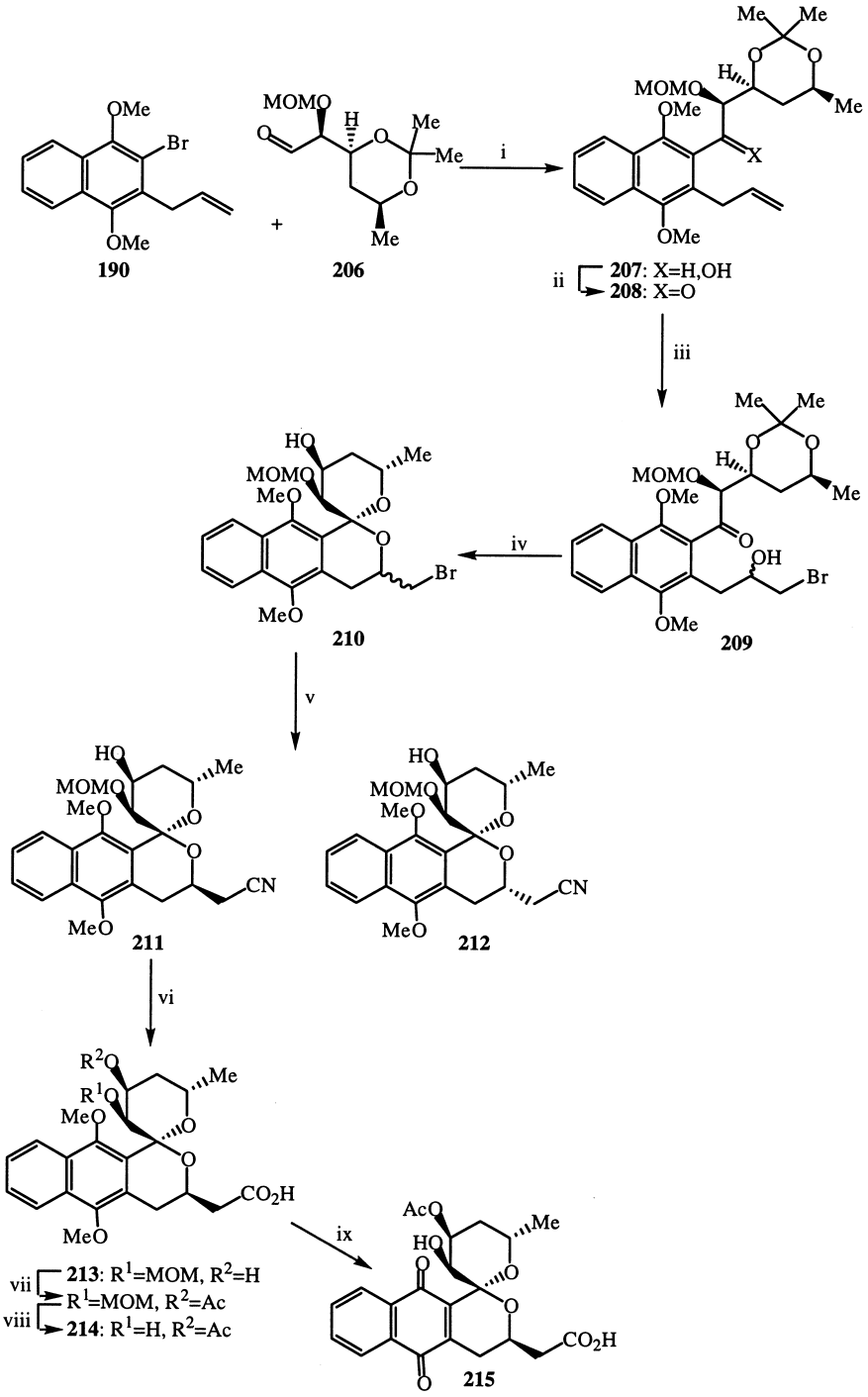
Of the four possible diastereomers (Fig. 4) formed in the intramolecular ketalisation reaction, spiroketal **a** was



(1)



Scheme 33. Reagents and conditions: (i) MOMCl, $PhNEt_2$, CH_2Cl_2, RT; (ii) THF, $LiAlH_4$, RT; (iii) PhCOCl, py, CH_2Cl_2, RT, then EtOH; (iv) $imid_2CS$, $ClCH_2CH_2Cl$, reflux; (v) *n*-Bu_3SnH, $PhCH_3$, N_2, reflux; (vi) 5% aq. KOH, MeOH, RT; (vii) $(COCl)_2$, CH_2Cl_2, −60°C, DMSO, then alcohol, Et_3N, −60 to 25°C.

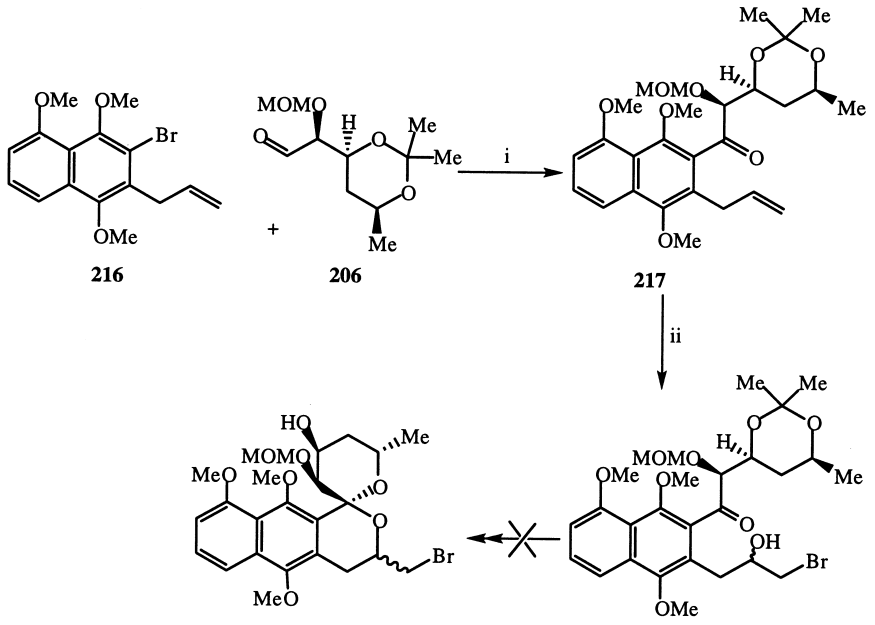


Scheme 34. Reagents and conditions: (i) THF, −78°C, N_2, Bu^{n}Li, **206**; (ii) CH_2Cl_2, PCC, RT; (iii) Me_2CO, 0°C, 2.7 M $HClO_4$, NBA (iv) 10% HCl, RT; (v) NaCN, DMF, 70°C; (vi) EtOH, 30% aq. KOH, 30% aq. H_2O_2, 40°C then reflux, then 10% HCl; (vii) Ac_2O, py, RT; (vii) 10% HCl, DME, 50°C; (ix) THF, AgO, 6 M HNO_3, RT.

assigned to **194**, **196** and spiroketal **c** was assigned to **195**, **197** after consideration of thermodynamic stability, nonbonding interactions and anomeric effects, with **a** being more stable than **c**.

(+)-9-Deoxygriseusin B **215** was then synthesised in a similar manner to the above racemic synthesis and the syntheses of nanaomycin A **18** and the eleutherins **5**, **9**.[54,55] A chiral carbohydrate precursor **206** was used to construct the spiro system, the synthesis of which began with 6-deoxy-3,5-*O*-isopropylidene-L-gulono-γ-lactone **202** (Scheme 33). The hydroxyl group of **202** was protected as a methoxymethyl ether before reduction of the lactone to produce diol **203**. Selective benzoylation and deoxygenation using Barton's methodology afforded benzoate **204** accompanied by alcohol **205**. Saponification of benzoate **204** followed by Swern oxidation resulted in the desired aldehyde **206**.

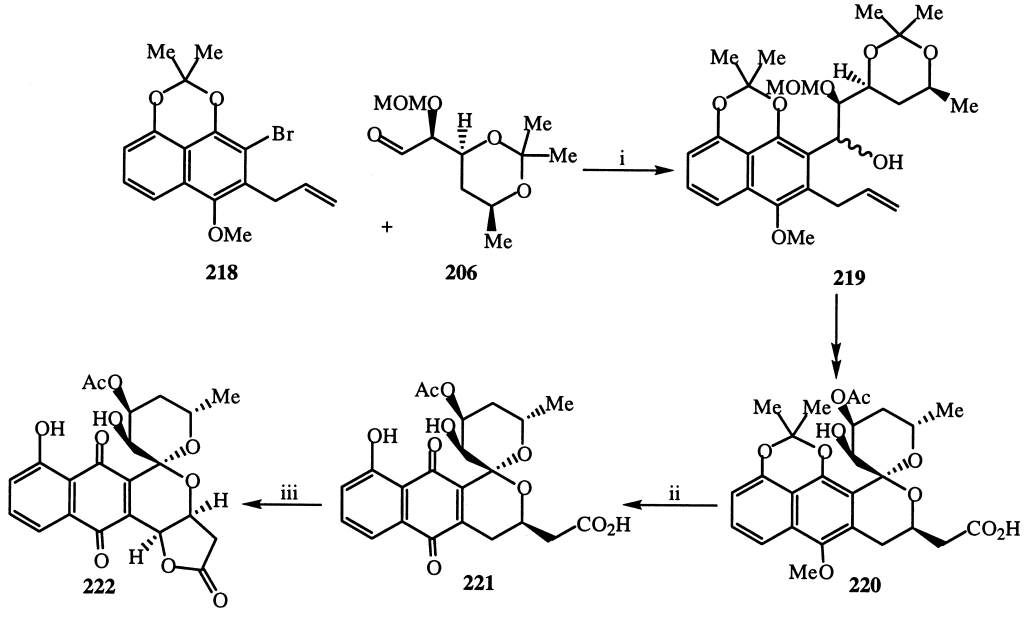
With the required aldehyde now available, the construction



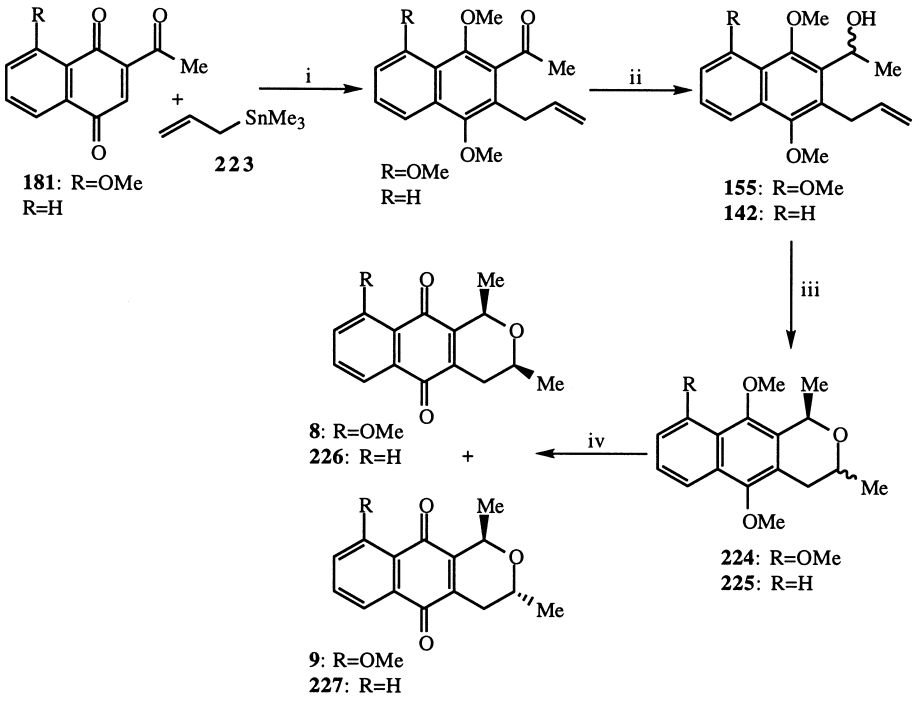
Scheme 35. Reagents and conditions: (i) a: THF, −78°C, N_2, Bu^{n}Li, **206**; b: CH_2Cl_2, PCC, RT; (ii) Me_2CO, 0°C, 2.7 M $HClO_4$, NBA.

of the pyranonaphthoquinone moiety commenced using allylnaphthalene **190**, prepared by allylation and reductive methylation of 2-bromonaphthoquinone (Scheme 34). Lithiation and coupling of allylnaphthalene **190** to aldehyde **206** afforded epimeric alcohols **207** which were oxidised to ketone **208**. Construction of the dioxaspiro ring system from this point was closely modelled on earlier work.[53] Reaction of ketone **208** with hypobromous acid to afford bromohydrin **209** and selective removal of the acetonide group from the side chain afforded a 1:1 mixture of epimeric bromoketals **210**, which were converted to nitriles **211** and **212** (2.2:1 ratio). The displacement conditions favoured the formation of nitrile **211** from nitrile **212**. Hydrolysis of nitrile **211** afforded acid **213** which required appropriate protecting group manipulation before conversion to the target quinone. Thus, acetylation of the free hydroxyl group followed by removal of the methoxymethyl group afforded alcohol **214** which, upon oxidative demethylation, furnished (+)-9-deoxygriseusin B **215**.

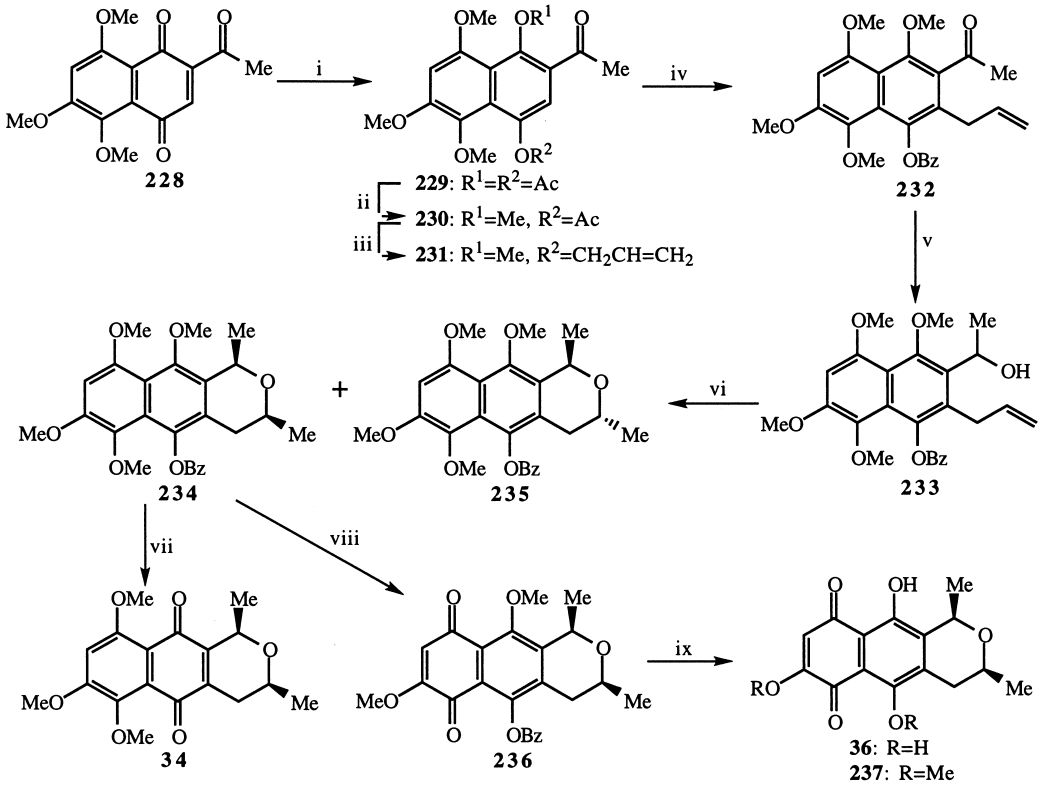
Similar methodology[53,56] was also used to construct the pentacyclic ring systems of (+)-griseusin A **222** and B **221** using allylnaphthalene **216** and aldehyde **206** (Scheme 35).[57] Lithiation of bromide **216** followed by addition of aldehyde **206** and oxidation furnished naphthylketone **217**. Intramolecular ketalisation of the corresponding bromohydrin, however, could not be achieved under a variety of conditions. This was presumed to be due to the steric



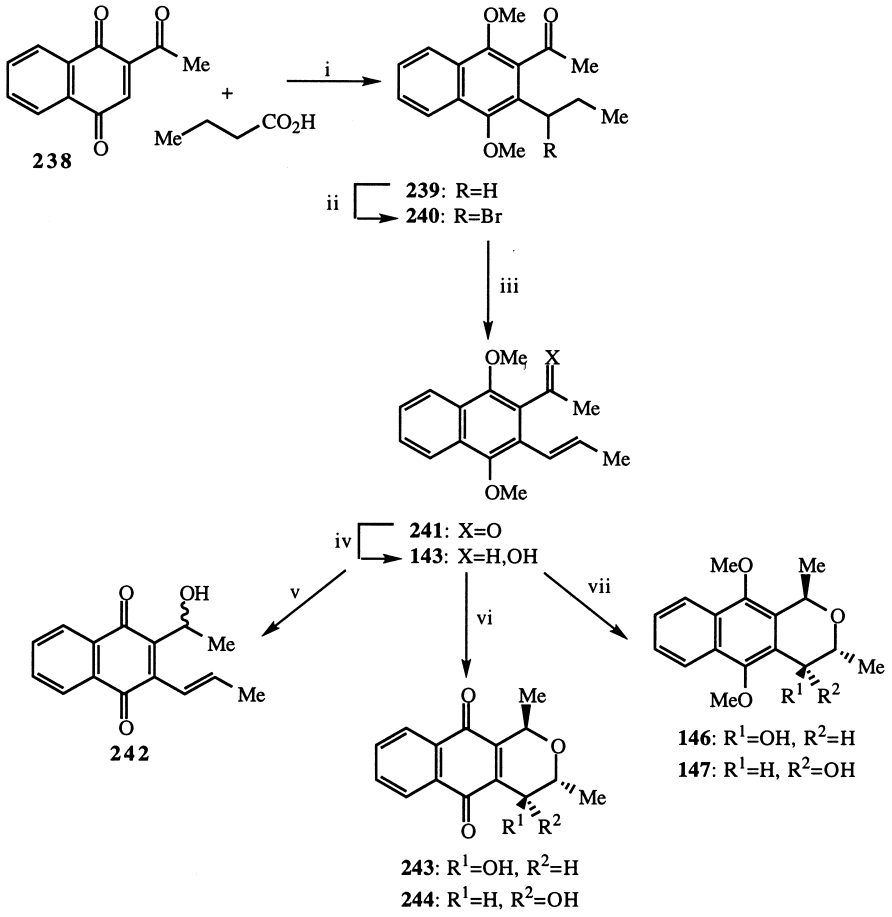
Scheme 36. Reagents and conditions: (i) a: THF, −78°C, N_2, Bu^{n}Li, **206**; RT, O_2.



Scheme 37. Reagents and conditions: (i) a: $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C to RT; b: MeI, K_2CO_3, Me_2CO; (ii) $LiAlH_4$, Et_2O, 0°C; (iii) a: $Hg(OAc)_2$, THF/H_2O, RT, then 3 M NaOH; b: $NaBH_4$, 3 M NaOH, RT (**155**) *or* a: PhSeBr, CH_2Cl_2, −78°C, H_2O, RT; b: Raney Ni, THF (**142**); (iv) aq. CAN, MeCN.



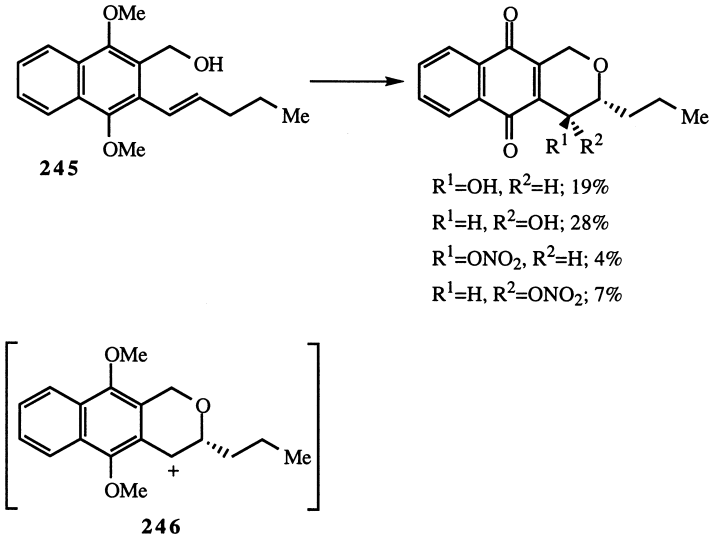
Scheme 38. Reagents and conditions: (i) a: CH_2Cl_2, aq. $Na_2S_2O_4$; b: Py, Ac_2O, 80°C; (ii) a: MeOH, KOH, RT; b: Me_2CO, K_2CO_3, Me_2SO_4, reflux; (iii) a: MeOH, KOH, RT; b: Me_2CO, K_2CO_3, allyl bromide, reflux; (iv) a: 125°C, N_2; b: Me_2CO, K_2CO_3, allyl bromide, reflux; (iv) a: 125°C, N_2; b: Me_2CO, K_2CO_3, BzBr, reflux; (v) Et_2O, $LiAlH_4$, RT; (vi) $Hg(OAc)_2$, aq. THF, RT, then 3 M NaOH, then $NaBH_4$; (vii) EtOAc, 10% Pd–C, conc. HCl, H_2, RT; b: aq. MeCN, CAN, RT; (vii) AgO, dioxane, 6 M HNO_3, RT; (ix) EtOH, conc. HCl, reflux.



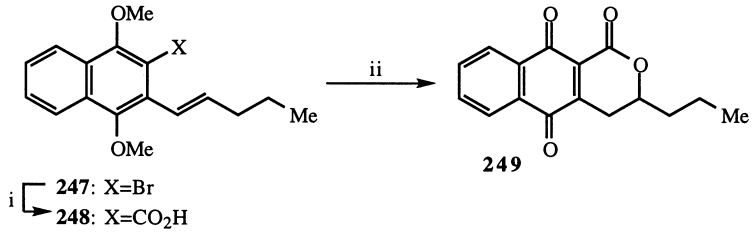
Scheme 39. Reagents and conditions: (i) a: CH_3CN, aq. $AgNO_3$, 65–70°C; b: Et_2O, aq. $Na_2S_2O_4$; c: dry acetone, K_2CO_3, $(MeO)_2SO_2$, reflux; (ii) NBS, $(C_6H_5Co)_2O_2$, CCl_4, heat; (iii) DMF, DBN, 45°C; (iv) excess $NaBH_4$, EtOH, RT; (v) AgO, dioxane, 6 M HNO_3, RT; (vi) CAN (4 equiv.), CH_3CN, H_2O; (vii) CAN (2 equiv.), CH_3CN, H_2O.

hindrance associated with the *peri* methoxy groups, and therefore an isopropylidene group was chosen to protect the two phenolic groups which was incorporated into allylnaphthalene **190** (Scheme 36).

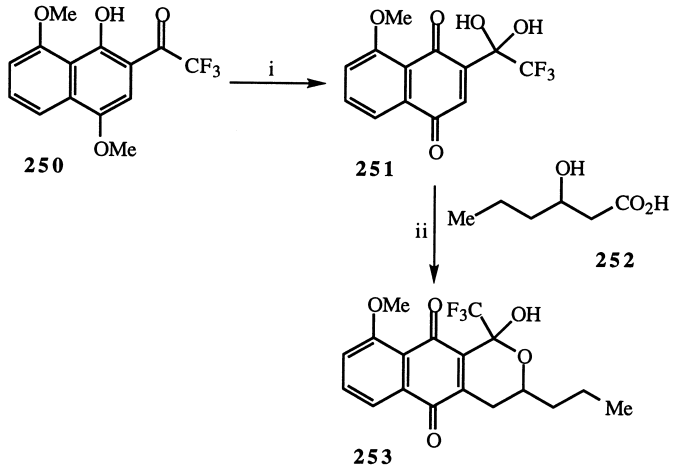
Coupling allylnaphthalene **218** with aldehyde **206** afforded the required carbinols **219**, which were carried through the synthetic sequence as for **207**, resulting in acid **220** as a single epimer. Silver(II)



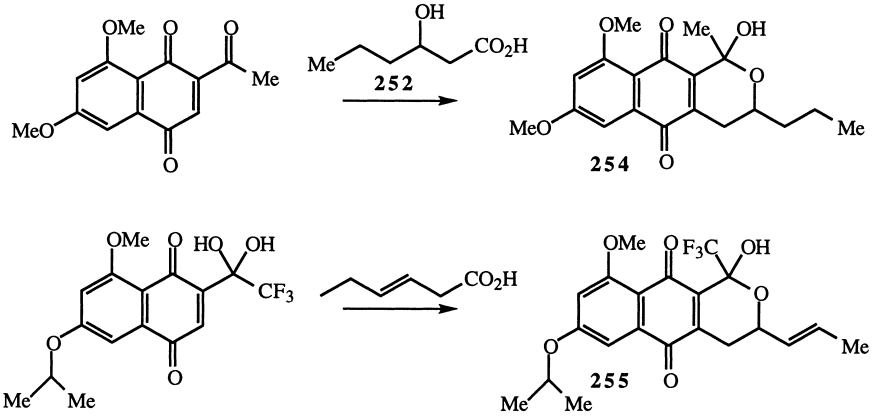
Scheme 40. Reagents and conditions: aq. CAN, MeCN.



Scheme 41. Reagents and conditions: (i) Et_2O, N_2, RT, Bu^nLi, CO_2, 5% NaOH; (ii) C_6H_{12}, hν.



Scheme 42. Reagents and conditions: (i) aq. CAN, MeCN; (ii) MeCN, aq. $AgNO_3$, **252**, 78°C, then aq. potassium peroxodisulphonate.

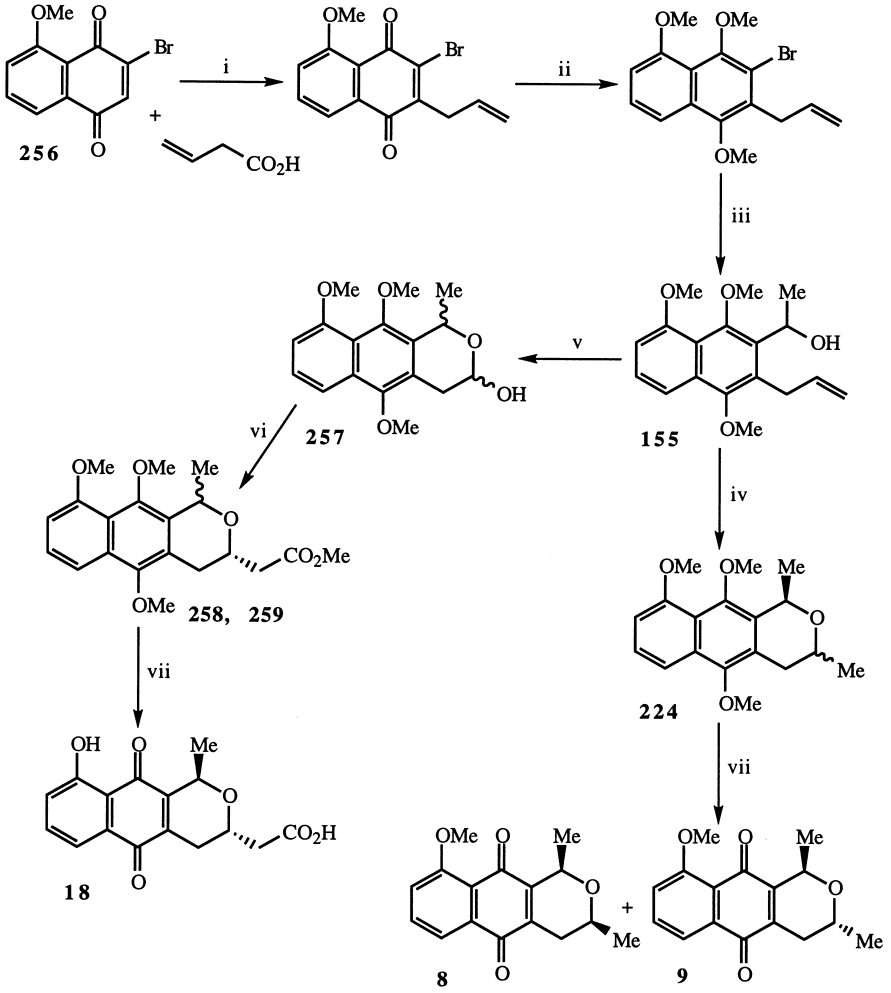


Scheme 43. Reagents and conditions: aq. $AgNO_3$, aq. potassium peroxodisulphonate, N_2, 78°C.

oxidation formed the corresponding quinone with concomitant deprotection of the naphthol affording (+)-griseusin B **221**. Aerial oxidation then resulted in cyclisation of the carboxylic acid side chain affording (+)-griseusin A **222**.

2.4.3. Other novel intramolecular cyclisation methods. Intramolecular oxymercuration of naphthalenol **155** was used to furnish the required pyranonaphthoquinone ring system in the synthesis of the eleutherins (Scheme 37).[52,58] Alcohol **155** in turn was assembled via nucleophilic addition of allyltrimethylstannane **223** to quinone **181** followed by reduction of the resultant ketone. Oxymercuration of alcohol **155** followed by borohydride reduction, afforded a 1:1 mixture of *cis* and *trans* pyran isomers **224** which were separated and oxidatively demethylated to afford (±)-eleutherin **8** and (±)-isoeleutherin **9**.

This mode of cyclisation has also been utilised in the syntheses[59] of racemic ventiloquinones E **34** and G **36** (Scheme 38). Reductive acetylation of quinone **228** afforded acetylnaphthalene **229**, which underwent selective methylation to give diacetate **230**. Selective hydrolysis of **230** followed by allylation of the resulting naphthol afforded ether **231** which, upon Claisen rearrangement followed by benzylation, provided ketone **232**. Reduction of **232** with lithium aluminium hydride furnished alcohol **233** which, upon cyclisation with mercuric acetate and sodium



Scheme 44. Reagents and conditions: (i) MeCN, $AgNO_3$, H_2O, $(NH_4)_2S_2O_8$, 60°C; (ii) a: aq. $NaHSO_3$, Et_2O; b: KOH, Me_2SO_4, RT to 65°C, (iii) THF, Bu^nLi, −78°C, MeCHO; (iv) $Hg(OAc)_2$, THF/H_2O, NaOH, RT; (v) OsO_4, dioxane/H_2O, RT then $NaIO_4$; (vi) NaH, DME, $(MeO)_2P(O)CH_2CO_2Me$, RT, **257**; (vii) a: aq. CAN, MeCN, RT; b: $AlCl_3$, CH_2Cl_2, RT; c: conc. H_2SO_4; d: conc. HCl.

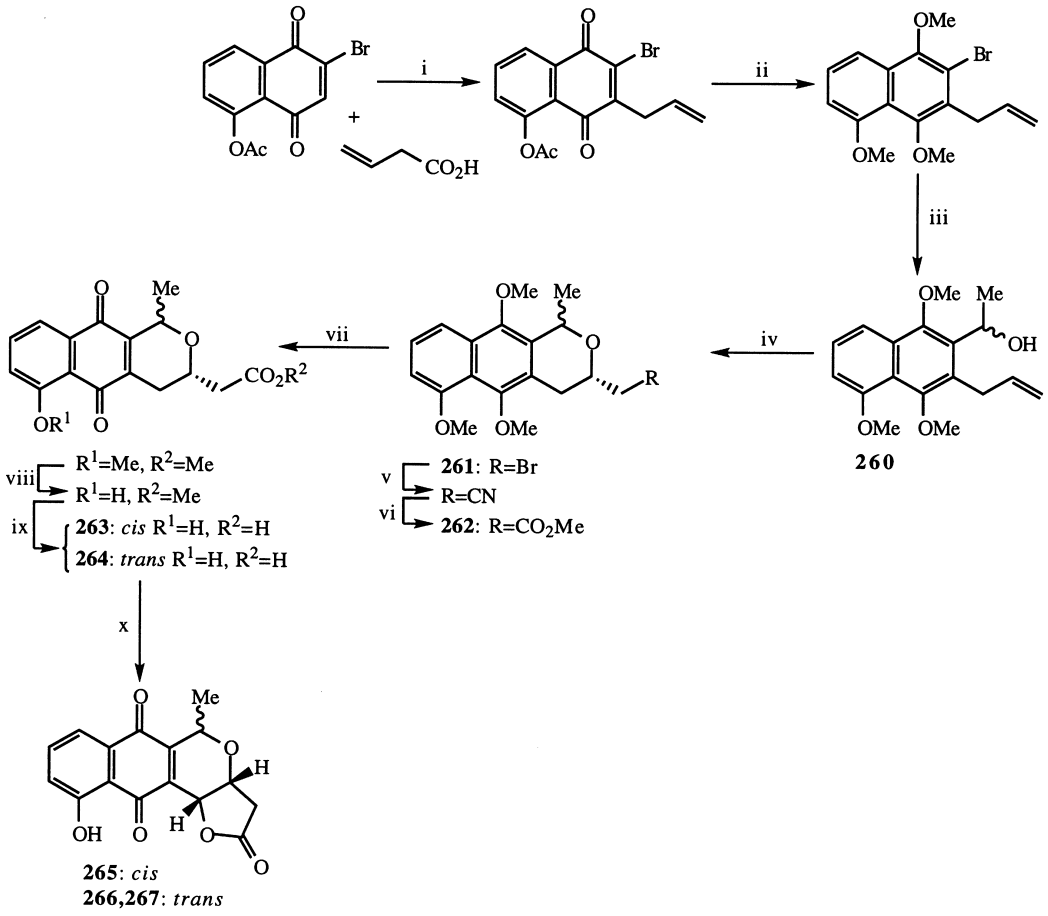
borohydride, gave a 1:1 mixture of *cis* and *trans* pyrans **234** and **235**. Removal of the benzyl group from **234** by hydrogenolysis, and subsequent oxidation using CAN, afforded (±)-ventiloquinone E **34**. Silver(II) oxidation of *cis* pyran **234** furnished *cis* quinone **236** which after treatment with ethanolic HCl produced (±)-ventiloquinone G **36**. Removal of the benzyl group from **236** gave a compound isomeric with ventiloquinone J **237**, thus confirming its structure.

The demethoxyeleutherins **226**, **227** (Scheme 37) were also prepared[52,58] in a similar manner to that described above. Cyclisation of alcohol **142** in this case was accomplished by phenylselenoetherification. The naphthopyrans **225** were isolated in a 2:1 *cis*:*trans* ratio and these were converted to demethoxyeleutherins **226**, **227** before separation.

A synthesis of the 7,9-dideoxy derivatives of quinone A **116** and quinone A′ **122** (from protoaphin cleavage) has been achieved[60,61] in which the correct stereochemistry about the pyran ring resulted from a novel cyclisation. 2-Acetyl-1,4-naphthoquinone **238** (Scheme 39) underwent free radical propylation and reductive methylation to give compound **239**. Benzylic bromination followed by dehydrobromination of bromide **240** yielded olefin **241**. Reduction of the ketone group followed by oxidative cyclisation of the resultant alcohol **143** afforded different products depending on the type and amount of reagent used.

Oxidative cyclisation of alcohol **143** using silver(II) oxide gave only the corresponding quinone **242** whereas 4 equiv. of CAN produced 7,9-dideoxy analogues **243**, **244** in a 1:3 ratio. Further experiments[61] indicated that the stereochemistry displayed was set up at cyclisation, and that cyclisation occurred *before* oxidation. Indeed, if only 2 equiv. of CAN were used, naphthopyrans **146** and **147** (5:2) were formed. The C-4 hydroxyl group prefers an axial position (**244**, **147**) but is also equatorial (**243**, **146**) due to its lesser bulk than a methyl group and the greater *peri* hydrogen bonding in an equatorial position.

A related naphthalene **245** was similarly oxidised with four equivalents of CAN (Scheme 40) and afforded five products;[61] two quinonoid alcohols, their respective nitrates and the corresponding quinone of **245**. The formation of these four pyranonaphthoquinones implied the intermediacy of carbonium ion **246** which is trapped competitively by water and nitrate. Further studies[49] indicated that the



Scheme 45. Reagents and conditions: (i) MeCN/H_2O, $AgNO_3$, ammonium peroxodisulphonate, 80°C; (ii) a: Et_2O, $Na_2S_2O_4$; b: KOH; c: Me_2CO, Me_2SO_4, K_2CO_3, reflux; (iii) THF, −78°C, Bu^{n}Li, MeCHO; (iv) EtOAc, NBA, RT; (v) NaCN, DMF, N_2, 70°C; (vi) MeOH, 0°C, HCl gas; (vii) aq. CAN, MeCN, RT; (viii) CH_2Cl_2, −78°C, BCl_3; (ix) conc. HCl, RT; (x) a: separate; b: MeOH/H_2O, air, RT.

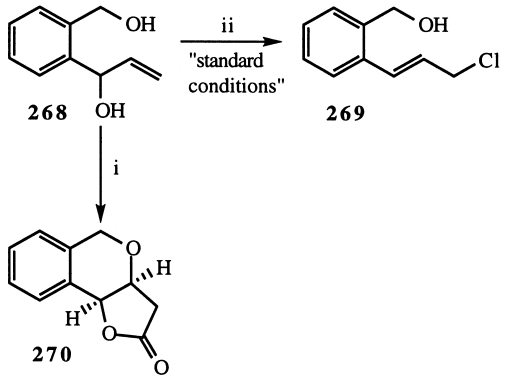
methoxy *ortho* to the alkenyl group played a key role in the cerium-promoted cyclisation. A radical cation mechanism was proposed leading ultimately to a carbocation like **246**.

Various pyranonaphthoquinones have been synthesised by potassium peroxodisulphonate and silver nitrate alkylation of functionalised quinones.[62–64] For example, bromonaphthalene **247** (Scheme 41) was converted to carboxylic acid **248** which upon irradiation underwent cyclisation to lactone **249**.[62]

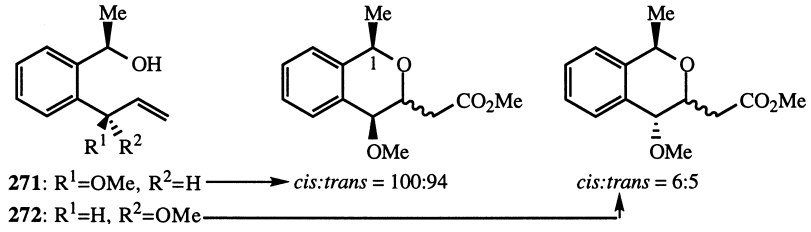
Using trifluoroacetic anhydride as an acetylating agent, naphthalene **250** was synthesised, converted by previously described methodology to quinone **251**, and then coupled to 3-hydroxyhexanoic acid **252** to give isochromane **253** (Scheme 42).[63]

Two quinones, **254** and **255** were formed[64] by coupling and subsequent cyclisation of 3-hydroxyhexanoic acid and *trans*-3-hexenoic acid, respectively (Scheme 43).

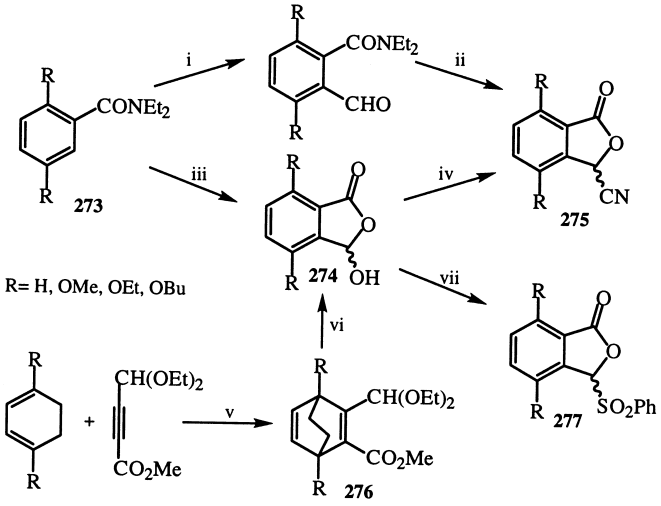
An alternative route[55] to nanaomycin A **18** began with free radical allylation of bromoquinone **256** (Scheme 44). Reductive methylation, lithiation and addition of acetaldehyde gave, rather than a naphthopyran, alcohol **155**, a common intermediate for several eleutherin and nanaomycin A **18** syntheses. The synthesis of the eleutherins was then achieved by acetoxymercuration/demercuration of alkene **155** to afford a mixture of naphthopyrans **224** which were separated and oxidised to (±)-eleutherin **8** and (±)-isoeleutherin **9**. (±)-Nanaomycin A **18** resulted from oxidative cleavage of the olefinic bond of alkene **155**, giving lactol **257** as a mixture of diastereomers. Wittig–Horner reaction furnished naphthopyrans **258**, **259**



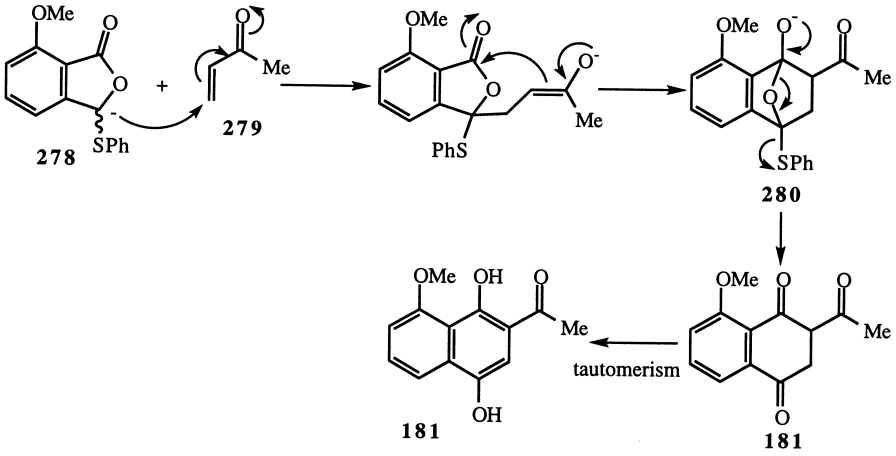
Scheme 46. Reagents and conditions: (i) $Pd(OAc)_2$ (1 equiv.), THF, CO; (ii) $PdCl_2$ (0.1 equiv.), $CuCl_2$ (3 equiv.), CO, THF.



Scheme 47. Reagents and conditions: $Pd(OAc)_2$ (1 equiv.), THF, CO.



Scheme 48. Reagents and conditions: (i) THF, −78°C, N_2, Bu^{s}Li, DMF, RT; (ii) a: KCN, 18-C-6, CH_2Cl_2, 0°C, TMSCN or aq. THF, KCN, 0°C, TsOH, RT; b: AcOH, RT or aq. THF, TsOH, reflux; (iii) a: THF, −78°C, TMEDA, Bu^{s}Li, DMF, RT; b: AcOH, 10% HCl, reflux; c: $NaHCO_3$ workup; (iv) a. aq. KCN, 0°C, then aq. HCl; b: $(COCl)_2$, MeCN, −12°C, DMF, then py; (v) $PhCH_3$, reflux; (vi) glacial AcOH, 5% HCl, 70°C; (vii) a: C_6H_6, PhSH, TsOH, reflux; b: MCPBA, CH_2Cl_2, RT.

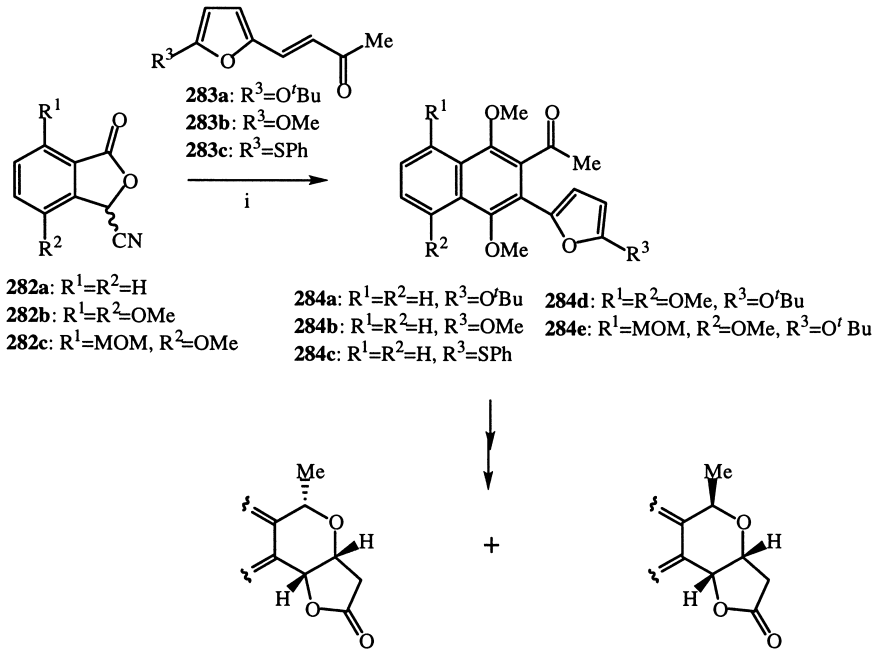


Scheme 49.

which were then treated as previously described (Section 2.4.2) to give (±)-nanaomycin A **18**.

A close structural isomer of alcohol **155**, namely alcohol **260**, was constructed using very similar methodology[55] and used to synthesise (±)-isokalafungin **266**, (±)-isonanaomycin A **264** and (±)-isonanaomycin D **267**, as well as their *cis* isomers (Scheme 45).[65]

Treatment of alcohol **260** with *N*-bromoacetamide formed the required dihydropyran ring affording a 1:1 mixture of *cis* and *trans* bromides **261**. The bromine was displaced by cyanide and the nitrile hydrolysed and subsequently methylated by hydrochloric acid in anhydrous methanol to ester **262**. Oxidation to the quinone, demethylation with boron trichloride and liberation of the carboxylic acid produced *cis* (**263**) and *trans* (**264**) (±)-isonanaomycin A. The

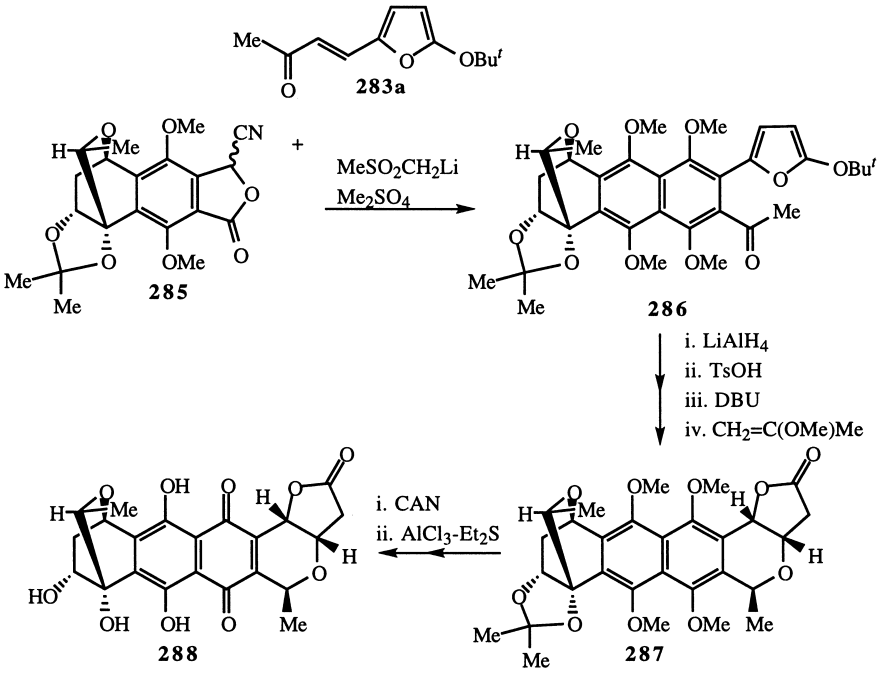


Scheme 50. Reagents and conditions: (i) a: $MeSOCH_2Li$, THF, −5 to −40°C; b: **283**, −20 to 0°C; c: aq. Na_2SO_4, Et_2O; d: Me_2SO_4, K_2CO_3, Me_2CO, reflux.

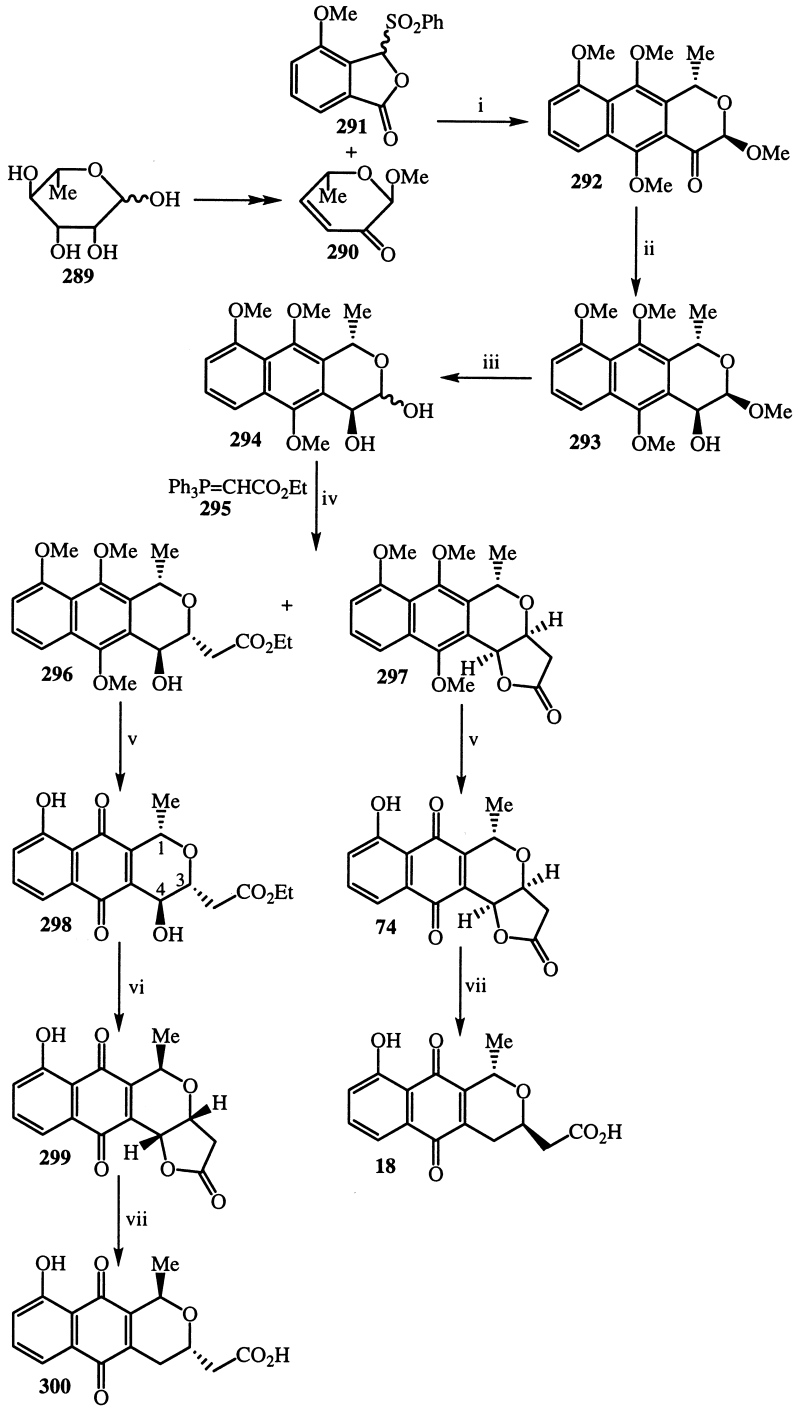
diastereomers were separated and the *cis* isomer **263** was converted by aerial oxidation to *cis* isonanaomycin D and *cis* isokalafungin **265** while the *trans* isomer **264** was transformed to the corresponding *trans* compounds **266** and **267**.

Intramolecular alkoxycarbonylation of hydroxyalkenes has also been used to prepare simple benzopyran lactones.[66] Model reactions investigating the stereoselectivity of the intramolecular alkoxycarbonylation reaction established the requirement for the use of a stoichiometric amount of palladium diacetate to afford the desired pyran **270**, with the *cis* isomer predominating over the *trans* in this example while standard catalytic conditions resulted in rearrangement of **268** to chloride **269** (Scheme 46).

The monomethyl ethers **271** and **272** (Scheme 47) gave a nearly equal ratio of *cis* and *trans* isomers suggesting that the free allylic hydroxyl group has a directing effect which favours the formation of a *cis* lactone, irrespective of the configuration at C-1.



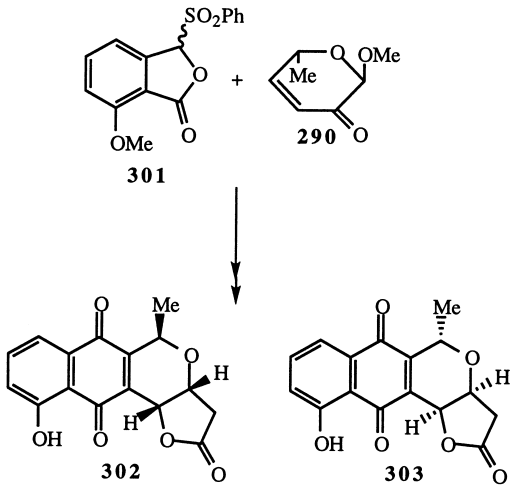
Scheme 51.



Scheme 52. Reagents and conditions: (i) a: ^{t}BuOLi, THF, −78°C to RT; b: Me_2SO_4, K_2CO_3, Me_2CO, 40°C; (ii) $NaBH_4$, MeOH, RT; (iii) 0.5 M HCl, AcOH, 75°C; (iv) PhMe, reflux; (v) a: aq. CAN, MeCN, RT; b: $AlCl_3$,CH_2Cl_2, 0°C to RT; (vi) C_6H_6, conc. H_2SO_4, 0°C to RT; (vii) PtO_2, H_2, EtOH.

2.5. Use of phthalide precursors

The use of organophthalides, phenylsulphanylphthalides and phenylsulphonylphthalides has been a common method to construct several pyranonaphthoquinone antibiotics. The cyanophthalides used in pyranonaphthoquinone syntheses (vide infra) are generally prepared[67,68] by directed *ortho*-lithiation of appropriately substituted aromatic amides **273**, followed by addition of a formyl group (Scheme 48). Formation of the cyanohydrin and subsequent cyclisation then results in the 3-cyanobenzofuranone **275**. Another method[69,70] forms the hydroxyphthalide **274** from amide **273**, which is then ring opened to the corresponding cyanohydrin and cyclised to give 3-cyanobenzofuranone **275**. The functionalised hydroxyphthalide **274** can also be generated by a Diels–Alder reaction to generate the bridged intermediate **276**.[69] Phenylsulphonylphthalide **277** is formed[71,72] from hydroxyphthalide **274**, oxidation of the sulphide with *m*-chloroperbenzoic acid giving the desired sulphone.



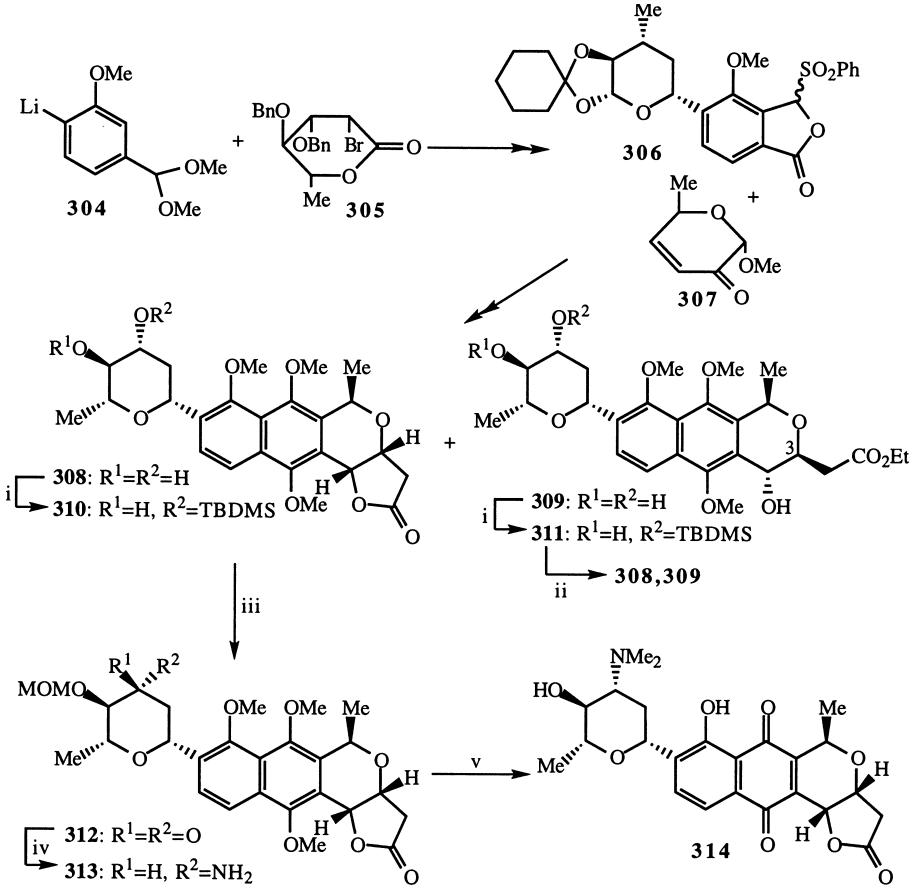
Scheme 53.

Phthalide annulation, which involves the reaction of phthalide anions and an appropriate Michael acceptor, has been employed as a convergent method for the construction of functionalised 1,4-dihydroxynaphthalene derivatives leading to a wide range of naphthoquinone and anthracycline antibiotics.

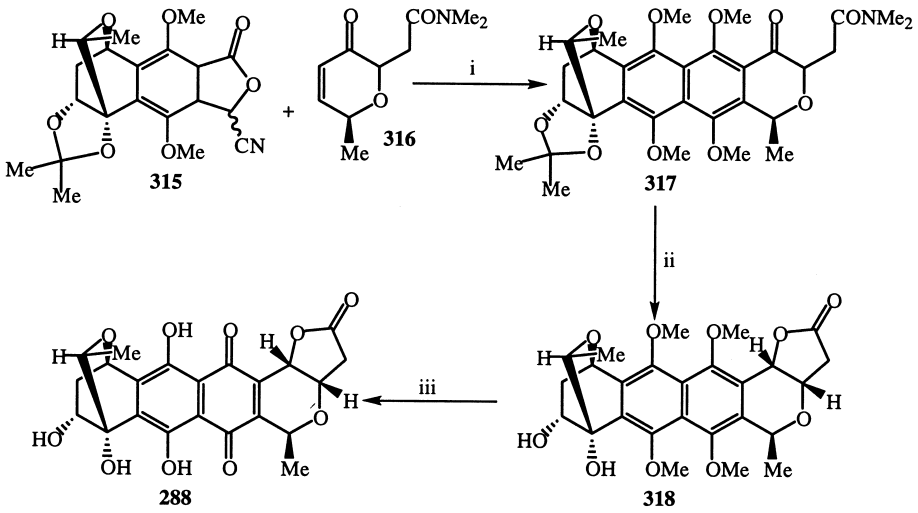
In its simplest form, this phthalide annulation sequence[73] produced the starting material, hydroquinone **181**, for the synthesis of racemic nanaomycin A **18**[33,51] described earlier (Scheme 31). Addition of methyl vinyl ketone **279** (Scheme 49) to phenylsulphanylphthalide anion **278** gives an intermediate bridged structure **280**, which is transformed to naphthydroquinone **181** via concomitant cleavage of the γ-lactone and loss of thiophenolate followed by tautomerism. Oxidation of **181** gives acetyl quinone **281**.

2.5.1. Use of Michael acceptor 4-(5-alkoxy-2-furyl)-3-buten-2-ones. Reaction of lithiated 3-cyanophthalides **282** with furyl-3-buten-2-one **283** and subsequent *O*-methylation of the resulting hydroquinones (Scheme 50) gave 2-acetyl-3-furylnaphthalenes **284**.[67] Reduction and deprotection/cyclisation of these compounds gave, for non-substituted naphthalenes **284a**,**b**, a mixture of *cis*- and *trans*- pyran-γ-lactones (*trans* favoured) and for substituted naphthalenes **284d**,**e**, only the *trans* epimer was produced.[74,75]

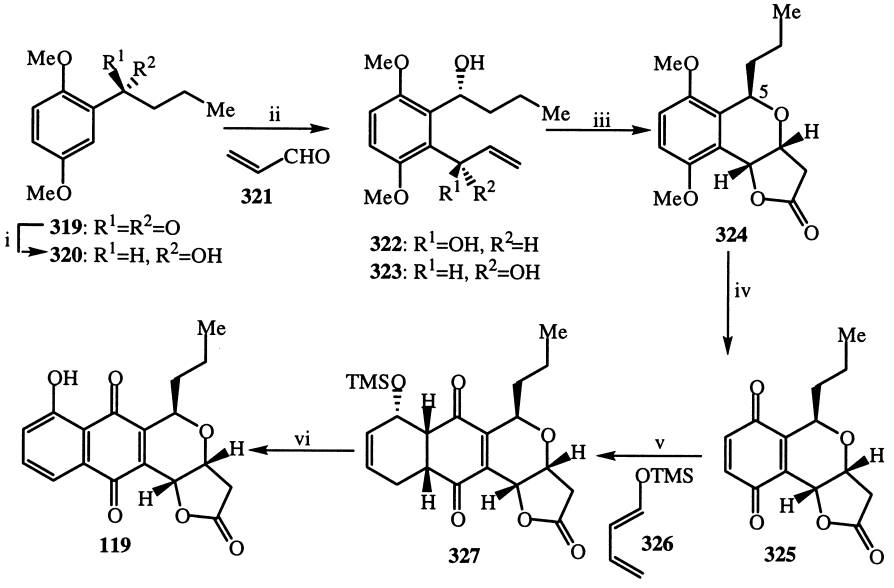
In the total synthesis of (±)-granaticin **288**[76] this same methodology was used to join the highly functionalised phthalide **285** (Scheme 51), that possesses the oxabicyclo system, and furylbuten-2-one **283a**, giving the *tert*-butoxyfuran precursor **286** for the required lactone ring. After methylation, the same series of reactions[75] used to form pyran-γ-lactones (Scheme 50) gave (±)-granaticin **288**



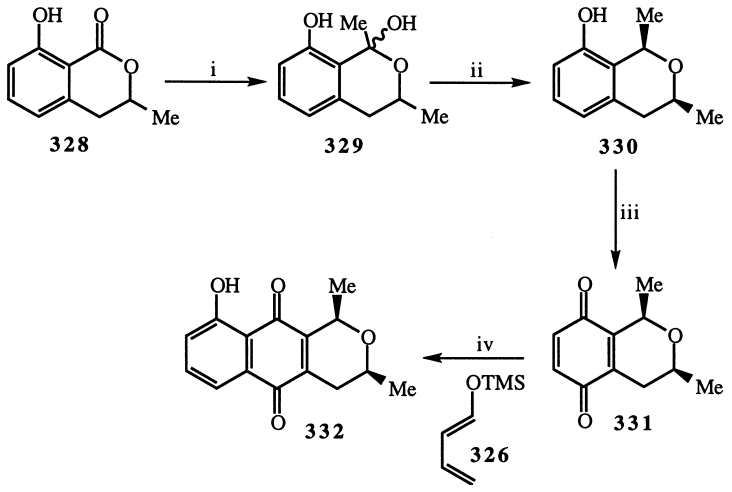
Scheme 54. Reagents and conditions: (i) TBDMSCl, imid, DMF; (ii) TsOH, PhMe, 70°C; (iii) a: MOMCl, Pr^i_2 NEt; b: Bu_4NF, THF; c: PCC, 3A, CH_2Cl_2, RT; (iv) a: $NH_2OH{\cdot}HCl$, Py; b: H_2, Raney Ni, EtOH; (v) a: 37% aq. HCHO, $NaBH_3CN$, AcOH, MeCN; b: CAN, H_2O, MeCN; c: $AlCl_3$, CH_2Cl_2.



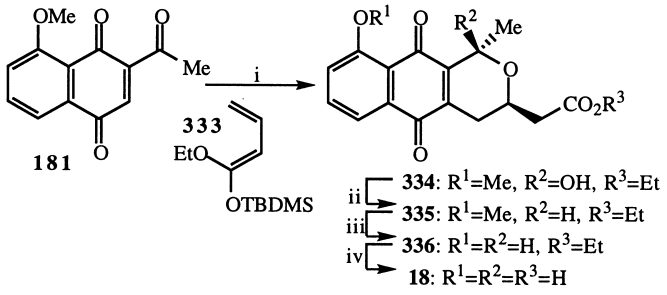
Scheme 55. Reagents and conditions: (i) $MeSOCH_2Li$, Me_2SO_4; (ii) $LiBBu^s_3H$ (2 equiv.), THF, −78°C, then Me_3SiCl (6 equiv.), THF, RT; (iii) a: $CH_2C(OMe)Me$, CAN; b: $AlCl_3$–Et_2S.



Scheme 56. Reagents and conditions: (i) THF, −25°C, (+)-Ipc_2BCl; (ii) Et_2O, Bu^nLi (2 equiv.), 0°C to RT, then −78°C, **321**; (iii) $Pd(OAc)_2$, CO, THF; (iv) AgO, THF, 6 M HNO_3, RT; (v) CH_2Cl_2, −78°C; (vi) Me_2CO, Jones reagent, 0°C.



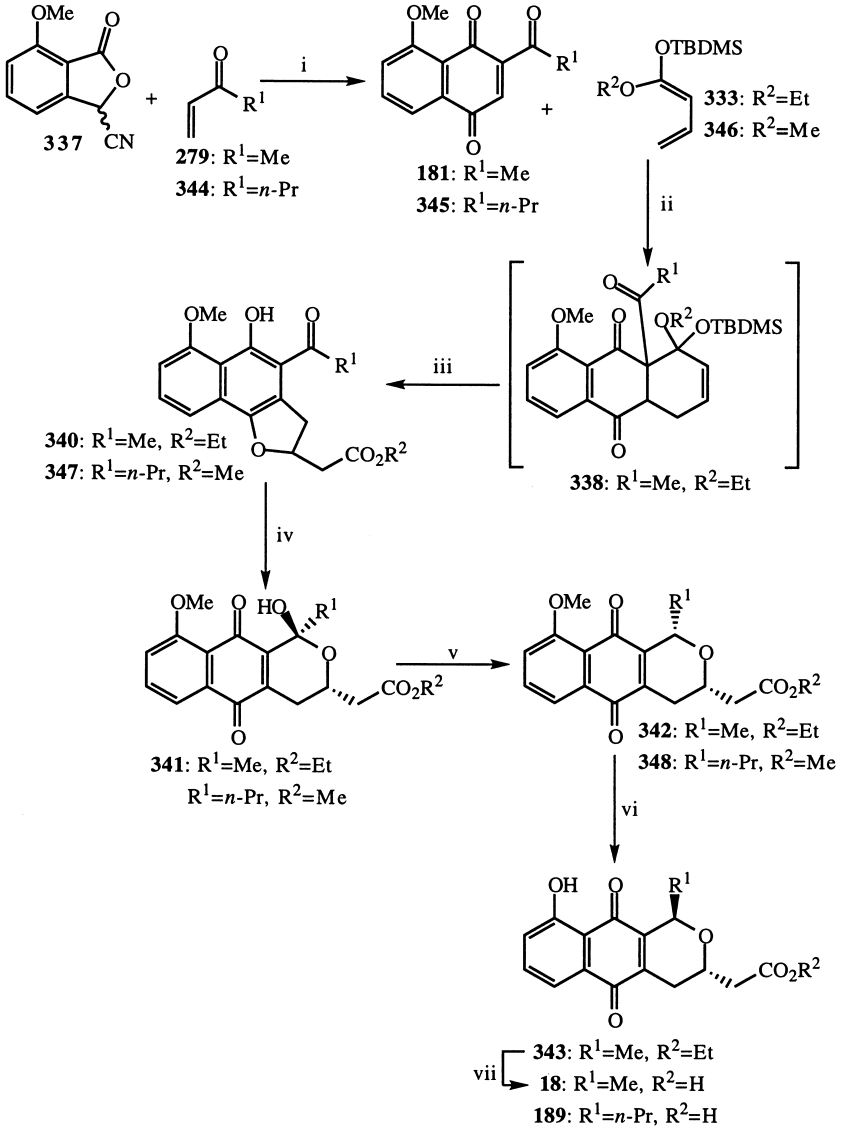
Scheme 57. Reagents and conditions: (i) Et_2O, −78°C, MeLi; (ii) CH_2Cl_2, −78°C, CF_3CO_2H, Et_3SiH, 0°C; (iii) Fremys salt; (iv) **326** then Et_3N.



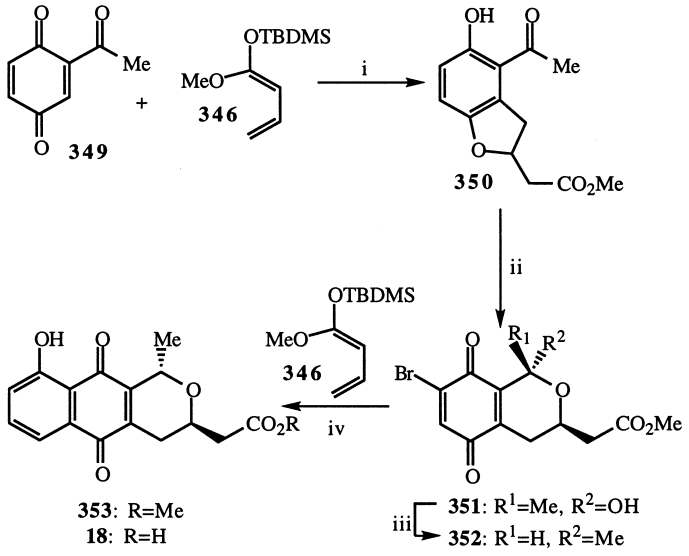
Scheme 58. Reagents and conditions: (i) a: F^-; b: aq. CAN, MeCN, RT; (ii) CH_2Cl_2, −78°C, CF_3CO_2H, Et_3SiH, 0°C; (iii) BBr_3, CH_2Cl_2, −78°C; (iv) MeOH, KOH.

as the major product. In the final stages, the tetramethoxynaphthalene moiety of compound **287** was oxidised by ceric ammonium nitrate to two naphthoquinones, and these were both demethylated using $AlCl_3$–Et_2S to give (±)-granaticin **288** (due to naphthazarin tautomerism).

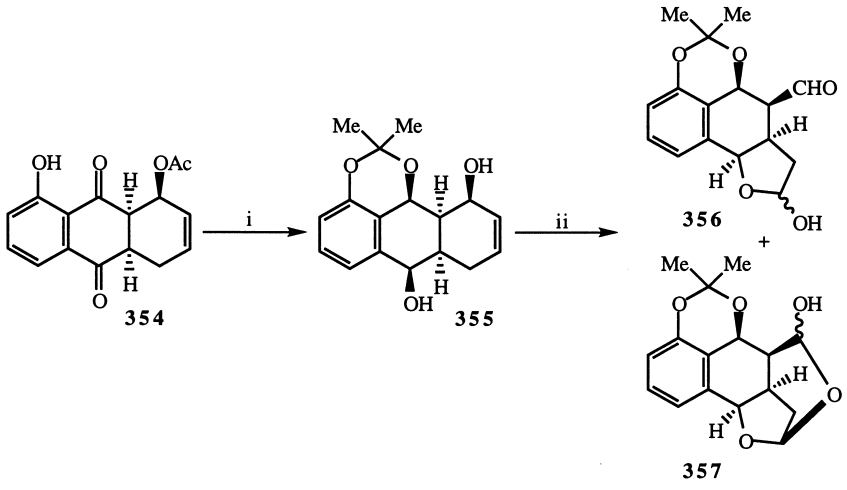
2.5.2. Use of a carbohydrate-based Michael acceptor. In the following pyranonaphthoquinone antibiotic syntheses, a Michael acceptor derived from a naturally occurring carbohydrate is used in the phthalide annulation step. The γ-lactone ring is formed via cyclisation of a hydroxy ester or hydroxy acid.



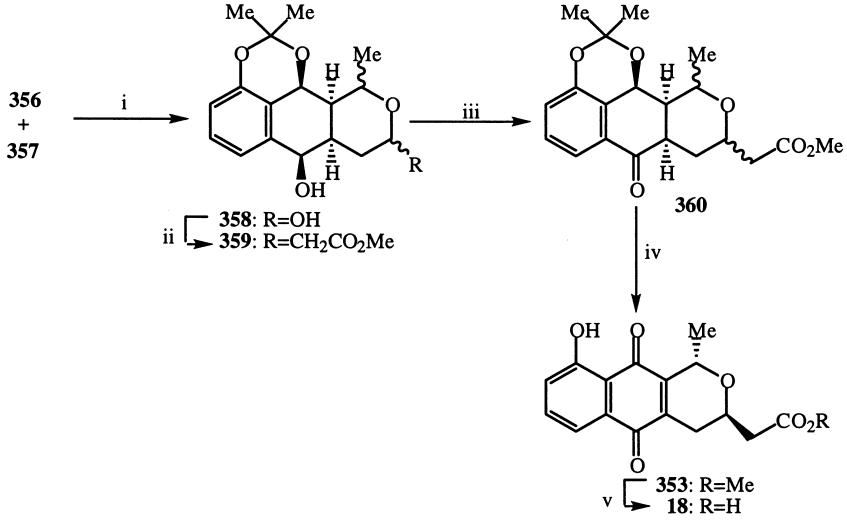
Scheme 59. Reagents and conditions: (i) a: DMSO, RT, KO^{t}Bu (3 equiv.); b: aq. CAN, MeCN, RT; (ii) CH_2Cl_2, −78°C, diene, RT; (iii) 0°C, MeCN, PO_4^{3-} buffer, Bu_4NF, RT; (iv) aq. CAN, MeCN, RT; (v) CH_2Cl_2, −78°C, CF_3CO_2H, Et_3SiH, RT; (vi) CH_2Cl_2, −78°C, BBr_3; (vii) NaOH, MeOH, RT.



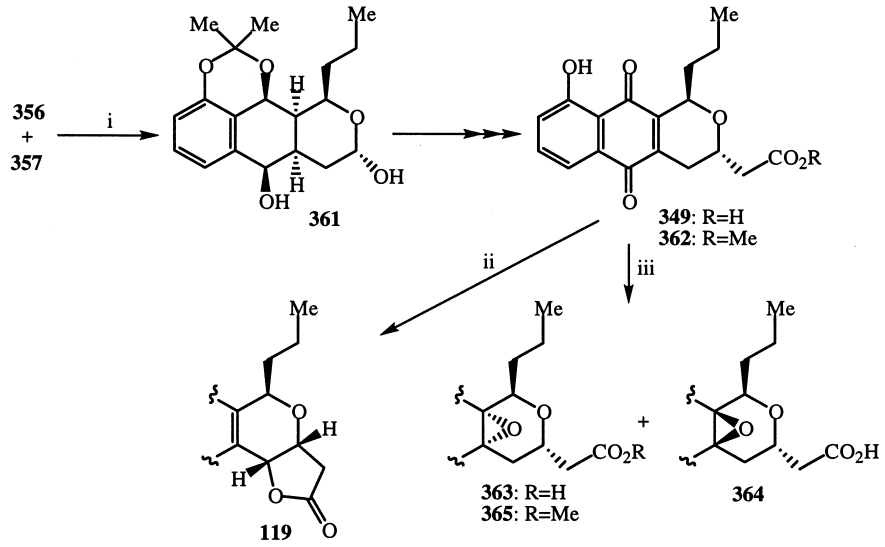
Scheme 60. Reagents and conditions: (i) CH_2Cl_2, −78°C, RT, 0°C, MeCN, PO_4^{3-} buffer, Bu_4NF, RT; (ii) a: CH_2Cl_2, RT, $TiCl_4$, Br_2 (2 equiv.); (iii) CH_2Cl_2, −78°C, Et_3SIH, $BF_3{\cdot}Et_2O$, RT; (iv) CH_2Cl_2, −78°C, RT, Et_3N, then MeCN, 5% HF, RT.



Scheme 61. Reagents and conditions: (i) a: $NaBH_4$, THF, 5°C; b: $Me_2C(OMe)_2$, $BF_3{\cdot}Et_2O$; c: $LiAlH_4$, Et_2O; (ii) a: OsO_4–$NaIO_4$, $^tBuOH/H_2O$; b: NaOAc, DABCO.



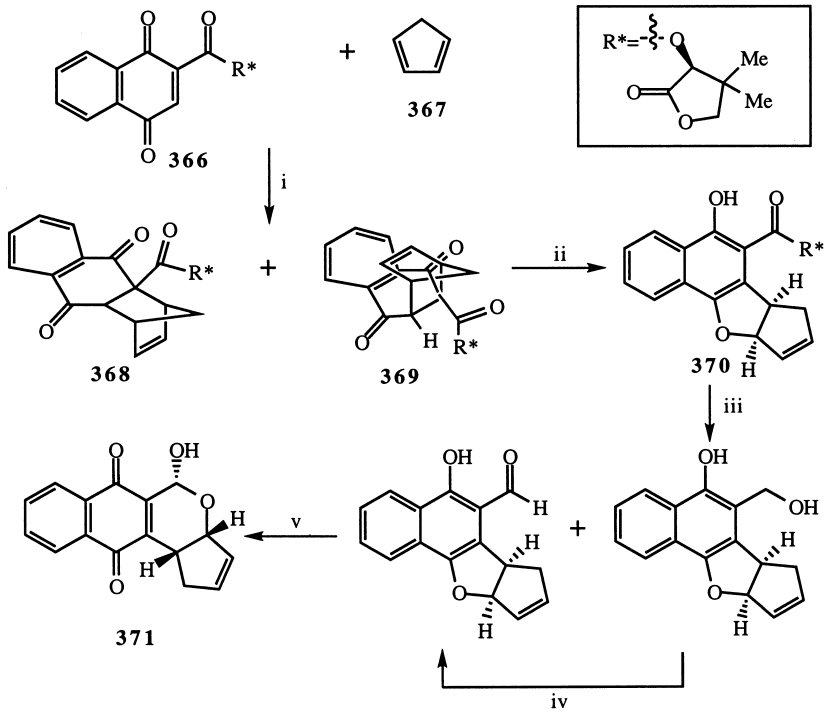
Scheme 62. Reagents and conditions: (i) MeMgI, Et_2O; (ii) $(EtO)_2P(O)CH_2CO_2Me$, Bu^nLi, THF; (iii) PCC, CH_2Cl_2, RT; (iv) DDQ, dioxane, TsOH, reflux; (v) KOH, $EtOH/H_2O$, RT.



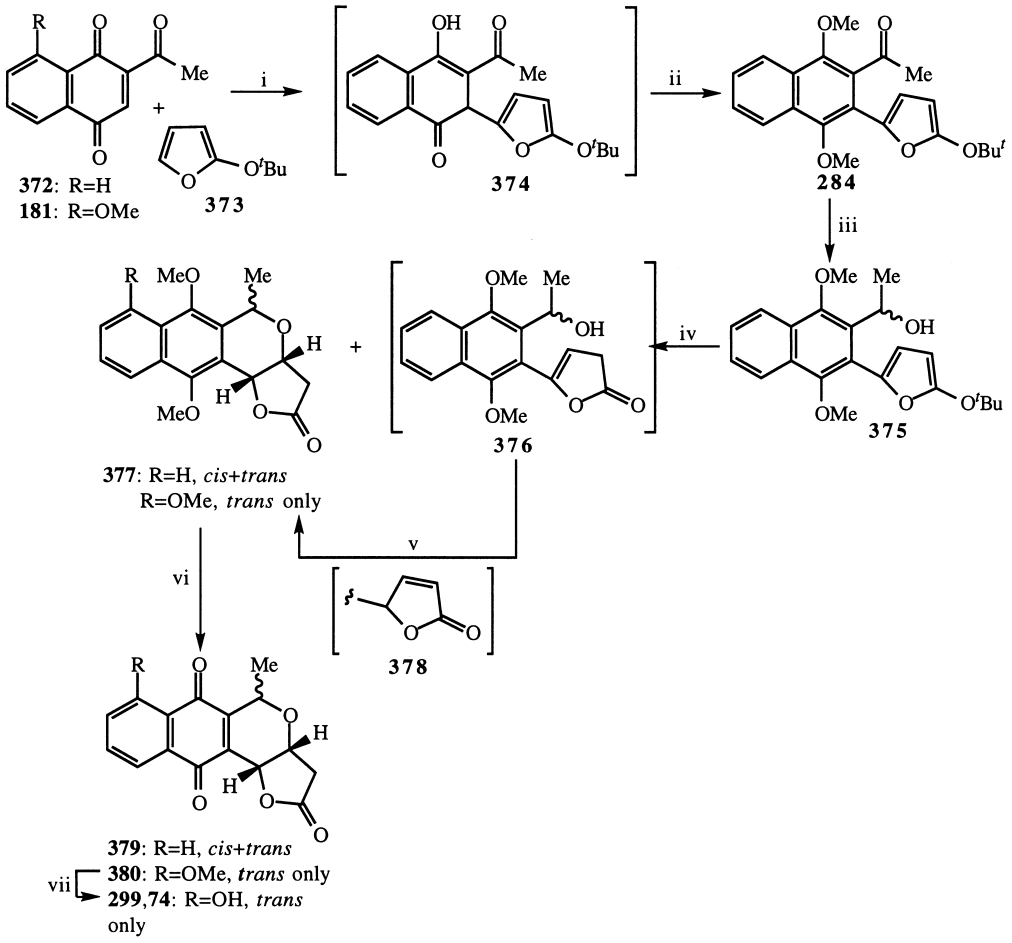
Scheme 63. Reagents and conditions: (i) $Pr^{n}MgBr$, Et_2O; (ii) $CHCl_3$, air, reflux; (iii) $^{t}BuO_2H$, Triton B, dioxane/EtOH, RT.

Enantiospecific total syntheses of nanaomycin D **288** and A **18** and their enantiomers kalafungin **299** and 4-deoxykalafunginic acid **300** were completed[77,78] using a common optically active intermediate **294**. Enone **290**, from which the stereochemistry of the products resulted, was derived from L-rhamnose **289** (Scheme 52) and condensed with phthalide **291** to give pyranonaphthalene **292** after methylation. Reduction of the ketone furnished alcohol **293** exclusively, acid hydrolysis of the hemiacetal giving the key compound **294**. Wittig reaction of **294** with ethoxycarbonylmethylenetriphenylphosphorane **295** gave ester **296** and lactone **297**, both resulting from intramolecular Michael cyclisation of an intermediate α,β-unsaturated ester and lactonisation to give lactone **297**. Oxidation and demethylation of lactone **297** gave nanaomycin D **288**, and hydrogenolysis afforded nanaomycin A **18**. Similar treatment of ester **296** gave quinone **298**, which was epimerised at C-1 and C-4 to the preferred 1,3-*trans* configuration and lactonised to kalafungin **299**. Hydrogenolysis of **299** provided 4-deoxykalafunginic acid **300**.

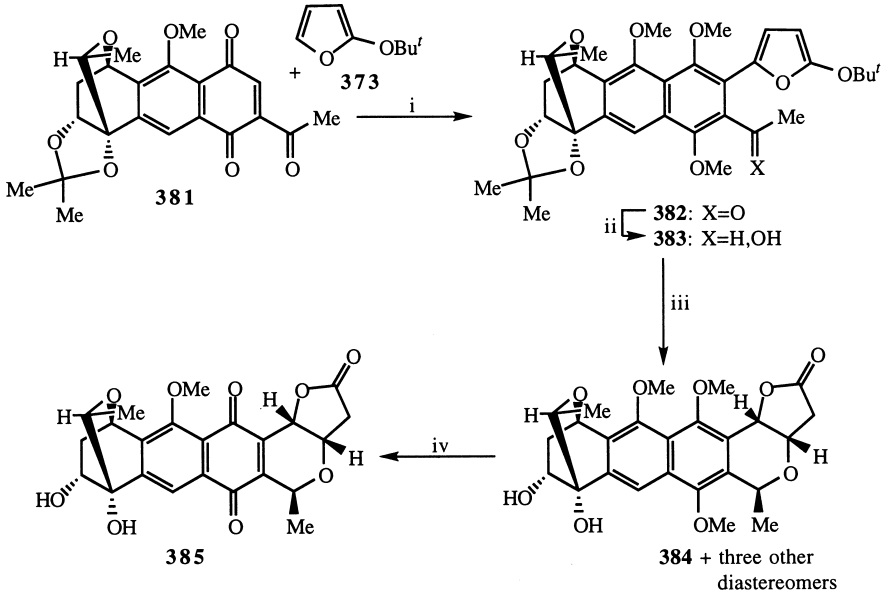
Using the same methodology, isokalafungin **302** and isonanaomycin D **303** were synthesised from the isomeric phthalide **301** and enone **290** (Scheme 53).[65]



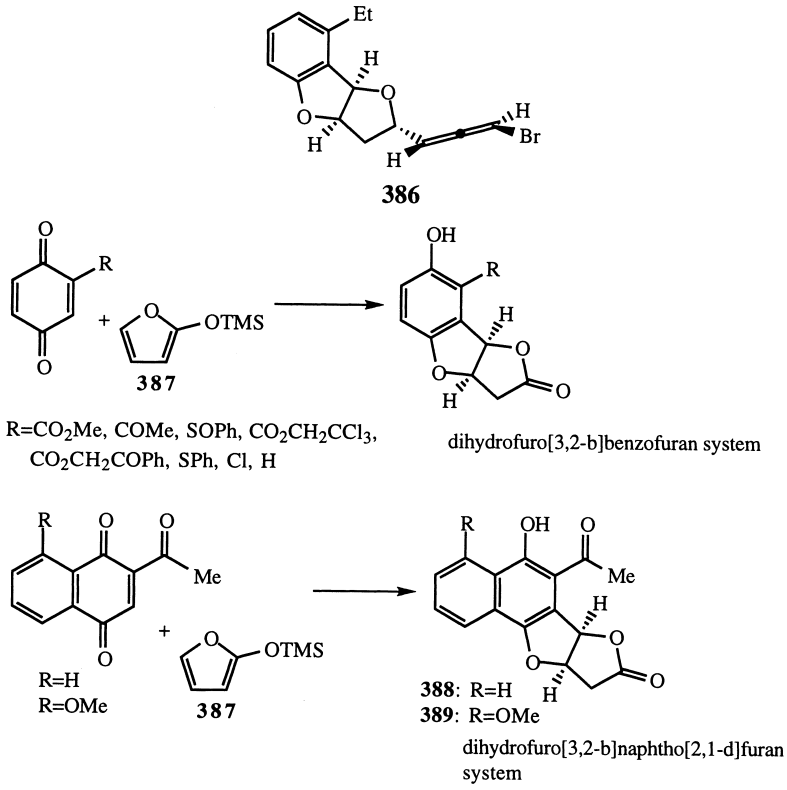
Scheme 64. Reagents and conditions: (i) $ZnCl_2$, CH_2Cl_2, −78°C; (ii) $SnCl_4$, CH_2Cl_2; (iii) $LiBH_4$; (iv) MnO_2, CH_2Cl_2; (v) AgO, HNO_3.



Scheme 65. Reagents and conditions: (i) $PhCH_3$, −78°C to RT; (ii) Me_2SO_4, K_2CO_3, Me_2CO, reflux; (iii) $LiAlH_4$, Et_2O, −10°C, N_2; (iv) CF_3CO_2H, CH_2Cl_2, 0°C to RT, N_2; (v) DBU or DBN, C_6H_6, RT; (vi) AgO, THF, 6 N HNO_3; (vii) BCl_3, CH_2Cl_2, −78°C.



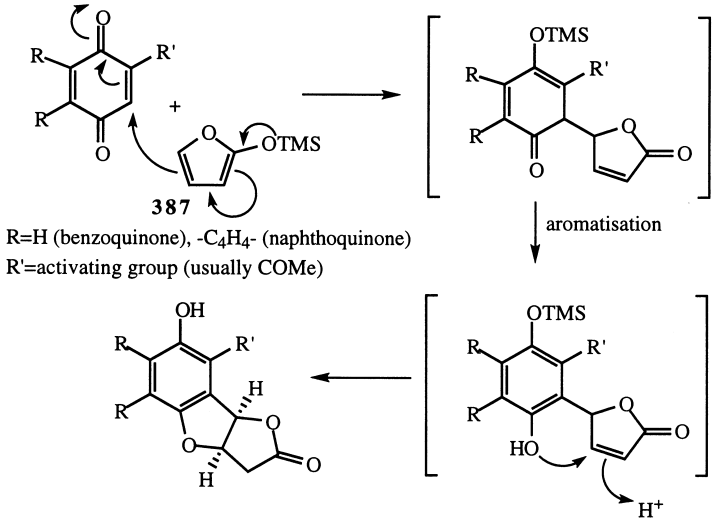
Scheme 66. Reagents and conditions: (i) a: Me_2CO, −70 to −10°C; b: Me_2SO_4, K_2CO_3, reflux; (ii) $LiAlH_4$, Et_2O, −50 to −30°C; (iii) a: TsOH, MeCN, RT, b: DBU, $PhCH_3/CH_2Cl_2$, −10°C; (iv) a: protection; b: aq. CAN, MeCN, RT; c: TsOH, MeCN, RT.



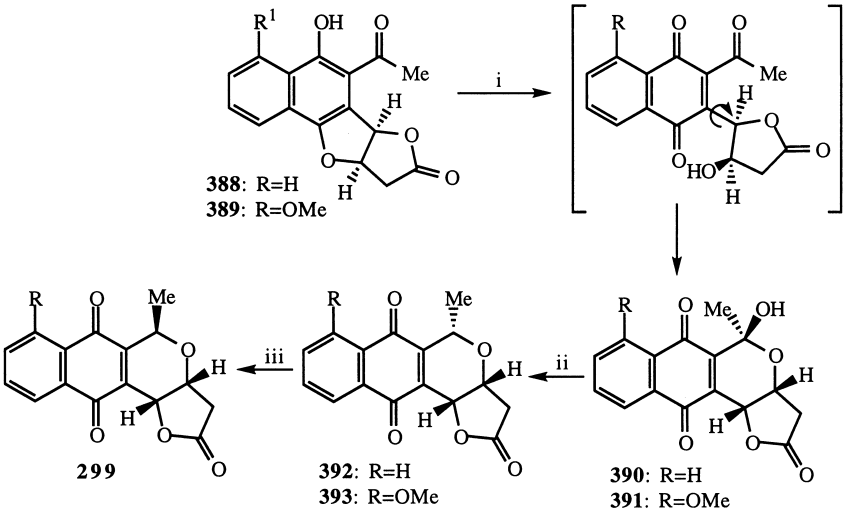
Scheme 67. Reagents and conditions: MeCN, 0°C, N_2, RT, MeOH.

Having been used by Tatsuta et al.[77,78] for the enantiospecific synthesis of nanaomycin D **288** and kalafungin **299** (Schemes 52 and 53, vide supra), this enone/phthalide strategy, was later extended to the synthesis of medermycin **314**.[79] The dimethylamino group on the C-glycoside fragment was introduced at a late stage in the synthesis.

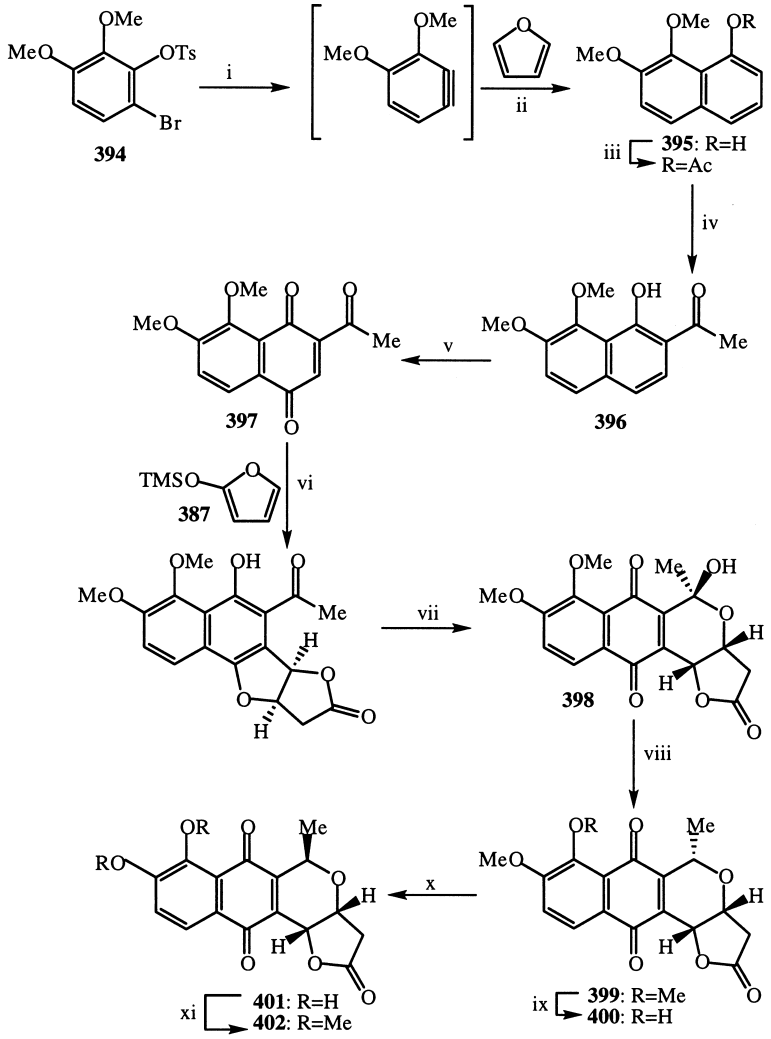
Lactone **305** (Scheme 54) was derived from the D-isomer of **289** (Scheme 52) by a three step sequence and coupled with lithiated acetal **304**, providing functionalised sulphonyl phthalide **306**.[77,78] Coupling of sulphonyl phthalide **306** and enone **307** (the enantiomer of enone **290**), followed by a standard sequence of reactions, afforded lactone **308** and ester **309**. The 3-hydroxyl groups were selectively protected as *tert*-butyldimethylsilyl ethers and undesired ester **311** was recycled to lactone **308** and ester **309** through *retro* Michael and Michael cyclisations at C-3. MOM protection, desilylation and oxidation of alcohol **310** to ketone **312** then allowed the amino group to be elaborated. Addition of hydroxylamine hydrochloride afforded the corresponding oxime which was reduced to amine **313**. Dimethylation of the amine, quinone formation and



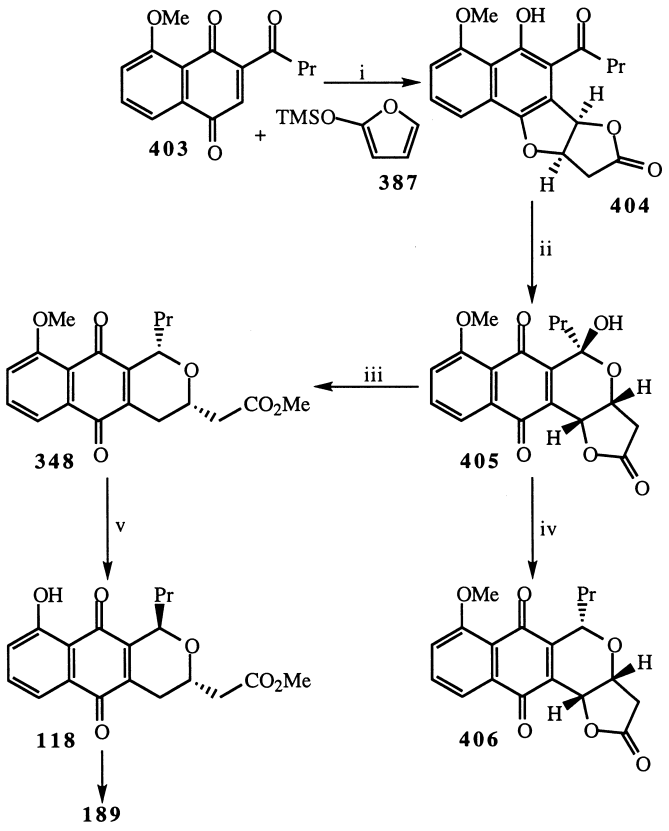
Scheme 68.



Scheme 69. Reagents and conditions: (i) aq. CAN, MeCN, RT; (ii) CH_2Cl_2, −78°C, N_2, TFA, Et_3SiH, RT; (iii) BBr_3 (excess), CH_2Cl_2, −78°C to RT.



Scheme 70. Reagents and conditions: (i) Bu^nLi, THF, −78°C; (ii) conc. HCl, MeOH, reflux; (iii) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2; (iv) $BF_3{\cdot}Et_2O$, 95°C; (v) AgO, dioxane, conc. HNO_3, RT; (vi) MeCN, 0°C, N_2; (vii) aq. CAN (2 equiv.), MeCN, RT; (viii) Et_3SiH, TFA, RT; (ix) BBr_3 (2 equiv.), CH_2Cl_2, −78°C to RT; (x) BBr_3 (excess), CH_2Cl_2, −78°C to RT; (xi) MeI, AgO, CH_2Cl_2.



Scheme 71. Reagents and conditions: (i) MeCN, 0°C, N_2, MeOH, RT; (ii) aq. CAN (2 equiv.), MeCN, RT; (iii) Et_3SiH, TFA, −78°C to RT; (iv) Pd/C, EtOAc, H_2, RT; (v) BBr_3 (10 equiv.), CH_2Cl_2, −78 to 0°C.

deprotection of the methoxy group then furnished medermycin **314**.

This methodology was further extended to the synthesis of unnatural (−)-medermycin[80] starting from L-rhamnose **289**.

Following the synthesis of (±)-granaticin **288**, Yoshii et al.[81] completed a stereocontrolled synthesis of naturally occurring granaticin **288** (Scheme 55). The synthesis employed a pentacyclic phthalide **315** (regioisomeric with **652**) and dihydropyranone **316**, having the correct absolute stereochemistry. Coupling of the two chiral fragments and methylation gave pyran **317**. Reduction of the ketone carbonyl group resulted in a *cis*-γ-hydroxyamide which upon lactonisation afforded the required γ-lactone **318**. Finally, oxidation and demethylation produced granaticin **288**.

2.6. Diels–Alder methodology

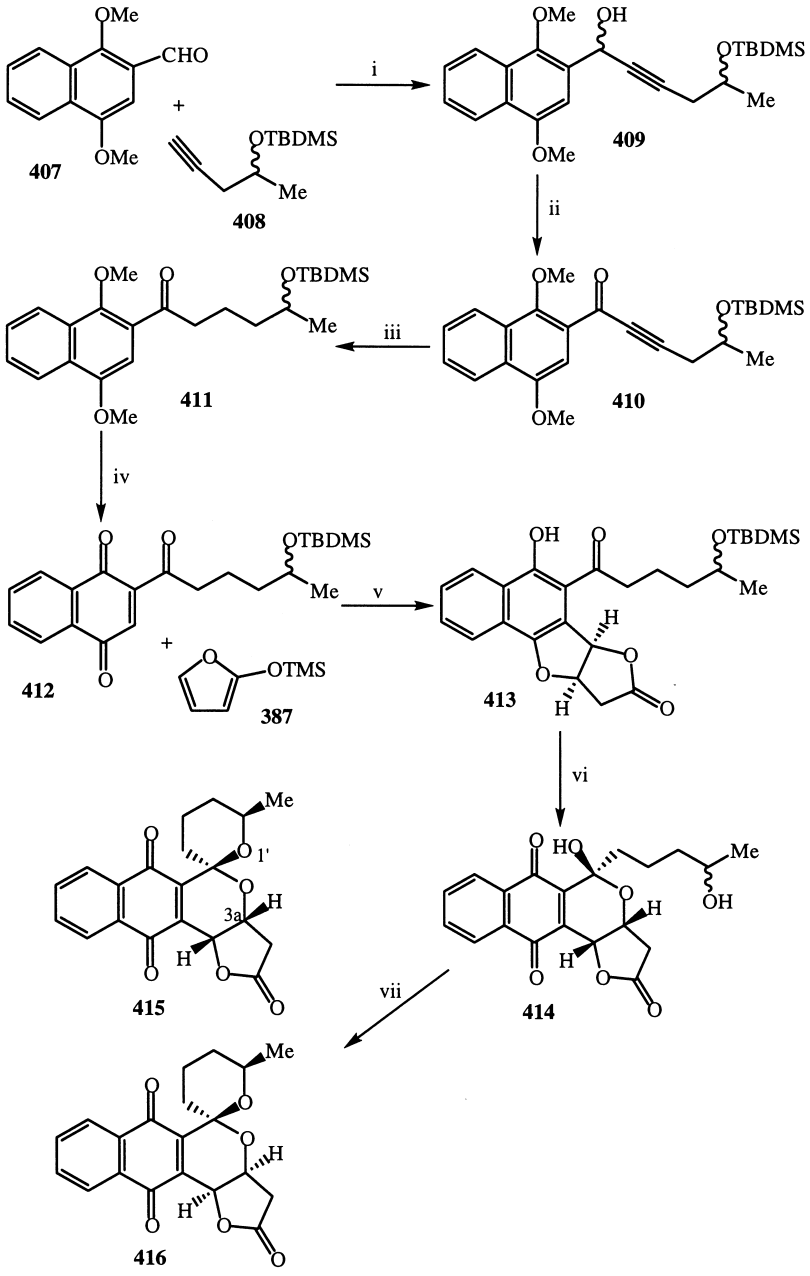
The Diels–Alder reaction has also been commonly used for the synthesis of pyranonaphthoquinone antibiotics. In each case, appropriately functionalised dienes and dienophiles have been utilised to furnish the required oxygenation pattern of the pyranonaphthoquinone skeleton.

A synthesis[40] of frenolicin B **119** (Scheme 56) began with the enantioselective reduction of ketone **319**. Metalation of alcohol **320** to give the dianion followed by reaction with acrolein **321** gave diols **322**, **323** in a 1:1.5 ratio, respectively. With the two side chains in place, palladium catalysed carbonylation and cyclisation of diol **323** produced lactone **324**, the isomeric diol giving a mixture of lactone **324** and its C-5 epimer. Oxidation of lactone **324** using silver(II) oxide provided benzoquinone **325**. Treatment of benzoquinone **325** with 1-((trimethylsilyl)-oxy)butadiene **326** then gave Diels–Alder adduct **327** which was immediately treated with Jones reagent to give frenolicin B **119**. No isomeric products were obtained from the cycloaddition, therefore the remote substituents on the dienophile conferred excellent regioselectivity on the reaction.

A simpler example was also provided by Kraus et al.[82] Lactol **329**, prepared by addition of methyl lithium to lactone **328**, underwent reduction to the *cis*-ether **330** (Scheme 57). Formation of quinone **331** using Fremys salt followed by cycloaddition to diene **326** gave racemic demethoxyeleutherin **332**.

In the synthesis of nanaomycin A **18**, a tandem Diels–Alder *retro* Claisen (DARC) reaction (Scheme 58) of naphthoquinone **181**[74] and ketene acetal **333**, gave hemiacetal **334** after oxidation. Reduction of hemiacetal **334** furnished cyclic ether **335**, which upon demethylation and isomerisation using boron tribromide gave the ethyl ester of nanaomycin A **336**. Finally, saponification produced (±)-nanaomycin A **18**.[83]

An alternative route[84] to (±)-nanaomycin A **18** used cyanophthalide **337** and methyl vinyl ketone **279**. Cyanophthalide **337** underwent Michael addition to methyl vinyl ketone **279** followed by intramolecular Claisen reaction



Scheme 72. Reagents and conditions: (i) **408**, THF, −78°C, Bu^{n}Li, then **407**, −78 to 60°C; (ii) excess MnO_2, CH_2Cl_2, RT; (iii) H_2, 5% Pd/C, EtOAc, RT; (iv) aq. CAN (1.9 equiv.), MeCN, RT; (v) MeCN, 0°C, N_2, RT, MeOH; (vi) aq. CAN (8 equiv.), MeCN, RT; (vii) CH_2Cl_2, CSA, reflux.

to give, after oxidation, quinone **181** (Scheme 59). Diels–Alder addition of diene **333** to quinone **181** gave intermediate **338**, which upon treatment in situ with fluoride ion underwent a *retro* Claisen reaction (Eq. (2)) to intermediate **339**, which immediately cyclised to furonaphthofuran **340**. Oxidation produced the quinone with simultaneous formation of a pyran ring. Reduction of the hemiacetal **341** to an ether afforded the *cis*-pyran **342** exclusively. Demethylation

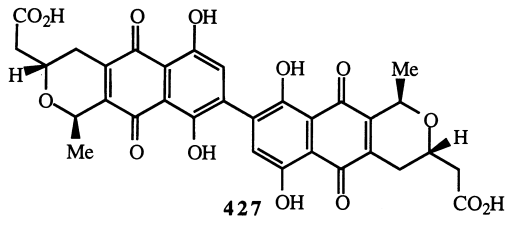


Figure 5.

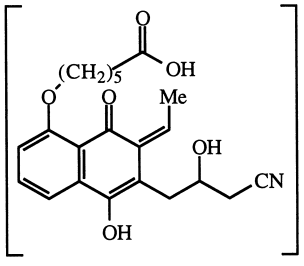
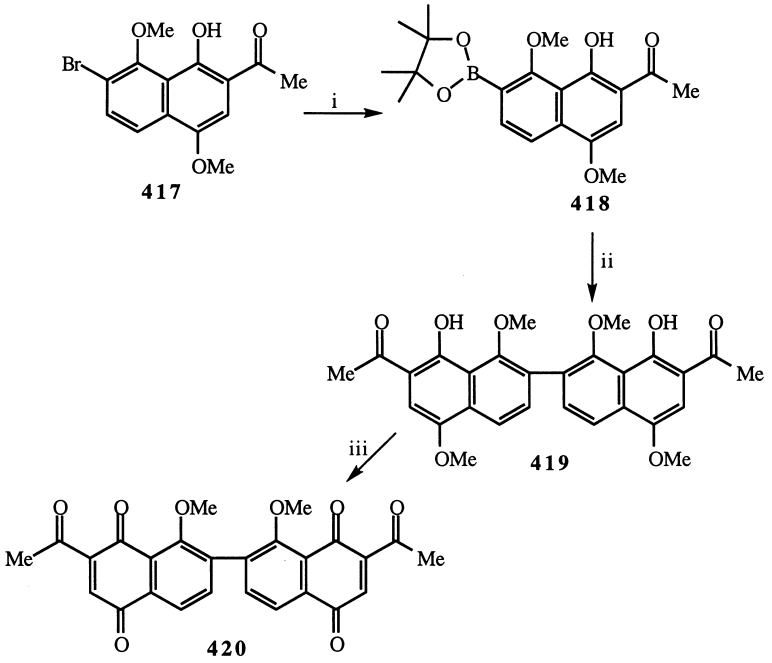
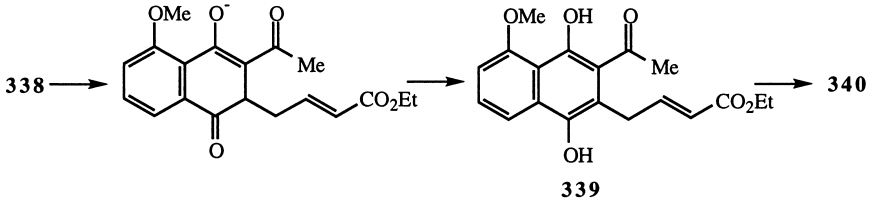


Figure 6.



Scheme 73. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, 120°C; (ii) $PdCl_2(dppf)$, CsF, diboron pinacolate, THF, reflux; (iii) CAN (4 equiv.), H_2O, CH_3CN.

and epimerisation to the *trans*-pyran **343** was then effected using boron tribromide giving (±)-nanaomycin A **18** after saponification. The synthesis of racemic deoxyfrenolicin **189** involved the same series of reactions detailed above, starting with propyl vinyl ketone **344**. Oxidation to quinone **345**, cycloaddition to diene **346** and *retro* Claisen reaction gave **347**, which was oxidised and reductively deoxygenated to pyran **348**. Deprotection/epimerisation and hydrolysis then afforded (±)-deoxyfrenolicin **189**.



(2)

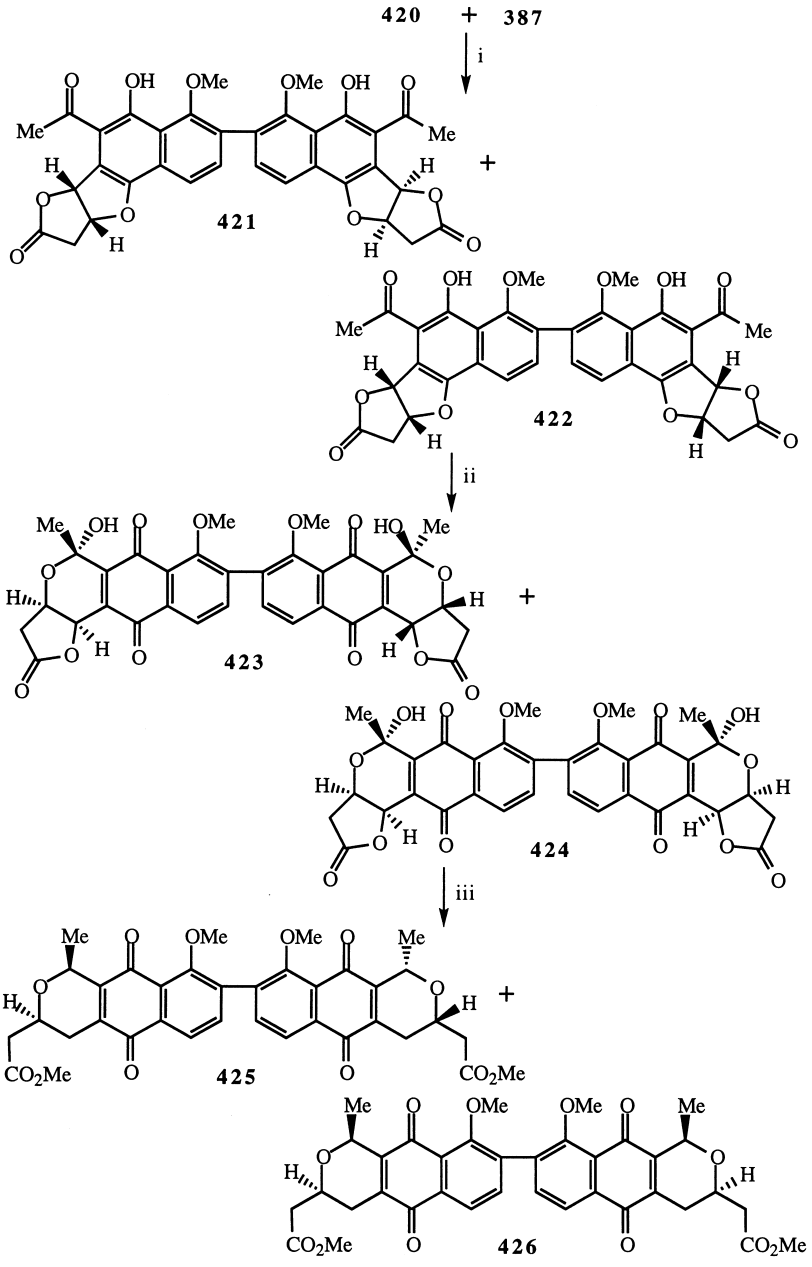
The preparation of quinone **353** as an intermediate for the synthesis of pyranonaphthoquinones, was also achieved by a Diels–Alder addition (Scheme 60).[85] Ester **350** was available by a one pot DARC reaction from quinone **349** and ketene acetal **346**. Bromination *ortho* to the phenol and oxidative rearrangement gave alcohol **351** which, after reductive removal of the hydroxyl group afforded quinone **352**. Further reaction with ketene acetal **346** formed the third ring of pyranonaphthoquinone **353**, which upon hydrolysis gave (±)-nanaomycin A **18**.

In the first synthesis of frenolicin **60**,[86] the Diels–Alder adduct **354** of juglone and 1-acetoxybutadiene was selectively reduced, protected and further reduced to diol **355** (Scheme 61). Lemieux–Johns oxidative cleavage of the double bond, followed by treatment with base, provided a mixture of aldehyde **356** and its hemiacetal **357**. From this mixture both nanaomycin A **18** and frenolicin **363** were synthesised as described below.

Nanaomycin A 18: Addition of methylmagnesium iodide to aldehyde **356** and its hemiacetal **357** gave alkylated product **358** as a diastereomeric mixture (Scheme 62). Wittig–Horner reaction of the alkylated product **358** produced ester **359** with the required carboxymethyl side chain, which was oxidised to give ketone **360**. DDQ oxidation and equilibration to the *trans*-isomer using toluenesulfonic acid gave pyranonaphthoquinone **353** which, after hydrolysis, afforded (±)-nanaomycin A **18**.

Frenolicin 363: In a similar manner the addition of *n*-propylmagnesium bromide to aldehyde **356** and its hemiacetal **357** gave hemiacetal **361** (Scheme 63). Treatment of hemiacetal **361** using a similar set of reactions as described above for hemiacetal **358** afforded (±)-deoxyfrenolicin **189**. (±)-Frenolicin B **119** was then formed by refluxing carboxylic acid **349** in chloroform whilst (±)-frenolicin **363** and (±)-*epi*-frenolicin **364** were obtained by epoxidation of carboxylic acid **349**. Epoxidation of ester **362** only produced (±)-*epi*-frenolicin methyl ester **365** due to the pyran ring adopting a conformation wherein the carboxymethyl side chain hindered approach to one face.

Recent studies by Brimble et al.[87] on an asymmetric variant of the Diels–Alder reaction investigated the potential of forming pyranonaphthoquinone antibiotics enantioselectively. The use of chiral auxiliaries (e.g. pantolactone) at C-2 of 1,4-naphthoquinone **366** resulted in high levels of asymmetric induction in Diels–Alder cycloadditions with



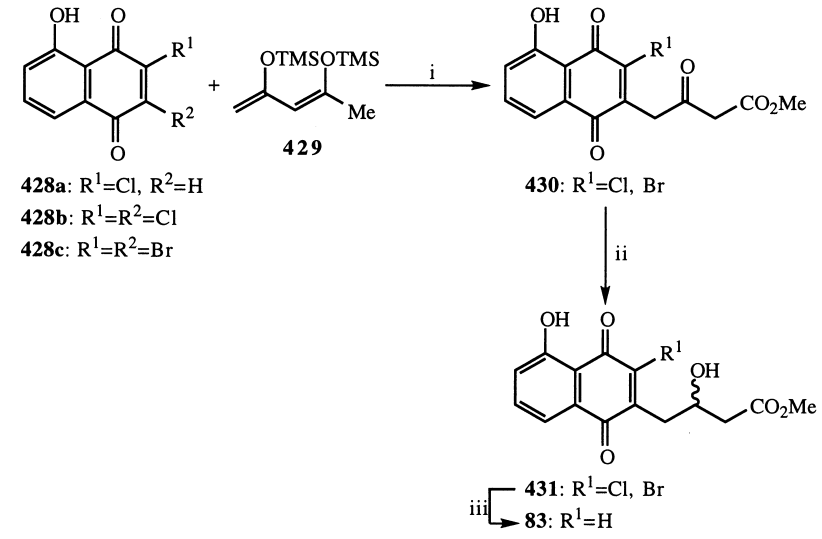
Scheme 74. Reagents and conditions: (i) a: CH_3CN, 0°C; b: silica gel, EtOAc–hexane; (ii) CAN, H_2O, CH_3CN, 0°C; (iii) a: 10% Pd/C, H_2, EtOAc; b: excess CH_2N_2, Et_2O; (iv) $CHCl_3$, H^+ trace, RT.

cyclopentadiene (Scheme 64). Diels–Alder adducts **368** and **369** were formed in a 1:45 ratio in this reaction. Fragmentation of adduct **369** resulted in furan **370** which after removal of the chiral auxiliary and oxidative rearrangement afforded a cyclopentannulated pyran **371** similar to that observed in naturally occurring pyranonaphthoquinone antibiotics.

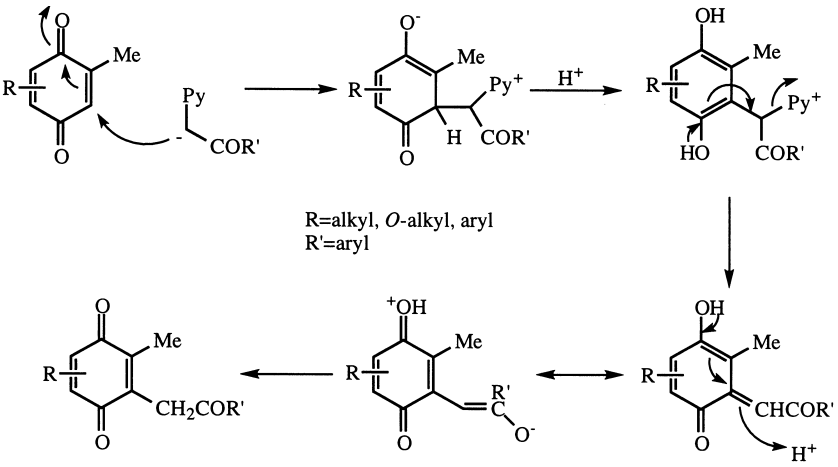
2.7. Conjugate addition to quinones

2.7.1. Addition of 2-*tert*-butoxyfuran. Methodology developed by Kraus et al.[88] used 2-*tert*-butoxyfuran **373** as a butenolide anion equivalent. Addition of 2-*tert*-butoxyfuran **373** to 2-acetyl-1,4-naphthoquinone **372** (Scheme 65) gave Michael adduct **374** which was methylated in situ to afford furan **284**.[89] Hydride reduction of furan **284** to alcohol **375** and deprotection of the *tert*-butoxy group gave a mixture of β,γ-unsaturated butenolide **376** and cyclised product **377** (2.7:1 ratio). The uncyclised butenolide **376** was isomerised to the 'unmasked' α,β-butenolide **378** and cyclised in situ using DBU. Oxidative demethylation gave (±)-7-deoxykalafungin **379** as a mixture of epimers. No stereocontrol at C-1 was exercised in this approach, however, epimerisation to the natural configuration was achieved using a Lewis acid.

In a similar manner[74] naphthoquinone **181** was transformed into pyranonaphthoquinone **380** as a *single* isomer, deprotection of which using boron trichloride, gave a racemic mixture of kalafungin **299** and nanaomycin D **74**. The addition of 2-*tert*-butoxyfuran **373** to naphthoquinone **181** took 24 h whereas rapid reaction was observed for naphthoquinone **372**. The deprotection/cyclisation sequence



Scheme 75. Reagents and conditions: (i) $ZnBr_2$ (R^1=Cl, R^2=H only), −78°C; (ii) $NaBH_4$, THF, −78°C; (iii) $SnCl_2$, HCl/MeOH, air.



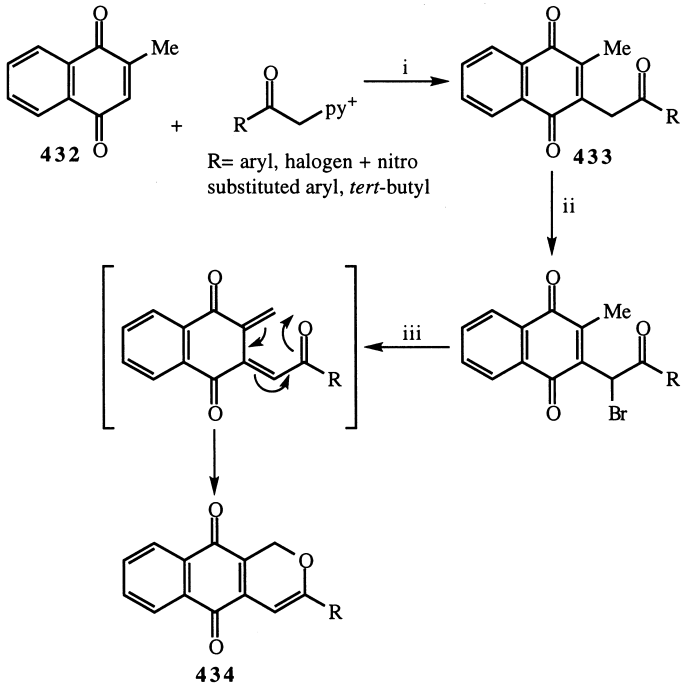
Scheme 76. Reagents and conditions: MeOH, Et_3N, RT, or CH_2Cl_2, K_2CO_3, 18-C-6.

was effected more easily for the methoxy analogue of furan **375**. The starting naphthoquinone **181** in this case was formed by a phthalide annulation reaction (Section 2.5). This sequence is a very direct route to the target compounds but has modest overall yield.

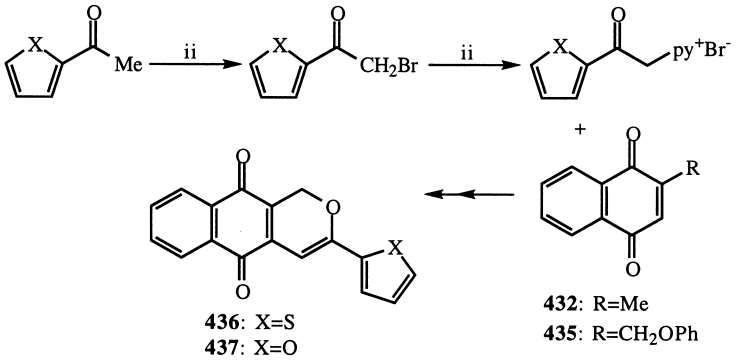
A close analogue of granaticin **74** was prepared[75] by addition of 2-*tert*-butoxyfuran **373** to advanced intermediate **381** (Scheme 66). The oxabicyclic ring system present in quinone **381** was assembled in a similar manner to that used for the synthesis of the simpler compound, sarubicin A **75**. Quinone **381** was generated from the corresponding dimethyl ether and was converted to ketone **382** after Michael addition of 2-*tert*-butoxyfuran **373** and subsequent methylation. Reduction of the acetyl group afforded a diastereomeric mixture of carbinols **383** which gave four diastereomeric pyranolactones (*trans*:*cis* 4:1) after a deprotection/cyclisation sequence. From this mixture, naphthopyran **384** was isolated and oxidised to pyrano-napthoquinone **385** after protection of the diol as an acetonide or carbonate. The oxabicyclic system could not withstand the *O*-demethylation conditions required, hence, (±)-granaticin **74** was not realised by this route.

2.7.2. Addition of 2-trimethylsilyloxyfuran. In synthetic studies by Brimble et al.[90,91] directed towards the fish anti-feedant panacene **386** the uncatalysed addition of 2-trimethylsilyloxyfuran **387** to C-2 activated quinones (Scheme 67) was examined. The work resulted in a facile entry to the *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-one and *cis*-6b,9a-dihydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one ring systems.

From the products isolated, it was envisaged that after initial 1,4-addition of 2-trimethylsilyloxyfuran **387** *ortho* to the activating group on the quinone ring, aromatisation, followed by a second 1,4-addition of the resulting phenoxy group onto the neighbouring butenolide moiety, had occurred, providing the desired heterocycle (Scheme 68). There were few examples of such furofuran ring systems occurring naturally, however it was found that a rearrangement could be effected to form the more common



Scheme 77. Reagents and conditions: (i) MeCN, Et_3N; (ii) CCl_4, Br_2, dark, RT; (iii) CH_2Cl_2, N_2, dark, Et_3N.



Scheme 78. Reagents and conditions: (i) Br_2; (ii) Et_2O, py, reflux.

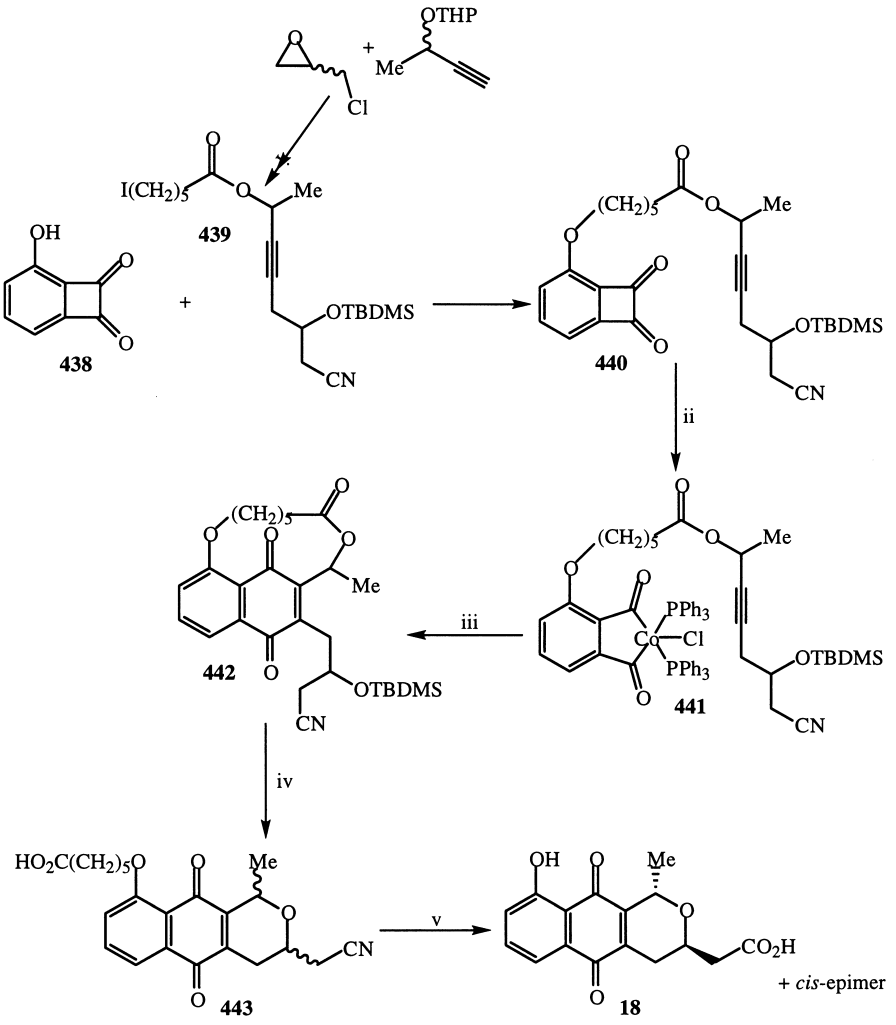
γ-pyranolactone, as found in the pyranonaphthoquinone family of antibiotics, and a synthesis of racemic kalafungin **299** was undertaken.[92,93] Thus, treatment of quinones **372**, **181** with 2-trimethylsilyloxyfuran **387** resulted in furonaphthofurans **388** and **389** which, upon addition of ceric ammonium nitrate (2 equiv.), afforded the desired pyranonaphthoquinones **390**, **391**, respectively (Scheme 69).

The lactols were reduced to ethers **392**, **393**, with a *cis*-relationship between the groups at C-5 and C-3a. Finally, treatment of ether **393** with an excess of boron tribromide resulted in demethylation with concomitant epimerisation at C-5 to afford kalafungin **299**.

The methodology demonstrated by the synthesis of ether **392** and kalafungin **299**[92,93] was applied to the arizonins[94,95] and the frenolicins.[96] A synthesis of 5-*epi*-arizonin B1 **400** and arizonin C1 **402** was accomplished by obtaining the appropriately substituted naphthoquinone **397** (Scheme 70).

Treatment of bromotosylate **394** with ^{n}BuLi in the presence of furan, followed by ring opening of the resultant dihydrofuran, gave 7,8-dimethoxynaphthalen-1-ol **395**. The acetate derived from naphthol **395** underwent Fries rearrangement to naphthol **396** using boron trifluoride etherate. Silver(II) oxide oxidation of naphthol **396** gave quinone **397**, which was transformed to hemiacetal **398** by the previously described methods. Reduction of hemiacetal **398** via axial delivery of hydride afforded 5-*epi*-arizonin C1 **400**, selective demethylation of which gave 5-*epi*-arizonin B1 **399**. Treatment of 5-*epi*-arizonin C1 **400**, with an excess of boron tribromide gave diol **401** which upon methylation afforded arizonin C1 **402**.

The necessity to epimerise the *cis*-lactones to *trans*-lactones using this annulation/rearrangement sequence was circumvented in the synthesis of (±)-deoxyfrenolicin **189**.[96] Adduct **404** (Scheme 71) was formed in good yield from the addition of 2-trimethylsilyloxyfuran **387** to quinone **403**, which, after oxidative rearrangement furnished hemiacetal

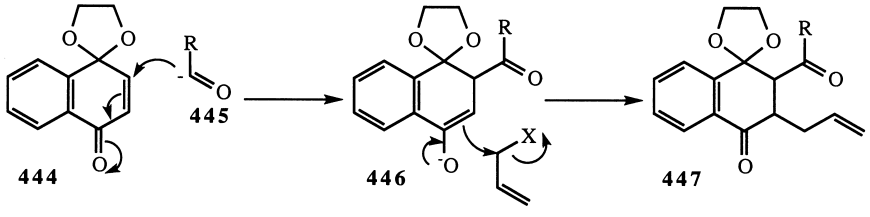


Scheme 79. Reagents and conditions: (i) MeCN, DBU, reflux, N_2; (ii) $Co(PPh_3)_3Cl$, C_6H_6, N_2, 40°C; (iii) MeCN, N_2, $AgBF_4$, reflux; (iv) a: Et_2O, 12 M HCl, Zn, N_2, RT; b: Ag_2O, Et_2O, RT; (v) a: CH_2Cl_2, $AlCl_3$, N_2; b: 50% H_2SO_4, N_2, 90°C.

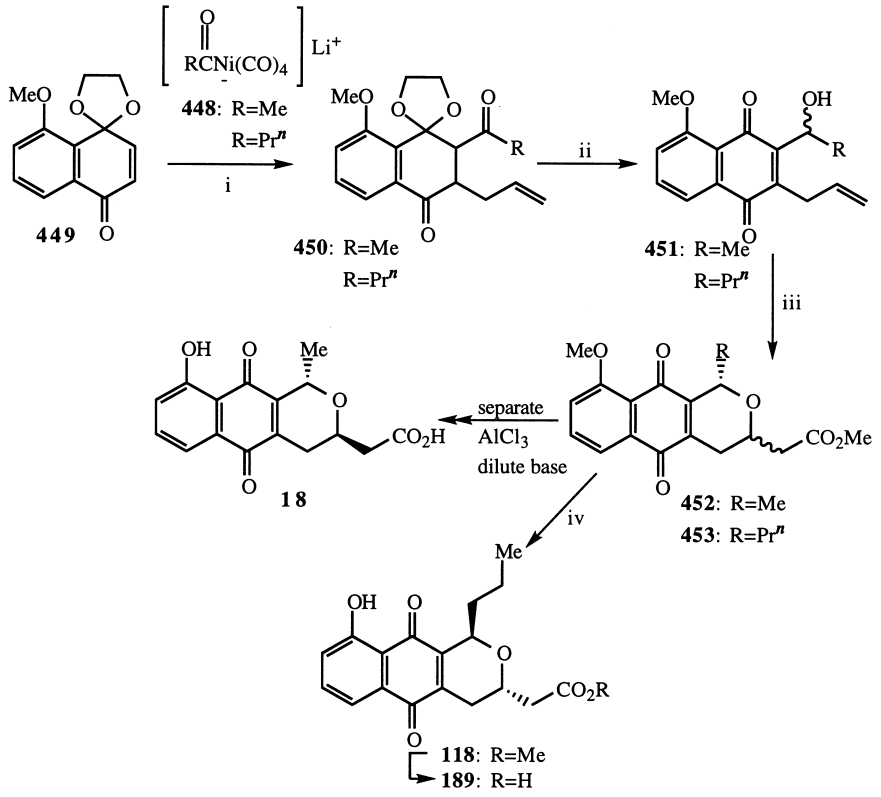
405. Attempts to reduce hemiacetal **405**, however, using triethylsilane/trifluoroacetic acid resulted in the decomposition of the desired product **406**. The instability of hemiacetal **406** was suggested to be due to the large propyl substituent being *cis* to the methylene group of the γ-lactone, creating unfavourable 1,3-interactions. The successful conversion of hemiacetal **405** to (±)-deoxyfrenolicin **189** was achieved by hydrogenation over palladium on charcoal affording methyl ester **348** after treatment with diazomethane. Deprotection of the *cis*-methyl ester **348** to the corresponding naphthol using boron tribromide also effected epimerisation at C-1, resulting in formation of *trans*-naphthol ester **118**. This hydrogenation, deprotection sequence developed for the synthesis of (±)-deoxyfrenolicin was also employed[96] to prepare (±)-nanaomycin A **47** from hemiacetal **391** (Scheme 69).

The furofuran annulation/oxidative rearrangement methodology has also been extended to the synthesis of more complex pyranonaphthoquinone antibiotics. The pentacyclic ring system present in griseusin A **222** (Scheme 36) was synthesised as outlined (Scheme 72).

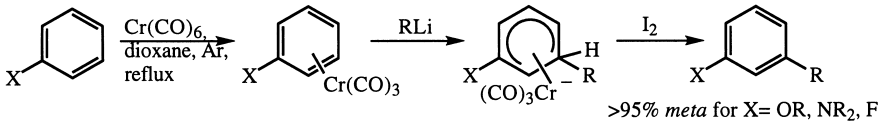
The assembly of spiroketals **415**[97,98] and **416** initially required the synthesis of naphthoquinone **412**. Thus, condensation of the lithium acetylide of **408** with 1,4-dimethoxy-2-formylnaphthalene **407** afforded alcohol **409** as an isomeric mixture. Oxidation using activated



Scheme 80.



Scheme 81. Reagents and conditions: (i) a: Et_2O, −50°C; b: allyl iodide, HMPA, RT; (ii) a: dioxane/6 M HCl, RT; b: $NaBH_4$, THF; c: DDQ, MeOH, 0°C; (iii) $PdCl_2(MeCN)_2$, $CuCl_2$ (3 equiv.), MeOH, CO, RT; (iv) BBr_3, CH_2Cl_2, 0°C.



Scheme 82.

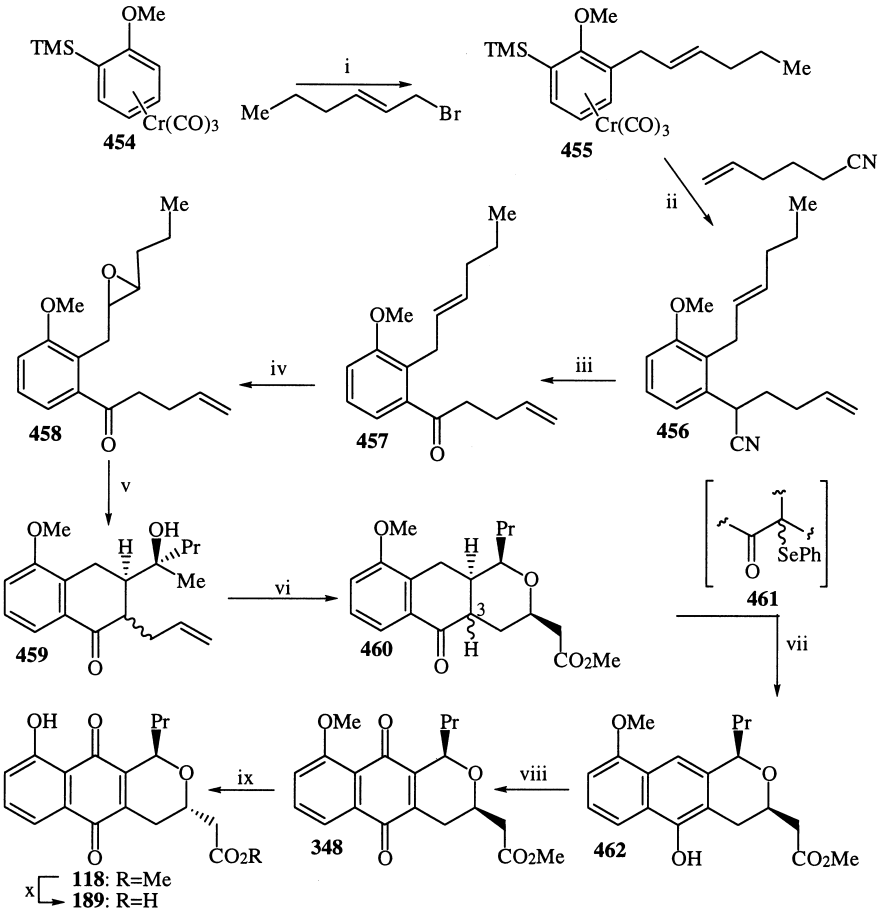
manganese dioxide gave ketone **410**, which was hydrogenated to compound **411** before oxidative demethylation to afford quinone **412**.

Addition of 2-trimethylsilyloxyfuran **387** to quinone **412** gave adduct **413** as a 1:1 isomeric mixture (^{1}H NMR). Rearrangement of the isomeric mixture of adducts and deprotection of the *tert*-butyldimethylsilyl group was accomplished by using excess ceric ammonium nitrate (8 equiv.). Treatment of the corresponding diol **414** with camphorsulphonic acid under reflux afforded two spiroketal isomers **415** and **416** which were easily separated by flash chromatography.

This methodology has also been extended recently to the synthesis of dimeric pyranonaphthoquinones.[99,100] The successful strategy made use of a novel double furofuran annulation reaction of a bisquinone **420**.[100] Bisquinone **420** in turn, was prepared by oxidation of binaphthol **419**. Suzuki–Miyaura coupling of bromide **417** with pinacol boronate **418** (made in situ by treatment of bromide **6** with diboron pinacolate) afforded biaryl **419** (Scheme 73).

Oxidation of biaryl **419** using ceric ammonium nitrate gave bisquinone **420**. Double annulation of bisquinone **420** with 2-trimethylsilyloxyfuran **387** then afforded a 1:1 mixture of adducts **421** and **422** which upon double oxidative rearrangement afforded hemiacetals **423** and **424** (Scheme 74). Hydrogenation of hemiacetals **423** and **424** resulted in reduction of the hemiacetal to a cyclic ether and ring opening of the γ-lactone. Treatment of the resultant bis-carboxylic acid with an ethereal solution of diazomethane afforded bis-methyl esters **425** and **426** which are closely related to the bis-methyl ester of actinorhodin **427** (Fig. 5).

2.7.3. Conjugate addition of diene 429. A recent synthesis[101] of alcohol **83**, a key intermediate in the synthesis of nanaomycin A **18** (Scheme 15), involved the addition of a strongly polarised diene **429** to several quinonoid dienophiles such as dibromide **428c** (Scheme 75). The use of such starting materials meant that conjugate addition dominated the conventional Diels–Alder reaction, resulting in the formation of bromide **430**. Reduction to alcohol **431** followed by dehalogenation gave



Scheme 83. Reagents and conditions: (i) THF, Ar, −30°C, Bu^{n}Li, then CuI, −30 to 0 to −30°C, bromide, RT; (ii) LDA, THF, −78°C, nitrile, HMPA, then **455**, −78 to 0 to −78°C, I_2 in THF, RT; (iii) LDA, THF, −78°C, then **456**, O_2, Me_2S; (iv) aq. $NaHCO_3$, CH_2Cl_2, 0°C, MCPBA; (v) a: LDA, THF, 0°C, **458**, TBDMSCl, HMPA, RT; b: CH_2Cl_2, RT, Ar, $BF_3{\cdot}Et_2O$; (vi) $PdCl_2$, $CuCl_2$, CO, MeOH, RT; (vii) a: $CH(OMe)_3$, $TsOH{\cdot}H_2O$, MeOH, RT, Et_3N; b: C_6H_6, RT, Ar, PhSeBr; d: CH_2Cl_2, −78°C, O_3, RT; (viii) Me_2CO, CrO_3; (ix) CH_2Cl_2, −78°C, Ar, BBr_3, −78 to 0°C; (x) MeOH, RT, aq. KOH.

alcohol **83** in an overall yield of 21% from dibromide **428**.

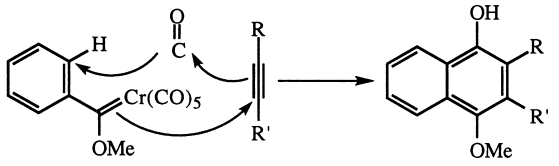
2.7.4. Michael addition of pyridinium ylides. Pyridinium ylides also provide a convenient method for introducing acetylmethyl and related residues on to quinone nuclei.[102] The pyridinium salts form nitrogen ylides in situ under very mild conditions as illustrated in Scheme 76.

Appropriate *N*-ylides were used to convert 2-methyl-1,4-naphthoquinone **432** into 3-(acylmethyl) derivatives **433**[102] which were then cyclised to naphtho[2,3-*c*]pyran-5,10-diones **434** by treatment with bromine followed by dehydrobromination with triethylamine (Scheme 77).[103]

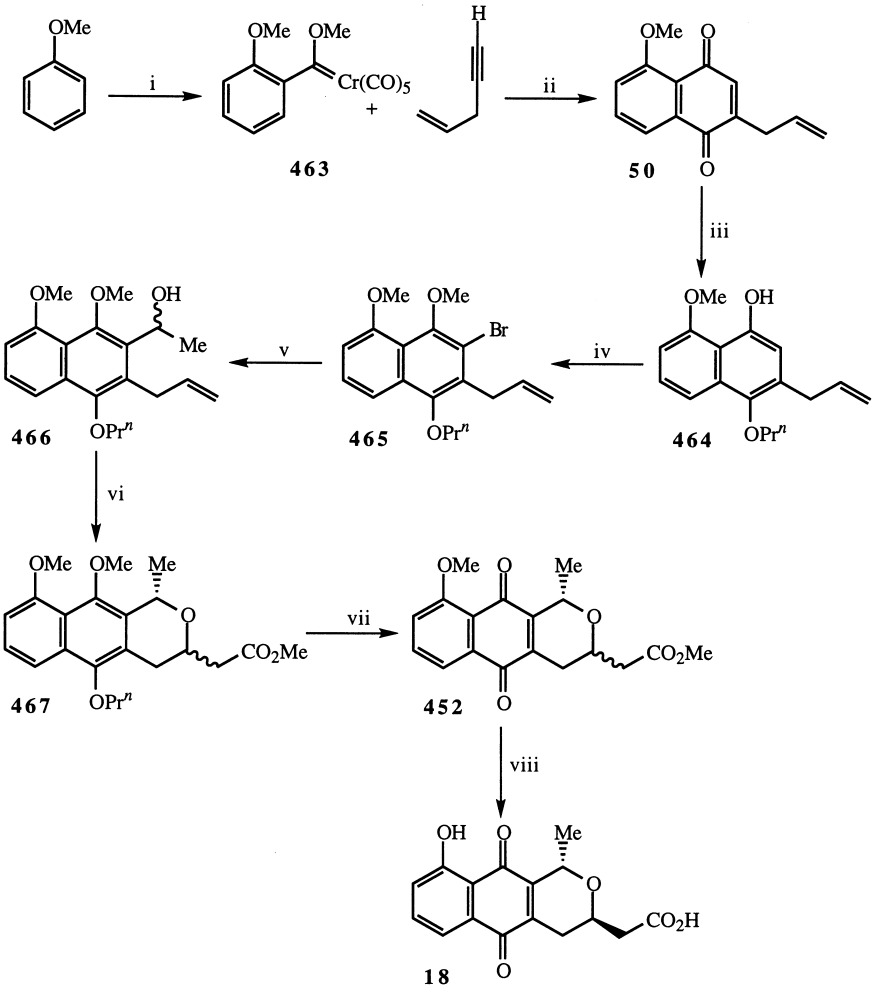
When thiophene and furan derivatives were employed instead of phenacyl ylides (Scheme 78), substitution into naphthoquinone **432** occurred smoothly and the bromination–dehydrobromination sequence was effective in producing pyran derivatives **436**, **437**.[104] When 2-phenoxymethyl-1,4-naphthoquinone **435** was used, the parallel product smoothly eliminated a phenoxide ion to form a quinone methide and, from there, the required naphthopyrandione.

2.8. Organometallic methodology

2.8.1. Regiospecific intramolecular alkyne insertion to phthaloylcobalt complexes. Liebeskind et al.[39,105] established a facile synthesis of (±)-nanaomycin A **18**, in which the naphthoquinone nucleus was constructed by intramolecular alkyne insertion into a phthaloylmetal complex. Phthaloylcobalt complexes were chosen for their ease of preparation, high yields, generality and cost effectiveness



Scheme 84.



Scheme 85. Reagents and conditions: (i) Et_2O, $Cr(CO)_6$, RT, then methyl fluorosulphonate (3 equiv.); (ii) a: THF, 45°C; b: aq. CAN, MeCN, RT; (iii) a: $Na_2S_2O_4$, Et_2O, H_2O; b: Pr^nI, Me_2CO, K_2CO_3; (iv) a: NBS, MeCN, −30°C, aq. Na_2SO_3 workup, RT; b: MeOH, NaOH, Me_2SO_4; (v) Et_2O, −78°C, Bu^nLi, −100°C, MeCHO; (vi) MeOH, $PdCl_2$, $CuCl_2$, CO then **467**, RT; (vii) aq. CAN, MeCN; (viii) a: $AlCl_3$, CH_2Cl_2, RT; b: conc. H_2SO_4, 0°C; c: aq. KOH, RT.

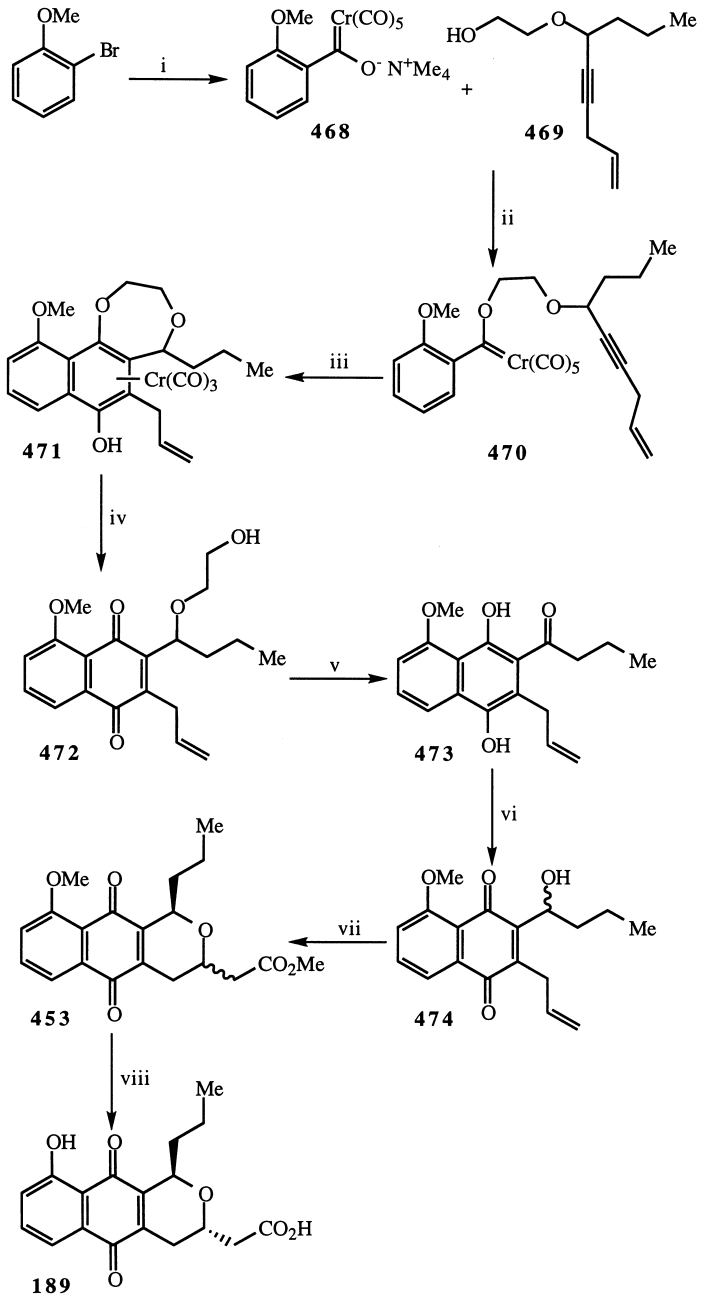
despite their requirement of activation by silver tetrafluoroborate before alkyne insertion. The appropriate functionality was introduced via a fully elaborated alkyne that was connected through a linking group to the phenol functionality of the phthaloyl ring. By judicious choice of the length of linking group, only the formation of the desired regioisomer was observed.

Condensation of phenol **438** and alkyne **439** (Scheme 79) gave the highly functionalised benzocyclobutenedione **440** with a pendant alkyne moiety. After insertion of cobalt, intramolecular cyclisation of the resultant phthaloylcobalt complex **441** was promoted by silver tetrafluoroborate, forming the macrocyclic quinone **442**. Pyran formation was then achieved by reduction with zinc and acid, yielding **443** as a mixture of diastereomers after oxidative work-up. The side chain was then detached and acid hydrolysis furnished (±)-nanaomyin A **18** and its *cis*-epimer in a 3:1 ratio. The critical pyran ring closure is thought to proceed via an *ortho*-quinone methide (Fig. 6).

2.8.2. Conjugate addition of acyl nickel carbonylate anions to quinone monoketals. In the synthesis of (±)-nanaomycin A **18** and (±)-deoxyfrenolicin **189**,[106,107] it was hoped that Michael addition of an acyl anion equivalent **445** (Scheme 80) to a quinone monoketal **444** would give an enolate anion **446**, which could be trapped by an allyl halide, thus attaching the two side chains to the quinone nucleus in a one pot reaction.

The resulting compound **447** could then be transformed into a pyranonaphthoquinone antibiotic by intramolecular alkoxycarbonylation. Generally, conjugate addition of reactive carbanions to quinone monoketals has led to reductive cleavage rather than addition.[106] Acylnickel carbonylate anions, generated in situ from nickel tetracarbonyl and alkyllithium reagents, however, were found to add to α,β-unsaturated ketones in a 1,4-fashion, and initial studies with quinone monoketals were promising.[107]

Addition of acylate anion **448** to juglone monoketal methyl ether **449** followed by allylation gave **450** (Scheme 81).[106] This was converted to quinone **451**, before alkoxycarbonylation to afford the *trans*-isomer of pyran **452** as the major product. Separation (by crystallisation) of the *trans*-isomer provided a formal synthesis of (±)-nanaomycin A **18**. In practice, quinone **451** is obtained more conveniently by allylstannane allylation of acetyl quinone **181** (Scheme



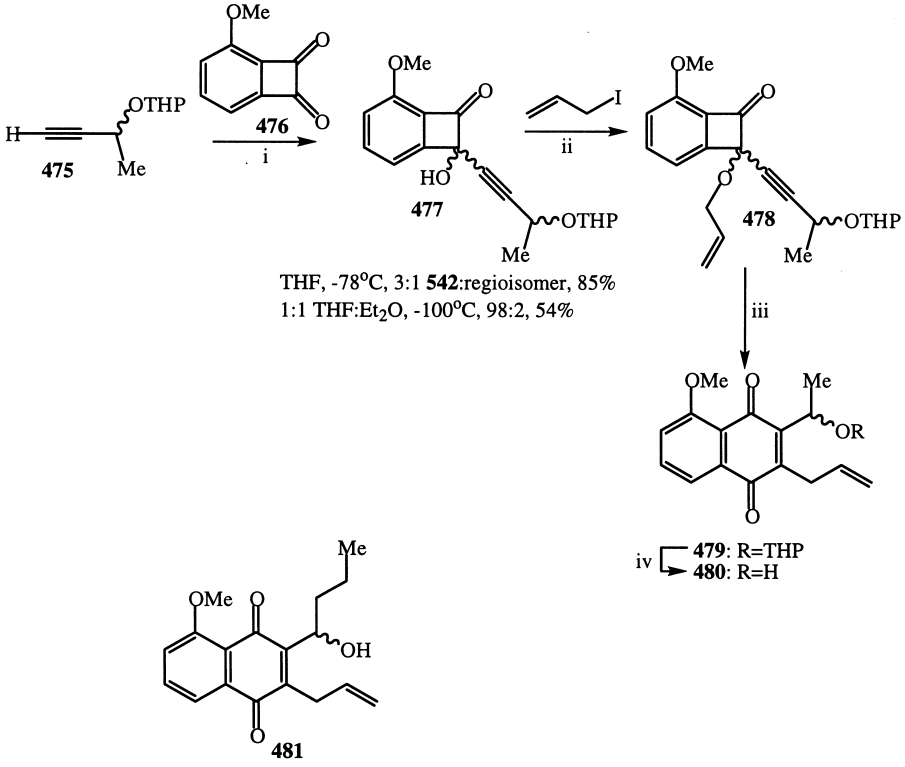
Scheme 86. Reagents and conditions: (i) a: Et_2O, −78°C, Bu^nLi, then $Cr(CO)_6$, RT; b: Me_4NBr, H_2O; (ii) MeCOCl, −20°C, CH_2Cl_2, RT; (iii) Et_2O, 35°C; (iv) DDQ, MeCN, RT; (v) 5 M H_2SO_4, MeOH, six days; (vi) a: $NaBH_4$, THF, RT; b: DDQ, MeOH, 0°C; (vii) $CuCl_2$ (3 equiv.), $PdCl_2(MeCN)_2$, MeOH, CO, RT; (viii) a: THF, −78°C, 3:1 **542**:regioisomer, 85% 1:1 THF/Et_2O, −100°C, 98:2, 54%

37), and the *cis*-isomer of pyran **452** can be equilibrated to the *trans* using concentrated acid.[30,33]

A parallel set of reactions yielded propyl substituted pyran **453** in a 3:1 *trans*:*cis* ratio. Treatment of this isomeric mixture with boron tribromide effected demethylation and complete isomerisation to the natural *trans*-isomer **118**. Removal of the ester group then afforded (±)-deoxyfrenolicin **189**.

2.8.3. Nucleophilic addition/oxidation using an arene–chromium complex. The addition of nucleophiles to arene–metal complexes which results in η^5-(cyclohexadienyl) metal species that can be manipulated into useful organic products has been well documented.[108] The most abundant and easily handled examples are arene–$Cr(CO)_3$ species which, upon treatment with oxidising agents afford substituted arene systems (Scheme 82). Useful regioselectivity can be achieved from the *meta*-directing influence of powerful resonance donor substituents, allowing the synthesis of several aromatic natural products.

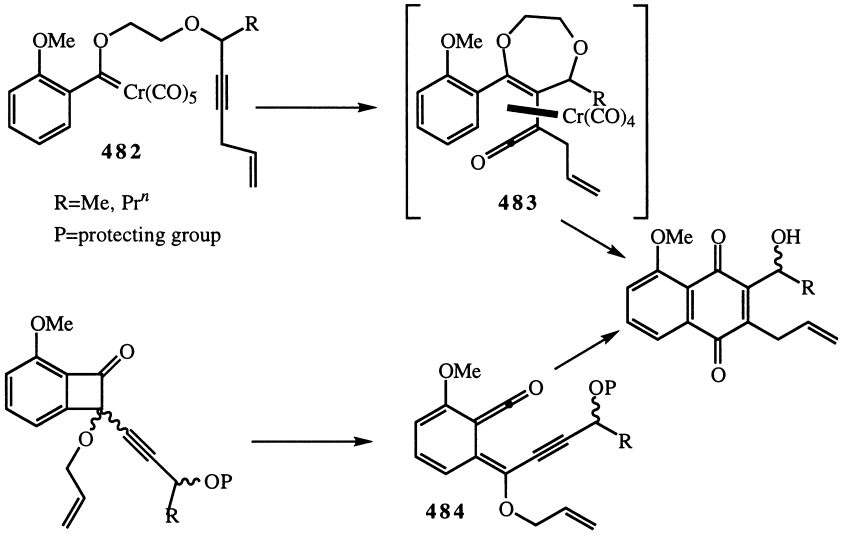
Trisubstituted arene complex **455**, prepared from [*o*-(trimethylsilyl)anisole]$Cr(CO)_3$ **454** was used for the synthesis of (±)-deoxyfrenolicin **189** (Scheme 83). The silyl substituent differentiated the two positions *meta* to



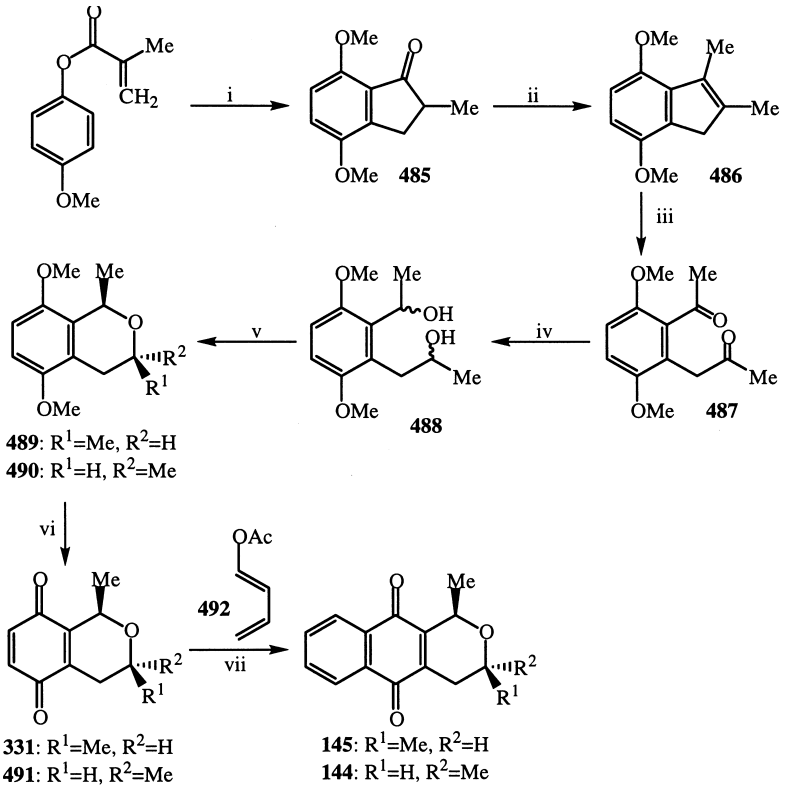
Scheme 87. Reagents and conditions: (i) THF, −78°C, Bu^{n}Li or 1:1 THF/Et_2O, −100°C, Bu^{n}Li, then add to **476**; (ii) Ag_2CO_3, dioxane; (iii) *p*-xylene, reflux; (iv) AcOH/THF/H_2O.

the methoxy group such that after addition of lithiated 5-cyanohex-1-ene, oxidation and protodesilylation nitrile **456** was produced. Oxidative removal of the cyano group gave ketone **457**. The first cyclisation was achieved after selective epoxidation of the disubstituted double bond to give epoxide **458**. Formation of the corresponding *Z*-silyl enol ether and subsequent Lewis acid catalysed opening of the epoxide ring then afforded alcohol **459** as a separable mixture of isomers (up to 82:18 *cis*:*trans*). Palladium catalysed intramolecular alkoxycarbonylation then resulted in a second cyclisation to afford pyran **460** as an epimeric mixture at C-3. Aromatisation of the central ring proved difficult and involved a multistep procedure leading to the α-phenylselenoxide **461** which fragmented to form naphthol **462**. Jones oxidation converted naphthol **462** to *cis*-quinone **348**, which upon demethylation, equilibrated to the *trans*-isomer **118**. Finally, saponification of pyran **118** afforded (±)-deoxyfrenolicin **189**.

2.8.4. Alkyne cycloaddition to chromium–carbene complexes [Cr(CO)$_5$]. An alternative strategy for the synthesis[108–110] of (±)-nanaomycin A **18** and (±)-deoxyfrenolicin **189** using organometallic chemistry relied on two key steps: cycloaddition of an alkyne to a carbene–chromium



Scheme 88.



Scheme 89. Reagents and conditions: (i) $AlCl_3$, NaCl, 90–180°C, N_2; (ii) Et_2O, MeMgI, 0°C to RT, HCl; (iii) OsO_4, dioxane/H_2O, RT then $NaIO_4$; (iv) Et_2O, $LiAlH_4$, reflux; (v) Et_2O, conc. HCl, 0°C; (vi) a: separate; b: aq. CAN, MeCN, RT; (vii) $PhCH_3$, RT then Na_2CO_3/aq. EtOH.

complex followed by intramolecular alkoxycarbonylation of an hydroxyalkene (Scheme 84). High regioselectivity and functional group compatibility are required in the alkyne cycloaddition, which is strongly influenced by steric effects of the alkyne substituents.

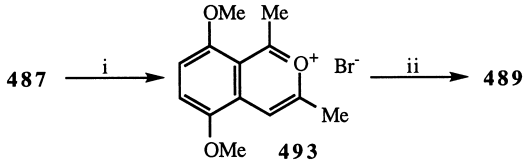
For (±)-nanaomycin A **18**, intermolecular reaction of allyl acetylene with chromium–carbene complex **463** (Scheme 85) followed by oxidation of the crude product gave naphthoquinone **50**. Only one regioisomer was isolated, with the orientation being consistent with that observed previously.[39,105,109] Reduction and alkylation afforded naphthalene **464** which after bromination and methylation afforded bromide **465**. Addition of acetaldehyde to the lithiated compound **465**, resulted in alcohol **466** which after intramolecular alkoxycarbonylation afforded naphthopyran **467** in a 3:2 *cis*:*trans* ratio. The isomers were separated and oxidised to the corresponding quinones **452**, from which (±)-nanaomycin A **18** was realised by epimerisation of *cis*-quinone **452**, demethylation and hydrolysis.[33,55]

A synthesis of (±)-deoxyfrenolicin **189** (Scheme 86) utilised an *intra*molecular cycloaddition to control the regioselectivity (vide supra for similar examples) and began with the quaternary ammonium salt **468**. Reaction with alkynol **469** gave the corresponding metal complex **470**, which slowly cyclised in refluxing ether to naphthol **471**. Removal of the chromium from naphthol **471** and oxidation produced quinone **472** which after acid treatment afforded ketone **473** by tautomerism to the quinone-methide followed by ketal formation and hydrolysis. Hydride reduction of ketone **473** and reoxidation produced naphthoquinone **474**. Alkoxycarbonylation gave the pyran isomers **453** (*cis*:*trans*=1:3), and demethylation/isomerisation with boron tribromide followed by hydrolysis furnished (±)-deoxyfrenolicin **189**.

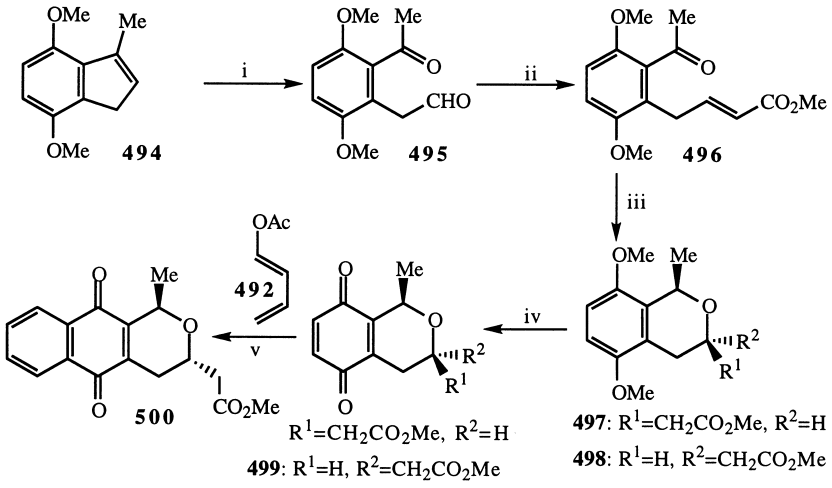
2.9. Electrocyclic ring opening of benzocyclobutanones

A different approach to the synthesis of a quinone nucleus was proposed by Liebeskind[111] and Moore.[112] The key reaction involved the electrocyclic ring opening of 4-substituted 4-hydroxycyclobutenones to conjugated ketenes, which then undergo thermal ring closure and rearrangement to form quinones or hydroquinones.

Starting from benzocyclobutenone **476**,[113] reaction with the lithium salt of protected 3-hydroxybut-1-yne **475** afforded alcohol **477** as a 2:1 mixture of diastereomers (Scheme 87).[114] The compounds differ stereochemically only at the chiral centre in the THP group and thus alkynylation is not



Scheme 90. Reagents and conditions: (i) HBr, AcOH; (ii) H_2, PtO_2, AcOH.

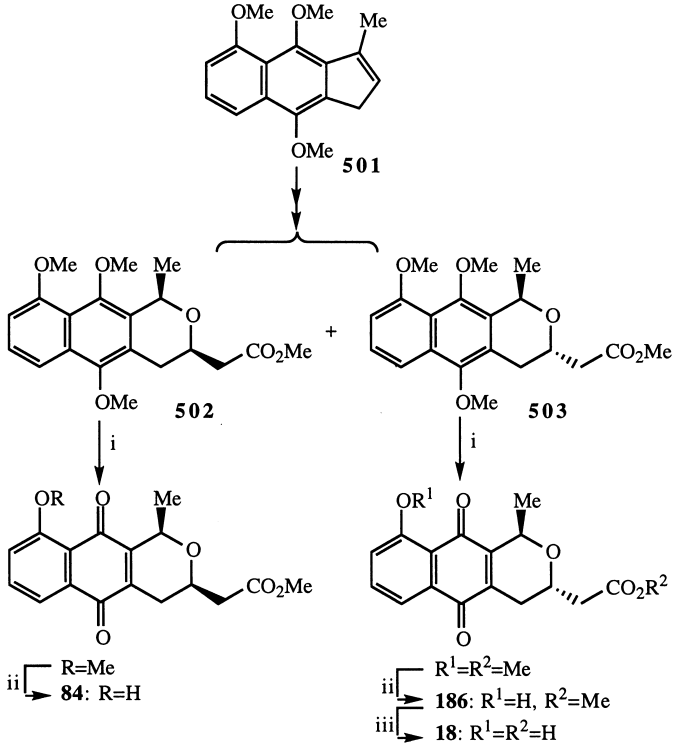


Scheme 91. Reagents and conditions: (i) OsO_4, dioxane/H_2O, RT then $NaIO_4$; (ii) $(Ph)_3P{=}CHCO_2Me$, C_6H_6, RT; (iii) $NaBH_4$, MeOH, 0°C to RT; (iv) aq. CAN, MeCN, RT; (v) $PhCH_3$, RT then Na_2CO_3/aq. EtOH.

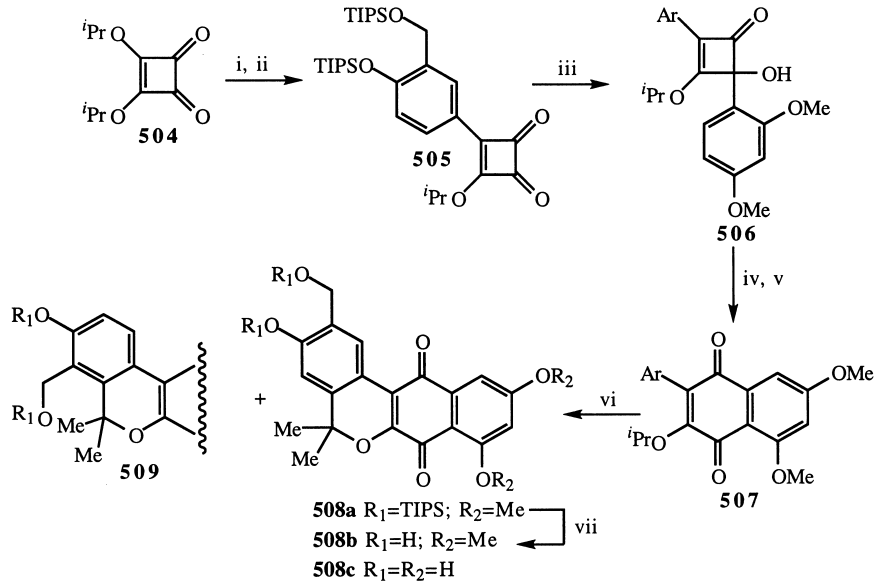
only regioselective for the more electron deficient and sterically less congested carbonyl, but also stereoselective in its approach. Optimum regiospecificity of 98:2 was achieved by changing solvent and temperature conditions, however, only a poor yield of alcohol **477** resulted.

Thermolysis of allyl ether **478** resulted in quinone **479** which upon deprotection afforded alcohol **480**. Quinone **481** was also made by the same procedure, starting from the appropriate acetylene. Quinones **480** and **481** have been used as key synthetic precursors of nanaomycin A **18** and deoxyfrenolicin **189**.

Upon comparison of this synthetic method with the related aryl carbene method[110] it can be seen that the regiochemical outcome of the cyclobutenone methodology is controlled in the initial alkynylation of the starting material, whereas with the aryl carbene method the tethered aryl carbene complex **482** dictates the result (Scheme 88). Both methods involve a conjugated ketene, intermediate **483** for the



Scheme 92. Reagents and conditions: (i) aq. CAN, MeCN, RT; (ii) $AlCl_3$, C_6H_6, RT; (iii) conc. HCl.



Scheme 93. Reagents and conditions: (i) Li-C_6H_3-4-OTIPS-3CH_2OTIPS, THF, −78°C; (ii) TFAA; (iii) Li-C_6H_3-2,4-OMe, THF, −78°C; (iv) *p*-xylene, 138°C; (v) Ag_2O, K_2CO_3; (vi) hν (40 W fluorescent lamp), DDQ, C_6H_6; (vii) TBAF.

carbene and intermediate **484** for the cyclobutenone synthesis.

2.10. Oxidative cleavage of benzindenes

In the synthesis[54] of deoxy analogues of the eleutherins (**5**, **6**) and nanaomycin A **18**, oxidative cleavage of indene **486** was used to form the pyran ring. Indene **486** in turn, was prepared by addition of methylmagnesium iodide to indanone **485** followed by acid treatment (Scheme 89). Oxidative cleavage produced a diketone **487** which was reduced to diol **488**. Acid catalysed cyclisation of diol **488** afforded a 1:2 ratio of isochromans **489** and **490**. Equilibration to the thermodynamically more stable *trans*-isomer **490** by methanesulphonic acid increased the *cis*:*trans* ratio to 1:4. Pure *cis*-pyran **489** could be obtained from diketone **487** by hydrogenation of oxonium salt **493** (Scheme 90). Oxidative demethylation of pyrans **489**, **490** gave the corresponding quinones **331** and **491**, benzannulation of which with 1-acetoxybuta-1,3-diene **492** gave, after sodium carbonate treatment of the initial four regioisomeric adducts, (±)-9-demethoxyeleutherin **145** and (±)-9-demethoxyisoeleutherin **144**.

In the synthesis of (±)-deoxynanaomycin A methyl ester **500** (Scheme 91),[54] indene **494** was oxidatively cleaved to the ketoaldehyde **495** then a selective Wittig reaction carried out on the aldehyde group. Reductive cyclisation of conjugated ester **496** produced benzopyrans **497** and **498** in a 1:3.5 ratio, respectively. Treatment of the major isomer **498** gave benzoquinone **499** and ultimately (±)-deoxynanaomycin A methyl ester **500**.

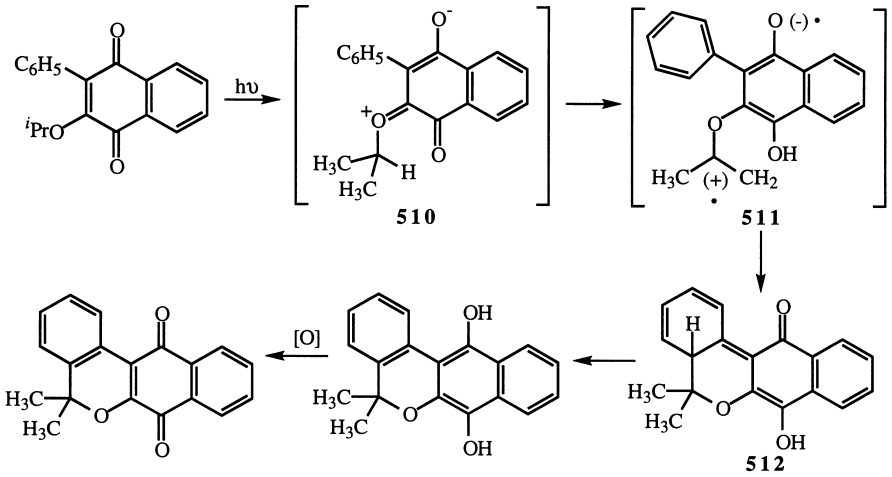
Using a similar series of reactions to that used in the synthesis of pyranonaphthoquinone **500**,[54] indene **501** was transformed[55] into (±)-nanaomycin A **18** (Scheme 92). As the additional aromatic ring was already part of the indene structure, no Diels–Alder reaction was required for this synthesis. The two naphthopyrans **502** and **503** were isolated in a 1:1.9 ratio (*cis*:*trans*). After conversion to their respective quinones, demethylation using aluminium trichloride gave naphthols **84** and **186**. Finally, hydrolysis of naphthol **186** produced (±)-nanaomycin A **18**.

2.11. Photoannulation strategy

Moore et al.[115] proposed a novel method for the construction of the pyranonaphthoquinone skeleton using a novel photoannulation reaction of a 2-aryl-3-alkoxy-1,4-naphthoquinone. In turn, the required parent naphthoquinone was made by a thermally induced ring expansion of a 4-arylcyclobutenone. This methodology was used for the synthesis of pyranonaphthoquinone **508b**, a dimethyl analogue of naphthgeranine E **508c** (Scheme 93).

The synthesis of pyranonaphthoquinone **508b** began by 1,2-addition of 5-lithio-2-(triisopropylsiloxy)benzyl triisopropylsilyl ether to diisopropyl squarate **504** followed by trifluoroacetic anhydride to afford a 'one pot' synthesis of cyclobutenedione **505**. Regiospecific addition to the more reactive carbonyl of cyclobutenedione **505** resulted in cyclobutenone **506** which upon thermolysis and oxidation afforded the required 2-aryl-3-alkoxy-1,4-naphthoquinone **507**. Photolysis of a benzene solution of naphthoquinone **507** in the presence of 2,3-dichloro-2,3-dicyano-1,4-benzoquinone afforded a 1:1 mixture of **508a** and its regioisomer **509**. Finally, desilylation of **508a** resulted in pyranonaphthoquinone **508b**.

The photoannulation reaction is envisaged to occur via intermediate **510** (Scheme 94) which, after proton transfer from the methine carbon of the isopropoxy group to the adjacent carbonyl and aromatisation would result in diradical **511**. Intramolecular ring closure to a quinone methide **512** followed by tautomerism to a hydroquinone and subsequent oxidation affords the required pyranonaphthoquinone skeleton.



Scheme 94.

References

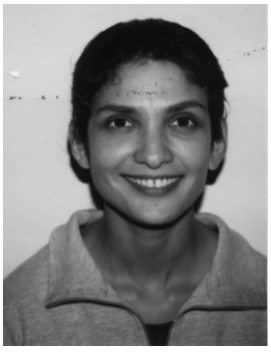
1. Thomson, R. H. *Naturally Occurring Quinones*; 2nd ed.; Academic Press: London, 1971, p 282 see also p 597.
2. Floss, H. G. In *Antibiotics*, Corcoran, J. W., Ed.; Springer: Berlin, 1981; Vol. 4, p 215 and references therein.
3. Floss, H. G.; Keller, P. J.; Beale, J. M. *J. Nat. Prod.* **1986**, *49*, 957.
4. Floss, H. G.; Beale, J. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 146.
5. Rohr, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 881.
6. Moore, H. W. *Science* **1977**, *197*, 527.
7. Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249; *Chem. Abstr. 96* 173661b.
8. Thomson, R. H. *Naturally Occurring Quinones*; 3rd ed.; Chapman & Hall: London, 1987, p 270.
9. Tisler, M. *Adv. Heterocycl. Chem.* **1989**, *45*, 37.
10. Thomson, R. H. In *The Total Synthesis of Natural Products*, Apsimon, J. Ed.; Wiley: New York, 1992; Vol. 8, p 324.
11. Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
12. Webb, A. D.; Harris, T. M. *Tetrahedron Lett.* **1977**, 2069.
13. Yamaguchi, M.; Nakamura, S.; Okuma, T.; Minami, T. *Tetrahedron Lett.* **1990**, *31*, 3913.
14. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273.
15. Tatsuta, K.; Kojima, N.; Chino, M.; Kawazoe, S.; Nakata, M. *Tetrahedron Lett.* **1993**, *34*, 4961.
16. Tatsuta, K.; Chino, M.; Kojima, N.; Shinojima, S.; Nakata, M.; Morooka, M.; Ohba, S. *Tetrahedron Lett.* **1993**, *34*, 4957.
17. Yamaguchi, A.; Okuma, T.; Nakamura, S.; Minami, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 183.
18. Gilbreath, S. G.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6172.
19. Mitscher, L. A.; Gollapudi, S. R.; Oburn, D. S.; Drake, S. *Phytochemistry* **1985**, *24*, 1681.
20. Blouin, M.; Beland, M. C.; Brassard, P. *J. Org. Chem.* **1990**, *55*, 1466.
21. Bergeron, D.; Brassard, P. *Heterocycles* **1992**, *34*, 1835.
22. Laatsch, H. *Liebigs Ann. Chem.* **1987**, 297.
23. Cameron, D. W.; Chan, H. W.-S. *J. Chem. Soc. (C)* **1966**, 1825.
24. Cameron, D. W.; Chan, H. W.-S.; Hildyard, E. M. *J. Chem. Soc. (C)* **1966**, 1832.
25. Blackburn, G. M.; Cameron, D. W.; Chan, H. W. S. *J. Chem. Soc. (C)* **1966**, 1836.
26. Eisenhuth, W.; Schmid, H. *Helv. Chim. Acta* **1958**, *41*, 2021.
27. Eisenhuth, W.; Schmid, H. *Experientia* **1957**, *13*, 311; *Chem. Abstr. 52*, 6296a.
28. Cameron, D. W.; Feutrill, G. I.; Pietersz, G. A. *Aust. J. Chem.* **1982**, *35*, 1481.
29. Pyrek, J. St.; Achmatowicz Jr., O.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673.
30. Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263.
31. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 2630.
32. Yoshii, E.; Kometani, T.; Nomura, K.; Takeuchi, Y.; Odake, S.; Nagata, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4779.
33. Naruta, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 609.
34. Dhokte, U. P.; Rao, A. S. *Synth. Commun.* **1991**, *21*, 1263.
35. Retamal, J. I.; Ruiz, V. M.; Tapia, R. A.; Valderrama, J. A.; Vega, J. C. *Synth. Commun.* **1982**, *12*, 279.
36. Masquelin, T.; Hengartner, U.; Streith, J. *Synthesis* **1995**, 780.
37. Masquelin, T.; Hengartner, U.; Streith, J. *Helv. Chim. Acta* **1997**, *80*, 43.
38. Cameron, D. W.; Crosby, I. T.; Feutrill, G. I. *Aust. J. Chem.* **1992**, *45*, 2025.
39. South, M. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 4181.
40. Kraus, G. A.; Li, J. *J. Am. Chem. Soc.* **1993**, *115*, 5859.
41. Giles, R. G. F.; Green, I. R.; Knight, L. S.; Son, V. R. L.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Chem. Commun.* **1991**, 287.
42. Cameron, D. W.; Cromartie, R. I. T.; Kingston, D. G. I.; Todd, A. R. *J. Chem. Soc.* **1964**, 51.
43. Giles, R. G. F.; Green, I. R.; Knight, L. S.; Son, V. R. L.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 865.
44. Cameron, D. W.; Schutz, P. E. *J. Chem. Soc. (C)* **1968**, 1801.
45. Cameron, D. W.; Crosby, I. T.; Feutrill, G. I.; Pietersz, G. A. *Aust. J. Chem.* **1992**, *45*, 2003.
46. Giles, R. G. F.; Green, I. R.; Hugo, V. I.; Mitchell, P. R. K. *J. Chem. Soc., Chem. Commun.* **1983**, 51.
47. Giles, R. G. F.; Green, I. R.; Hugo, V. I.; Mitchell, P. R. K.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2309.
48. Giles, R. G. F.; Green, I. R.; Hugo, V. I.; Mitchell, P. R. K.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2383.

49. Giles, R. G. F.; Green, I. R.; Pestana, J. A. X. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2389.
50. Elsworth, J. F.; Giles, R. G. F.; Green, I. R.; Ramdohr, J. E.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2469.
51. Dhokte, U. P.; Rao, A. S. *Synth. Commun.* **1988**, *18*, 597.
52. Uno, H. *J. Org. Chem.* **1986**, *51*, 350.
53. Masamoto, K.; Takeuchi, Y.; Takeda, K.; Yoshii, E. *Heterocycles* **1981**, *16*, 1659.
54. Kometani, T.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1191.
55. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.
56. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4725.
57. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 2311.
58. Naruta, Y.; Uno, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1277.
59. de Koning, C. B.; Giles, R. G. F.; Green, I. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2743.
60. Chorn, T. A.; Giles, R. G. F.; Mitchell, P. R. K. *J. Chem. Soc., Chem. Commun.* **1981**, 534.
61. Chorn, T. A.; Giles, R. G. F.; Green, I. R.; Mitchell, P. R. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1249.
62. Giles, R. G. F.; Reuben, M. K.; Roos, G. H. P. *South African J. Chem.* **1979**, *32*, 127.
63. Giles, R. G. F.; Green, I. R.; Niven, M. L.; Yorke, S. C.; Hugo, V. I. *South African J. Chem.* **1986**, *39*, 46.
64. Hugo, V. I. *Synth. Commun.* **1994**, *24*, 2563.
65. Hoffmann, B.; Schonebaum, A.; Lackner, H. *Liebigs Ann. Chem.* **1993**, 333.
66. Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171.
67. Nomura, K.; Okazaki, K.; Hori, K.; Yoshii, E. *Chem. Pharm. Bull.* **1986**, *34*, 3175.
68. Li, T. T.; Wu, Y. L.; Walgrove, T. C. *Tetrahedron* **1984**, *40*, 4701.
69. Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.
70. Krohn, K. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 37.
71. Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318.
72. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061.
73. Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263.
74. Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439.
75. Nomura, K.; Hori, K.; Ishizuka, M.; Yoshii, E. *Heterocycles* **1987**, *25*, 167.
76. Nomura, K.; Okazaki, K.; Horo, K.; Yoshii, E. *J. Am. Chem. Soc.* **1987**, *109*, 3402.
77. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *J. Antibiot.* **1985**, *38*, 680.
78. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699.
79. Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.* **1990**, *31*, 5495.
80. Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T.; Nakata, M. *J. Antibiot. (Tokyo)* **1991**, *44*, 901; *Chem. Abstr. 115*, 232643h.
81. Okazaki, K.; Nomura, K.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1989**, 354.
82. Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.
83. Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.
84. Li, T.; Wu, Y. L.; Walsgrove, T. C. *Tetrahedron* **1984**, *40*, 4701.
85. Kraus, G. A.; Shi, J. *J. Org. Chem.* **1990**, *55*, 1105.
86. Ichihara, A.; Ubukata, M.; Oikawa, H.; Murakami, K.; Sakamura, S. *Tetrahedron Lett.* **1980**, *21*, 4469.
87. Brimble, M. A.; McEwan, J. F.; Turner, P. *Tetrahedron: Asymmetry* **1998**, 1239.
88. Kraus, G. A.; Sugimoto, H. *J. Chem. Soc., Chem. Commun.* **1978**, 30.
89. Kraus, G. A.; Roth, B. *J. Org. Chem.* **1978**, *43*, 4923.
90. Brimble, M. A.; Gibson, J. J. *Tetrahedron Lett.* **1987**, *28*, 4891.
91. Brimble, M. A.; Brimble, M. T.; Gibson, J. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 179.
92. Brimble, M. A.; Hodges, R. A.; Stuart, S. J. *Tetrahedron Lett.* **1988**, *29*, 5987.
93. Brimble, M. A.; Stuart, S. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 881.
94. Brimble, M. A.; Pythian, S. J. *Tetrahedron Lett.* **1993**, *34*, 5813.
95. Brimble, M. A.; Phythian, S. J.; Prabaharan, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2855.
96. Brimble, M. A.; Lynds, S. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 493.
97. Brimble, M. A.; Nairn, M. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 169.
98. Brimble, M. A.; Nairn, M. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 579.
99. Brimble, M. A.; Duncalf, L. J.; Phythian, S. J. *Tetrahedron Lett.* **1995**, *36*, 9209.
100. Brimble, M. A.; Neville, D.; Duncalf, L. J. *Tetrahedron Lett.* **1998**, *39*, 5647.
101. Cameron, D. W.; Crosby, I. T.; Feutrill, G. I. *Tetrahedron Lett.* **1992**, *33*, 2855.
102. Aldersley, M. F.; Dean, F. M.; Nayyir-Mazhir, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1753.
103. Aldersley, M. F.; Dean, F. M.; Hamzah, A. S. *Tetrahedron Lett.* **1986**, *27*, 255.
104. Aldersley, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. E.; Ennis, D. S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2163.
105. Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Iyer, S.; Leeds, J. P. *Tetrahedron* **1985**, *41*, 5839.
106. Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. *J. Org. Chem.* **1982**, *47*, 4382.
107. Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. *J. Org. Chem.* **1985**, *50*, 5566.
108. Semmelhack, M. F. *Pure Appl. Chem.* **1981**, *53*, 2379.
109. Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850.
110. Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*, 5803.
111. Liebeskind, L. S.; Iyer, S.; Jewell Jr., C. F. *J. Org. Chem.* **1986**, *51*, 3065.
112. Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.
113. South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815.
114. Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174.
115. Onofrey, T. J.; Gomez, D.; Winters, M.; Moore, H. *J. Org. Chem.* **1997**, *62*, 5658.

Biographical Sketch

Margaret Brimble received her B.Sc. in 1982 and her M.Sc. (Hons) in 1983 from the University of Auckland, New Zealand. She was then awarded a Commonwealth Scholarship to study in the United Kingdom and received her Ph.D. in 1986 from the University of Southampton. She then took up her initial academic appointment as a lecturer in chemistry at Massey University, New Zealand, in 1986. After spending a semester as a visiting professor at the University of California, Berkeley, she moved to the University of Sydney in 1994 where she was promoted to a Reader in organic chemistry in 1998. In 1999 she then returned to New Zealand to take up the Chair in Organic Chemistry at the University of Auckland. Her main areas of research focus on the synthesis of natural products containing bis-spiroacetal ring systems and the synthesis of pyranonaphthoquinone antibiotics. She has been awarded the New Zealand Institute of Chemistry Easterfield Medal and the Royal Society of New Zealand Hamilton Prize.

Michael Nairn obtained his Ph.D. from Massey University, New Zealand, in 1996 under the supervision of Margaret Brimble. His Ph.D. research focused on the synthesis of the pyranonaphthoquinone antibiotic, griseusin A. This research was extended by postdoctoral work at the University of Sydney, Australia, looking at the bioreductive alkylation properties of this class of compound. In 1998 he joined a collaborative project between SmithKline Beecham Pharmaceuticals and the Research School of Chemistry, The Australian National University, Canberra, working on the preparation of new bacterial anti-infective agents and the development of enzyme inhibitors.



Hishani Prabaharan received her undergraduate education at the University of Auckland, New Zealand, where she completed her M.Sc. in chemistry in 1995 working with Margaret Brimble on the synthesis of the pyranonaphthoquinone antibiotics kalafungin and arizonin C1. She then undertook Ph.D. studies at the University of Sydney working with Margaret Brimble on the synthesis of the polyether antibiotics salinomycin and CP44,161. Hishani received her Ph.D. in 1999 and her current research interests lie in the use of asymmetric metal mediated transformations for organic synthesis.