SYNTHESIS OF HONGCONIN AND RELATED NAPHTHO[2,3-*c*]PYRANS

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BY

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SYNTHESIS OF HONGCONIN AND RELATED

NAPHTHO [2,3-c] PYRANS

ABSTRACT

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The naphtho[2,3-c]pyran occurs frequently in nature as derivatives of the 5,10 - quinones. The most common examples include the eleutherins and protoaphins. These naturally occurring compounds have been found to possess antibiotic activity through the process of bioactivation. The possibility of appropriately substituted compounds functioning as bioreductive alkylating agents provides a logical model that has a great deal of predictive power.

The thesis deals with the synthesis of some naphtho[2,3-c]pyrans to be tested biologically; the challenge being to design compounds in a biologically inactive form which become activated only subsequent to an *in-vivo* transformation.

Chapter One describes and compares a high yielding synthesis of a naphtho[2,3-c]pyran, hongconin, to a previous route.[18] Racemic hongconin (29) has been synthesised from adduct (43) formed by reaction between 1-methoxycyclohexa-1,4-diene (41) and 1,4-benzoquinone (42). The key steps

includes Fries and Claisen rearrangements, base and cerium(IV) initiated pyran ring formation, C-4 pyran ring hydroxylation and silver(II) mediated oxidation. The target compound (29) was tested *in vitro* for antimicrobial activity and compared to the results obtained for isoeleutherin (2) and its 9-demethoxy analoque (30).

The spectral data, melting points and yields of the individual compounds is as described in Chapter Two.

To my parents Johannes and Angie Oosthuizen whose love and support steered me

*in the right direction, making my study career possible.*

GENERAL INTRODUCTION

Several naturally occurring quinones contain the naphtho[2,3-c]pyran ring system. These pyranquinones are widely distributed in sea urchins and related marine animals, certain fungi and lichens. Many are present in bark or roots of the higher plants, or in animal tissues, where they occur only in very low concentration and are masked by other pigments.[1]

The epimeric naphtho[2,3-c]pyran -5,10-quinones, eleutherin (1) and isoeleutherin (2) were first isolated from the tubers of *Eleutherine bulbosa* by Schmid and co - workers.[2-4]
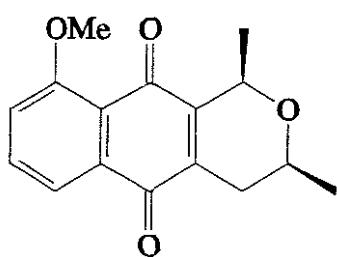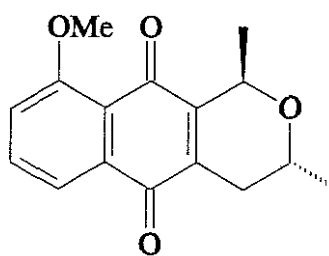
(1)   (2)
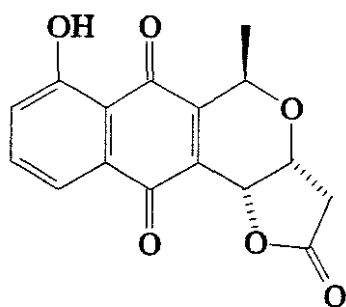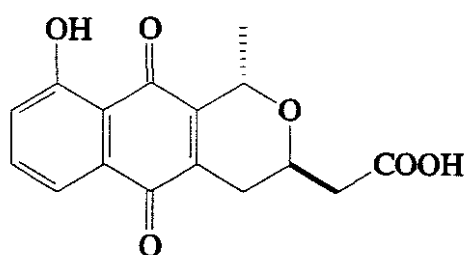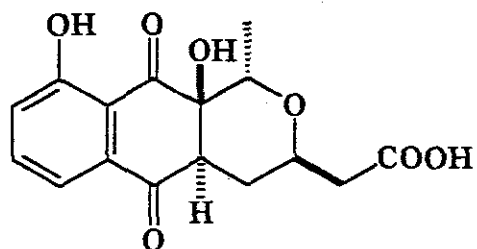
Other naturally occurring compounds include kalafungin[5](3), the nanaomycins[6,7] (4)-(7), -naphthocyclinone[8] (8) and extended quinones[9] (9)-(10).

Kalafungin   (3)   Nanaomycin A   (4)

Nanaomycin B (5)
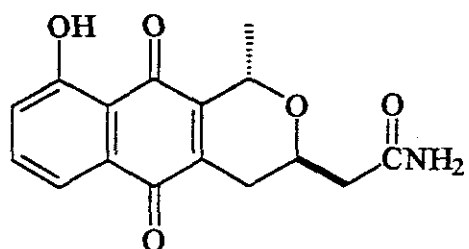
Nanaomycin C (6)
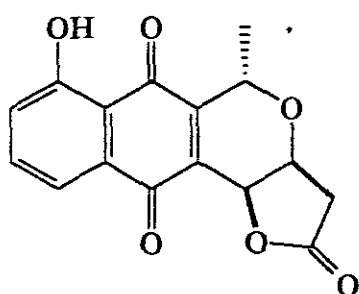
Nanaomycin D (7)
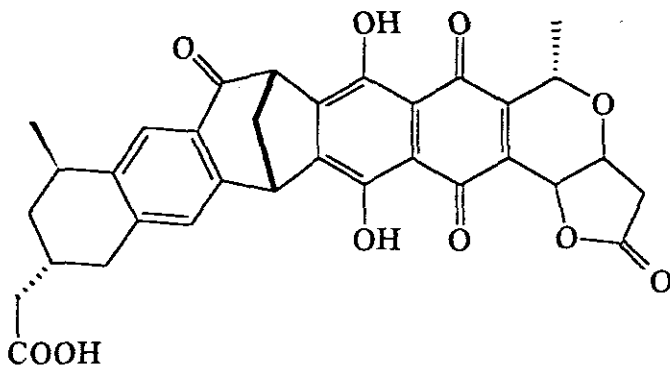
ɣ - Naphthocyclinone (8)
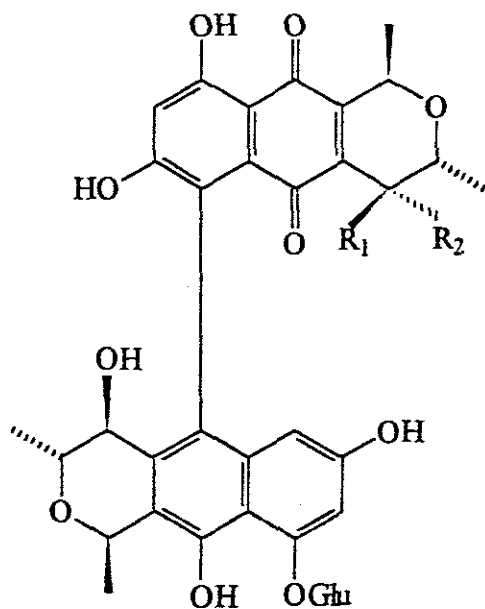
Protoaphin-*fb* (9) R_1 = OH ; R_2 = H
Protoaphin-*sl* (10) R_1 = H ; R_2 = OH

Moore[10] has reviewed numerous compounds that can act as bioreductive alkylating agents *via* quinone methide formation, that is, biologically inactive compounds can become potent alkylating agents after they undergo a reduction *in-vivo* to an active hydroquinone which functions as a bis-alkylating agent.

A number of naturally occurring quinones contain the fused pyrano- -lactone moiety such as that found in the antibiotic nanaomycin D (7).

The proposed mechanism of action for these quinones is illustrated in **SCHEME A** (overleaf) using nanaomycin D (7) as example.

(7)

(11)

(13)

(12)

2 H⁺

(14)
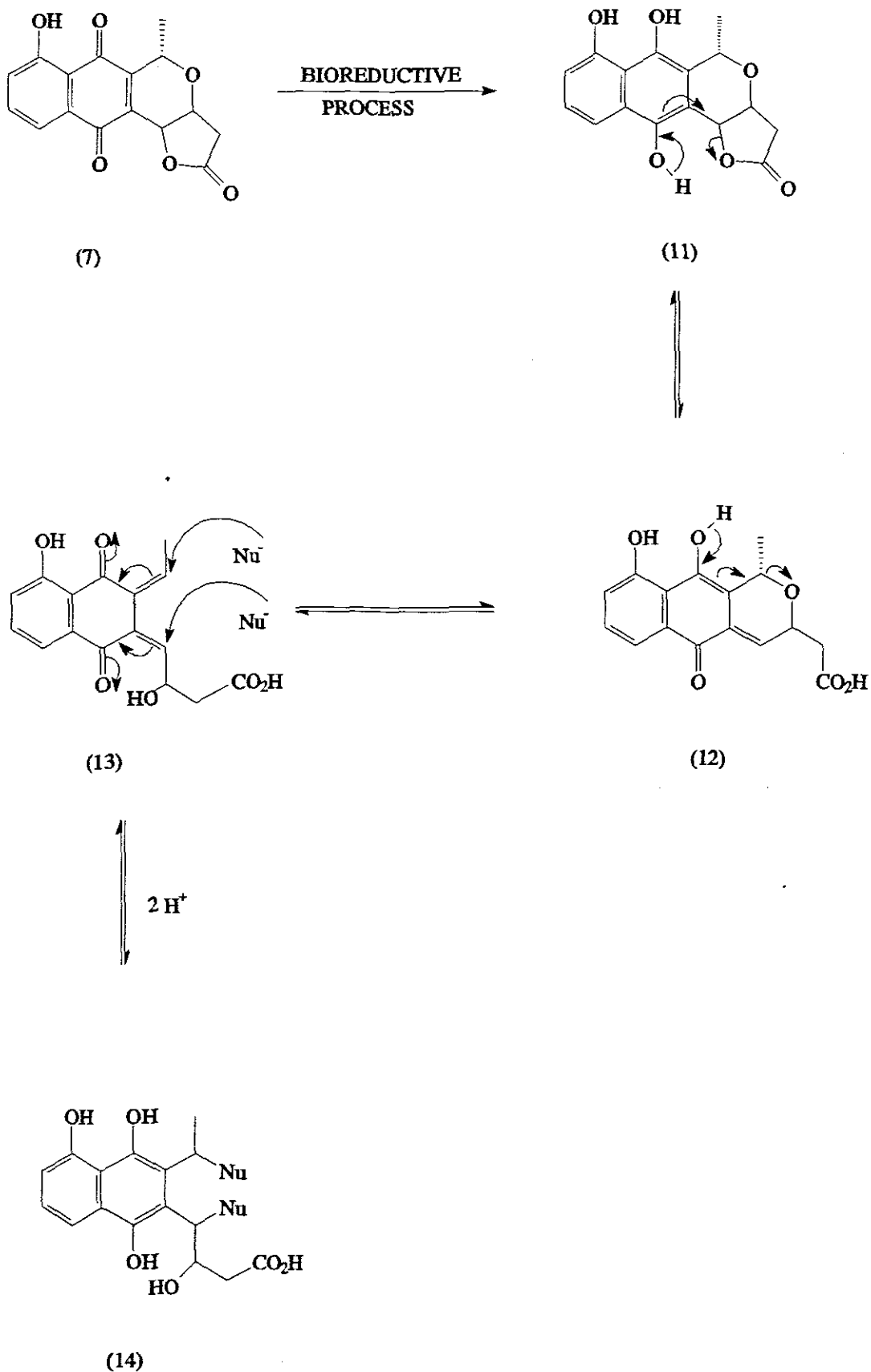
BIOREDUCTIVE PROCESS: **SCHEME A**

After *in-vivo* reduction of the quinone (7) to the hydroquinone (11), the quinone

methide (12) is formed through ring opening of the fused pyrano- -lactone moiety,

after which opening of the heterocyclic ring affords (13). The resulting quinone

methide(13) could act as a Michael-type acceptor to nucleophiles (Nu) which may

be certain nucleophilic centres in the D.N.A. or R.N.A. molecule, thereby binding

the nucleic acid, as in (14) and preventing cell growth.[11]

Research has shown that the naphtho[2,3-*c*]pyran ring system could well be

biologically active through the process of bioreductive alkylation. According to the

above proposed mechanism, the eleutherins (1) and (2) might also undergo

bioreduction and consequently act as bioreductive alkylating agents.
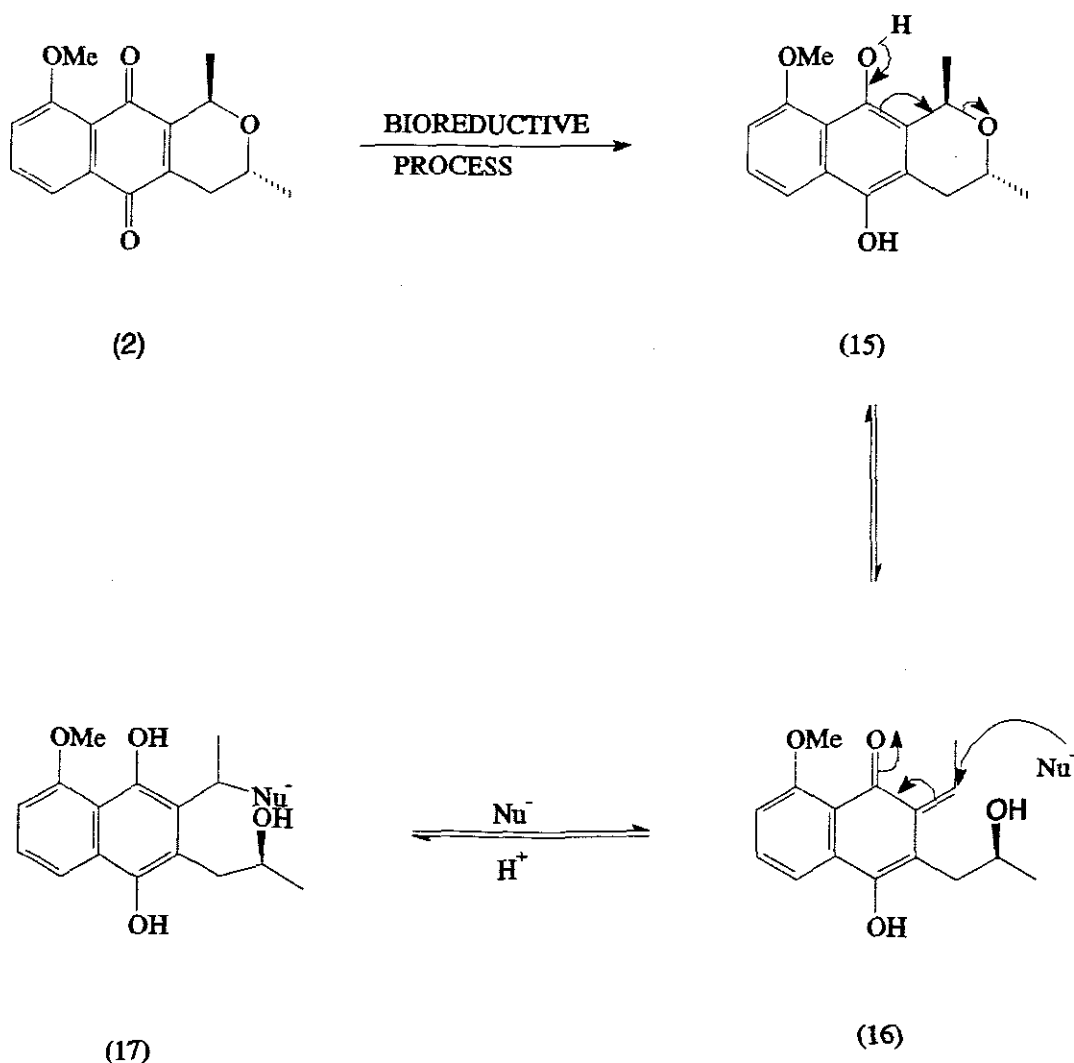
SCHEME B

Professor Robin Giles and colleagues at the University of Cape town investigated the possible laboratory synthesis of some naturally occurring quinones of the eleutherin type, and were the first to synthesise C-4 hydroxylated naphtho[2,3-c]pyran-5,10-quinones.

Spontaneous cyclisation to the quinone (20) was attempted by treating the alcohol (18) with argentic oxide.[12] It was found that the attempted cyclisation afforded only one product namely the quinonoid alcohol (19), which exhibited little proclivity towards cyclisation.

OMe

OH

OMe

(18)

O

OH

O

(19)

O

O

O

(20)

O

O

OH

(21)

O

O

O

OH
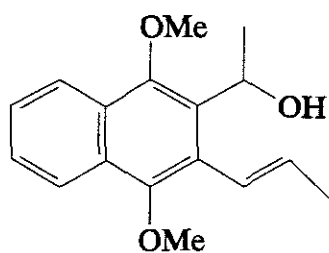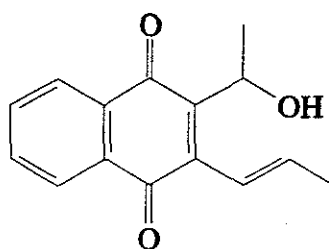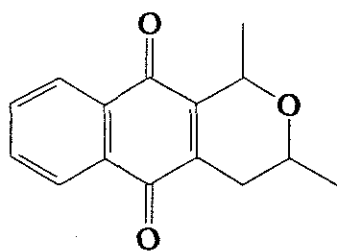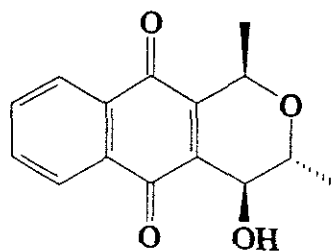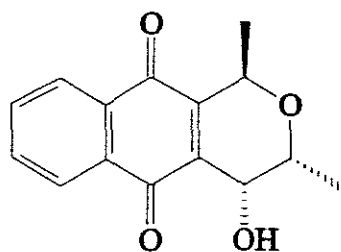
(22)

Giles further found that oxidation of the alcohol (18) with 4 molar equivalents cerium(IV) ammonium nitrate (CAN) afforded a mixture of the two diasteriomeric naphthopyranquinones (21) and (22) as their racemates.

The same alcohol, when treated with 2 molar equivalents cerium(IV) ammonium nitrate (CAN) afforded a mixture of the two racemic naphthopyrans (23) and (24).[13]
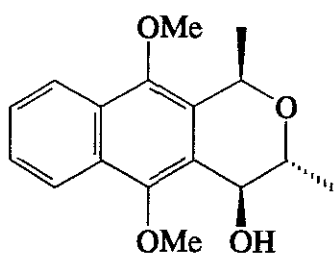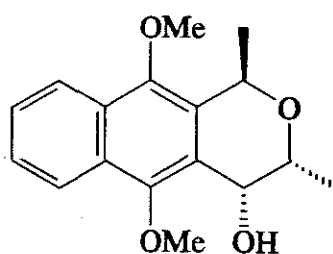
(23)   (24)

Compounds (23) and (24) afforded the quinones (21) and (22) respectively when further treated with 2 molar equivalents CAN.

Thus the one-step conversion of the naphthalene dimethyl ether (18) to the naphtho[2,3-c]pyran-5,10-quinones (21) and (22) respectively was of considerable value since these products are the 7,9-dideoxy derivatives of quinone A (25) and quinone A′ (26) respectively and possess the correct relative stereochemistry about the pyran ring at C-1, C-3 and C-4.[14]
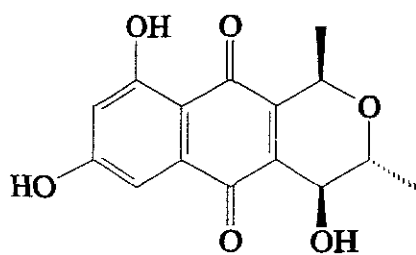
(25)
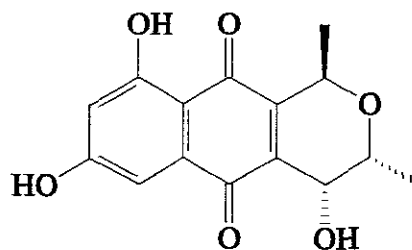
(26)

Compounds (25) and (26) possess the correct structure to be converted to the naturally occurring protoaphin - *fb* (9) and protoaphin - *sl* (10) respectively.

Protoaphin-*fb* (9) was first isolated from the heamolymph of the bean aphid, *Aphis fabae Scop.* and the isomeric protoaphin-*sl* (10) was isolated from the willow aphid, *Tuberolachnus salignus.*[15]

Another method of synthesising naphthopyrans was achieved by base-induced cyclisation of naphthyl alcohols of the type (27). Giles and co-workers[16] treated the unconjugated alkenyl alcohol (27) with potassium *t*-butoxide in N,N-dimethyl formamide (DMF) at 60°C for 15 minutes under nitrogen atmosphere to give the naphtho[2,3-*c*]pyran (28) in high yield. The conjugated isomer (18) cyclised equally well under the same conditions.
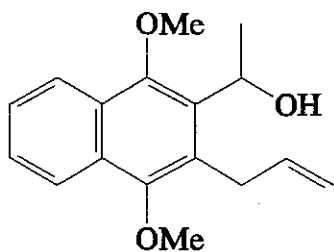
(27)
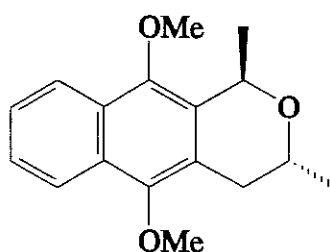
(28)

These reactions are of considerable importance, since the two methyl groups on the pyran ring can be obtained virtually exclusively *trans*.

The above methodology was used in this study for the construction of the [2,3-*c*]pyran ring.

The objective of this project was the total synthesis of the naphtho[2,3-*c*]pyran, hongconin (29) as the racemate for antimicrobial evaluation. It was envisaged that by comparing the antimicrobial activity of (29) (if any) with that of isoeleutherin (2) and its 9-demethoxy analogue (30) a better understanding of a possible molecular structure - activity relationship of these compounds would be gained.
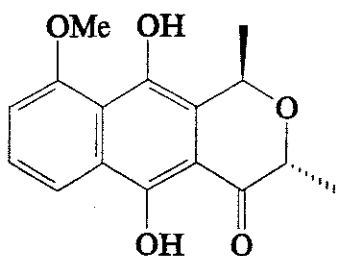
(29)
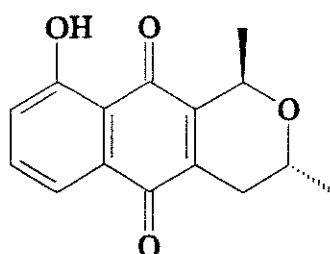
(30)

Chapter One deals with the synthesis of hongconin (29), a naphtho[2,3-c] pyran, which was isolated from the rhizome of *Eleutherin americana* Merr. et. Heyne (Iridaceae) in 1981, along with three known naphthalene derivatives, eleutherol (31), eleutherin (1) and isoeleutherin (2).[17-19] These four naphthalene derivatives showed the effect of increasing coronary flow on isolated guinea pig heart.
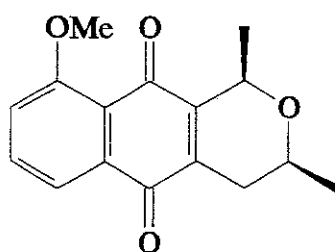
(1)
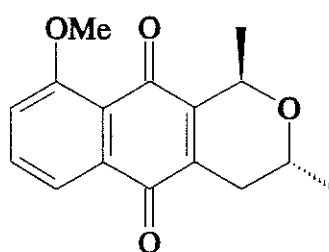
(2)
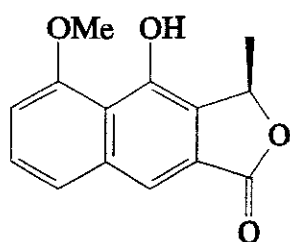
(31)

The rhizome of this plant was used as a folk medicine for the treatment of coronary disorders in southern China.[20] The biological activity of hongconin was confirmed by pharmacological tests using isolated guinea pig heart and shown to be effective to *angina pectoris*.[21]

The natural occurrence of (29) is low, thus the availability of quantities for more exhaustive testing is dependent on the development of a convenient synthetic route.

CHAPTER ONE

THE TOTAL SYNTHESIS OF HONGCONIN (29)

Kraus[18] recently reported the total synthesis of racemic hongconin (29) where the key steps include the methylation of a benzylic alcohol, the formation of a pyran ring, and the regioselective formation of a naphthalene ring *via* a Diels-Alder reaction.

The route involved the reaction of the alcohol (32) with *n*-butyllithium, followed by treatment with acrolein at -78°C, to afford an inseparable mixture of diols (33) and (34).
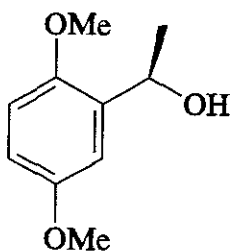
(32)
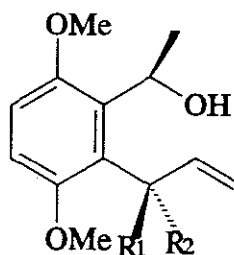
(33) R_1 = OH ; R_2 = H

(34) R_1 = H ; R_2 = OH

After treating the diols with mercuric acetate [$Hg(OAc)_2$] in aqueous THF[22], the resulting mercurials were reduced with sodium borohydride ($NaBH_4$) to provide a 5:1 ratio of the alcohols (35) and (36) respectively.

OMe

(35)

OMe OH

.

OMe

(36)

OMe OH
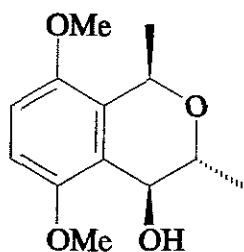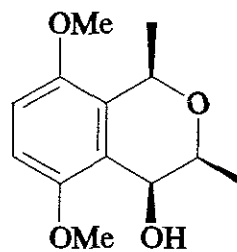
Alcohol (35) was then oxidised with pyridinium chlorochromate (PCC) to the ketone

(37) in high yield which was then further oxidised by the method of Rapoport

(AgO/HNO$_3$)[23] to afford the benzoquinone (38).

OMe

(37)

OMe O

O

(38)

O O
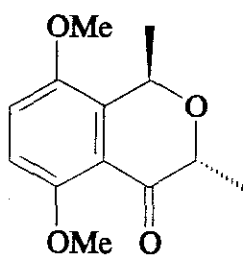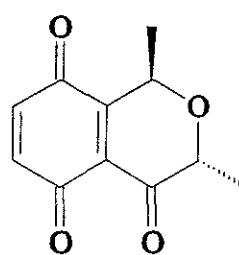
By the addition of a substituent X (such as halogen or sulfoxide)[24,25], the

regioselective cycloaddition reactions of quinones and dienes can be controlled,

for example.
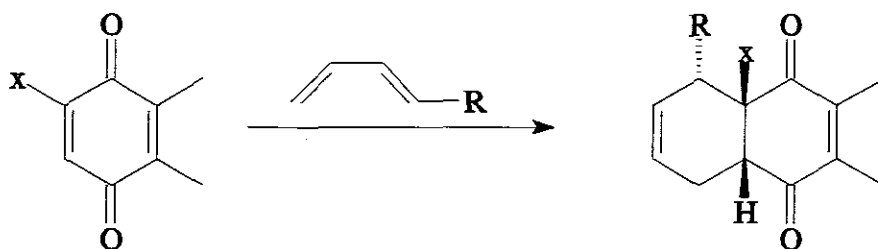
Thus the influence of functional groups not directly attached to the atoms undergoing a Diels-Alder reaction[26], was evaluated through the reaction of benzoquinone (38) with 1-[(trimethylsilyl)oxy] butadiene in dichloromethane for 24 hours at -78°C followed by treatment of the unpurified adduct with Jones reagent in acetone at 0°C to afford compound (39) in low yield.
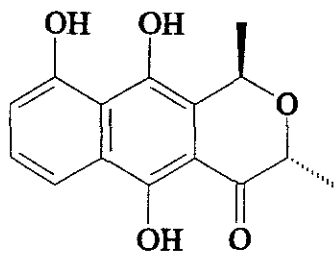
(39)
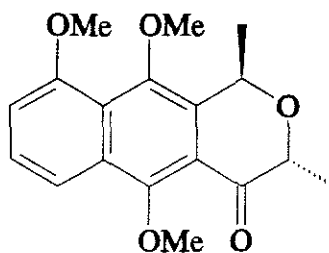
(40)

It was found that the carbonyl group in the pyranone ring exerted a large influence on the regioselectivity of the above reaction.

Methylation of compound (39) generated a triether (40) which was oxidised with argentic oxide [Ag(II)O/HNO$_3$], immediately followed by reduction with Na$_2$S$_2$O$_4$ to afford hongconin (29)

Our synthetic route for the synthesis of hongconin (29) is depicted in **SCHEME C** (overleaf), the first step being a regioselective cycloaddition *via a* Diels-Alder reaction.

SCHEME C

(41)   (42)   (43)   (44)

(47)   (46)   (45)

(48)   (49)

SCHEME C cont.

(50)

(51)

(54)

(53)

(52)

(55)

(56)

(40)

TARGET COMPOUND (29)
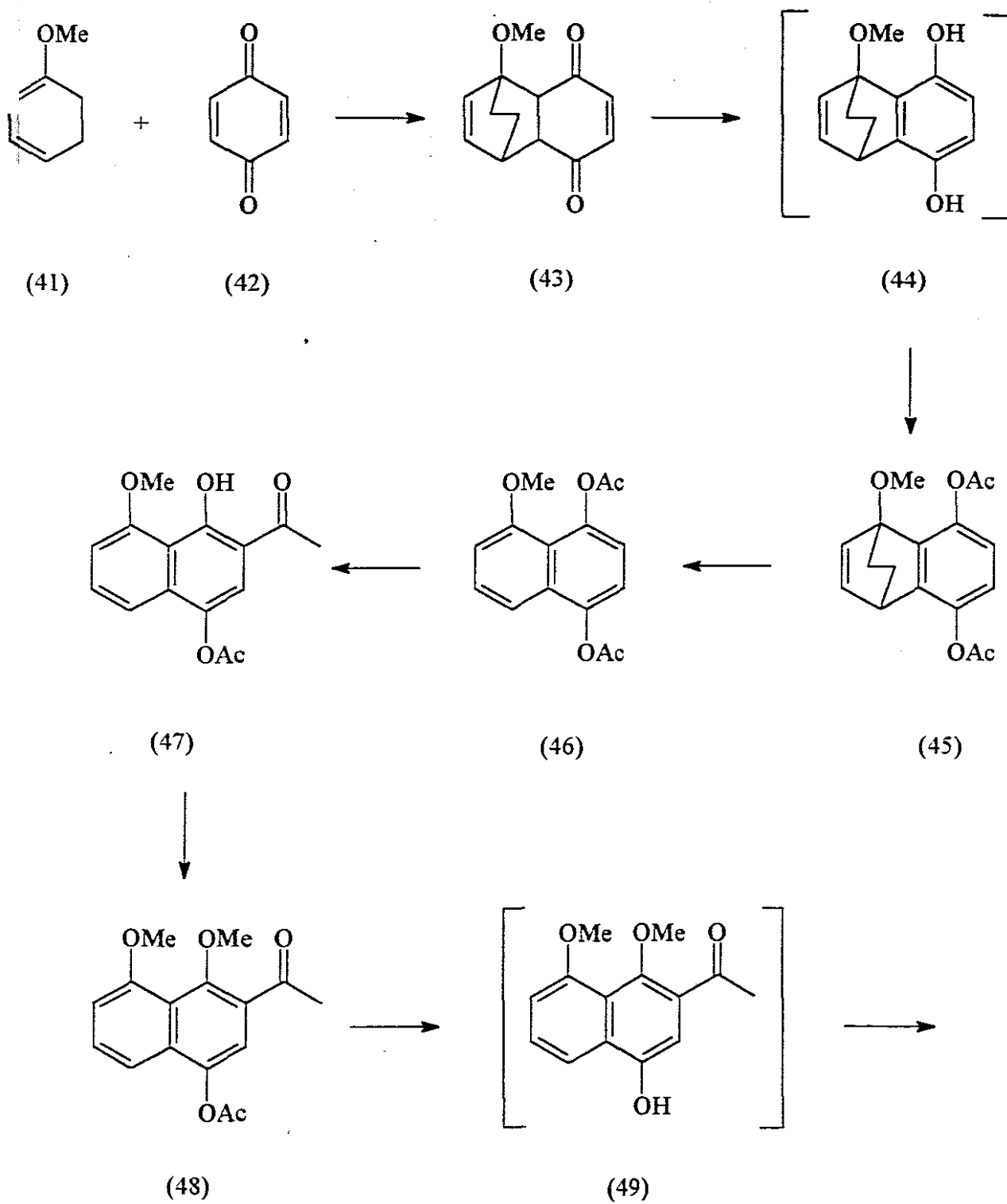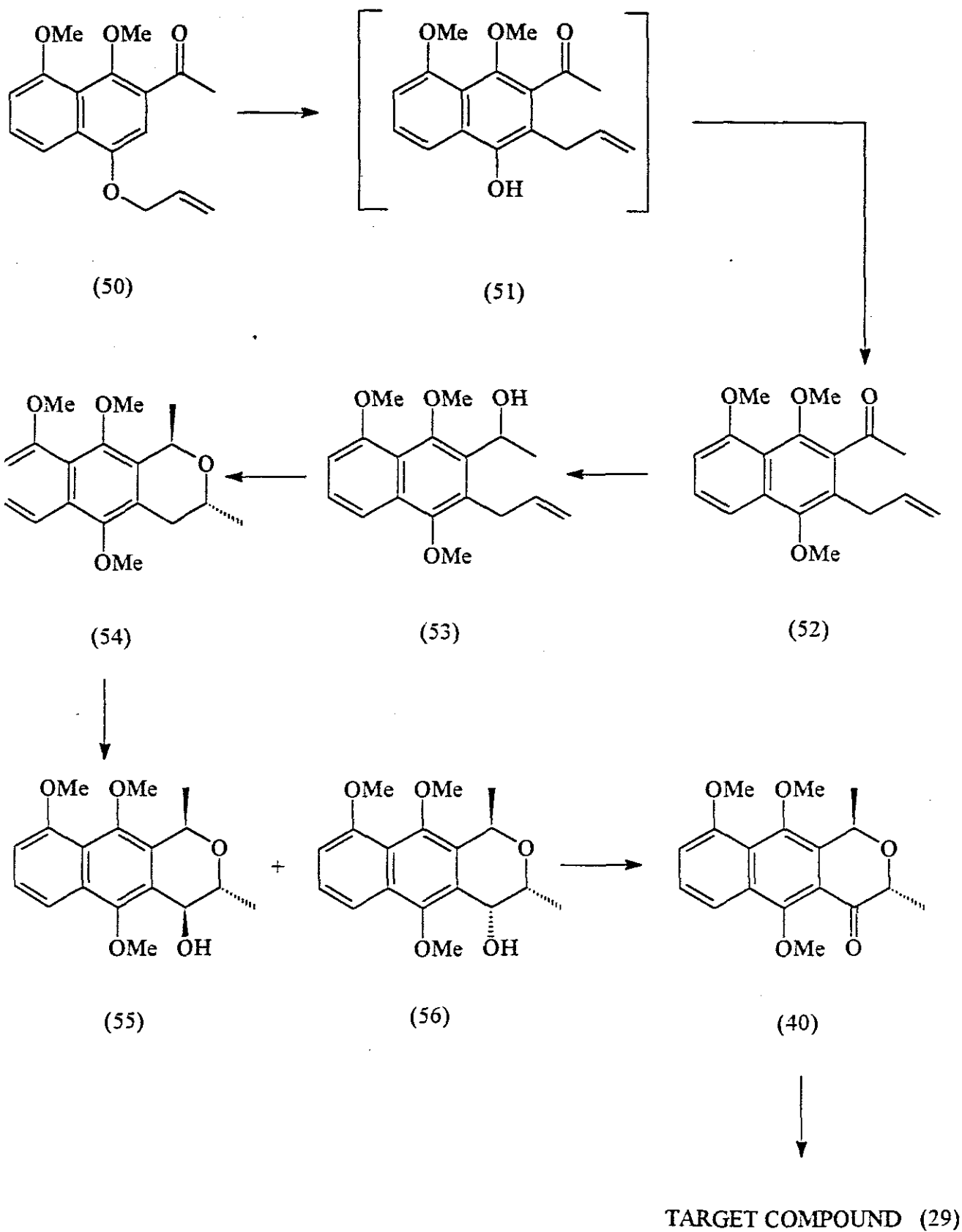
The Diels-Alder adduct (43)[28] was obtained in good yield by the addition of portions of recrystallised 1,4-benzoquinone (42) to 1-methoxycyclohexa-1,3-diene (41) in benzene and heated under reflux for 2½ hours. Although the diene mixture (41) contains up to 35% of the non-conjugated diene (57), the reaction still gave fair to good yields of the crystalline adduct (43).

OMe   OMe

65%   35%
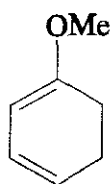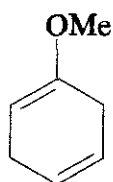
(41)   (57)

The portionwise addition of benzoquinone to the diene solution minimised the formation of quinhydrone which may interfere during work-up and contaminate the adduct (43).

Compound (43), was enolised with potassium carbonate in dry acetone to give the diol (44).

To avoid decomposition, diol (44) was immediately treated with acetic anhydride and pyridine to afford the diacetate (45) in good yield (71%).

The ethano - bridge of compound (45) was thermally eliminated (200 - 220°C) to yield the diacetate (46) in high yield. (96%)

The next step was to convert the diacetate (46) to compound (47) by means of a Fries rearrangement reaction.

Read and Ruiz[29] treated the 1,4-Diacetoxy naphthalene (58) with a solution of zinc chloride and glacial acetic acid under reflux for 30 min to afford the 4-acetoxy-2-acetyl-1-naphthol (59) in a 78% yield.
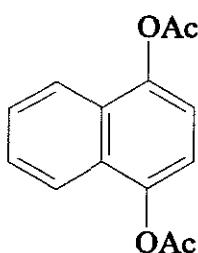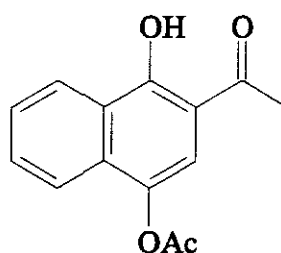
(58)   (59)

The same reaction conditions as above were employed to convert the diacetate (46) to compound (47), but extremely low yields were obtained.

Treatment of the diacetate (46) with boron trifluoride etherate afforded mainly the product (47) of *ortho* rearrangement[28] which was supported by the lowfield singlet at δ 14.08 in the ^{1}H n.m.r. spectrum which corresponds to the hydroxyl group hydrogen-bonded to the carbonyl - oxygen of the acetyl group at C-3. The

structure of compound (47) was thus confirmed by comparing its ^{1}H n.m.r.
spectrum and melting point with that of material obtained *via* an alternative route.[30]

The infrared spectrum of compound (47) shows the absence of a strong hydroxy
absorption band in the region 4000 - 3000 cm^{-1}. This phenomenon was also
observed in the infrared spectrum of 2-hydroxyacetophenone (60)[11], most likely due
to the strong intramolecular H-bonding in the molecule.
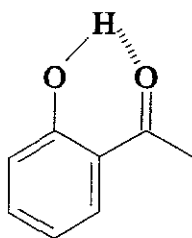
(60)

A minor product was also formed, which was isolated and identified as the
unstable naphthoquinol (61).
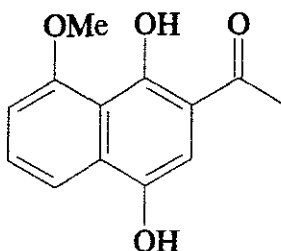
(61)

The ¹H n.m.r. spectrum of the quinol (61), (being almost insoluble in deuterated chloroform), was recorded in deuterated acetone as solvent. An important feature of this spectrum is the low field singlet at δ 13.40 due to strong intramolecular hydrogen bonding between the hydroxyl at C-4 and the carbonyl oxygen of the acetyl group at C-3, and a broad signal at *ca.* δ 6.00 due to the hydoxyl at C-1. Both signals disappeared upon addition of deuterium oxide.

Due to the instability of quinol (61) it was converted to the monoacetate (47) by acetylation of the crude reaction mixture with distilled acetic anhydride (1 molar equiv.) and pyridine (1 molar equiv.) in chloroform containing zinc-dust; the function of the latter being to convert any of quinone (62), which may arise by aerial oxidation of compound (63), a by-product of the Fries rearrangement, to the acetate (64) by reductive monoacetylation.
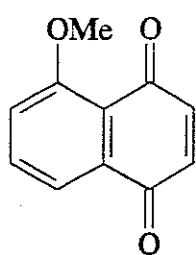
(62)
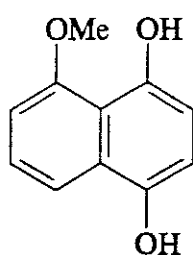
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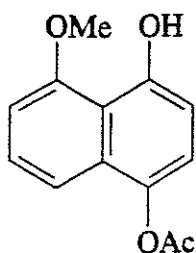
(64)
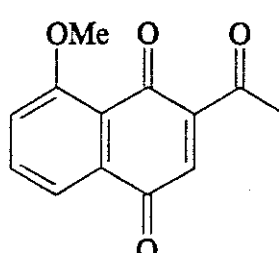
(65)

At the same time, any of the quinone (65) which may similarly be obtained by oxidation of hydroquinone (61), would be converted to (47).

The monoacetate (47) was methylated by refluxing with a large excess of distilled methyl iodide (10 molar equiv.) and potassium carbonate (5 molar equiv.) in acetone for 5 hours under nitrogen. Yields of 90% were regularly obtained throughout.

Alkaline hydrolysis of the methylated product (48), afforded the unstable intermediate (49).

Because of its instability, the intermediate was not chromatographed, but dissolved in acetone and refluxed with allylbromide (3 molar equiv.) in the presence of potassium carbonate (3 molar equiv.) for 3 hours to afford compound (50) as a bright yellow solid.

In the next step compound (50) underwent a thermal Claisen rearrangement (200-210°C) to afford the intermediate (51), which was immediately methylated in the usual way to the trimethyl ether (52) (91%).

The ^{1}H n.m.r. spectrum of this product showed *inter alia* a doublet of doublets (J 1 and 6Hz) at δ 3.56 due to the methylene protons of the propenyl chain at C-2 which are coupled to the olefinic protons. The terminal olefinic protons resonated as a two-proton multiplet centred at δ 4.75 - 5.20, whereas the C-2 vinylic proton resonated as a one proton multiplet at δ 5.60 - 6.26.

The reaction of (52) with lithium aluminium hydride (LiAlH$_4$) in dry ether at room temperature afforded the corresponding alcohol (53) in high yield. (80%)

The ^{1}H n.m.r. spectral features of (53) corresponded entirely to those reported earlier by Kometani et al.[31]

The non-conjugated alcohol (53) was then dissolved in DMF and treated with potassium t-butoxide (5 molar equiv.) under nitrogen at room temperature for 10 minutes to afford the naphtho[2,3-c]pyran (54).

It is very important that for this reaction all moisture is eliminated and only freshly distilled DMF and sublimed potassium t-butoxide are used.

The ^{1}H n.m.r. spectrum of the naphtho[2,3-c]pyran (54) showed inter alia, a three-proton doublet (J 6Hz) at δ 1.40; another three-proton doublet (J 6.5Hz) at δ 1.65; a one-proton doublet of doublets (J 11 and 17Hz) at δ 2.59, another one-proton doublet of doublets (J 3.5 and 17Hz) at δ 3.07; a one-proton multiplet at δ 4.05 - 4.23, and a one-proton quartet (J 6.5Hz) centred at δ 5.34.

Thus the above spectroscopic data supported the assignment of structure (54) to the product in which the partially unsaturated pyran ring may be represented as in FIGURE 1[32] (overleaf).
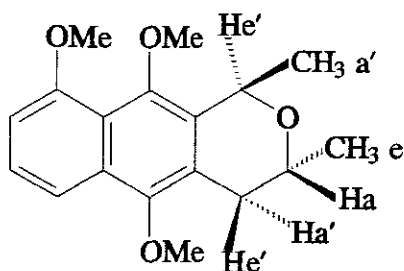
(54)
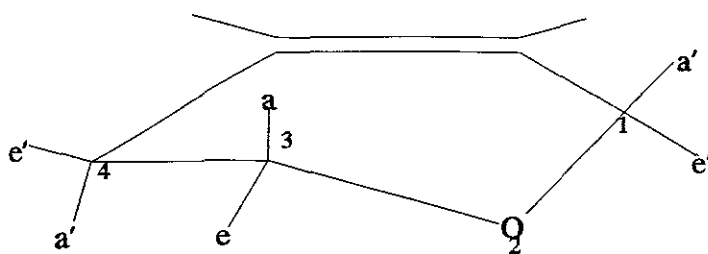
FIGURE 1

The shape of the pyran ring is distorted from that of the normal chair geometry in order to accommodate the trigonal carbon atoms of the aromatic ring.

The symbols a′ and e′ denote *pseudo*-axial and *pseudo*-equatorial configurations of the bonds in question in the chair-like conformation of the partially unsaturated ring. A useful tool for determining the stereochemistry of protons on adjacent carbon atoms is to use the Karplus equation.[33;34]

The substituents attached to C-3 occupy normal equatorial (e) and axial positions (a), but those attached to C-1 and C-4 are imperfectly staggered and are said to occupy *pseudo*-equatorial (e') and *pseudo*-axial (a') positions.

The doublet at δ 1.40 is due to the methyl group at C-3, which occupies the less crowded equatorial position, coupled to 3-H. The doublet at δ 1.65 is as a result of the C-1 *pseudo*-axial methyl coupled to the adjacent hydrogen at C-1 of the pyran ring. The doublet of doublets which resonate at δ 2.59 represent the *pseudo*-axial 4-H which is geminally coupled to the *pseudo*-equatorial 4-H, as well as vicinally coupled to axial 3-H. The coupling constant of 11 Hz (Jvic) between 3-H and 4-H confirmed the former axial since the relatively large coupling constant implies a large dihedral angle (ϕ) between the axial 3-H and one of the hydrogens at C-4. The coupling constant of 17 Hz represents the geminal coupling between the two hydrogens at C-4. The doublet of doublets at δ 3.07 is due to the *pseudo*-equatorial 4-H which again is geminally coupled to the *pseudo*-axial 4-H and vicinally coupled to the axial 3-H. The smaller coupling constant of 3.5 Hz (Jvic) indicates a smaller dihedral angle between the one 4-H and 3-H. The multiplet at δ 4.05 - 4.23 is due to the axial 3-H, whereas the quartet at δ 5.34 is due to 1-H coupled to the *pseudo*-axial methyl group.

The magnitude of Jvic, being a function of the dihedral angle (ϕ) between 3-H and 4-H, is also given by the Karplus equation, which frequently agrees with the observed values.

FIGURE 2 summarised in a qualitative manner the dependence of Jvic on the dihedral angle (ϕ).

Karplus equations:

ϕ between 0° and 90°   :   Jvic $= 8.5 \cos^2 \phi - 0.28$

ϕ between 90° and 100°   :   Jvic $= 9.5 \cos^2 \phi - 0.28$
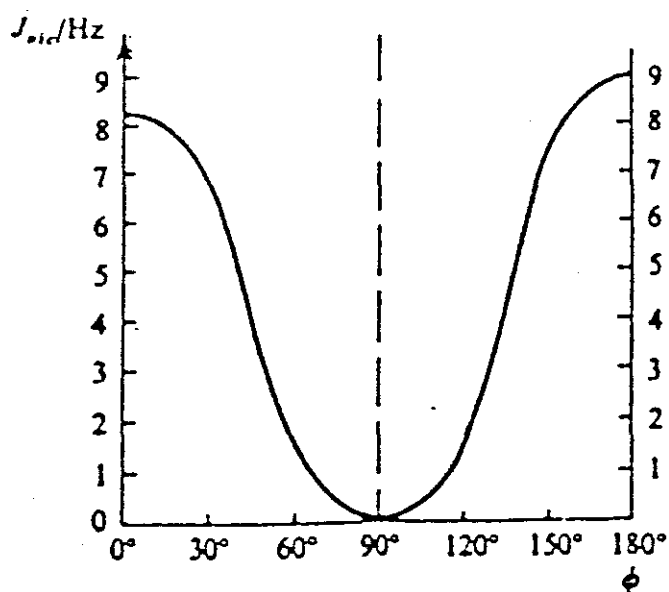
FIGURE 2: Variation of vicinal coupling constant J_{vic}, with dihedral angle ϕ
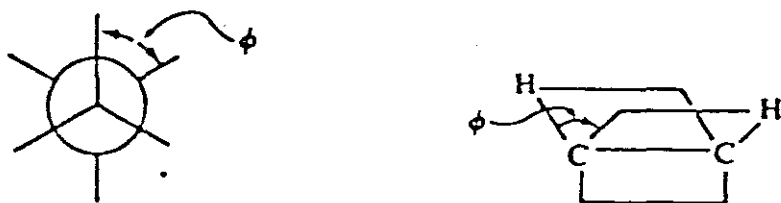
FIGURE 3: Graphical explanation of Karplus's equation

The largest vicinal couplings arise with protons in the *trans* co-planar position (ϕ = 180°), while vicinal coupling for *cis* co-planar protons are almost as large (ϕ = 0°). In contrast very small couplings arise between protons at 90° to each other.

This base-induced cyclisation also yielded small amounts of the *cis*-isomer (66).
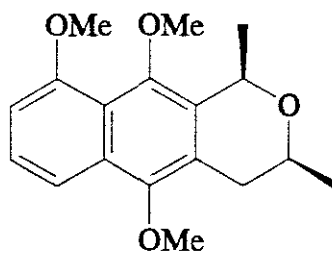
(66)

The [1]H n.m.r spectrum allows for certain distinctions to be made between the *cis* and the *trans* isomer.[31]

The 3-H multiplets differ substantially in chemical shift; those for the *trans* isomer (54) fall in the range at δ 3.90 - 4.30, while 3-H in the *cis* isomer (66) appear at δ 3.50 - 3.80. The chemical shift of the 1-H quartets also differ with the *trans* isomer resonating at *ca.* δ 5.30 while 1-H of the *cis* isomer occurs at *ca.* δ 5.20.

Existing methods[22,31] for preparing naphthopyrans always give a mixture, however the method we applied here can be used selectively to provide the *trans* isomer in high yield.

We attempted cyclisation and hydroxylation in one step by dissolving the non-conjugated alcohol (53) in dimethyl sulphoxide (DMSO) and passing dry air through the stirred solution for 5 minutes. However, the alcohol did not dissolve in the DMSO and N,N-dimethylformamide (DMF) was used as substitute. Potassium *t*-butoxide (4 molar equiv.) was added and the solution stirred for 20 minutes under a stream of air. A further quantity of potassium t-butoxide (2 molar equiv.) was added and the mixture stirred for a further 20 minutes to afford a mixture of the *trans*-dimethylnaphthopyran (54) with small amounts of the *cis* isomer (66) as well as the diasteriomeric 4-hydroxypyrans (55) and (56) in low yields.
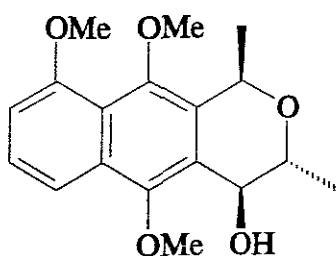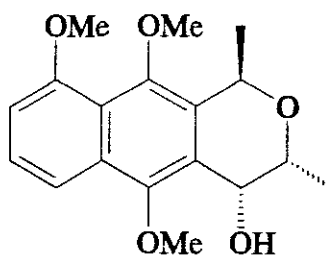
(55)   (56)

By first cyclising the alcohol (53) to the naphthopyran (54) followed by hydroxylation using the above method, the 4-hydroxypyrans (55) and (56) were obtained in a combined yield of 73% (based on unrecovered starting material) in a ratio of approximately 4:1 respectively.

Thus, under these conditions compound (55), in which the hydroxyl occupies the *pseudo*-equatorial position (e'), was more abundant than (56) in which the hydroxyl group is *pseudo*-axial (a').

The stereochemistry at the chiral centres of the isomeric compounds (55) and (56) was also established by (i) the reasonable assumption that the C-3 methyl adopts the less crowded equatorial position and (ii) the magnitude of vicinal coupling (J_{vic}) between 3-H and 4-H as observed in their individual ^{1}H n.m.r. spectra.

In the case of compound (55) the vicinal coupling constant of 8 Hz between 3-H and 4-H confirmed the latter as *pseudo*-axial.

For the isomeric (56), the smaller vicinal coupling constant of 2Hz indicated a smaller dihedral angle (ϕ) between 3-H and 4-H, which with 3-H again axial, confirmed the 4-H as being *pseudo*-equatorial and thus the hydroxyl as *pseudo*-axial.

Since long range coupling between 1-H and 4-H is too small to be measured, it was more difficult to assign configuration at C-1. However, the stereochemistry at C-1

for (55) was readily established by comparing its ^{1}H n.m.r. spectral data of the

smaller J value of 1-H (1.4Hz) to that published for quinones (21) and (22).[12,13]
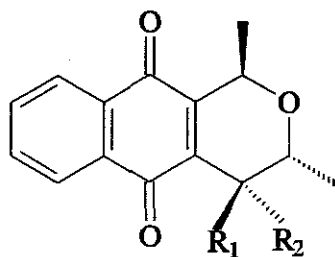
(21) R$_1$ = OH ; R$_2$ = H

(22) R$_1$ = H ; R$_2$ = OH

It is known that measurable long-range coupling of the type (H-C-C=C-C-H),

occurs by the operation of a mechanism involving presumably hyperconjugation

and σ-π electron interaction.[35]

In compounds (21) and (22) the C-H bonds at C-1 and C-4 assume different

conformations with respect to the plane of C=C of the quinone ring. Karplus[33] has

shown that long-range coupling of this type will be a maximum between C-H bonds

which are perpendicular to the plane defined by the double bond and almost zero

between C-H bonds in the plane of the double bond.

Compound (21) showed a doublet of quartets at δ 4.92 (J 7 and 1.5Hz), a doublet

of doublets at δ 4.47 (J 8 and 1.5Hz), and a doublet of quartets at δ 3.90 (J 8 and

6.5Hz). The signals being respectively due to 1-H, 4-H, and 3-H. The large

coupling constant between 3-H and 4-H (8 Hz) indicates an arrangement close to

trans-diaxial between these two protons, the C-3 methyl and C-4 hydroxy groups therefore being equatorial and *pseudo*-equatorial respectively.

The smaller coupling constant in each case is thus undoubtedly due to the long-range coupling discussed above between *pseudo*-equatorial 1-H and *pseudo*-axial 4-H. No long-range coupling was observed for compound (22) between the 1-H and 4-H protons confirming 1-H as *pseudo*-equatorial and thus C-1 methyl as *pseudo*-axial.[13]   ,

Thus the ^{1}H n.m.r. spectrum of compound (55) included a broad singlet at δ 4.20 (which disappeared on addition of deterium oxide) due to the C-4 hydroxy group, and a one-proton doublet (J 8.5Hz) at δ 4.76 due to the *pseudo*-axial 4-H which is vicinally coupled to the axial 3-H. The resonance of the latter appeared at *ca.* δ 3.97 as a doublet of quartets (J 6.5 and 8.5Hz). The large coupling constant (8.5Hz) as with (21), indicates an arrangement close to *trans*-diaxial between 3-H and 4-H, the C-3 methyl and C-4 hydroxy groups therefore being equatorial and *pseudo*- equatorial respectively.

The next step was to oxidise the 4-hydroxypyrans (55) and (56) to the trimethoxy ketopyran (40).
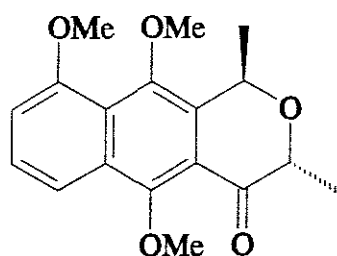
(40)

Pyridinium dichromate (PDC) has been shown to be very useful in the oxidation of alcohols and is easily prepared in quantity by dissolving chromium trioxide (CrO_3) in a minimum of water, adding pyridine and collecting the precipitate as a stable bright orange solid.[36]

PDC oxidant was used by Van Eeden[37] to oxidise the dimethoxyhydroxypyran (67) to the 4-oxopyran (68).
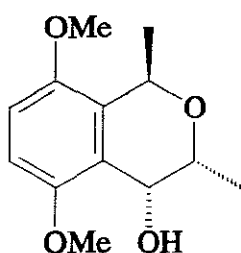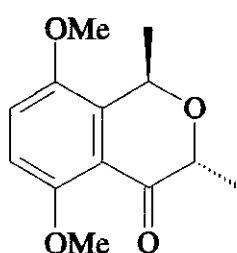
(67)   (68)

Thus the diasteriomeric mixture of (55) and (56) was treated with PDC (10 molar equiv.) under nitrogen and left stirring for 15 hours at room temperature. We expected a better yield than the 37% obtained earlier by Van Eeden[37], since compounds (55) and (56) are more electron rich, however 44% was the best yield obtained.

We replaced PDC with pyridinum chlorochromate (PCC) in an attempt to obtain better yields. PCC is a highly efficient readily available, stable reagent and prepared by adding chromium trioxide (CrO_3) to 6M HCl rapidly with stirring. The homogenous solution is cooled to 0°C and pyridine is added to give a yellow orange solid.[38]

A mixture of compounds (55) and (56) was slowly added to a stirring suspension of PCC (4 molar equiv.) and celite (to increase the reaction surface) in dichloromethane at 0°C. The reaction mixture was warmed to room temperature and left stirring for 15 hours to afford the ketopyran (40) in a yield of 84%.

Based on its spectroscopic properties, structure (40) was confirmed. The ¹H n.m.r. showed the following spectral features: a three-proton doublet (J 7Hz) at δ 1.50 is due. to the methyl group at C-3 which adopts the less crowded equatorial position, coupled to 3-H. The doublet at δ1.67 is due to the C-1 *pseudo*-axial methyl coupled to the adjacent hydrogen at C-1 of the ring. The quartet at δ 4.58 and δ 5.49 correspond to the coupling of 3-H and 1-H to the protons at C-3 and C-1 respectively.

In the benzo-series[37] it was decided to oxidise the dimethoxyketopyran (68) to the quinone (69) using argentic oxide [Ag(II)O/HNO_3] as an oxidant. The quinone (69) formed could then easily be reduced to the hongconin derivative (70).

(68) ⟶ (69) ⟶ (70)
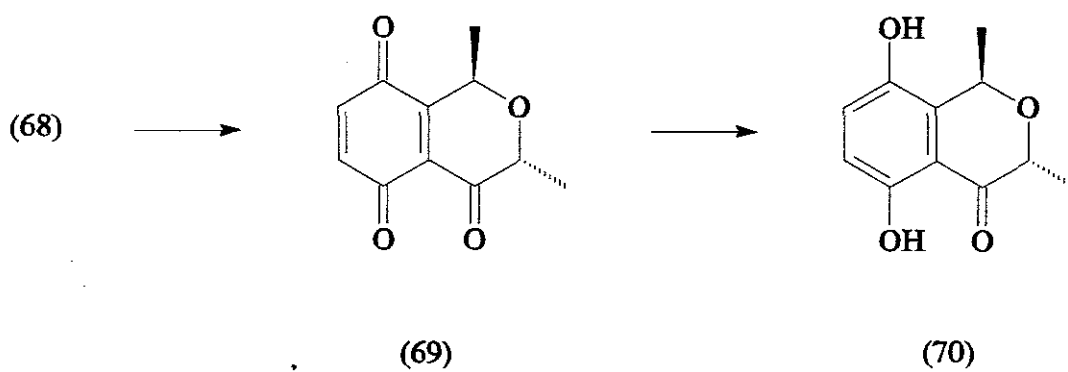
This was what was expected according to the mechanism outlined by Snyder and Rapoport[23]. (**SCHEME D** overleaf)

SCHEME D
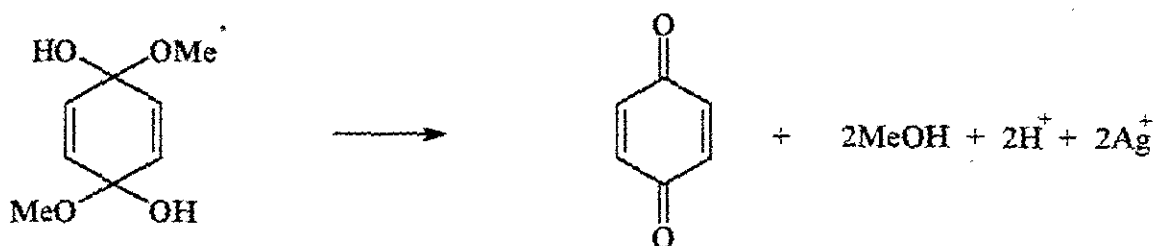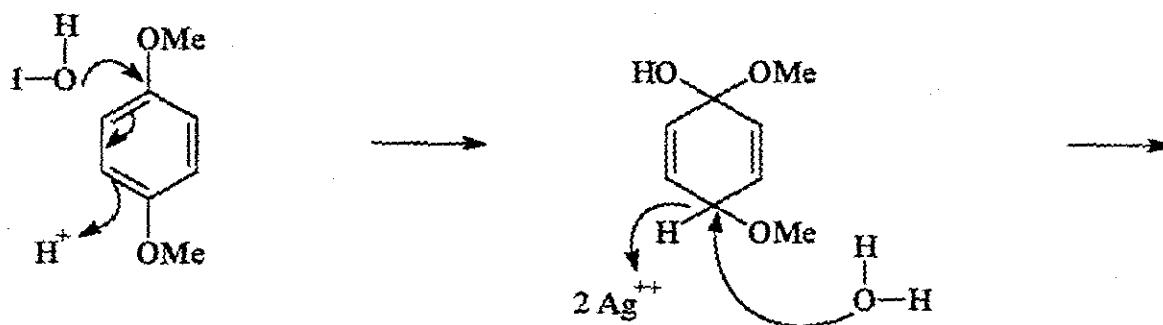
OR
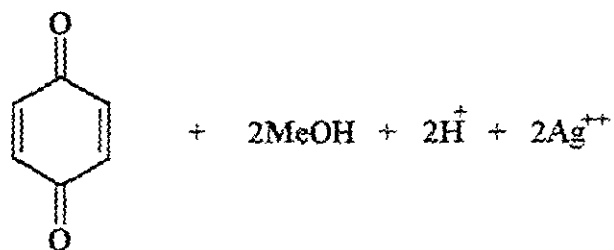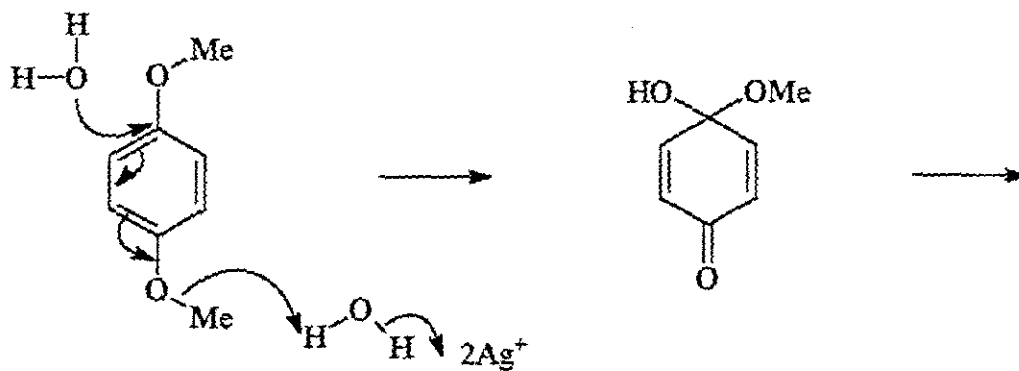
After the reaction of compound (68) with argentic oxide and upon close inspection of the spectroscopic data, it was evident that the target compound (70) was formed instead of the expected quinone intermediate (69).

The ^{1}H n.m.r. spectrum showed *inter alia* two singlets at δ 4.92 and δ 11.30 which disappeared on addition of deterium oxide.

Using the same reaction conditions as in the benzo-series the trimethoxyketopyran (40) was dissolved in dioxane and argentic oxide added (5 molar equiv.), after which the reaction mixture was treated with nitric acid (6M) and left stirring for 15 minutes at room temperature. Upon inspection of the spectroscopic data and comparing it with that of compound (70) it was confirmed that hongconin (29) was formed in one step in a low yield of 37%. According to mass spectroscopic data analysis it seemed as if some quinone (71) indeed formed.
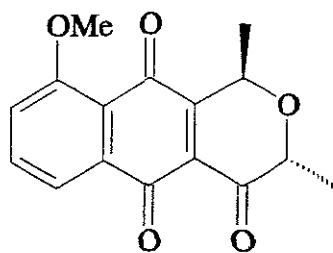
(71)

The ^{1}H n.m.r. of hongconin showed inter alia two D_2O exchangeable singlets at δ 8.97 and 12.80, and a doublet at δ 1.55 (J 7Hz) and 1.64 (J 7Hz) corresponding to the protons of the two methyl groups at C-3 and C-1 respectively.

The I.R. spectrum showed absorption at 3400 cm^{-1} corresponding to the hydroxy group and a carbonyl absorption at 1735 cm^{-1}.

No explanation as yet can be given as to why the trimethoxyketopyran (40) did not undergo oxidation to the expected intermediate (71) (as proposed by the mechanism of Snyder and Rapoport[23]), but it is thought that the intramolecular H-bonding stabilises the hydroquinone and thus favours the formation of the product (29).

Compounds (40) and (29) were evaluated for antimicrobial activity but showed no activity against some selected Gram positive and Gram negative organisms.

n order to compare the antimicrobial activity of (40) and (29) with that of other structurally related naphthopyrans it was decided to prepare compounds (2) and 30).

soeleutherin (2) was readily synthsised from pyran (54) by treatment with CAN as irst reported by Kometani et al[31].

Finally compound (30) was obtained from (2) by Lewis acid (AlCl₃) mediated demethylation at 0°C. It was noted that when demethylation was performed at room temperature, the *cis* isomer (72) also formed.
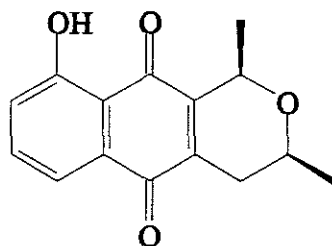
(72)

Since the Rf values of (30) and (72) are identical their relative abundance was established by ¹H n.m.r. integration. [64:36 = 3:2]

The ¹H n.m.r. spectrum allows for definitive distinctions to be made between the *cis* and the *trans* isomer. The 3-H multiplets differ substantially in chemical shift; Those for the *trans* isomer (30) fall in the range at δ 3.90 - 4.05 while 3-H of the *cis* isomer (72) appears at δ 3.50 - 3 69. The chemical shift of the 1-H quartets also differ with that of the *trans* isomer resonating at *ca.* δ 4.99 while the 1-H of the *cis* isomer occurs at *ca.* δ 4.83.

The antimicrobial activities of (40), (29), (2) and (30) as evaluated through the Bauer-Kirby method are shown in **Table 1**.

TABLE 1

RELATIVE INHIBITION ACTIVITY OF COMPOUNDS (40, (29), (2) AND (30)

ORGANISMS SABS Culture No.	Number of Organisms per ml.	Dose of compound in μmol.	Compound (40) in albumin. Inhibition Zone in mm	Compound (29) in albumin. Inhibition Zone in mm.	Compound (2) in albumin. Inhibition Zone in mm.	Compound (30) in albumin Inhibition Zone in mm.
GRAM + Staphylococcus aureus SATOC Sta 10	7.2×10^{12}	2.81 1.40 0.70	- - -	- - -	19 15 15	17 14 14
Bacillus Subtilus SATOC BOC 96	1.4×10^{9}	2.81 1.40 0.70	11 - -	- - -	19 15 15	12 - -
Candida albicans fungus	1.2×10^{7}	2.81 1.40 0.7	- - -	- - -	22 20 20	- - -

TABLE 1 cont.

ORGANISMS SABS Culture No.	Number of Organisms per ml.	Dose of compound in μmol.	Compound (40) in albumin. Inhibition Zone in mm.	Compound (29) in albumin. Inhibition Zone in mm.	Compound (2) in albumin. Inhibition Zone in mm.	Compound (30) in albumin. Inhibition Zone in mm.
GRAM- *Pseudomonas aeruginosa* SATOC Pse 13	3.9×10^{10}	2.81 1.40 0.70	- - -	- - -	- - -	- - -
Proteus mirabilis SATOC Pre 1	5.5×10^{9}	2.81 1.40 0.70	- - -	- - -	- - -	- - -
Eschericia coli SATOC ESC 20	3.6×10^{13}	2.81 1.40 0.70	- - -	- - -	- - -	- - -

CHAPTER TWO

EXPERIMENTAL

GENERAL:

H n.m.r. spectra were recorded on a 60 MHz Varian 360 Spectrometer and a Varian 200 MHz Spectrometer at ambient temperatures in deuterochloroform using tetramethylsilane as internal standard. Mass Spectra were recorded on a modified AEI analyzer (902) at 70 eV and an ion source temperature between $180^{\circ}C$ and $220^{\circ}C$. Infrared spectra were measured for nujol mulls on a PYE UNICAM SP3 - 200 infrared spectrophotometer. Melting points are quoted uncorrected and were recorded on a Fischer-John apparatus.

Column chromatography was carried out on dry packed columns with Merck Kieselgel 60 (70 - 230 mesh) as adsorbent. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 F_{254}, while thin layer chromatography (t.l.c) was carried out on aluminium plates coated with the same material.

Light petroleum refers to the fraction of boiling point 60 - 80°C, and ether to diethyl ether.

Anhydrous magnesium sulphate ($MgSO_4$) was used to dry the organic solvents after extraction procedures. Most organic solvents and liquid reagents were distilled immediately before use.

As in the text some solvents and reagents have been abbreviated. DMF, CAN, PCC, Ag(II)O refers to N,N-dimethylformamide, cerium(IV) ammoniumnitrate, pyridinium chlorochromate, and argentic oxide respectively.

The phrase "residue obtained upon work-up" refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

5,8-Diacetoxy-1,4-ethano-1,4-dihydro-1-methoxynaphthalene. (45)

A solution of 1-methoxycyclohexa-1,3-diene **(41)** (7.661g, 0.07 mol) and 1,4-benzoquinone

(42) (4.40g, 0.0407mol) in dry benzene (50ml) was heated under reflux in a nitrogen

atmosphere for $2^{1}/_{2}$ hours. The solvent was evaporated to give an oily residue to which

was added dry acetone (100ml) and potassium carbonate (12.49g, 2 equiv.). The mixture

was vigorously stirred under reflux in a nitrogen atmosphere for 2 hours, cooled, filtered

and the solvent evaporated under reduced pressure.

Acetic anhydride (18.46g, 4 equiv.) and pyridine (14.31g, 4 equiv.) were added and the

solution was refluxed for 1 hour in a nitrogen atmosphere afterwhich it was cooled, the

solid filtered off and chromatographed (eluent 20% ethyl acetate in light petroleum) to

afford compound **(45)** (9.649g, 71%) as a white solid. m.p. 146 - 147°C (light petroleum)

(Lit.[28] 147 - 148°C)

(Found: C, 67.5; H, 6.1%. $C_{17}H_{18}O_5$ requires C, 67.55; H, 5.96%)

Vmax. 1750cm^{-1}(C = O); δ_H 1.40 - 1.80 (4H, m, 2 x CH_2), 2.24 and 2.33 (3H each, s, 2

x CH_3), 3.55 (3H, s, OCH_3) 3.75 - 3.95 (1H, m, 4-H), 6.25 - 6.56 (2H, m, 2- and 3-H),

6.65 and 6.85 (1H each, 2 x d, J 8Hz each, 6- and 7-H).

1,4-Diacetoxy-5-methoxynaphthalene. (46)

Compound **(45)** (202mg, 0.669 mmol) was heated in a nitrogen atmosphere (oil bath 220°C) for 40 minutes. Chromatographic purification of the residue (eluent 20% ethyl acetate in light petroleum) afforded compound **(46)** as white crystals (175mg, 95.5%). m.p. 122 - 123°C (light petroleum). (Lit.[28] 122 - 123°C)

(Found: C, 65.9; H, 5.3%. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.1%)

Vmax. 1760cm^{-1}(C=O); δ_H 2.33 and 2.41 (3H each, s, 2 x CH_3), 3.83 (3H, s, OCH_3), 6.80 - 7.50 (5H, m, 2-,3-,6-,7- and 8-H).

1-Acetoxy-3-acetyl-5-methoxy-4-naphthol. (47)

Compound **(46)** (2.005g, 0.0073 mol) was stirred in boron trifluoride-diethyl ether (5ml) for 45 minutes at 60°C (oil bath temperature) in a nitrogen atmosphere. The reaction

mixture was thrown onto ice (50ml) and extracted exhaustively with dichloromethane. The organic phase was dried (MgSO₄) and the solvent evaporated. Acetic anhydride (0.746g, 1 equiv.), pyridine (0.578g, 1 equiv.), dry chloroform (50ml) and zinc dust (4g) [to ensure that any quinone present by oxidation of **(61)** was reduced to the hydroquinone level] were added. The mixture was gently boiled with vigorous stirring under nitrogen for 1 hour, cooled, poured into water (50ml) and exhaustively extracted with dichloromethane. The organic phase was briefly shaken with water (40ml) containing concentrated hydrochloric acid (2ml). The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate in light petroleum) to afford the naphthol **(47)** (1.685g, 84%) as yellow needles identical to the material obtained *via* alternative route.[30] m.p. 130 - 131°C (methylene chloride - light petroleum). (Lit.[30] 130 - 131°C)

(Found: C, 65.5; H, 5.1%. $C_{15}H_{14}O_5$ requires C, 65.7; H , 5.1%)

Vmax. 1750 and 1620cm⁻¹(C=O); δ_H 2.44 (3H, s, Ar-OCO$\underline{CH_3}$), 2.67 (3H, s, Ar-CO$\underline{CH_3}$), 4.05 (3H, s, OCH₃), 6.94 (1H, d, J 8Hz, 6-H), 7.32 (1H, d, J 8Hz, 8-H), 7.45 (1H, s, 2-H), 7.54 (1H, t, J 8Hz, 7-H), and 14.08 (1H, s, OH, D₂O exchangeable).

1-Acetoxy-3-acetyl-4,5-dimethoxynaphthalene. (48)

Compound **(47)** (0.770g, 0.0028 mol) in dry acetone (50ml) was treated with an excess of potassium carbonate (1.939g, 5 equiv.) and iodomethane (3.991g, 10 equiv.) and the mixture refluxed with vigorous stirring for 5 hours. The reaction mixture was then cooled, filtered, the solvent evaporated under reduced pressure, and the residue chromatographed (eluent 20% ethyl acetate in light petroleum) to afford compound **(48)** (0.760, 94%). m.p. 105 - 106°C (light petroleum).

(Found: C, 66.5; H, 5.45%. $C_{16}H_{16}O_5$ requires C, 66.67; H, 5.55%)

Vmax. 1765 and 1670cm^{-1}(C = O); δ_H 2.40 (3H, s, Ar-OCO$\underline{CH_3}$), 2.77 (3H, s, Ar-CO$\underline{CH_3}$), 3.90 and 4.03 (3H each, s, 2 x OCH$_3$), 6.95 (1H, dd, J 3 and 7Hz, 6-H), 7.35 - 7.60 (3H, m, 2-,7-, and 8-H)

3-Acetyl-1-allyloxy-4,5-dimethoxynaphthalene. (50)

Compound **(48)** (1g, 0.0035 mol) was dissolved in methanolic potassium hydroxide

(0.25%, 30ml) and stirred for 10 minutes at room temperature. Thereafter the reaction

mixture was quenched with water (200ml), stirred and acidified using dilute hydrochloric

acid (lithmus paper). The reaction mixture was exhaustively extracted with dichloromethane

and the residue obtained upon work-up gave the crude intermediate **(49)** which was

dissolved in dry acetone (50ml) and treated with allylbromide (1.27g, 3 equiv.) and

potassium carbonate (1.44g, 3 equiv.). The reaction mixture was then refluxed under a

nitrogen atmosphere for 3 hours, afterwhich it was cooled and filtered. Evaporation of the

solvent and chromatography (eluent 15% ethyl acetate in light petroleum) afforded product

(50) (0.801g, 81%) as yellow crystals. m.p. 69 - 70°C

(Found: C, 71.2; H, 6.1%. $C_{17}H_{18}O_4$ requires C, 71.33; H, 6.3%)

Vmax. 1670cm^{-1}(C=O); δ_H 2.80 (3H, s, Ar-COC$\underline{H_3}$), 3.87 and 4.07 (3H each, s, 2 x

OCH$_3$), 4.72 (2H, dt, J 2 and 6Hz, C$\underline{H_2}$CH=CH$_2$), 5.18 - 5.76 (2H, m, CH$_2$CH=C$\underline{H_2}$), 5.82

- 6.55 (1H, m, CH$_2$C$\underline{H}$=CH$_2$), 6.90 (1H, dd, J 2 and 7Hz, 6-H), 7.10 (1H, s, 2-H), 7.50

(1H, t, J 8Hz, 7-H), 7.97 (1H, dd, J 3 and 8Hz, 8-H).

3-Acetyl-1,4,5-trimethoxy-2-prop-2-enylnaphthalene. (52)

Compound **(50)** (0.521g, 0.0018 mol) was immersed in an oil bath (preheated to 220°C) under a nitrogen atmosphere for 35 minutes to afford the intermediate **(51)** which was cooled, dissolved in dry acetone (50ml) and treated with potassium carbonate (2.01g, 8 equiv.) and methyl iodide (2.07g, 8 equiv.). The reaction mixture was then refluxed for $1^{1}/_{2}$ hours under a nitrogen atmosphere, cooled and filtered. Evaporation of the solvent and chromatography (eluent 20% ethyl acetate in light petroleum) afforded compound **(52)** (0.496g, 91%) as yellow crystals. m.p. 54 - 55°C (light petroleum). (Lit.[39] obtained as a pale yellow oil)

(Found: C, 72.0, H, 6.6%. $C_{18}H_{20}O_4$ requires C, 72.0, H, 6.7%).

Vmax. 1690(C=O), 1620cm^{-1}(C=C); δ_H 2.60 (3H, s, Ar-CO$\underline{CH}_3$), 3.56 (2H, dd, J 1 and 6Hz, $\underline{CH}_2$CH=CH$_2$), 3.78, 3.87 and 4.00 (3H each, s, 3 x OCH$_3$), 4.75 - 5.20 (2H, m, CH$_2$CH=$\underline{CH}_2$), 5.60 - 6.26 (1H, m, CH$_2\underline{CH}$=CH$_2$), 6.89 (1H, dd, J 2 and 8Hz, 6-H), 7.44 (1H, t, J 8Hz 7-H), and 7.70 (1H, dd, J 2 and 8Hz, 8-H).

3-(1-Hydroxyethyl)-1,4,5-trimethoxy-2-prop-2-enylnaphthalene. (53)

Compound **(52)** (1g, 0.0033 mol) disolved in dry ether (10ml) was added dropwise over 3 minutes to a stirred suspension of lithium aluminium hydride (1.27g, 10 equiv.) and dry ether. The mixture was stirred for a further 30 minutes, afterwhich it was worked-up by addition of saturated ammonium chloride (dropwise), dried ($MgSO_4$) and filtered. Evaporation of the solvent and chromatography (eluent 20% ethyl acetate in light petroleum) afforded product **(53)** (0.804g, 80%) as white crystals.

m.p. 81 - 82°C (light petroleum). (Lit.[31] obtained as an oil)

(Found: C, 71.75; H, 7.4%. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%)

Vmax. 3470(OH), 1620cm^{-1}(C=C); δ_H 1.62 (3H, d, J 6Hz, Ar-CHOH$\underline{CH_3}$), 3.50 - 3.80 (2H, m, $\underline{CH_2}$CH=CH$_2$), 3.84, 3.90, and 3.99 (3H each, s, 3 x OCH$_3$), 4.15 (1H, s, Ar-CH$\underline{OH}$CH$_3$, D_2O exchangeable), 4.78 (1H, d, J 2Hz, Ar-$\underline{CH}$OHCH$_3$), 4.95 - 5.25 (2H, m, CH$_2$CH=$\underline{CH_2}$), 5.74 - 6.40 (1H, m, CH$_2$$\underline{CH}$=CH$_2$), 6.88 (1H, d, J 8Hz, 6-H), 7.38 (1H, t, J 8Hz, 7-H), 7.70 (1H, d, J 8Hz, 8-H).

(±)trans-3,4-Dihydro-5,9,10-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran. (54)

Compound **(53)** (367mg, 1.216 mmol) was disolved in dry DMF (20 ml) and dry nitrogen was passed through the solution for 5 minutes. Potassium *t*-butoxide (682mg, 5 equiv.) was added and the mixture stirred in a nitrogen atmosphere for 10 minutes at room temperature. The mixture was exhaustively extracted with ether and the residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate in light petroleum) to afford the product **(54)** (315mg, 86%) as light yellow crystals. m.p. 91 - 92°C (light petroleum) (Lit.[31] 99.5 - 100.5°C)

δ_H 1.40 (3H, d, J 6Hz, 3-CH$_3$), 1.65 (3H, d, J 6.5Hz, 1-CH$_3$), 2.59 (1H, dd, J 11 and 17Hz, 4-Ha'), 3.07 (1H, dd, J 3.5 and 17Hz, 4-He'), 3.80, 3.84 and 4.00 (3H each, s, 3 x OCH$_3$), 4.05 - 4.23 (1H, m, 3-H), 5.34 (1H, q, J 6.5Hz, 1-H), 6.82 (1H, d, J 8Hz, 8-H), 7.35 (1H, t, J 8Hz, 7-H), and 7.66 (1H, dd, J 1 and 8Hz, 6-H).

(±)(1R,3R,4S)-3,4-Dihydro-4-hydroxy-5,9,10-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (55), and (±)(1R,3R,4R)-3,4-Dihydro-4-hydroxy-5,9,10-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (56).

Compound (54) (155mg, 0.513 mmol) was dissolved in dry DMF (20ml) and potassium *t*-butoxide (230mg, 4 equiv.) was added. Air was passed over the reaction mixture which was stirred at room temperature for 20 minutes. A further quantity of potassium *t*-butoxide (115mg, 2 equiv.) was added and the mixture was stirred for a further 20 minutes. Water was added to the reaction mixture and the organic layer exhaustively extracted with ether. The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate in light petroleum) to afford firstly product (55) (91mg, 56%) as an light yellow oil. (Lit.[40] obtained as an oil). This was followed by the epimeric (56) (21mg, 13%) also obtained as an oil. (Lit.[40] 170 - 173°C)

For (55).

(Found: C, 67.7; H, 6.8%. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.95%)

δ_H 1.43 (3H, d, J 6.5Hz, 3-CH$_3$), 1.70 (3H, d, J 7.5Hz, 1-CH$_3$), 3.80, 3.97 and 4.01 (3H each, s, 3 x OCH$_3$), *ca.* 3.97 (1H, dq, J 6.5 and 8.5Hz, 3-H, partially obscured by CH$_3$), 4.20 (1H, broad singlet, OH, D$_2$O exchangeble), 4.76 (1H, d, J 8.5Hz, 4-H), 5.26 (1H, q, J 7.5Hz, 1-H), 6.88 (1H, d, J 8Hz, 8-H), 7.40 (1H, t, J 8Hz, 7-H) and 7.64 (1H, d, J 8Hz, 6-H).

For **(56)**.

(Found: M$^+$ 318.1473 C$_{18}$H$_{22}$O$_5$ requires M$^+$ 318.1467).

δ_H 1.43 (3H, d, J 6Hz, 3-CH$_3$), 1.61 (3H, d, J 7Hz, 1-CH$_3$), 2.22 (1H, d, J 8Hz, OH, D$_2$O exchangeble), 3.81, 4.02, and 4.05 (3H each, s, 3 x OCH$_3$), 4.14 (1H, dq, J 2 and 6Hz, 3-H), 4.76 (1H, dd, J 2 and 8Hz, 4-H, collapsed to d, J 2Hz on D$_2$O exchange), 5.34 (1H, q, J 7Hz, 1-H), 6.89 (1H, d, J 8Hz, 8-H), 7.40 (1H, t, J 7Hz, 7-H), and 7.72 (1H, d, J 8Hz, 6-H).

(±)(1R,3R)-5,9,10-trimethoxy-1,3-dimethyl-4-oxo-(1H,3H)-naphtho[2,3-c]pyran. (40)

A mixture of compounds **(55)** and **(56)** (40mg, 0.126 mmol) was dissolved in dichloromethane (10ml) and added dropwise to a suspension of PCC (0.108g, 4 equiv.) and celite (0.5g) in dichloromethane (10ml) at 0°C. The reaction temperature was slowly raised to room temperature and stirred for 15 hours. The PCC was then filtered off and the residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate in light petroleum) to afford the product **(40)** as bright yellow crystals (33.4mg, 84%). m.p. 80 81°C (light petroleum).

(Found: M$^+$, 316.1303 C$_{18}$H$_{20}$O$_5$ requires M$^+$, 316.1311).

Vmax. 1695cm^{-1}(C=O); δ_H 1.50 (3H, d, J 7Hz, 3-CH$_3$), 1.67 (3H, d, J 7Hz, 1-CH$_3$), 3.84,

3.98 and 4.00 (3H each, s, 3 x OCH$_3$), 4.58 (1H, q, J 7Hz, 3-H), 5.49 (1H, q, J 7Hz, 1-H),

7.01 (1H, d, J 8Hz, 8-H), 7.43 (1H, t, J 8Hz, 7-H), 7.94 (1H, d, J 8Hz, 6-H).

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(±)(1R,3R)-5,10-Dihydroxy-9-methoxy-1,3-dimethyl-4-oxo-(1H,3H)-naphtho[2,3-c]pyran.

(29)

Compound **(40)** (154mg, 0.487 mmol) was dissolved in dioxane (10 ml), afterwhich

silver(II)oxide (320mg, 5 equiv.) was added to the stirred reaction mixture. Nitric acid (6M)

was added dropwise until the Ag(II)O has dissolved. The reaction mixture was stirred for

a further 10 minutes, quenched with water and the organic layer exhaustively extracted

with dichloromethane. The residue obtained upon work-up was chromatographed (eluent

25% ethyl acetate in light petroleum) to afford product **(29)** (50.7mg, 36%) as a yellow

solid. m.p. 119 - 121°C

(Found: M$^+$ 288.0985 C$_{16}$H$_{16}$O$_5$ requires M$^+$ 288.0998).

Vmax. 3400(OH), 1735cm^{-1}(C=O); δ_H 1.55 (3H, d, J 7Hz, 3-CH$_3$), 1.64 (3H, d, J 7Hz, 1-CH$_3$), 4.08 (3H, s, OCH$_3$), 4.58 (1H, q, J 7Hz, 3-H), 5.48 (1H, q, J 7Hz, 1-H), 7.00(1H, d, J 8Hz, 8-H), 7.38 (1H, t, J 8Hz, 7-H), 8.04 (1H, d, J 8Hz, 6-H), 8.97 (1H, s, 10-OH, D$_2$O exchangeable), 12.80 (1H, s, 5-OH, D$_2$O exchangeable).

(±) Isoeleutherin. (2)

CAN (0.461g, 2 equiv.) dissolved in H$_2$O (5 ml) was added dropwise to a stirred solution of compound **(54)** (127mg, 0.421 mmol) dissolved in acetonitrile (20 ml). Stirring was continued for a further 20 minutes, whereafter the reaction mixture was quenched with water and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluent 25% ethyl acetate in light petroleum) to afford product **(2)** (110mg, 96%). m.p. 151 - 152°C (Lit[4] 154.5 - 155.5^{o}C)

(Found: M$^+$ 272.1040 C$_{16}$H$_{16}$O$_4$ requires M$^+$272.1048)

Vmax. 1660cm^{-1}(C=O); δ_H 1.37 (3H, d, J 6Hz, 3-CH$_3$), 1.53 (3H, d, J 7Hz, 1-CH$_3$), 2.22 (1H, dddd, J 2 and 10 and 19Hz, 4-Ha'), 2.68 (1H, dd, J 3.5 and 19Hz, 4-He'), *ca.* 3.63 - 4.30 (1H, m, 3-H, obscured by CH$_3$), 5.00 (1H, dq, J 2 and 7Hz, 1-H), 7.26 (1H, dd, J 1.2 and 8Hz, 8-H), 7.64 (1H, t, J 8Hz, 7-H), 7.74 (1H, dd, J 1.5 and 8Hz, 6-H).

(±)_trans_-3,4-Dihydro-9-hydroxy-1,3-dimethyl-1H-naphtho[2,3-_c_]pyran-5,8-quinone (30)

Compound **(2)** (40mg, 0.147 mmol) dissolved in dichloromethane (15 ml) was treated with

an excess aluminium chloride (25 molar equiv.) and stirred for 1 hour at 0°C. The reaction

mixture was exhaustively extracted with chloroform and the residue obtained upon work-up

was chromatographed (eluent 20% ethyl acetate in petroleum ether) to afford compound

(30) as a bright yellow solid (38mg, 100%). m.p. 159 - 161°C.

(Found: M^+, 258.0912 $C_{15}H_{14}O_4$ requires M^+, 258.0892).

Vmax. 1660, 1645, and 1620cm^{-1}; δ_H 1.34 (3H, d, J 6Hz, 3-CH$_3$), 1.54 (3H, d, J 7Hz, 1-

CH$_3$), 2.22 (1H, dddd, J 2 and 10 and 19Hz, 4-Ha'), 2.74 (1H, dd, J 3.1 and 19Hz, 4-He'),

_ca_. 3.90 - 4.05 (1H, m, 3-H), 4.99 (1H, dq, J 2 and 7Hz, 1-H), 7.22 (1H, dd, J 2.3 and

8Hz, 8-H), 7.52 - 7.62 (2H, m, 6- and 7-H), 12.00 (1H, s, OH, D$_2$O exchangeble).

SUMMARY

To our knowledge, Kraus *et al*[18] is the only group to have published a synthesis of racemic hongconin (29) which involved 9 steps. Due to the low overall yield (8%) of Kraus' route an alternative route was devised. Although our route involves 13 steps it afforded a higher overall yield (29%).

The biological evaluations performed on compounds (40) and (29) showed no activity towards any of the organisms, while compounds (2) and (30) inhibited the growth of Gram positive organisms alone.

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