# A Total Synthesis Approach Towards a Novel Furoquinolinone Natural Product Isolated from the Rutaceae Family

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# Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Karl-Fredrik Lindahl

# Preface

Unless otherwise stated, the results in this thesis are those of the author. Parts of this work have appeared elsewhere.

**Refereed Journal Publications**

*"Synthesis of 5-methylfuro[3,2-c]quinolin-4(5H)-one via palladium catalysed cyclisation of N-(2-iodophenyl)-N-methyl-3-furamide"*

Karl-Fredrik Lindahl, Anthony Carroll, Ronald J. Quinn and Justin A. Ripper, *Tetrahedron Lett.* **2006**, *47*, 7493-7495

**Conference Proceedings**

Poster presentation:

"Studies towards the synthesis of Furo[3,2-*c*]quinolinone alkaloids"

Karl-Fredrik Lindahl, Anthony Carroll, Ronald J. Quinn and Justin A. Ripper, "Connect2005", RACI Conference in Sydney 2005

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# List of Abbreviations

| | |
|---|---|
| +ve | Positive |
| -ve | Negative |
| °C | Degrees Celsius |
| amu | Atomic mass units |
| aq | Aqueous |
| $CDCl_3$ | Deuterated chloroform |
| $CHCl_3$ | Chloroform |
| $CH_3I$ | Methyliodide |
| $cm^{-1}$ | Wave numbers |
| DCM | Dichloromethane |
| DEE | Diethyl ether |
| DIBALH | Diisobutyl aluminium hydride |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCE | Dichloroethane |
| DMA | *N,N*-Dimethylacetamide |
| DMF | Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| DMSO- $d_6$ | Deuterated DMSO |
| eq | Equivalent(s) |
| EI | Electron Impact |
| ESI | Electrospray Ionisation |
| FTIR | Fourier Transform Infrared Spectroscopy |
| g | Gram |

| | |
|---|---|
| COSY | Gradient Correlation Spectroscopy |
| HMBC | gradient Heteronuclear Multiple Bond Correlation spectroscopy |
| HSQC | gradient Heteronuclear Single Quantum Correlation spectroscopy |
| HPLC | High Performance Liquid Chromatography |
| HRMS | High Resolution Mass Spectrometry |
| h | Hour(s) |
| Hz | Hertz |
| *i-* | *ipso* |
| $IC_{50}$ | Concentration required for 50 % enzyme inhibition |
| IR | Infrared spectroscopy |
| KBr | Potassium bromide |
| LDA | Lithium diisopropyl amide |
| $LiAlH_4$ | Lithium aluminium hydride |
| *m-* | *meta* |
| M | Moles/litre |
| *m*-CPBA | *meta*-Chloroperoxybenzoic acid |
| mg | Milligram |
| $MgSO_4$ | Magnesium sulfate |
| MHz | Megahertz |
| min | minute/s |
| mL | Millilitre |
| mmol | Millimoles |
| M.p. | Melting point |

| | |
|---|---|
| mol | Moles |
| nmol | Nanomoles |
| $Et_3N$ | Triethylamine |
| NBS | *N*-Bromosuccinimide |
| NCS | *N*-Chlorosuccinimide |
| NIS | *N*-Iodosuccinimide |
| NMP | *N*-methylpyrrolidone |
| NMR | Nuclear Magnetic Resonance |
| *p-* | *para* |
| ppm | Parts per million |
| Rec | Recovered |
| $SOCl_2$ | Thionyl chloride |
| SEM | trimethylsilylethoxymethyl |
| TBACl | Tetrabutylammonium chloride |
| TBAF | Tetrabutylammonium fluoride |
| *t-* or *tert-* | Tertiary |
| TFA | Trifluoroacetic acid |
| $Tf_2O$ | Trifluoromethanesulfonic anhydride |
| TLC | Thin Layer Chromatography |
| THF | Tetrahydrofuran |
| µL | Microliter |
| µmol | Micromoles |

# Acknowledgements

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A BIG thank you to my family; Bengt, Elisabeth and Kalle, on the other side of the world, and to my girlfriend Kristine Nilsson, for great support and patience throughout the PhD project.

# Abstract

Furo- and pyranoquinolinone containing natural products have been isolated from the Rutaceae family sine the 1960's[1] and 1970's[2] and have shown to exhibit a range of biological activities such as antifungal, antibacterial, antiviral, antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, antiarrythmic and sedative properties. Due to this, synthetic strategies have been developed to afford some of the selected natural products. In the course of extracting natural products at Natural Product Discovery (Brisbane, QLD, Australia), one natural product, **1.01**, was isolated from the species *Euodia asteridala* (Rutaceae) and was of interest because of the ongoing screening of that class of molecules and the synthetic challanges involved. The natural product **1.01** consists of a furoquinolinone core with a cyclopropane ring fused onto the C2-C3 carbons of the furan ring, and a *gem* dimethyl functionality off the quarternary carbon of the cyclopropane ring. This thesis explores a total synthesis approach to compound **1.01**, with focus on a new synthetic strategy to afford the furoquinolinone core structure as a key intermediate.

In Chapter one, syntheses of other natural products are shown together with precedent synthetic strategies of the furo- and pyranoquinolinone core structures. The overall approach for the synthesis of the natural product **1.01** is outlined incorporating the new approach for synthesising the furoquinolinone core structure. Related chemistries are referenced, discussed and taken into account for all the proposed synthetic steps.

Abstract

In Chapter two, the *N*-methyl protected form of the furoquinolinone core structure, being the *N*-methyl key intermediate 5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one (**1.30**), was synthesised through a Heck mediated C-C coupling. The optimised Heck coupling reaction conditions included the use of the less common palladium catalyst, palladium oxide, together with additive, base and a polar solvent to afford the desired *N*-methyl key intermediate **1.30**, in a 89 % yield. Using the corresponding bromo and chloro precursors for the synthesis of **1.30**, showed a relative reactivity trend of I>Br>Cl. A second key intermediate, the *O*-methyl protected furoquinolinone core structure 4-methoxyfuro[3,2-*c*]quinoline (**2.01**), was synthesised via an *N*-SEM protected derivative 5-((2-(trimethylsilyl)ethoxy)methyl)furo[3,2-*c*]quinolin-4(5*H*)-one (**2.02**). Using the Heck type coupling conditions developed for substrate **1.30**, the *N*-SEM protected material **2.02** was afforded in a yield of 87 %. Deprotection of **2.02** and concomitant conversion to the desired methyl enol ether protected substrate **2.01**, was achieved in a yield of 63 % over three steps.

In Chapter three, reactivity of the *exo* double bond of the furan ring in the furoquinolinone key intermediates, **1.30** and **2.01**, was investigated with the diazo reagents 2-diazopropane, ethyl 2-diazopropanoate and dimethyl diazomalonate. No reaction was observed when investigating the reaction of 2-diazopropane with either substrate **1.30** or **2.01**. However, the desirable cyclopropane ring carbon skeleton was installed when reacting ethyl 2-diazopropanoate with substrate **1.30** or **2.01** giving cyclopropanated products ethyl 5,7-dimethyl-6-oxo-5,6b,7,7a-tetrahydro-6*H*-cyclopropa[4,5]furo[3,2-*c*]quinoline-7-carboxylate (**3.01**) and ethyl

6-methoxy-7-methyl-7,7a-dihydro-6b*H*-cyclopropa[4,5]furo[3,2-*c*]quinoline-7-carboxylate **3.02**, respectively. Reaction of the *N*-methyl substrate **1.30** with dimethyl diazomalonate, gave no detectable cyclopropanated material, but interestingly two novel insertion products dimethyl 3-(3-methoxy-2-(methoxycarbonyl)-3-oxoprop-1-enyl)-5-methyl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2,2(3*H*)-dicarboxylate (**3.03**) and tetramethyl 3-(2,2-*bis*(methoxycarbonyl) -5-methyl-4-oxo 2,3,4,5tetrahydrofuro[3,2-*c*]quinolin-3-yl)cyclopropane-1,1,2,2-tetracarboxylate (**3.04**) were obtained. Structure **3.03** showed addition of two dimethyl malonate carbenes, while the minor component's structure **3.04** showed addition of three dimethyl malonate carbenes. While reaction of the *O*-methyl substrate **2.01** with dimethyl diazomalonate gave no cyclopropanated material, a pyrano substrate dimethyl 5-methoxy-2*H*-pyrano[3,2-*c*]quinoline-2,2-dicarboxylate (**3.05**) was isolated instead. This product showed that addition of one dimethyl malonate carbene had occurred. Synthesis of a third key intermediate containing a methyl ester functionality linked to the C-3 position of the furan ring of **1.30**, was attempted by using the newly developed synthetic approach. This gave however only low yields of the desired product methyl 5-methyl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-3-carboxylate (**3.08**). The synthesis of this third key intermediate **3.08** as a whole was therefore discarded. For the investigation of the *exo* double bond of the furan ring of substrates **1.30** and **2.01** to be complete, electrophilic aromatic substitution reactions such as; bromination, Vilsmeier Haak formylation and Friedel Crafts acetylation, were conducted. The *N*-methyl protected substrate **1.30** showed high reactivity towards bromination conditions and two products, a *mono*-brominated 2-bromo-5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one (**3.12**) and a *bis*-brominated 2,8-dibromo-5-methylfuro[3,2-

*c*]quinolin-4(5*H*)-one (**3.13**) product, were isolated in a ratio of 65:35. After optimisation, the *mono*-brominated substrate **3.12** was selectively synthesised and isolated in a 94 % yield. The other two selected reagents showed poor reactivity towards the *N*-methyl substrate **1.30**. The *O*-methyl substrate **2.01** showed poor site selectivity under bromination conditions and the protecting group, the methyl enol ether, was cleaved to give a mixture of products. However, the *mono*-brominated product 2-bromo-5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one (**3.14**) was isolated in a 23 % yield. The other two selected reagents showed even lower site selectivity and converted the *O*-methyl key intermediate **2.01** to its precursor in excellent yields (100 % conversion using formylation, and 80 % conversion using acetylation conditions).

In Chapter four, the ester functionality of the cyclopropanated material **3.01** was reduced to a neopentyl alcohol 7-(hydroxymethyl)-5,7-dimethyl-5,6b,7,7a-tetrahydro-6*H*-cyclopropa[4,5]furo[3,2-*c*]quinolin-6-one (**4.01**). Preliminary results when attempting to deoxygenate the alcohol, gave ring opened rearrangement products 2-isopropyl-5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one (**4.04**) and 2-isopropenyl-5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one (**4.05**) being isomers of the natural product almeine. The product **4.04** was a result of a cyclopropane collapse to give an isopropene unit off the C-2 carbon of the furoquinolinone core structure. Further, the product **4.05** consisted of an isopropanyl unit off the C-2 carbon. A study was undertaken using other literature methods to give the *gem* dimethyl functionality under various conditions, however after numerous attempts the desired product was not afforded. It was discovered though that using either

thioacetic acid or thiobenzene as nuchleophiles under Mitsunobu conditions, the neopentyl alcohol functionality was able to be displaced to give the corresponding thio esters *S*-[(5,7-dimethyl-6-oxo-5,6b,7,7a-tetrahydro-6*H*-cyclopropa[4,5]furo[3,2-*c*]quinolin-7-yl)methyl]ethanethioate (**4.06**) and 5,7-dimethyl-7-[(phenylsulfanyl)methyl]-5,6b,7,7a-tetrahydro-6*H*-cyclopropa[4,5]furo[3,2-*c*]quinolin-6-one (**4.09**) in a 74 and 65 % yield, respectively. Several attempts to reductively cleave the thio esters to give the *gem* dimethyl functionality failed. Finally, in an alternative strategy to install the *gem* dimethyl functionality, it was envisaged the neopentyl alcohol could first be oxidised to the corresponding aldehyde followed by reduction to give the desired product. When this strategy was attempted, only complex mixtures were observed with indication of a ring opened byproduct.

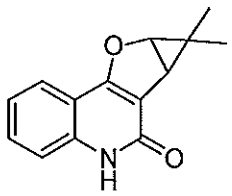
In Chapter five, a new synthesis strategy was elaborated on to give the natural compound **1.01**. This strategy incorporated a vinyl alkylation of an *O*-methyl protected compound 4-hydroxy-2-methoxyquinoline-3-carbaldehyde (**5.04**) prepared by literature methods, using 1-bromo-2-methylpropene. This was envisaged to be followed by a novel tandem cyclisation/cyclopropanation reaction to furnish the natural product carbon scaffold. Several attempts to install the vinyl ether onto **5.04** failed, and therefore the strategy was modified. The phenol type alcohol (**5.04**) was first alkylated with an appropriate allyl group (1-bromo-2-methylprop-2-ene) to give compound 2-methoxy-4-[(2-methylprop-2-en-1-yl) oxy]quinoline-3-carbaldehyde (**5.13**), which was then envisaged to be isomerised to the corresponding vinyl ether 2-methoxy-4-[(2-methylprop-1-

enyl)oxy]quinoline-3-carbaldehyde (**5.03**). Even though several attempts were made to isomerise the allyl ether to the corresoponding vinyl ether **5.03** using literature methods, no product was able to be observed. The outlined synthetic strategy was however, proven to be sound since the tandem cyclisation/cyclopropanation reaction for the model case **5.13**, gave the desired product 2-methoxy-9a-methyl-1,1a,9,9a-tetrahydrocyclopropa[4,5]pyrano[3,2-*c*]quinoline (**5.14**).

# Chapter 1

## 1.1 Introduction

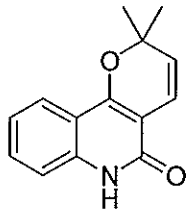
In the course of extracting and isolating natural products at Natural Product Discovery in Brisbane (Australia), a novel quinolinone alkaloid **1.01** was isolated from the species *Euodia asteridala* (Rutaceae family). The molecule has a quinolinone core structural unit, which consists of two six membered rings, with a fused furan ring in the angular [3,2-*c*]-position. On the exocyclic face of the furan ring system is a *gem* dimethyl containing fused cycloproprane ring. This class of compounds has been shown to be biologically active and have the potential of being antifungal, antibacterial, antiviral, antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, antiarrythmic and sedative agents.[3-9]




**1.01**

The number of quinoline alkaloids isolated from plants from the Rutaceae family is greater than 200[6,10,11] but only approximately 60 of these are quinolinones.[12] At present there are limited syntheses of this class of compounds and therefore it

became of interest to develop new synthetic methods to produce compounds of this type. Interestingly, a close relative to this class of molecules is the pyranoquinolinones, whose derivatives are commonly co-extracted with the furoquinolinones. One natural compound of particular note, with regards of the structural features of **1.01**, is flindersine (**1.02**) which has been isolated from *Haplophyllum suaveolens*.[13] Flindersine (**1.02**) contains a quinolinone unit as does **1.01**, but has a fused pyrano ring instead of a furan ring in the [3,2-*c*]-position, and thus is merely a constitutional isomer of **1.01**.



**1.02**

The structural differences between the two natural products **1.01** and **1.02** are interesting since both have the same chemical formula, and as mentioned, furo- and pyranoquinolinones are commonly extracted from the same species. The chemistry of furo- and pyranoquinolinones is frequently inter-related e.g., **1.01** and **1.02** are structural isomers, and therefore the chemistry of these two classes will be reviewed.

## 1.2 The chemistry of furo- and pyranoquinolinones

### 1.2.1 Furoquinolinones

As mentioned the quinolinone alkaloids can be broadly divided in to two general classes; the furoquinolinones and the pyranoquinolinones. Table 1 summarises all the angular natural product furoquinolinones that have been reported.[12]

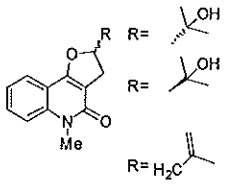
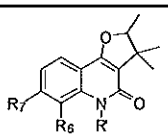
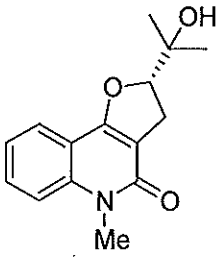
| Species | Alkaloid | Entry | Ref. | |
|---|---|---|---|---|
| *Araliopsis soyauxii* | (R)-Araliopsine | 1a | 7, 8, 14, 15 |  R=  |
| *Araliopsis soyauxii* | (S)-Araliopsine | 1b | " | R=  |
| *Almeida guyanensis* | Almeine | 2 | 16 | R=  |
| *Acronychia oligophylebia* and *Euxylophora* | Oligophyline | 3a | 18, 19 |  R'=Me, $R_6$=$R_7$=H |
| " | Oligophylicine | 3b | " | R'=$R_7$=H, $R_6$=OMe |
| " | Oligophylicidine | 3c | " | R'=H, $R_6$=$R_7$=OMe |
| *Euxylophora paraensis* | Demethyloligophyline | 3d | " | R'=$R_6$=$R_7$=H |

**Table 1**

Table 1 is also divided into two general subclasses. Those furoquinolinones that have been synthesised (entries **1a-b** and **2**) and those that have not (entries **3a-d**).

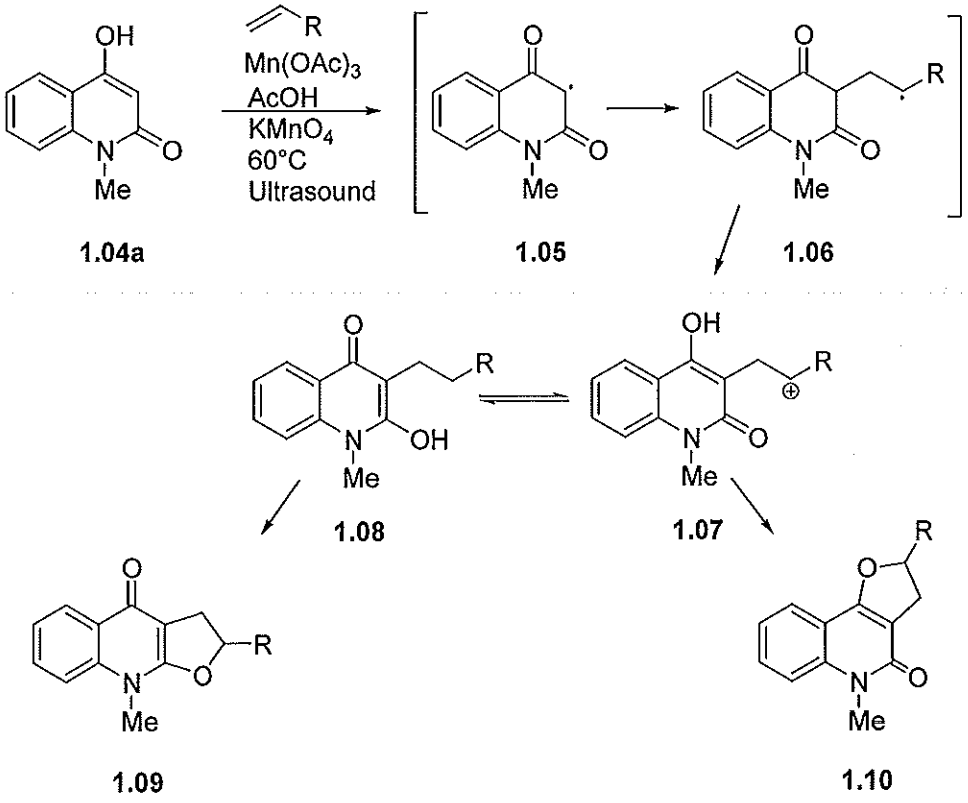
The first example of a furoquinolinone that has been synthesised is the angular quinolinone alkaloid araliopsine (**1.03**), which was isolated from the root bark of *Araliopsis soyauxii*[14] (Rutaceae) in its (*S*)-form, as shown in Figure 1.1.



**(1.03)**
**araliopsine**

**Figure 1.1**

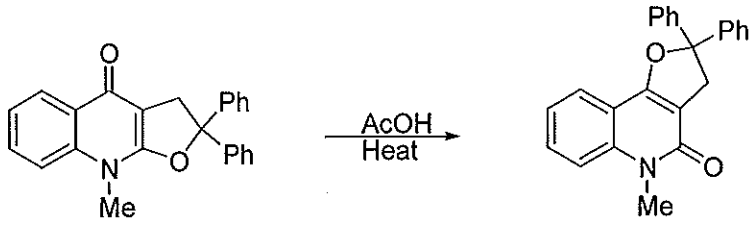
A recent technique for the synthesis of araliopsine (**1.03**) was developed by Bar *et al.*,[15] where the commercially available 4-hydroxy-1-methyl-2(1*H*)-quinolone (**1.04a**) was used as starting material (Scheme 1.1). This was treated with manganese(III)acetate and an appropriate alkene, to mediate a radical alkylation which was followed by oxidation and cyclisation to trap the carbocation formed (Scheme 1.1.)




**Scheme 1.1**

Scheme 1.1 also outlines the two possible outcomes of the reaction – either the linear furoquinolinone (**1.09**) or the angular furoquinolinone (**1.10**). The authors discovered that this regiochemistry could be affected by the nature of the R group of the alkene. If the R group was aryl a mixture of both linear and angular forms were produced, while if the R group was alkyl the angular form predominated. When the R group was an electron withdrawing group, such as a carbonyl group, the authors noted no reaction occurred giving only unreacted starting material. The reason why the reaction failed in this case was suggested to be due to the poor electrophilic nature of the radical in **1.05** being unable to react, and also, having an electron withdrawing group R in the radical intermediate **1.06** would hinder oxidation to the carbocation **1.07**, further impeding the reaction.

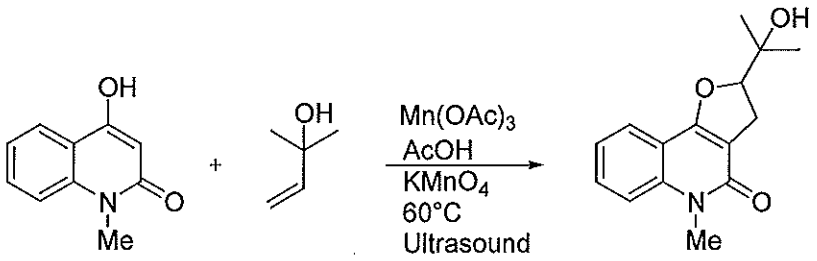
The explanation for the difference in regio chemical outcome based upon the electronic properties of the R group was unclear. However, molecular orbital calculations suggested that the linear form was thermodynamically less stable than the angular form.[15] This was supported by the observed slow isomerisation of **1.11** to **1.12** upon heating in acetic acid,[15] as shown in Scheme 1.2.




**1.11** **1.12**

**Scheme 1.2**

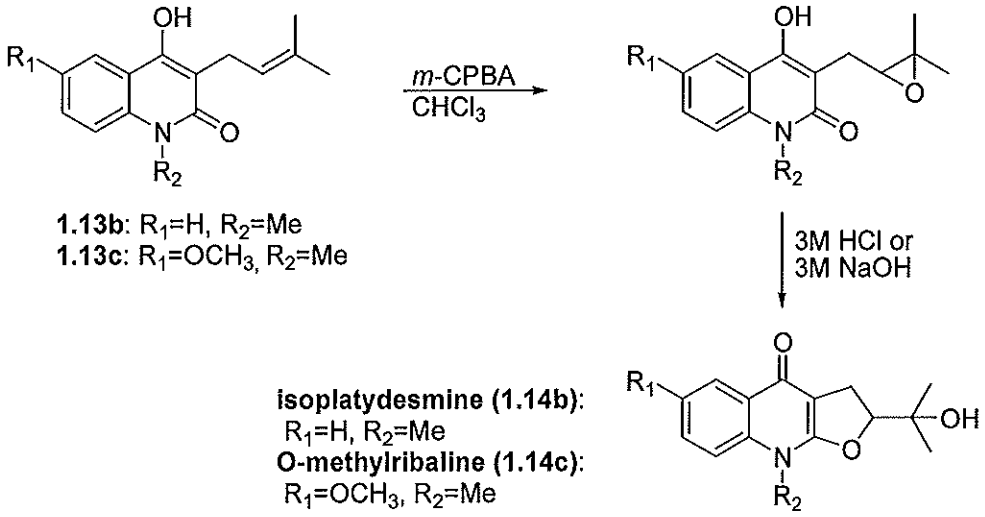
Due to the favourable outcome of unconjugated alkenes giving angular furoquinolinones, the authors were able to synthesise (±) araliopsine (**1.03**), using 4-hydroxy-1-methyl-2(1*H*)-quinolone (**1.04a**) and 2-methyl-3-buten-2-ol, in a 40 % yield (Scheme 1.3).



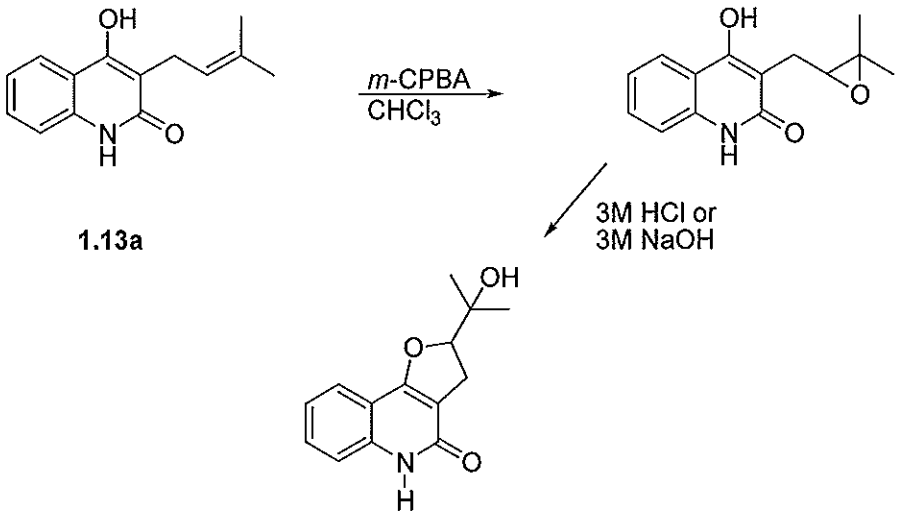

**1.04a** **(1.03) (±) araliopsine**

**Scheme 1.3**

Other syntheses of furoquinolinones have been investigated by Butenschön *et al.*[5] Their interest was in the voltage gated potassium channel Kv1.3 as an attractive target for immunosuppression. Naturally occurring benzofurans, coumarins, acridones and furoquinolinones were identified as potential leads, and thus methods for the synthesis of these compounds were required. The synthetic method developed for making the desired natural compounds and their analogues was by using 4-hydroxy-3-(3-methylbut-2-enyl)quinolin-2-ones **1.13a-c**.[16-19] Oxidative cyclisation of **1.13b** and **1.13c** with *m*-chloroperbenzoic acid, followed by ring closure of the intermediate epoxide through treatment with either 3M hydrochloric acid or 3M sodium hydroxide yielded the linear dihydrofuro[2,3-*b*]quinolinones isoplatydesmine (**1.14b**) and *O*-methylribaline (**1.14c**), as shown in Scheme 1.4. However, when **1.13a** was subjected to the same conditions, exclusively **1.15a** (*N*-demethylaraliopsine) was formed, as shown in Scheme 1.5.



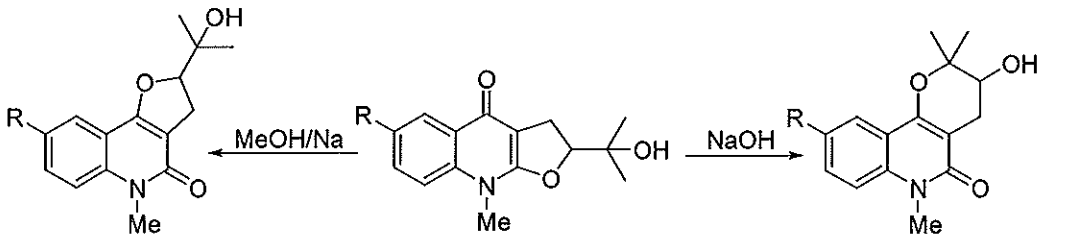

**Scheme 1.4**




**Scheme 1.5**

Further, James *et al.*[20] studied the rearrangement of the linear dihydrofuroquinolinones **1.14a** and **1.14b**. They found that when **1.14a** and **1.14b** were treated with sodium methoxide in methanol, the angular dihydrofuroquinolinones, racemic araliopsine (**1.03**) and the methoxy derivative **1.15c**, were produced (Scheme 1.6). When **1.14a** and **1.14b** were treated with

aqueous sodium hydroxide however, the angular dihydropyranoquinolinones, racemic pseudoribalinine (**1.20a**) and its methoxy derivative **1.20b** was produced (Scheme 1.6). This exemplifies the inter-related chemistry of furo- and pyranoquinolinones.



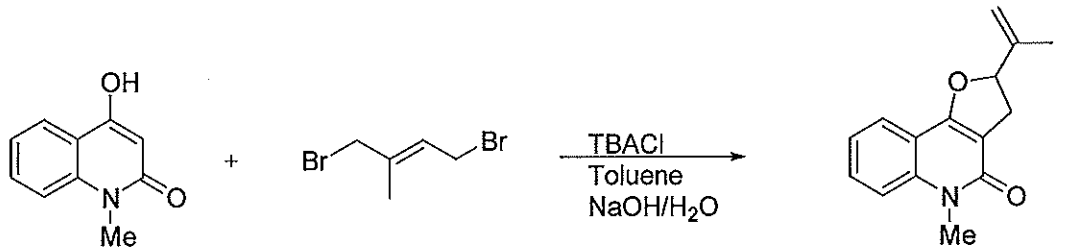

**(±) araliopsine (1.03)**: R=H
**1.15c**: R=$OCH_3$

**1.14a,b**

**pseudo-ribalinine (1.20a)**: R=H
**1.20b**: R=$OCH_3$

**Scheme 1.6**

The other furoquinolinone alkaloid shown in Table 1 that has been synthesised, is almeine (**1.21**), which was first isolated from the stem and root barks of *Almeidea guyanensis*.[21] Reisch *et al.*[22] synthesised (±) almeine by treating 4-hydroxy-1-methyl-2(1*H*)-quinolone (**1.04a**) with (*E*)-1,4-dibromo-2-methylbut-2-ene in the presence of the phase transfer catalyst tetrabutylammonium chloride (TBACl). This furnished (±) almeine (**1.21**) in a 42 % yield (Scheme 1.7).

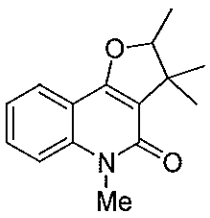



**1.04a**

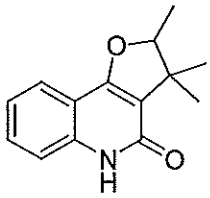
**(±) almeine (1.21)**

**Scheme 1.7**

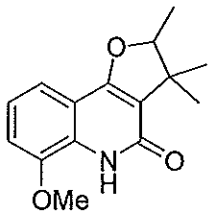
The second section of Table 1 summarises the angular furoquinolinone compounds that have been isolated but not yet synthesised. Oligophyline was islolated from the roots of *Acronychia oligophylebia*[23] and the heartwood from *Euxylophora paraensis*[24] (Rutaceae), while its closely related derivative demethyloligophyline has only been reported to be isolated from the heartwood of *Euxylophora paraensis*.[24] Oligophylicine and oligophylicidine, in contrast, have both only been isolated from the roots of *Acronychia oligophylebia*.[23]



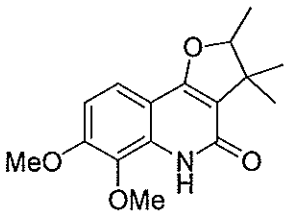

**oligophyline**




***N*-demethyloligophyline**

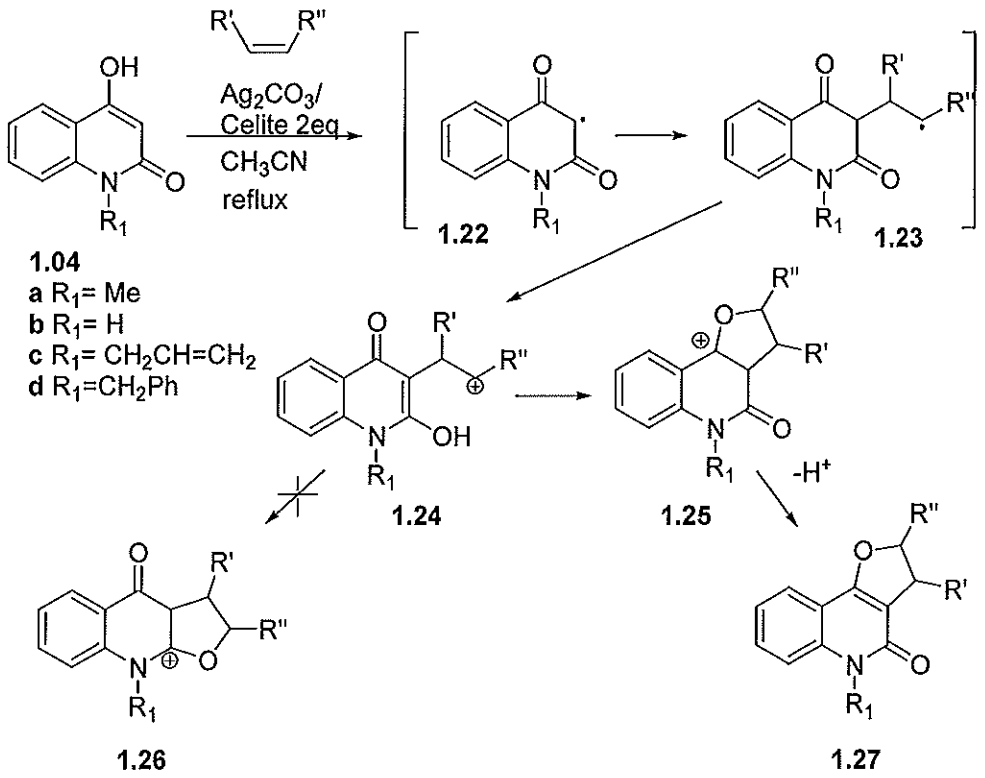



**oligophylicine**



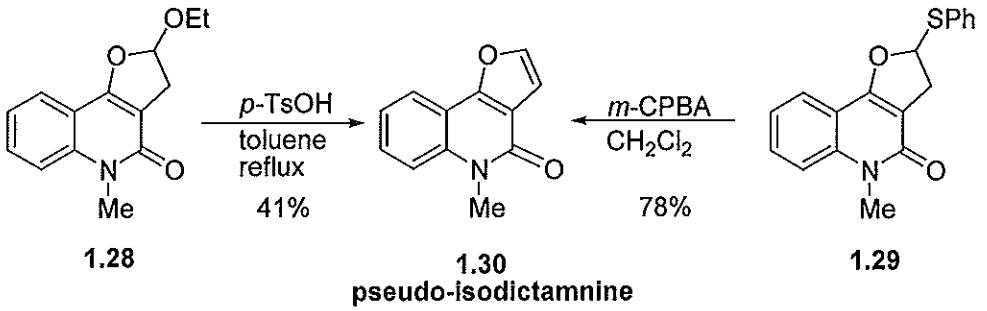

**oligophylicidine**

There have been related syntheses reported on angular furoquinolinone core structures which are similar to the natural products found in nature. Lee *et al.*[25,26] investigated the synthesis of dihydrofuroquinolinone (and furoquinolinone) derivatives by performing a radical alkylation and oxidative cyclisation on 4-hydroxy-2-quinolones **1.04a-d**, which is similar to the synthesis of the natural product araliopsine **1.03**. Thus the use of a variety of suitable alkenes in the presence of two equivalents of silver carbonate/Celite (Fétizon reagent) and the starting materials, **1.04a** and (**1.04b-d**),[27] yielded products **1.27a-d**.



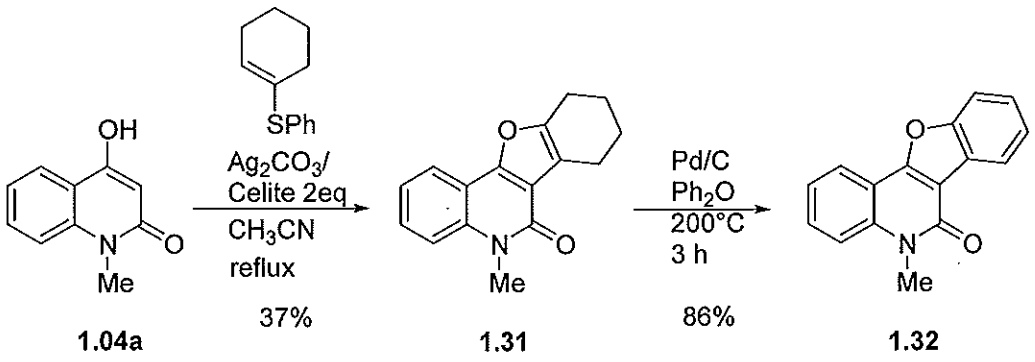

**Scheme 1.8**

By analogy of the synthesis of araliopsine **1.03** as described earlier by Bar *et al.*,[15] the reaction mechanism (Scheme 1.8) is explained in a similar fashion with the only difference being that silver carbonate is the radical source instead of manganese(III)acetate. The dihydrofuroquinolinones synthesised using this approach were also investigated for further conversion to the corresponding furoquinolinones. Thus as shown in Scheme 1.9, pseudo-isodictamnine (**1.30**) could be synthesised by either acid catalysed reactions on the ether **1.28** using *p*-toluenesulfonic acid, or by treatment of the thioether **1.29** with *m*-CPBA.




**Scheme 1.9**

An interesting outcome of this approach was also the synthesis of benzofuroquinolinone (**1.32**) which is the analogue of the natural compound benzosimuline. Treatment of the furoquinolinone **1.04a** with cyclohexenyl(phenyl)sulfane in the presence of silver carbonate/Celite, gave **1.31** as a single product. Further treatment of **1.31** with palladium on carbon in phenyl ether afforded benzofuroquinolinone **1.32** (Scheme 1.10).

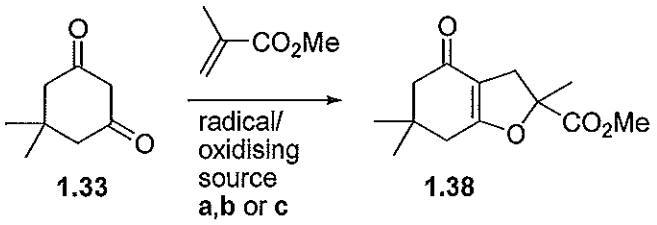



**Scheme 1.10**

An investigation of various oxidants in the radical alkylation/oxidative cyclisation on 1,3-dicarbonyl compounds was performed by Lee *et al.*[28] This was a preliminary study for determining the best methodology for synthesising

dihydrofuran, dihydrofurocoumarin, dihydrofuroquinolinone, dihydrofurophenalenone and furonaphthoquinone natural products.

To illustrate the relative efficiency of the different oxidants used prior in the literature, three test reactions were performed using dimedone (**1.33**) as a substrate, methacrylate as the alkylating alkene and three different metal salts as the radical/oxidising source, as shown in Scheme 1.11.



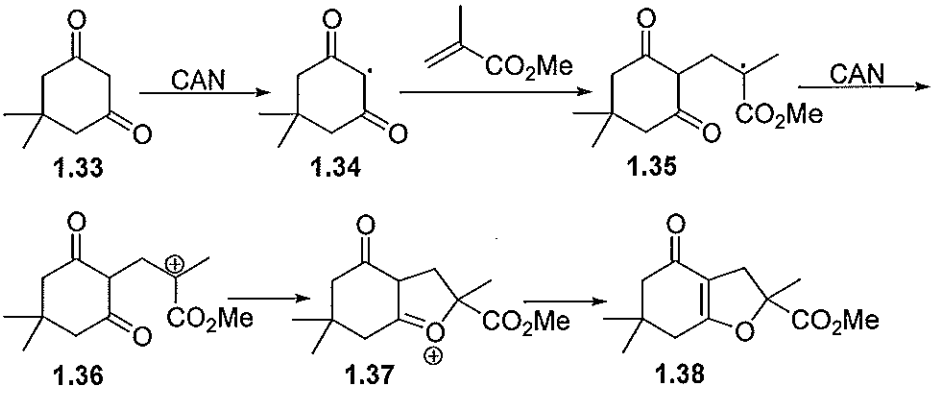

**1.33** **1.38**

| Oxidant | Solvent | T(°C) | Time(h) | Yield(%) |
|---|---|---|---|---|
| **(a)**:$Mn(OAc)_3 \cdot H_2O$ | AcOH | 80°C | 3 | 0 |
| **(b)**:$Ag_2CO_3$/Celite | $CH_3CN$ | reflux | 3 | 8 |
| **(c)**:$Ce(NH_4)_2(NO_3)_6$ | $CH_3CN$ | 0°C | 3 | 88 |

**Scheme 1.11**

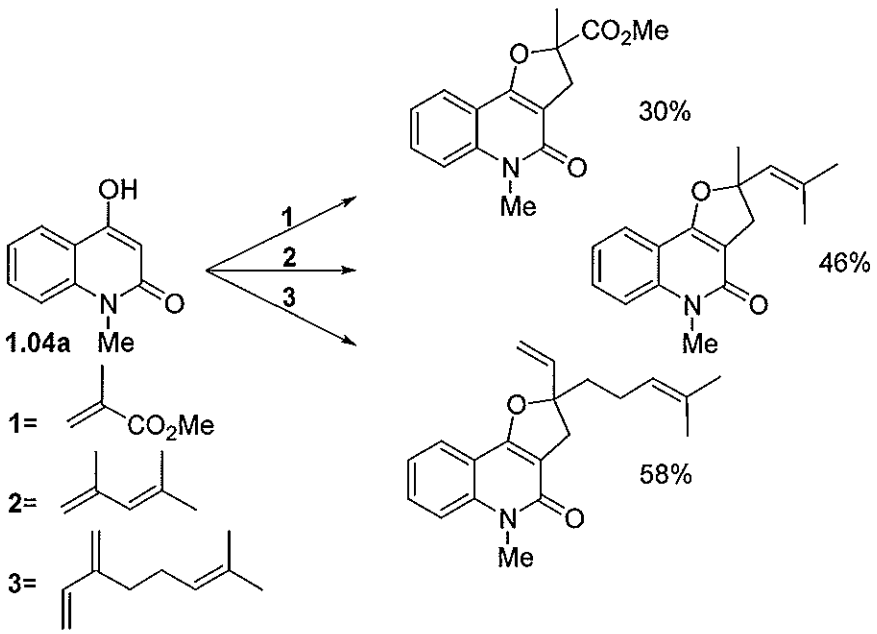
It was found that CAN, acting as a radical/oxidising source, was superior to the other two salts used in these test reactions. The suggested reaction mechanism[28] was similar to the previously discussed radical reaction mechanisms regarding the manganese(III) acetate[15] and the silver carbonate[25,26] reactions. The dimedone (**1.33**) is first oxidised by CAN to generate the radical **1.34**, followed by attack of methylacrylate to form another radical **1.35**. This intermediate radical adduct **1.35** is then oxidised to a carbocation **1.36** by CAN once more. Cyclisation then occurs

to form the charged cyclised product **1.37** which then undergoes loss of a proton to furnish the final product **1.38**, as shown in Scheme 1.12.




**Scheme 1.12**

The dihydrofuroquinolinones in Scheme 1.13 were then synthesised using this methodology. Thus the commercially available 4-hydroxy-1-methyl-2(1*H*)-quinolone (**1.04a**) was treated with CAN to mediate a radical alkylation by using two types of alkenes; acyclic *α,β*-unsaturated esters and conjugated dienes. This afforded the desired dihydrofuroquinolinones (Scheme 1.13).



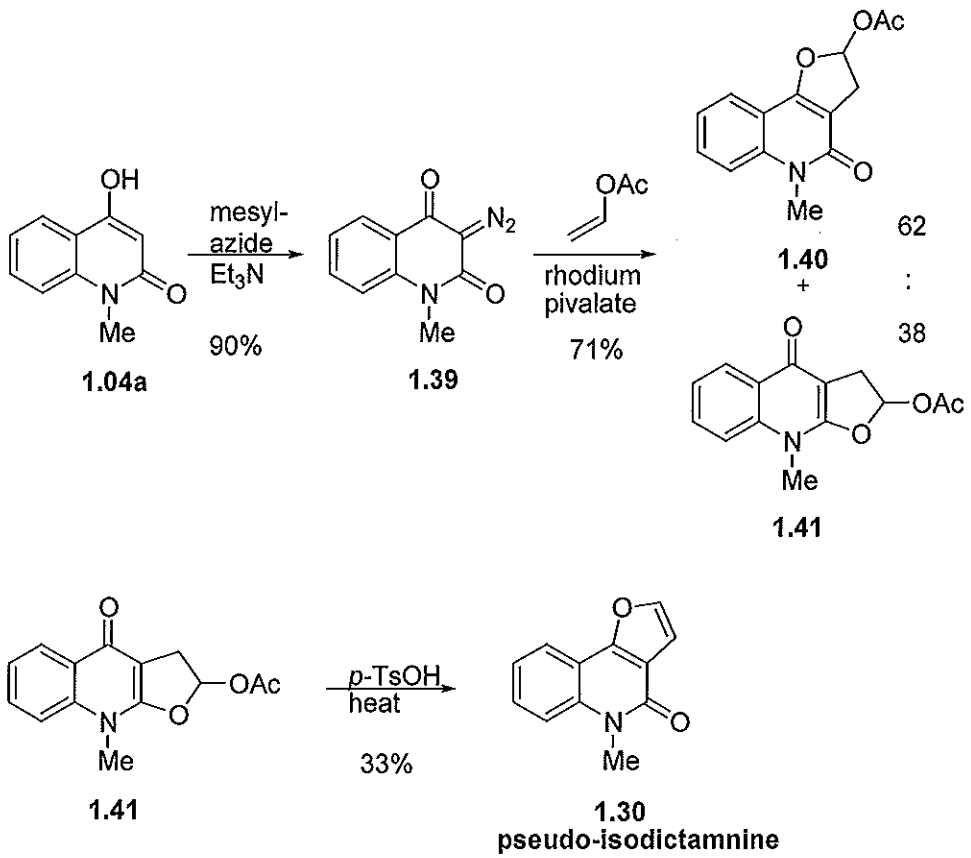

Reaction conditions: **1.04a** 1 eq., CAN 2.2 eq., alkene(**1**, **2** or **3**) 5 eq. in MeCN, 0°C, 3 h.

**Scheme 1.13**

The reactions gave low to moderate yields with no reported regioisomers (*eg.*, linear form of the dihydrofuroquinolinone) and, in addition, no detected 1,2- or 1,4-nitroxy adducts originating from the use of CAN.[29]

An alternate approach to the synthesis of furoquinolinones was investigated by Pirrung *et al.*[9] where a rhodium mediated dipolar cycloaddition of diazoquinolidiones with alkenes and alkynes respectively furnish the dihydro- and furoquinolinones in moderate to good yields, as shown in Scheme 1.14. Performing diazotization of the starting material 4-hydroxy-1-methyl-2(1*H*)-quinolone (**1.04a**) with mesyl azide in ethanol gives the intermediate product **1.39** in 90 % yield. Treatment of the freshly made diazoquinolidione **1.39** with a large excess of vinyl acetate in the presence of rhodium(II) pivalate as catalyst, gave a mixture of two dihydrofuroquinolinone regioisomers, **1.40** and **1.41**, where the angular isomer was favoured (62:38). The angular furoquinolinone isomer, pseudo-isodictamnine

(**1.30**), was then interestingly able to be accessed by heating **1.41** in the presence of a catalytic amount of *p*-toluenesulfonic acid, also shown in Scheme 1.14.




**Scheme 1.14**

### 1.2.2 Pyranoquinolinones

A higher number of molecules is observed in the angular pyranoquinolinone class of molecules[12] with greater substitution found around the three six membered core structure. Flindersine and its derivatives are presented in Table 2

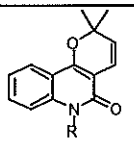
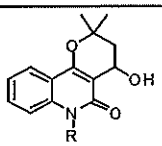
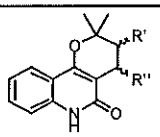
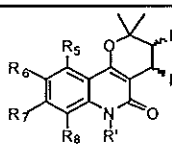
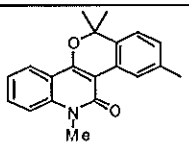
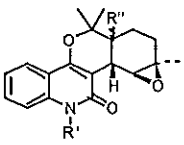
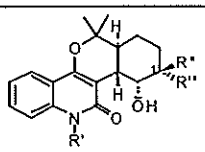
| Species | Alkaloid | Entry | | |
|---|---|---|---|---|
| *Flindersia australis, Haplophyllum perforatum and several others* | Flindersine | 4a |  | R=H |
| *Fagara chalybea, Atalantia roxburghiana and several others* | *N* -Methylflindersine | 4b | | R=Me |
| *Haplophyllum buxbaumii* | *N* -hydroxymethylflindersine | 4c | | $R=CH_2OH$ |
| *Zanthoxylum simylans* | *N* -Acetoxymethylflindersine | 4d | | $R=CH_2OAc$ |
| *Haplophyllum suaveolens* | Haplophylline | 4e | | $R=CH_2OCOCHC(CH_3)_2$ |
| *Geijera balansae* | 4'-Hydroxy-3',4'-dihydroflindersine | 5a |  | R=H |
| *Euxylophora paraensis* | 2,3,4,6-Tetrahydro-4-hydroxy-2,2,6-trimethyl -5H-pyrano[3,2-c]quinolin-5-one | 5b | | R=Me |
| *Geijera Balansae* | 3',4'-Dihydroxy-3',4'-dihydroflindersine | 6a |  | R'=OH R''=OH (*R,R*) |
| | | 6b | | R'=OH R''=OH (*S,S*) |
| | | 6c | | R'=OH R''=OH (*R,S*) |
| *Ravenia spectabilis* | Ravesilone | 7a |  | R'=Me,$R_1$=$R_2$=dihydro $R_5$=$R_6$=$R_7$=H,$R_8$=OH |
| *Zanthoxylum simulans* | Zanthodioline | 7b | | $R_1$=OH $R_2$=OH R'=Me,$R_5$=$R_6$=$R_7$=H $R_8$=OMe |
| *Araliopsis tabouensis* | Araliopsinine | 7c | | $R_1$=OH $R_2$=OH R'=Me,$R_5$=$R_6$=H $R_7$=$R_8$=OMe |
| *Zanthoxylum simulans* | Benzosimuline | 8 |  | |
| *Eriostemon australasius* | *trans* -Erioaustralasine | 9a |  | R'=$CH_2OAc$, R''=H |
| " | *cis* -Erioaustralasine | 9b | | R'=$CH_2OAc$, R''=H |
| *Halfordia kendack* | deacetoxy-trans-erioaustralasine | 9c | | R'=$CH_3$, R''=H |
| | | | | |
| *Halfordia kendack* | Erioaustralasine hydrate | 10a |  | R'=$CH_2OAc$, R''=Me, R'''=OH |
| " | Deacetoxy-trans-erioaustralasine hydrate | 10b | | R'=Me, R''=Me, R'''=OH |
| " | Deacetoxy-trans-1-epierioaustralasine hydrate | 10c | | R'=Me, R''=OH, R'''=Me |
| | | | | |

**Table 2**

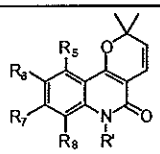
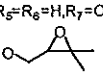
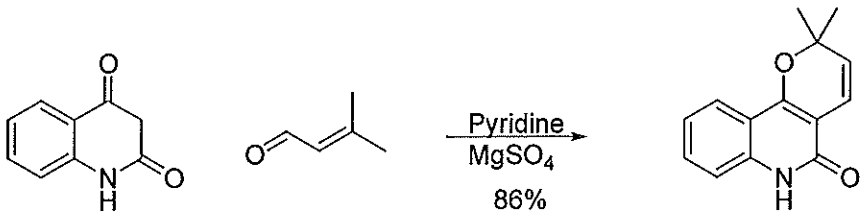
| Species | Alkaloid | Entry | | |
|---|---|---|---|---|
| *Haplophyllum acutifolium* | Haplophytine A | **11a** |  | $R'=R_6=R_7=R_8=H, R_5=OMe$ |
| *Haplophyllum perforatum* | Haplamine | **11b** | | $R'=R_5=R_7=R_8=H, R_6=OMe$ |
| *Agathosma* | *N* -Methylhaplamine | **11c** | | $R'=Me, R_5=R_7=R_8=H, R_6=OMe$ |
| *Vepris bilocularis* | 7-Methoxyflindersine | **11d** | | $R'=R_5=R_6=R_8=H, R_7=OMe$ |
| *Oricia renieri* | 7-Methoxy-N-methylflindersine | **11e** | | $R'=Me, R_5=R_6=R_8=H, R_7=OMe$ |
| *Vepris bilocularis* | 7-Prenyloxyflindersine | **11f** | | $R'=R_5=R_6=R_8=H$ $R_7=OCH_2CHC(CH_3)_2$ |
| " | *N* -Methyl-7-prenyloxyflindersine | **11g** | | $R'=Me, R_5=R_6=R_8=H$ $R_7=OCH_2CHC(CH_3)_2$ |
| *Zanthoxylum monophyllum* | Desmethylzanthophylline | **11h** | | $R'=CH_2OAc, R_5=R_6=R_7=H$ $R_8=OH$ |
| " | Zanthophylline | **11i** | | $R'=CH_2OAc, R_5=R_6=R_7=H$ $R_8=OMe$ |
| *Myrtopsis macrocarpa* | 8-Methoxyflindersine | **11j** | | $R'=R_5=R_6=R_7=H$ $R_8=OMe$ |
| *Zanthoxylum bungeanum* | Zanthobungeanine | **11k** | | $R'=OMe, R_5=R_6=R_7=H$ $R_8=OMe$ |
| *Vepris stolzii* | 8-(3,3-Dimethylallyloxy)-N-methylflindersine | **11l** | | $R'=Me, R_5=R_6=R_7=H$ $R_8=OCH_2CHC(CH_3)_2$ |
| *Oricia suaveolens* and *Oricia renieri* | Oricine | **11m** | | $R'=Me, R_5=R_6=H$ $R_7=R_8=OMe$ |
| *Haplophyllum telephioides* | 8-Hydroxy-6-methoxy flindersine | **11n** | | $R'=R_5=R_7=H$ $R_6=OMe, R_8=OH$ |
| *Vepris louisii, Vepris stolzii and Oricia renieri* | Veprisine | **11o** | | $R'=Me, R_5=R_6=H$ $R_7=R_8=OMe$ |
| *Vepris stolzii* | 8-(3,3-Dimethylallyloxy)-7-methoxy-N-methylflindersine | **11p** | | $R'=Me, R_5=R_6=H, R_7=OMe$ $R_8=OCH_2CHC(CH_3)_2$ |
| " | 8-(2,3-Epoxy-3,3-Dimethylallyloxy)-7-methoxy-N-methylflindersine | **11q** | | $R'=R_5=R_6=H, R_7=OMe$ $R_8=$  |

**Table 2 cont.**

One of the earlier approaches towards the syntheses of pyranoquinolinones was taken by Groot *et al.*[30] where the key step was a condensation of an $\alpha,\beta$-unsaturated aldehyde with a 1,3-diketone in a one-pot synthesis. Flindersine, which has been isolated from *flindersia australis* (among others), was able to be synthesised using this methodology in a 86 % yield, as shown in Scheme 1.15.




**1.42** **(1.43) flindersine**

**Scheme 1.15**

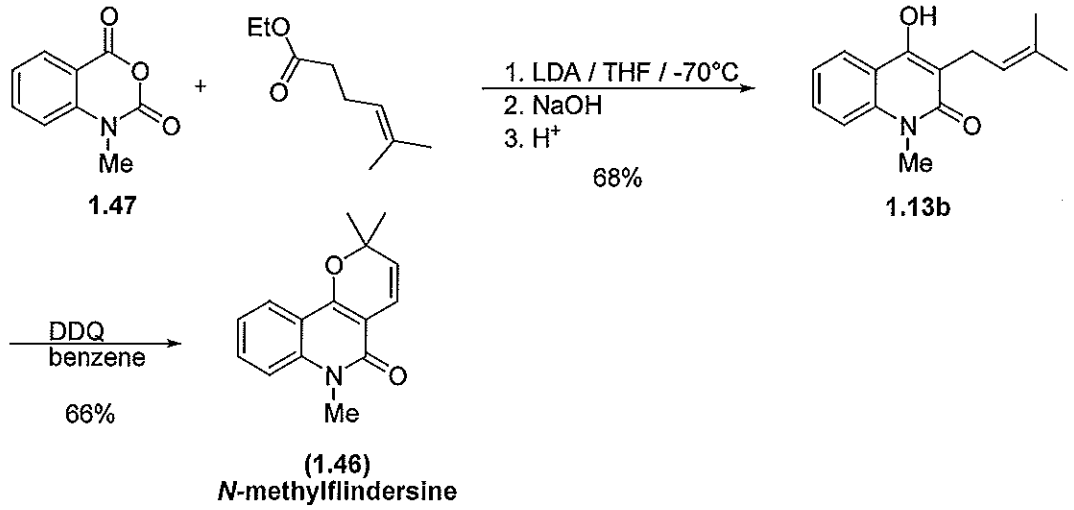
Some time later Watters *et al.*[31] used this approach to synthesise the natural alkaloids Veprisine (**1.44**) and 8-(3,3-dimethylallyloxy)-*N*-methylflindersine (**1.45**) (Figure 1.2), which were originally isolated from *Vepris louisii.*[32,33] The starting materials for the synthesis of these compound, **1.44** and **1.45**, were prepared by condensation of the corresponding aniline derivatives and malonic acid in the presence of phosphorus oxychloride.[34]

**(1.44) veprisine** **(1.45) 8-(3,3-dimethylallyloxy) -*N*-methylflindersine**

**Figure 1.2**

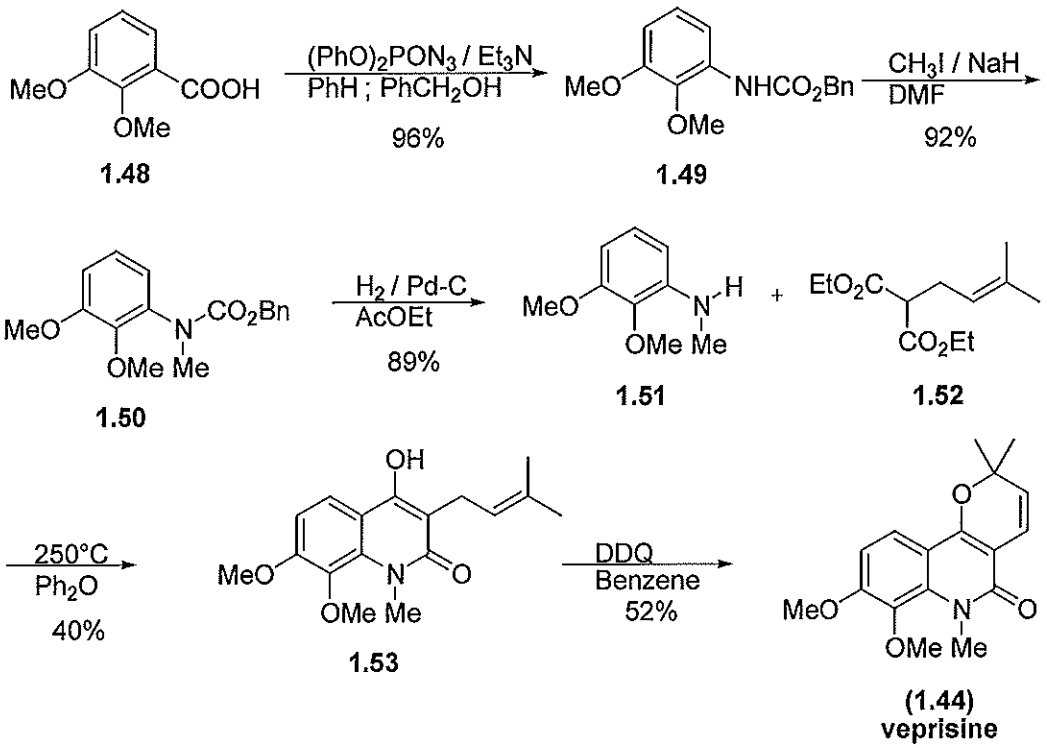
Kamikawa *et al.*[35] investigated the antagonist activity of flindersine (**1.43**), *N*-methylflindersine[27,36,37] (**1.46**) and veprisine (**1.44**) against SRS-A[35] and were therefore interested in developing a synthetic approach in order to access larger amounts of these compounds. The method chosen involved a DDQ

oxidation/cyclisation step of **1.13b** to give *N*-methylflindersine **1.46**. Compound **1.13b** was synthesised by the method of Coppola,[37] which involved reaction of the enolate of 5-methyl-4-hexeneoate with *N*-methylisatoic anhydride (**1.47**), as shown in Scheme 1.16.



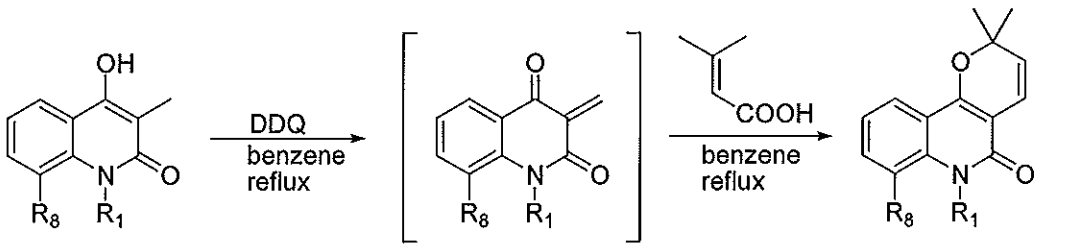

**Scheme 1.16**

Veprisine (**1.44b**) was also synthesised using this strategy of a DDQ oxidation/cyclisation, of the precursor **1.53**, as shown in Scheme 1.17. Compound **1.53** was synthesised by condensation of the *N*-methylaniline **1.51** (prepared in three steps from the benzoic acid **1.48**) and the malonate derivative **1.52**.




**Scheme 1.17**

As shown in Scheme 1.18, Kumar *et al.*[38] considered the use of heterocyclic quinone methides (**1.55**) for the synthesis of flindersine (**1.43**), *N*-methylflindersine (**1.46**) and 8-methoxyflindersine (**1.56**). The 3-methylene-2,4-(1*H*, 3*H*)quinoline dione methide (**1.55**) is generated by refluxing 4-hydroxy-3-methyl-2-(1*H*)quinoline (**1.54**) with DDQ in benzene. This was then treated with dimethyl acrylic acid which undergoes cyclisation[39,40] to furnish the product, as shown in Scheme 1.18. The yields were 68 % for flindersine, 70 % for 8-methoxyflindersine and 80 % for *N*-methylflindersine.

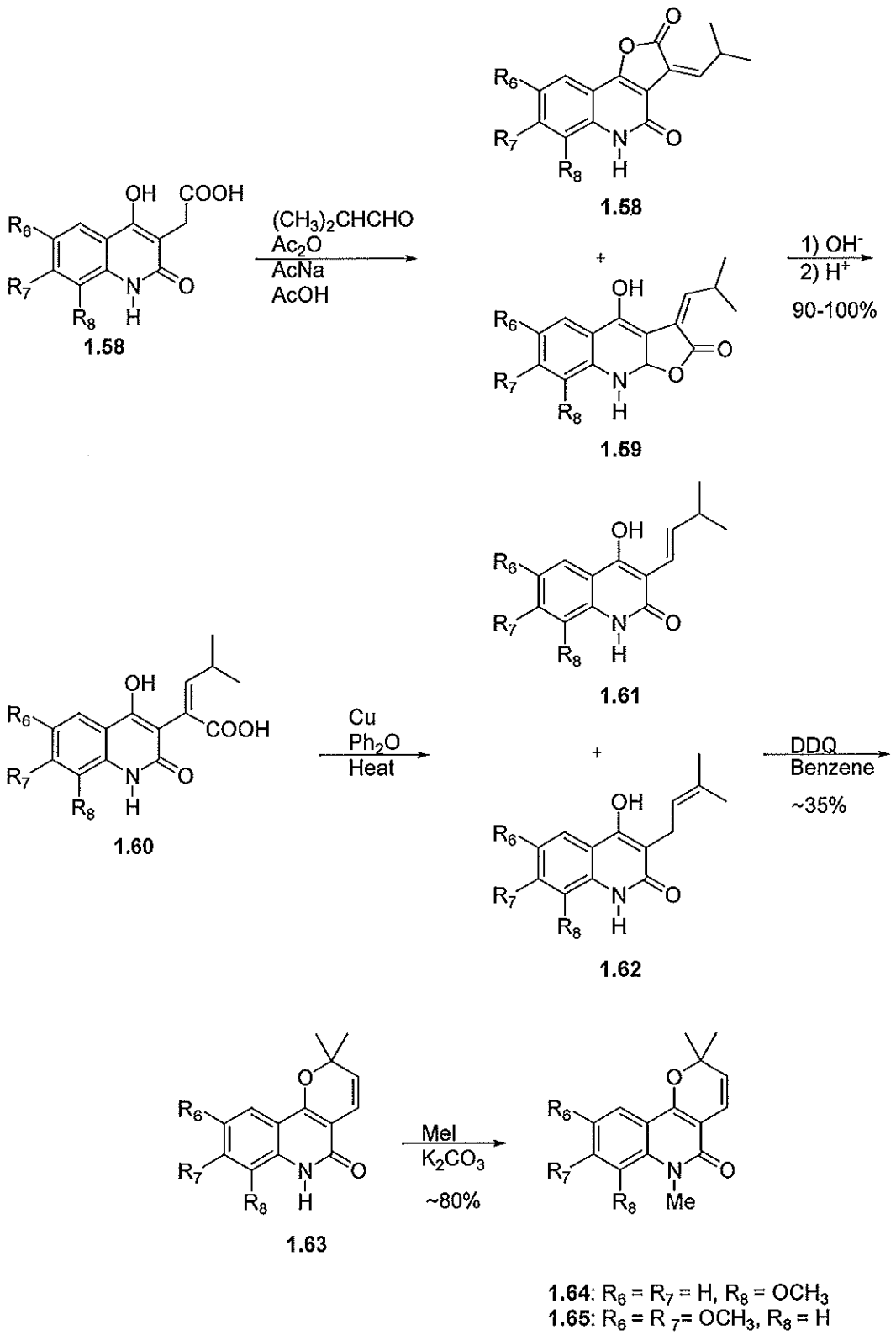



**1.54** **1.55**

**(1.43)**: $R_1 = R_8 = H$
**(1.46)**: $R_1 = CH_3$, $R_8 = H$
**(1.56)**: $R_1 = H$, $R_8 = OCH_3$

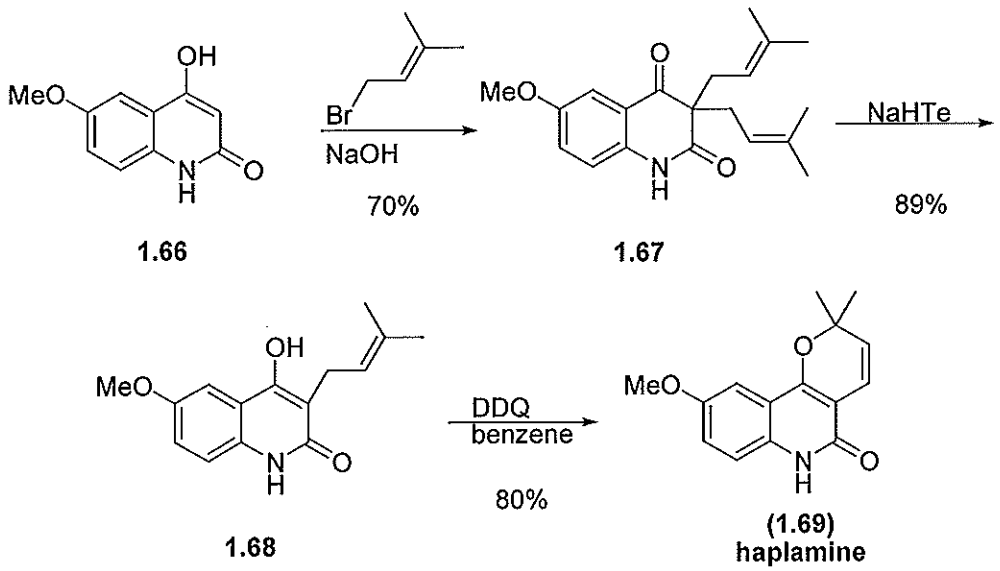
**Scheme 1.18**

Ramesh *et al.*[41] reported a method for the synthesis of several pyranoquinolinone alkaloids including zanthobungeanine[42] (**1.64**) and oricine[27,43] (**1.65**), as shown in Scheme 1.19. Condensation of 4-hydroxy-2-quinolinone-3-acetic acid (**1.57**) with isobutyraldehyde gave a mixture of two lactones, **1.58** (70 %) and **1.59** (20 %), where **1.59** was identified as a linear isomer and hence **1.58** was presumed to be an angular isomer. Upon treatment of both **1.58** and **1.59** with hot alkali followed by acidification, the same acid **1.60** was found to be formed. Decarboxylation of the acid **1.60** by heating with copper powder in diphenyl ether gave the two isomers, **1.61** and **1.62** in ~30 % yield respectively, which without further purification were treated with DDQ to furnish the cyclised product **1.63**. *N*-Methylation of **1.63** gave zanthobungeanine (**1.64**) and oricine (**1.65**) depending upon the substitution pattern of **1.63**, in overall, less than 20 % yield (Scheme 1.19).


OH
COOH
R6
R7
R8
N
H
O
1.58
(CH3)2CHCHO
Ac2O
AcNa
AcOH
1.58
1.59
1) OH-
2) H+
90-100%
1.61
1.60
Cu
Ph2O
Heat
DDQ
Benzene
~35%
1.62
1.63
MeI
K2CO3
~80%
Me
1.64: R6 = R7 = H, R8 = OCH3
1.65: R6 = R 7= OCH3, R8 = H

**Scheme 1.19**

Shobana *et al.*[44] reported a shorter, more efficient, approach to pyranoquinolinone alkaloids such as in the example of the synthesis of haplamine[45] (**1.69**), as shown in Scheme 1.20. Treatment of 4-hydroxyquinolin-2(1*H*)one with an excess of prenyl bromide in an alkali solution gave the *bis* prenylated quinolone (**1.67**) in a 70 % yield. Partial deallylation of **1.67** by sodium hydrogen telluride in boiling ethanol furnished the mono prenylated compound **1.68** in an 89 % yield. **1.68** was then oxidised by DDQ in boiling benzene to undergo dehydrocylisation to afford the product haplamine (**1.69**).




**Scheme 1.20**

### 1.2.3 Other furo- and pyranoquinolinone alkaloids

Table 3 summarises other more complex quinolinones that have been isolated from nature.[12] Some of these natural products have been synthesised,[46] however, these syntheses will not be considered and the Table merely illustrates the relative complexity shown by these compounds within nature.

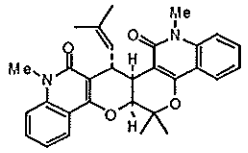
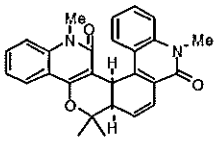
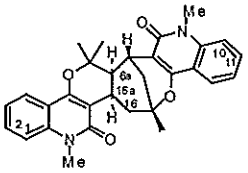
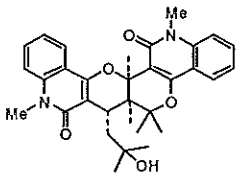
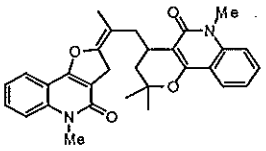
| Species | Alkaloid | Entry |
|---|---|---|
| *Melicope ptelefolia* | Melicobisquinolinone A |  |
| " | Melicobisquinolinone B |  |
| | | |
| *Euxylophora paraensis* | Paraensidimerine A |  |
| " | Paraensidimerine C | 16*a*-epimer |
| " | Paraensidimerine E | 6*a*,16*a*-diepimer |
| | Paraensidimerine F | 6*a*-epimer |
| | Paraensidimerine G | 16,16*a*-didehydro |
| *Vepris louisii* | Vepridimerine A | |
| *Vepris louisii and Oricia renieri* | Vepridimerine B | 1,2,10,11-tetramethoxy |
| *Araliopsis tabouensis* | Araliopdimerine C | 1,2,10,11-tetramethoxy 16,16*a*-didehydro |
| *Euxylophora paraensis* | Paraensidimerine B |  |
| " | Paraensidimerine D | 1'-dehydro,2'-deoxy |
| *Ptelea trifoliata* | Pteledimeridine |  |
| | | |

**Table 3**

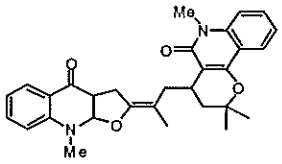
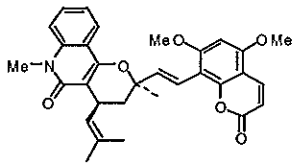
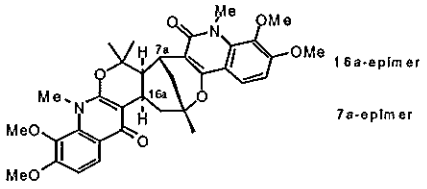
| Species | Alkaloid | Entry | |
|---|---|---|---|
| *Ptelea trifoliata* | Pteledimerine | |  |
| *Toddalia asiatica (Toddalia aculeata)* | Toddacoumalone | |  |
| *Vepris louisii and Oricia renteri* | Vepridimerine C | |  |
| *Vepris louisii* | Vepridimerine D | 16a-epimer | |
| *Synthetic* | Vepridimerine E | 7a-epimer | |

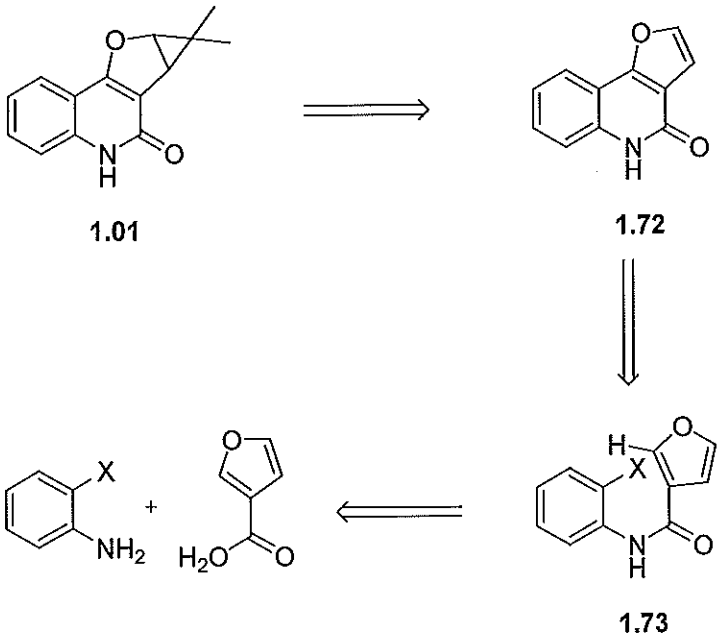
**Table 3 cont.**

### 1.2.4 Summary

When considering the examples that have been shown of the synthesis of the furo- and pyranoquinolinones in general, common strategies can be seen to be emerging. In general the approach taken involves some type of alkylation of a 1,3-dicarbonyl system followed by a cyclisation step to install either a furan- or pyrano moiety. It was envisaged that a potential new method for synthesising the furoquinolinone core structural unit could be developed which did not follow these common strategies. This method may have advantages over the examples shown as it could provide an alternative route to quinolinone alkaloids, in general. Also, once the new method for the synthesis of the furoquinolinone core structure has been developed, it can then be used as an intermediate towards attempting the synthesis of the natural product **1.01**.

## 1.3 Synthetic approach of the natural product 1.01

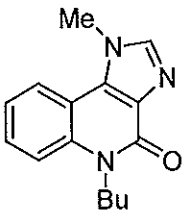
The proposed synthesis of the natural compound **1.01** is represented in Scheme 1.21 retrosynthetically. This Scheme includes a strategy for preparing the furoquinolinone core structural unit via a new approach. The furoquinolinone core **1.72** can be envisaged by disconnection of the two bonds of the cyclopropane ring of the natural compound **1.01**, and has previously been recognised as a potential key intermediate for this class of molecules.[25,26,47] Further, the synthesis of **1.72** can be envisaged by a intramolecular heck type coupling of **1.73**, where the precursor can be made by a simple amide coupling of an *ortho* haloaniline and 3-furoic acid. Thus the key features of the synthesis of the natural compound **1.01** will be the intramolecular heck coupling which in one step creates the tricyclic furquinolinone core structure **1.73**, and the cycolpropanation step, which may be achieved with the use of carbene chemistry as will be discussed.




**Scheme 1.21**

### 1.3.1 Synthesis strategy of the key intermediate

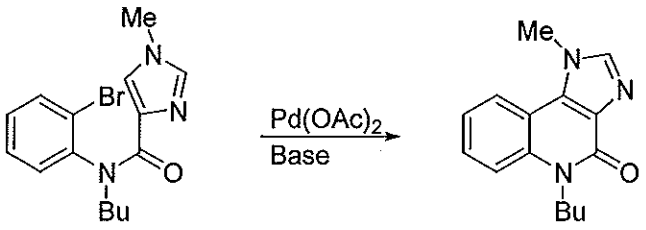
As shown there have been limited synthetic strategies to this class of compounds and alternative approaches may be advantageous. Kuroda *et al.*[48] presented a method of synthesising the heterocyclic quinolinone core structure (**1.70**) using an imidazole as the substitution group which resembles that of the furan ring, as shown in Figure 1.3.




**1.70**

**Figure 1.3**

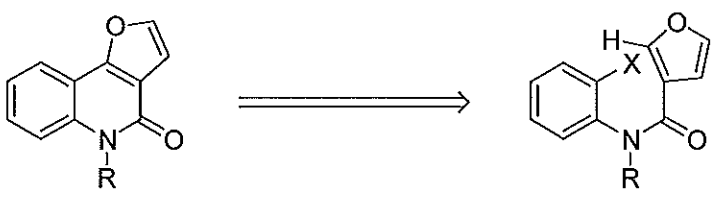
The key step in the synthesis of the quinolinone **1.70** was a palladium catalysed cyclisation of the *N*-phenyl-1*H*-imidazole-4-carboxamide derivative (**1.71**) in the presence of base in a polar solvent, as shown in Scheme 1.22.




**1.71** **1.70**

**Scheme 1.22**

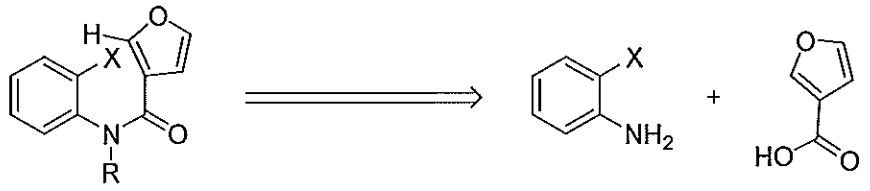
Intramolecular cyclisation for the formation of key intermediate **1.72** (Scheme 1.23) could be achieved using a palladium catalysed C-C coupling reaction,[49] radical cyclisation[50] or the use of photo induced cyclisation,[51] which has been used for the synthesis of similar heterocyclic systems. Considering the approach taken by Kuroda *et al.*,[48] it was envisaged that the palladium catalysed cyclisation could work as a key step for the synthesis of the furan ring system by performing the ring cyclisation on the amide **1.73**, shown retrosynthetically in Scheme 1.23. This would give the tricyclic core **1.72** as the key intermediate in the synthesis of compound **1.01**.




**1.72** **1.73**

**Scheme 1.23**

As mentioned, the amide precursor (**1.73**) for the cyclisation to the core structure can be derived from a haloaniline and the corresponding acid, as shown in Scheme 1.24.




**1.73**

**Scheme 1.24**

### 1.3.1.1 Amide couplings with acids and amines

Synthesising bicyclic structures with an amide incorporated have previously been explored with regards to investigation of natural products syntheses.[52] One way to facilitate the amide coupling of acids with amines is to use a coupling reagent[53-55] e.g., DCC or EDC, as shown in Figure 1.4. The reagent HOBt is commonly added to facilitate the amide coupling when these reagents are used.

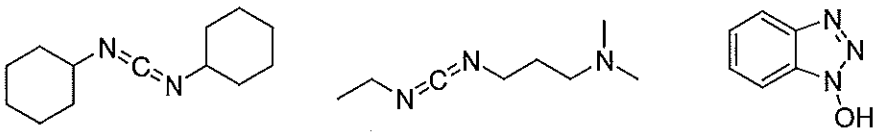
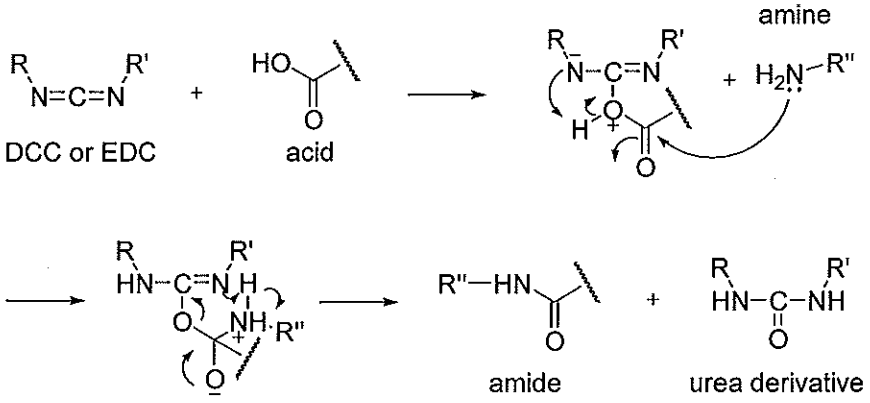



**Figure 1.4**

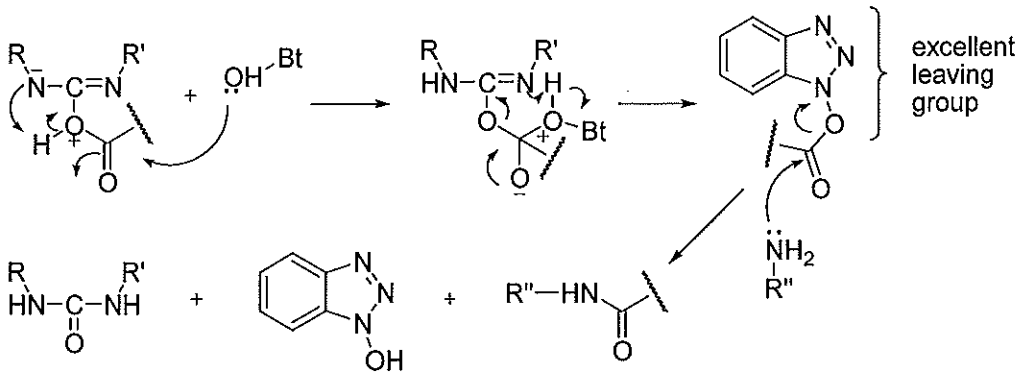
DCC and EDC are close relatives to each other, both sharing the same carbodiimide functionality, and hence, both have the same mechanism which is summarised in Scheme 1.25. The hydroxyl group of the acid is activated by the

carbodiimide which makes the carbonyl carbon of the acid more electrophilic, facilitating "attack" of the amine, as shown in Scheme 1.25.




**Scheme 1.25**

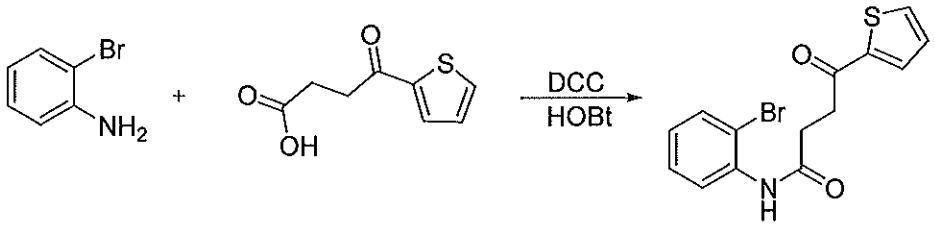
The reagent HOBt is often used in combination with either DCC or EDC to further facilitate the reaction. The addition of HOBt is to further activate the electrophilic carbonyl carbon to "attack" from the corresponding amine. This is achieved by the reagent first reacting with the carbodiimide activated carbonyl to produce an activated ester. This intermediate is then "attacked" by the amine to furnish the amide coupled product, as shown in Scheme 1.26.




**Scheme 1.26**

The driving force for reactions involving DCC or EDC, is the irreversible formation of the urea derived side product. Further, when the hydroxybenzotriazole reagent (HOBt) is employed, an excellent leaving group is formed which further promotes formation of the desired amide product, and consequently acts as the driving force of the reaction.

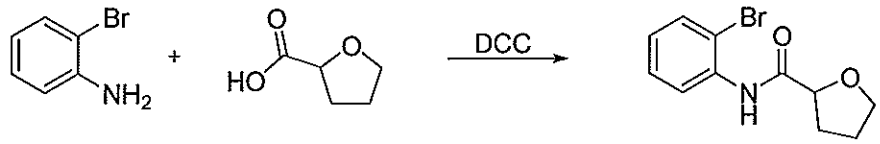
Raposo and co-workers[56] utilised the reagents DCC and HOBt, to couple a bromoaniline with a thiophene acid derivative to give the amide product in a yield of 53 %, as shown in Scheme 1.27.




**Scheme 1.27**

The reaction of the corresponding 2-iodoaniline under the exact same conditions was investigated and gave similar results. In both reactions, HOBt was used to further facilitate the coupling.

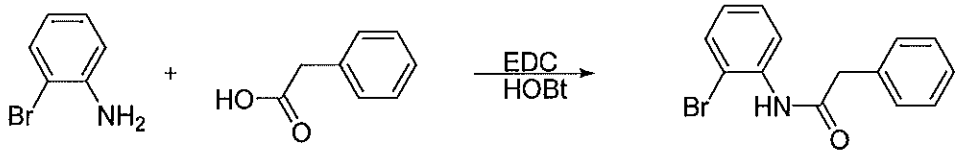
Lee and co-workers[57] demonstrated the utility of the coupling reagent DCC in the synthesis of the amide coupled product of 2-bromoaniline and tetrahydro-2-furancarboxylic acid, as shown in Scheme 1.28.




**Scheme 1.28**

The reaction was performed without further additives such as HOBt, however, only giving in this case a yield of 41 %.

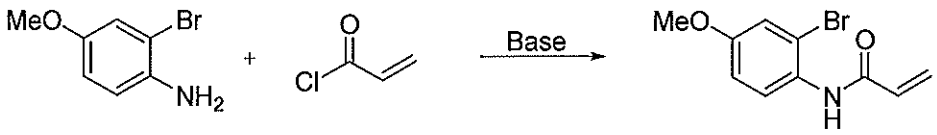
Evindar and co-workers[58] employed a similar procedure, as Raposo *et al.*,[56] in the synthesis of haloanilides as precursors for the formation of benzoxazoles. This procedure utilised both the coupling reagent EDC and HOBt to give a yield of 55 % of the desired product, as shown in Scheme 1.29.




**Scheme 1.29**

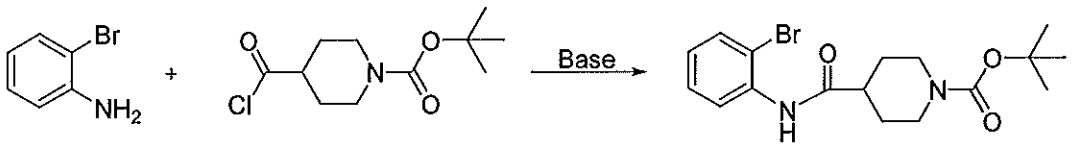
Another way of synthesising amides is by first converting the acid to its corresponding acid chloride, and then reacting this with the corresponding amine.[59,60] By converting the acid to its corresponding acid chloride, the carbonyl carbon becomes comparably more electrophilic, and this then can be utilised in the amide coupling.

Escolano and co-workers[52] published their synthetic investigation of pyrroloquinolinones, a close relative of the furoquinolinone class of molecules. In view of the outlined synthetic strategy they suggested, an amide coupled product was required in order to access the core structure for further investigation. The haloaniline was treated with the commercially available acryloyl chloride and base, to furnish the amide coupled product in a 93 % yield, as shown in Scheme 1.30.




**Scheme 1.30**

A convenient synthetic route to spiro[indole-3,4'-piperidin]-2-ones was prepared by Freund and co-workers.[61] The synthetic approach incorporated an amide coupling of *N*-Boc-isonipecotic acid and 2-bromoaniline. Initial attempts were made in coupling the 2-bromoaniline with the acid by using coupling reagents such as DCC and EDC etc., but only low yields were achieved. The *N*-Boc-isonipecotic acid was then converted to its acid chloride derivative, followed by treatment with 2-bromoaniline and base to afford the desired product in a 71 % yield, as shown in Scheme 1.31.



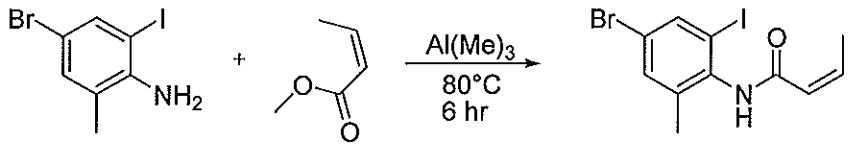

**Scheme 1.31**

In this report, Freund *et al.*[61] found that the acid chloride derivative gave a superior yield in forming the desired amide coupled product, as compared to using the well known coupling reagents (DCC, EDC. etc.)

A third method for synthesising amides is by direct aminolysis of esters. Although the direct conversion of esters to amides is potentially a useful synthetic operation, the required conditions can sometimes be the limit for several reasons.[62] As a remedy for the complications sometimes encountered with direct aminolysis, there are a few reagents[63-66] available to promote and facilitate the coupling under milder conditions, including the most commonly used trimethyl aluminium[67]

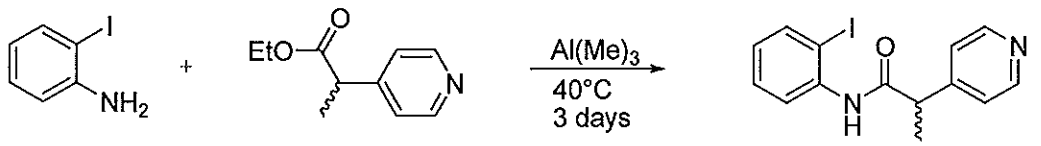
Basha and co-workers[67] reported the use of the reagent trimethylaluminium, for the coupling of esters with amines under mild reaction conditions. The generality of the reaction procedure was tested on a variety of compounds, and high yields of the desired products were observed. The key step is the pre-treatment of the amine with trimethylaluminium, followed by addition of the ester.

In the course of investigating low-temperature heck reactions of *o*-iodoacrylanilides, Lapierre and co-workers[68] were interested in synthesising a particular acrylamide. When employing the reported method from Basha *et al.*,[67] the desired amide coupled product was afforded in a yield of 90 %, but by using slightly higher reaction temperatures in a shorter period of time (Scheme 1.32).




**Scheme 1.32**

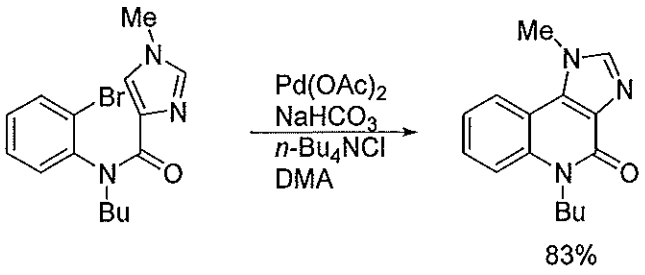
In the total synthesis of the anticancer alkaloid ellipticine, Pedersen and co-workers[69] also utilised the methodology from Basha *et al.*,[67] when synthesising a desired amide coupled product (Scheme 1.33). The starting material, 2-iodoaniline, was treated with trimethylaluminium followed by addition of ethyl 2-(4-pyridyl)acetate, to furnish the desired product in a 81 % yield, as shown in Scheme 1.33.




**Scheme 1.33**

### 1.3.1.2 The Heck type coupling in related reactions

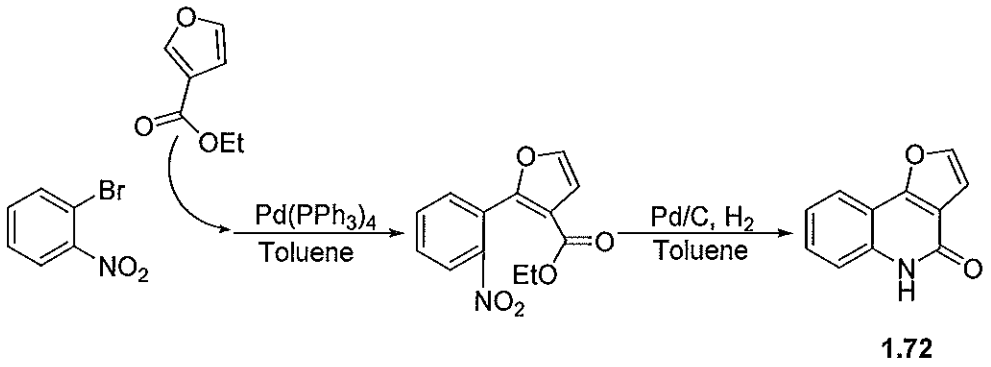
The most crucial step in achieving the furoquinolinone core structure **1.72**, was envisaged to be the intramolecular heck type coupling of the amide precursor **1.73**. In the work of Kuroda *et al.*,[48] a tethered amide linked imidazole group was used for the intramolecular C-C coupling (Scheme 1.34). In this coupling palladium acetate was employed as catalyst in the presence of sodium hydrogen carbonate, an additive and DMA as solvent. This gave the desired cyclised product in a 83 % yield, as shown in Scheme 1.34.




**Scheme 1.34**

The optimised conditions for the cyclisation of the imidazole derivative were found through a screening process where different solvents, bases, temperatures and catalyst loadings were altered. Kuroda *et al.*[48] found the best yields were obtained by using the additive TBACl with sodium bicarbonate as base. Palladium acetate was found to give the best yields as compared to using palladium triphenylphosphine tetrakis or palladium chloride. Also, the reaction required high temperatures (150 °C) and the use of a polar solvent such as DMA. No difference was observed in yield when using higher catalyst loadings.

Glover *et al.*[47] reported a new approach of synthesising the furoquinolinone core structure **1.72**. In contrast to the proposed strategy, a bimolecular heck type coupling of 1-bromo-2-nitrobenzene and ethyl-3-furoate, in the presence of base and palladium triphenylphosphine as catalyst, was used in the first step to afford the biaryl coupled derivative. In the second step, a reductive amide coupling furnished the furoquinolinone core structure **1.72** in an overall yield of 60 %, as shown in Scheme 1.35 .



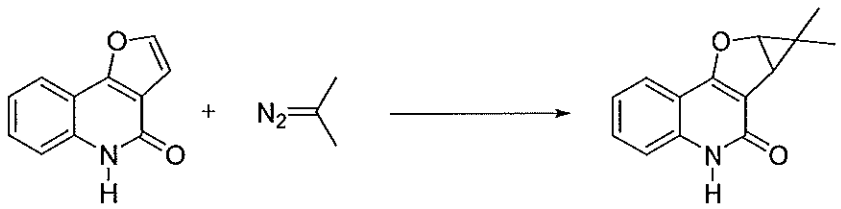

**1.72**

**Scheme 1.35**

The optimised conditions for the biaryl coupling were found through a screening process using 3-bromonitrobenzene and ethyl-3-furoate as substrates. This did not give the desired furoquinolinone core structure, however, did give the optimised conditions for the biaryl coupling reaction using similar substrates i.e., the use of 3-nitrobenzene instead of 2-nitrobenzene. The screening process involved the use of different catalysts, bases and solvents. It was discovered that depending on wether a polar or a non polar solvent was used in the biaryl coupling reaction, different regio isomers were favoured. When using a non polar solvent such as toluene

together with palladium triphenylphosphine as catalyst, the 2-aryl coupled product was shown to be the major product. When using a polar solvent such as NMP in the presence of a "ligandless" palladium catalyst such as palladium on carbon, the 5-aryl coupled product was shown to be the major outcome. Other bases such as triethylamine, only afforded low conversions to the 5-aryl coupled product. The conclusion of the screening was that the catalyst and the solvent were the most pertinent factors in optimising the biaryl coupling reaction.

With the double bond in key intermediate **1.72**, this functional group is likely to be the most reactive site for further functionalisation. For the novel alkaloid **1.01** there is a possibility the double bond in **1.72** can undergo a cyclopropanation reaction using an appropriate diazo reagent i.e., 2-diazopropane,[70] to give the desired frame work, as shown in Scheme 1.36.

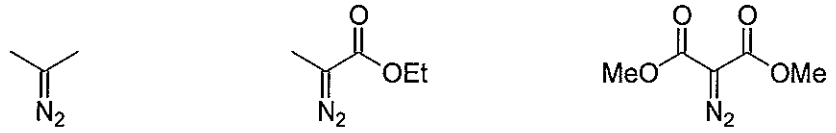



**1.72** **1.01**

**Scheme 1.36**

Of some concern, was that no literature precedent was found regarding installation of a cyclopropane ring functionality that contained a *gem* dimethyl group on a furoquinolinone core structure, or even on a simple furan ring. If this is due to the lack of reactivity of the 2-diazopropane with furan type systems, then the desired product would not be given by this approach, and therefore alternative strategies

may be required. Diazo reagents such as ethyl 2-diazopropanoate and dimethyl diazomalonate (Figure 1.5) have previously been used on furan type systems, as will be discussed. Use of such reagents will provide the necessary carbon frame work of the natural product, but subsequent functional group manipulation will be required. Also, it will be of interest regardless of the outcome of using 2-diazopropane, to be able to compare the reactivity of the furquinolinone core with various diazo reagents (Figure 1.5).




2-diazopropane ethyl 2-diazopropanoate dimethyl diazomalonate

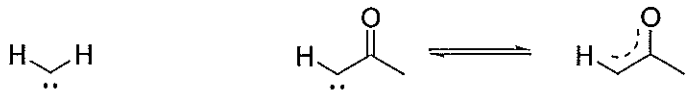
**Figure 1.5**

### 1.3.3 Carbene chemistry

#### 1.3.3.1 Historical perspective of diazocompounds

In a review by Marchand et al.,[71] carbene chemistry is described as an advancing area since it became of interest in the late 1940's and early 1950's.[71] In that time, the very reactive methylene carbene species was studied through the photolytic decomposition of diazomethane to explore its chemical and physical properties.[72,73] The synthetic utility was not of great value at the time owing to the difficulties of controlling the very reactive carbene species and consequently showed lack of selectivity in organic reactions. As a remedy for this problem, it was found that a more stabilised carbene could be generated if substituting one of the carbene methylene hydrogens with an electron stabilising group. This can be done by using

a heteroatom or a heteroatom containing group with an unshaired pair of electrons, such as an carbalkoxycarbene as depicted below.



non-stabilised methylene carbene

stabilised carbalkoxy carbene

The resulting carbene intermediate exhibits greater selectivity towards different substrates and could be rendered as a synthetic viable tool in organic chemistry.[71] Carbalkoxycarbenes have been known since the mid 1880's[74,75] but attention was not drawn until 1950's when mechanistic understanding was sought to explain various reaction outcomes and hence to make carbenes a more useful tool in organic chemistry.[71] The generation of a carbenoid complex, has been known for more than 100 years,[76] where heterogeneous copper bronze and cupric sulfate dominated until the 1960's. These catalysts were replaced with the homogeneous catalysts *bis*(acetylacetonato)copper(II)[77] as well as (trialkyl and triaryl phosphite)copper(I).[78] Between the years of 1960 and 1980, new transition metal catalysts of various constitutions such as; $Cu(I)L_n$, $Cu(II)L_n$, $Pd(II)L_n$ and $Rh(II)L_n$ were developed[79] and more or less supplanted the thermal and photolytical methods in generating carbenes.[80] In recent times, one of the most frequently used class of catalysts for cyclopropanation of double bonds, is various rhodium and copper complexes. These are all well documented in the literature. Also focus has been given in particular to developing metal ligands that stereoselectively introduce a cyclopropane ring on alkenes, and also, control the selectivity of cyclopropanation[80-103] over the CH-insertion reaction.[80-83,85-99,101,104]

### 1.3.3.2 Generation of Carbenes

There are several ways of generating carbenes and thereby installing a cyclopropane ring onto double bonds. Three methods frequently encountered in literature involving the generation of a carbene, are through a Simmon Smith[105] type reaction; the use of dihalogen compounds with strong base[106] or; the decomposition of diazo compounds. The decomposition of diazo compounds[71] can either be photolytically, thermally or metal induced.

### 1.3.3.3 The catalytic cycle in the carbenoid formation when using a diazo compound with a metal catalyst

A metal carbenoid complex generated from diazo reagents with electron withdrawing groups (on the carbon adjacent to carbene carbon) produces a highly electrophilic carbene amenable to participate in various types of reactions.[107] At the other end of the spectrum, carbenes generated with electron donating groups adjacent to the carbene centre (e.g. a methyl group) are less stabilised and are therefore less electrophilic in nature. Even though a metal complexed carbene differs from a free carbene derived photolytically, the inherent properties caused by the substituents adjacent to the carbene carbon centre follow the same trend.[80] The metal complexed carbene can be depicted as shown in Figure 1.6, where the R-groups enhance the electrophilic character of the carbene if R is an electron withdrawing group.

$$L_nM{=}CR_2 \rightleftharpoons L_n\overset{-}{M}\text{-}\overset{+}{C}R_2$$

**Figure 1.6**

As shown in Figure 1.7, transition metal compounds react as electrophiles with diazo compounds to form intermediate **I** which facilitates loss of nitrogen gas and thus a metal stabilised carbene **II** is generated. The metal stabilised carbene **II** can then react with an electron rich substrate, to give in this case a cyclopropanated product, and regeneration of the transition metal to complete the catalytic cycle (Figure 1.7).

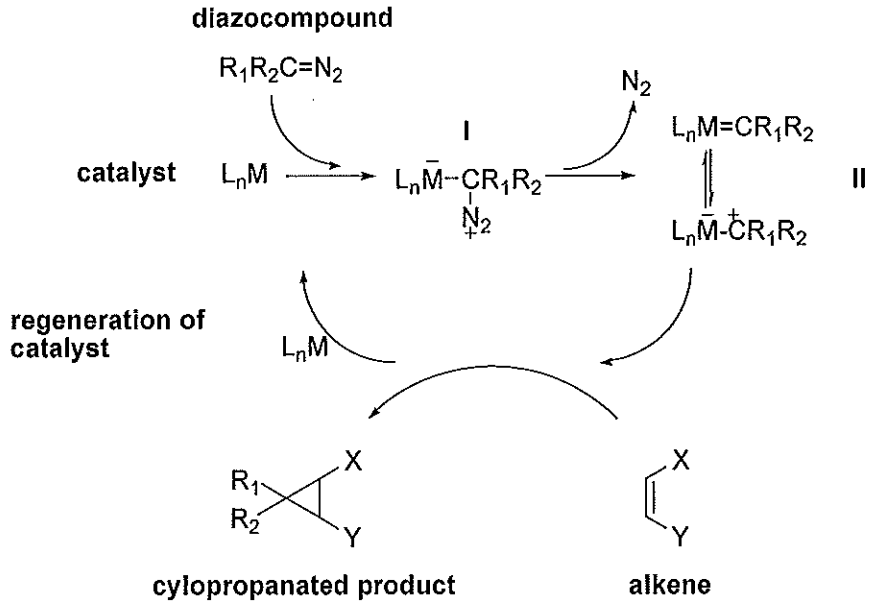
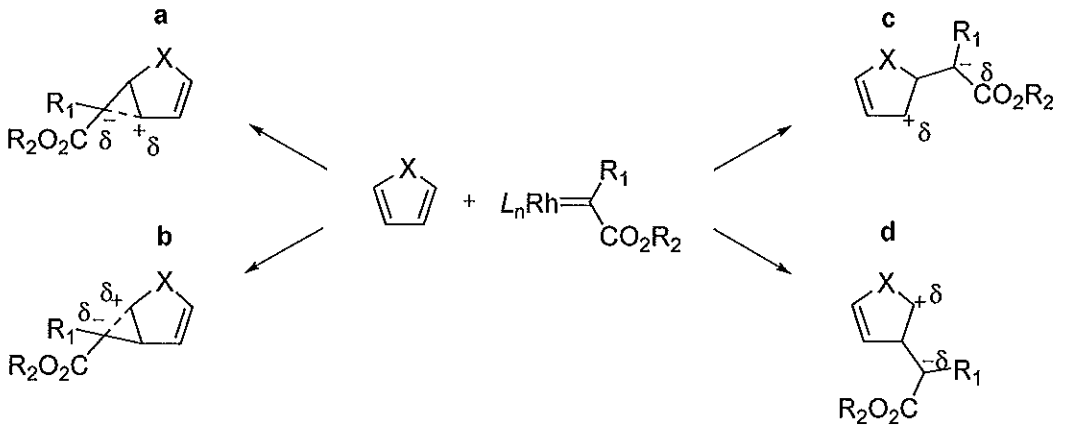



**Figure 1.7**

### 1.3.3.4 Mechanistic view

Several mechanistic interpretations[108,109] of the decompositions of diazo compounds with simple furans/substituted furans in the presence of dirhodium tetraacetate (and without[110,111]) as catalyst, have been published in the literature through the years. However, the latest mechanistic view reported by Davies *et*

*al.*,[112] showed that there are four possible intermediates able to be produced after the addition of the carbenoid complex to a heterocycle, as shown in Scheme 1.37.




**Scheme 1.37**

According to Davies *et al.*,[112] depending on the type of carbenoid and the heterocycle being used, the different intermediates **a** to **d** are favoured. It is explained that the cyclopropanation reaction is a concerted reaction with a build-up of a positive charge at either the C-2 or C-3 position, such as intermediates **a** or **b**. Alternatively, if the heterocycle and the carbenoid are effective at charge stabilisation, zwitterionic intermediates such as **c** and **d** can be formed. A variety of different products can be explained with respect to this mechanistic interpretation.

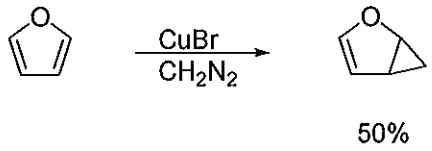
### 1.3.4 Frequently used diazo reagents on simple furans/substituted furans

Heterocycles such as simple furans readily react with different types of carbenes to form a variety of compounds such as cyclopropanated and ring opened dienal materials. Literature precedent reveals the frequent use of diazomethane and ethyl

diazoacetate, as carbene precursors, with furan/substituted furans as substrates. Further, it shows the variety of different products that can be synthesised depending upon the substrate and the catalyst used. Although these reagents will not give the carbon frame work for the natural product **1.01**, they do demonstrate the use and the versatility of carbene chemistry as a tool for installing, not only cyclopropane rings, but also other functionalities such as dienal type structures.

### 1.3.4.1 Using diazomethane

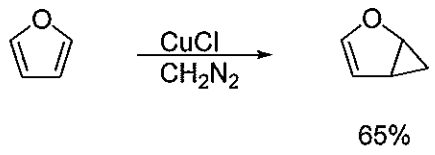
An early report can be found by Eugen Muller *et al.*,[113] exploring the metal catalysed reaction of diazomethane with simple furans where the diazomethane reagent was made separately and subsequently was added to the reaction mixture. The reaction afforded the cyclopropanated product in 50 % yield when copper bromide was employed as catalyst, as shown in Scheme 1.38.




**Scheme 1.38**

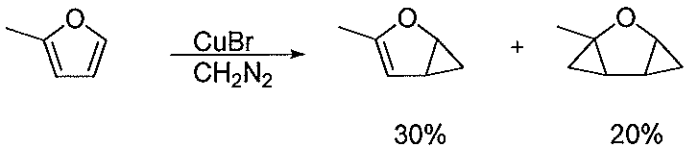
This reaction was later on revisited by Rainer Herges[114] in the pursuit of optimising the reaction protocol, due to serious accidents in the lab when handling pure diazomethane in large scale. Initial efforts, using the Simmon-Smith[115] type of cyclopropanations or ethereal solutions of diazomethane in the presence of CuCl, only resulted in poor yields. By using furan as solvent (which is immiscible with water) and generating the diazomethane in situ in a two phase system,[114] the yield

of the cyclopropanated product was able to be improved to 65 %, as shown in Scheme 1.39.



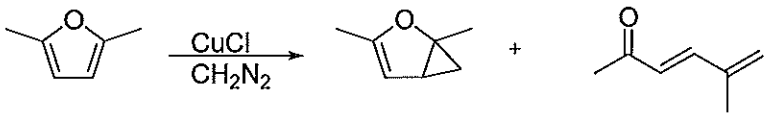

**Scheme 1.39**

Substituted furans have also been investigated with the copper based decomposition of diazomethane, in particular 2-methylfuran,[116] 2,5-methylfuran[117] and 2-tertbutylfuran.[117] In the case of 2-methylfuran, two isomers of cyclopropanated products were isolated, as shown in Scheme 1.40.



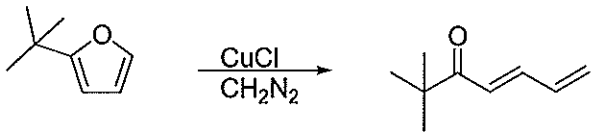

**Scheme 1.40**

Cyclopropanation occurred, in preference, on the unsubstituted side of the furan ring, giving the predominant mono cylopropanated product in 30 %, and the *bis* cyclopropanated product in 20 %. Interestingly, when 2,5-dimethylfuran was treated under similar conditions, only a mono cyclopropanated product could be isolated. However, an additional ring opened product was also observed i.e., diene carbonyl formation, as shown in Scheme 1.41.




**Scheme 1.41**

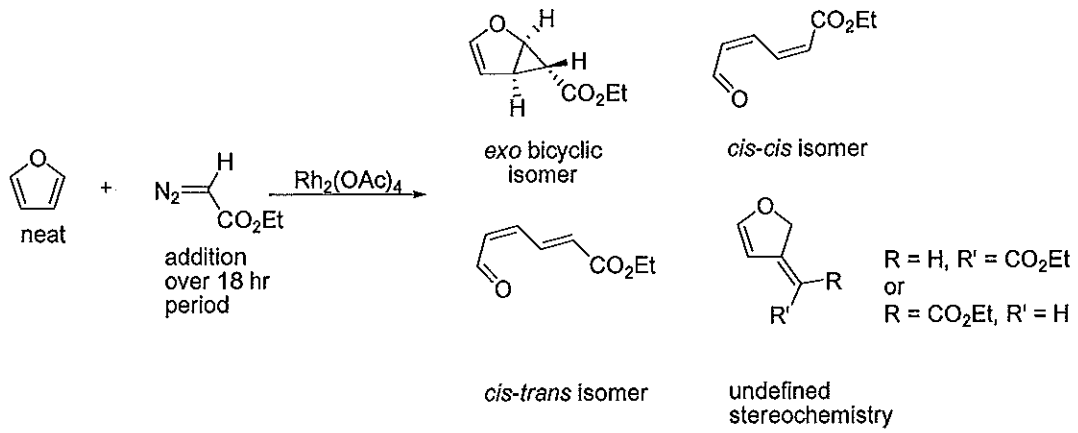
In addition, when treating 2-tertbutylfuran under the same reaction conditions, only diene carbonyl formation was afforded, as shown in Scheme 1.42.




**Scheme 1.42**

### 1.3.4.2 Using ethyl diazoacetate

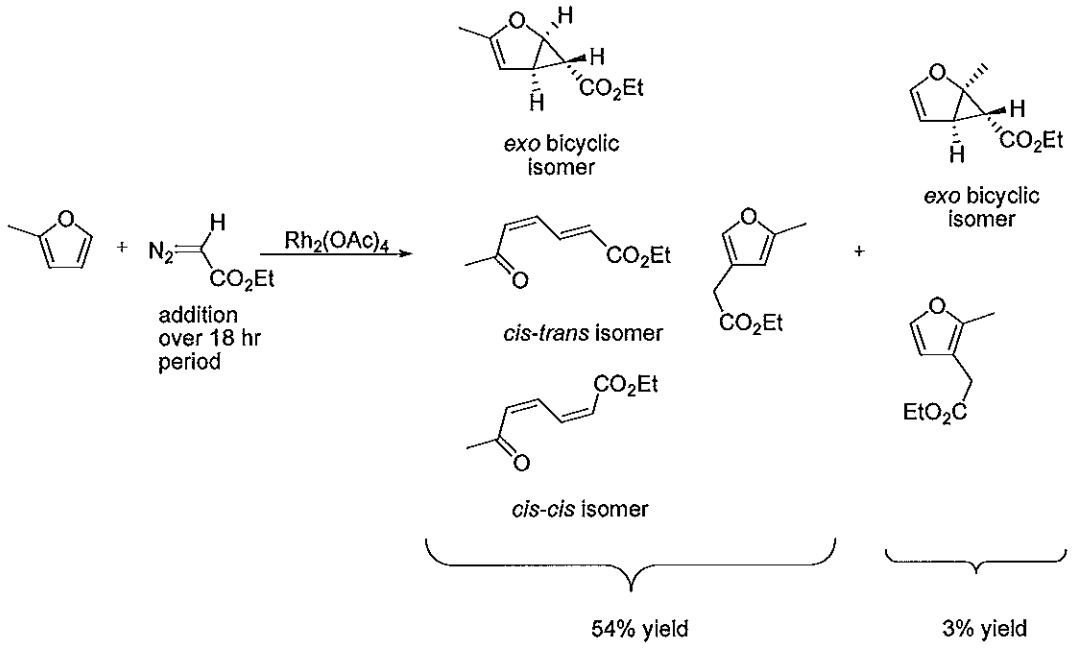
Studies of metal catalysed reactions of furans with diazo compounds have been conducted several times by Wenkert *et al.*[108,118-121] They investigated the reaction of simple furan, 2-methyl furan and 2,5-dimethylfuran as substrates, with ethyl diazoacetate as the carbene precursor.[118] When ethyl diazoacetate was added to neat furan in the presence of catalytical amounts of dirhodium tetraacetate as metal catalyst, four different products were isolated, as shown in Scheme 1.43.




**Scheme 1.43**

The products were, after silica based chromatography, identified as the *exo* isomer of the bicyclic product, the *cis-trans* and *cis-cis* dienals, and 3-alkylidene-2,3-dihydrofuran in a single stereoisomer in ratios of 17:10:5:1 respectively, and all in a total yield of 66 %.

When 2-methylfuran was used as the substrate and treated under the same conditions as the previous reaction, a different mixture of products was observed, as shown in Scheme 1.44.

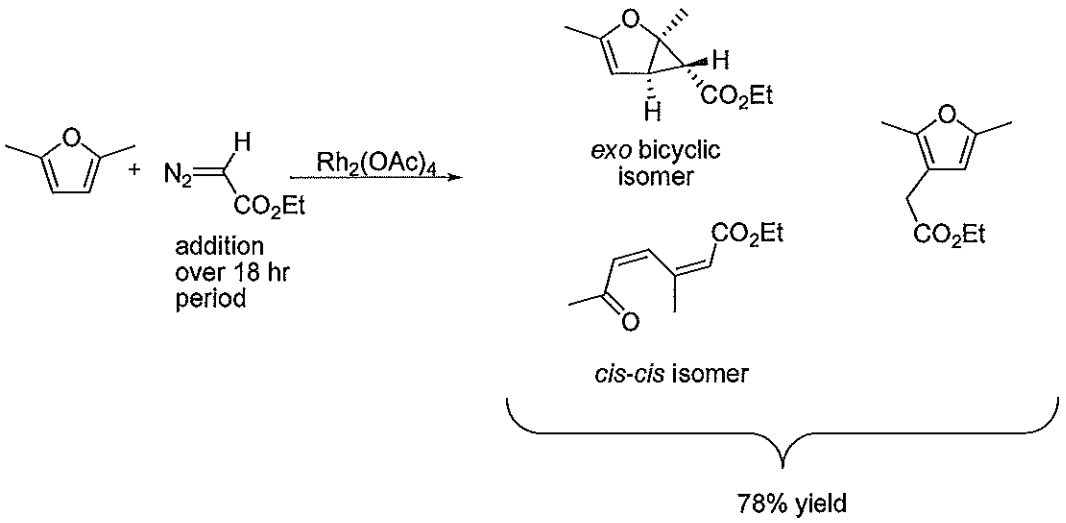



**Scheme 1.44**

The products in this after alumina based chromatography, were identified as the *cis-trans* and *cis-cis* dienals, the *exo* isomer of the bicyclic product, and the 4-CH-

insertion product in ratios of 31:12:10:1 respectively, and all in a total yield of 54 %, together with a 2:1 mixture of the *exo* isomer of the bicyclic product and the 3-CH-insertion product, in a total yield of 3%. It was also observed in the latter mixture in Scheme 1.44, that attack of the carbenoid complex was observed on the substituted side of the furan ring to give a second *exo* bicyclic isomer. However, due to the observed ratio of the two *exo* bicyclic isomers, and that only one constitutional dienal isomer was isolated from the reaction mixtures, it was noted that the attack of the carbenoid complex was in overall highly favoured on the less substituted side of the furan ring.

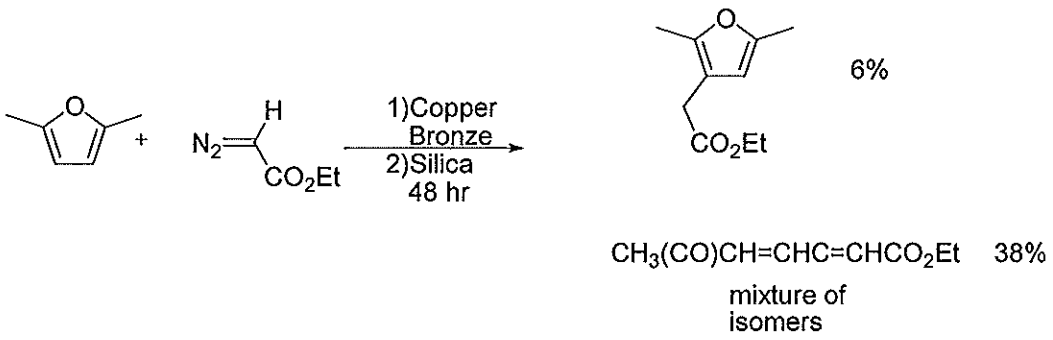
Finally, when 2,5-dimethylfuran was used as the substrate under the previous described conditions, three different products were isolated, as shown in Scheme 1.45.




**Scheme 1.45**

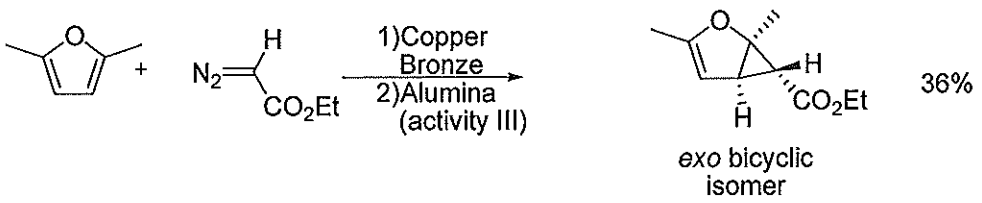
The products were, after alumina based chromatography, identified as the *cis-cis* dienal, the *exo* isomer of the bicyclic product, and the CH-insertion product in the ratio of 9:6:1 respectively, and all in a total yield of 78 %.

Previously Wenkert *et al.*[122] discovered, when using copper bronze as the catalyst for the decomposition of ethyl diazoacetate with 2,5-dimethylfuran as the substrate, the importance of the type of isolation procedure that was applied when the reaction was finished. As can be shown in Scheme 1.46, if the reaction mixture is left on silica for 48 hr before chromatography, the cyclopropanated material could not be detected in any of the fractions. As shown in Scheme 1.46, the products were identified as a mixture of dienal isomers (38 %) and as the CH-insertion product (6 %).



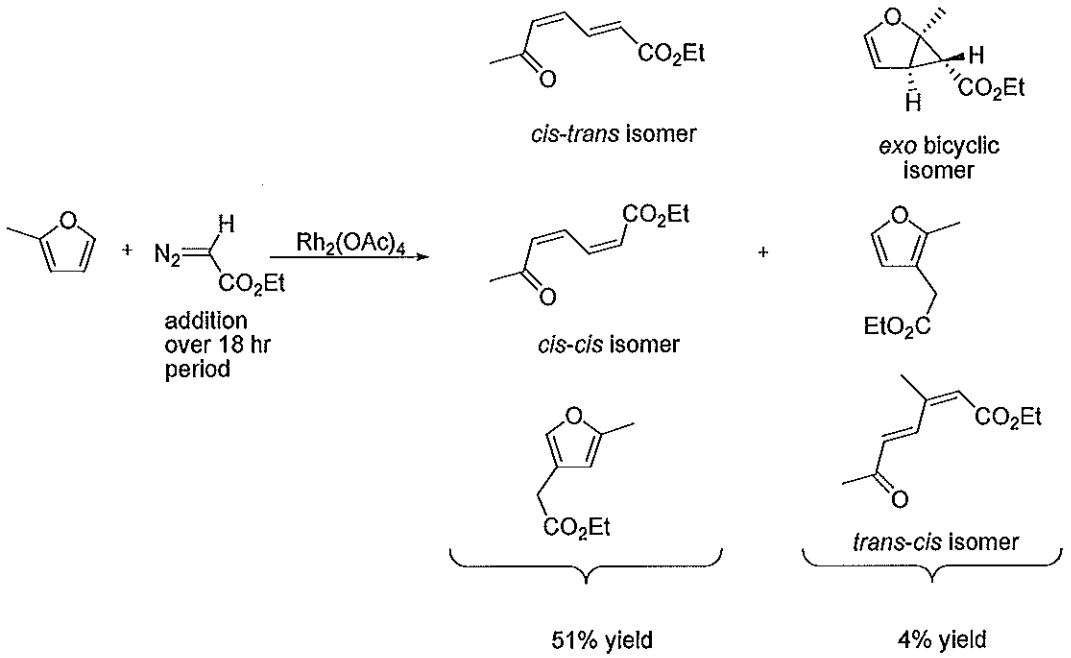

**Scheme 1.46**

When repeating the above described reaction, but replacing the silica with alumina and performing the isolation immediately after the reaction was completed, a single product of the bicyclic *exo* isomer was isolated in 36 %, as shown in Scheme 1.47.




**Scheme 1.47**

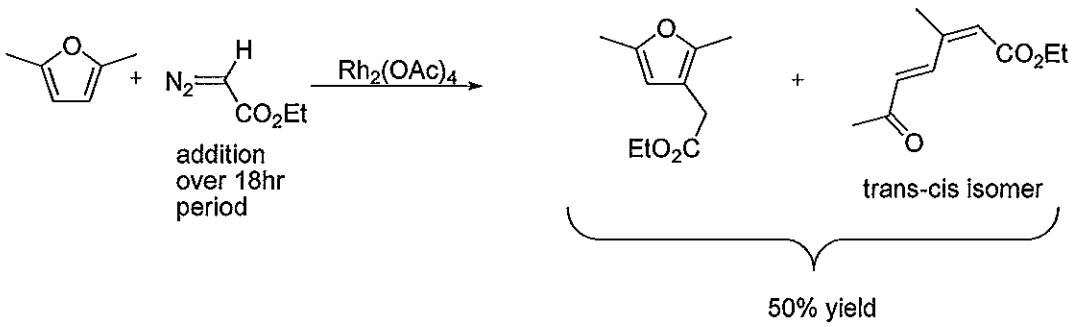
In the light of the importance of different isolation procedures, the reaction of 2-methylfuran with ethyl diazoacetate (Scheme 1.44) was repeated, replacing alumina with silica in the chromatography step (Scheme 1.48). This produced a different mixture of products as compared to when alumina was used for chromatography step.




**Scheme 1.48**

The products were identified as the *cis-trans* and *cis-cis* dienals and the 4-CH-insertion product in ratios of 38:12:1 respectively, and all in a total yield of 51 %, together with a 2:1:1 mixture of the *exo* bicyclic isomer, the 3-CH-insertion product and the *trans-cis* isomer in a total yield of 4 %.

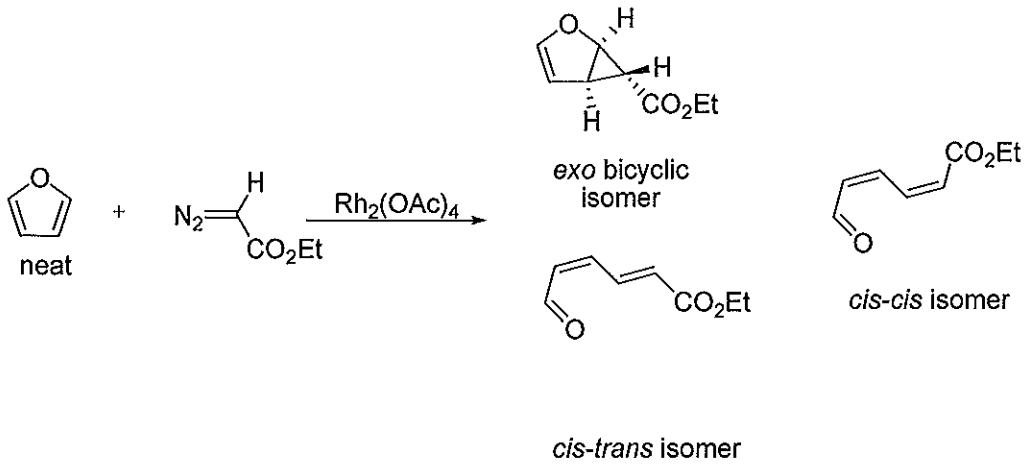
Furthermore, repeating the reaction with 2,5-methylfuran as substrate (Scheme 1.45) and using alumina instead of silica in the chromatography step, a different mixture of products was observed, as shown in Scheme 1.49.




**Scheme 1.49**

The products were identified as the *trans-cis* and the 3-CH-insertion product in ratios of 16:1 respectively and all in a total yield of 50 %.

Matlin and co-workers[109] also investigated the decomposition of the ethyl diazoacetate with simple furans. In contrast to Wenkert *et al.*,[118] rhodium catalyst was added to a mixture of ethyl diazoacetate and neat furan. The reaction was completed after 1 hr to afford three different products, as shown in Scheme 1.50.



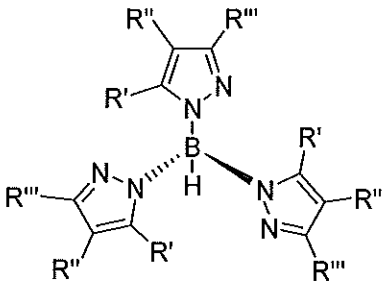

**Scheme 1.50**

The products were, after silica based chromatography, identified as the *exo* isomer of the bicyclic product, the *cis-trans* and *cis-cis* dienals in ratios of 6:1:1 respectively, and, interestingly no 3-alkylidene-2,3-dihydrofuran type products were isolated. Complete consumption of the carbene precursor was observed.

In more recent years, copper induced decomposition of diazocompounds with furans have found renewed interest,[123-125] and so with new optimised conditions, it can be employed giving similar conversion ratios to rhodium catalysts. Not only have yields been improved but also the greater interest of asymmetric syntheses has laid the ground for investigating different sources of copper ligands to be used in order to induce and control such a task. A vast number of chiral ligands are known to date and some of the most successful ones include: binaphthyls,[126-128] bisoxazolines[129-132] (both exhibiting a $C_2$-symmetry axis), phosphinooxazolines[133-135] and ferrocenyl[136-138] ligands.

In the view of this progressing area of copper catalysts and ligands, Caballero *et al.*[139] recently investigated the decomposition of ethyl diazoacetate with furans under copper induced conditions. Their investigative focus was emphasised on influencing the stereoselectivity in cyclopropanation reactions of furan type double bonds with chiral ligands. In particular, a trispyrazolylborate ligand with the general formula[140] $Tp^{x}Cu$ was shown to be very active with various substituents (R', R'', R'''), as shown in Table 5.

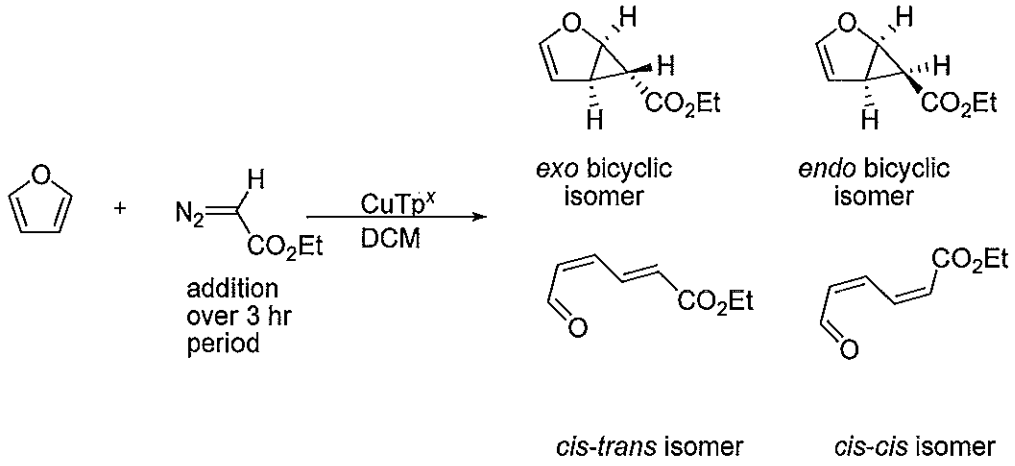
$Tp^x$ =



| $Tp^x$ | R' | R'' | R''' |
|---|---|---|---|
| | | | |
| $Tp^{Br3}$ | Br | Br | Br |
| $Tp^{Ms}$ | H | H | 2,4,6-$Me_3C_6H_2$ |
| $Tp^{Cy}$ | H | H | $C_6H_{11}$ |
| Tp* | $CH_3$ | H | $CH_3$ |

**Table 5**

The ratio from nearly 1:1 of cyclopropanation/diene formation in the rhodium case was improved to a 3.2:1 ratio of cyclopropanation/diene formation using the optimised copper conditions with various $Tp^x$ ligands.[139] Additionally, for the first time, the *endo* isomer of the bicyclic product was isolated and its properties investigated, as shown in Scheme 1.51.




**Scheme 1.51**

The ratio of the four different components produced under the copper catalysed conditions as shown in Scheme 1.51, varied depending on what type of ligand was being employed. When using the Tp* ligand, the products were identified as the *cis-trans*, and the *cis-cis* dienals, and the *exo*, and the *endo* bicyclic isomers in the ratio of 43:8:30:5, all in a total yield of 86 %. Thus, the *endo* bicyclic isomer could for the first time be isolated in a 5 % yield.

**1.3.4.3 Summary**

In the case of using diazomethane as the carbene precursor with furan/substituted furan, the bicyclic product was isolated in moderate to good yields. Copper chloride was reported to be the best catalyst, giving a yield of 65 % when using a simple furan as the substrate. Increasing substitution on the furan scaffold induced ring opened dienal type products upon treatment with diazomethane under the described conditions when using either copper- bromide or chloride as catalyst. When using a tert butyl group as the substituent on the C-2 position of the furan ring, solely the ring opened dienal type product was observed. Further, attack of the carbenoid complex was favoured on the unsubstituted side of the furan scaffold.

In the cases reviewed where 2-methylfuran or 2,5-dimethylfuran were treated with ethyl diazoacetate, different mixtures of products were obtained depending upon wether silica or alumina based adsorbents were used in the chromatography step. The acidity of the silica based system in the purification step supposedly induced the ring opening of the furan ring to mainly give dienal isomers with no detectable bicyclic product according to Wenkert *et al.*[118] In contrast, when repeating the reaction using 2-methylfuran or 2,5-dimethylfuran as substrate under the same

reaction conditions previously described, the bicyclic *exo* isomer could be isolated after alumina based chromatography in both cases.[118] However, the reaction of simple furan as a substrate and ethyl diazoacetate in the presence of dirhodium tetraacetate as catalyst, afforded the *exo* bicyclic isomer after silica based chromatography for both Wenkert *et al.*[118] and Matlin *et al.*,[109] highlighting its difference in reactivity to that of substituted furans. Also, a recent discovery by Caballero *et al.*,[139] showed the possibility, when using copper catalysed decomposition of ethyl diazoacetate with simple furans, to synthesise the *endo* isomer of the bicyclic product for the first time.

### 1.3.5 Cyclopropanation reactions with diazopropane, ethyl 2-diazopropanoate and dimethyl diazomalonate

As mentioned earlier, it is required to be able to install the cyclopropane ring with a *gem* dimethyl functionality to afford the natural product **1.01**. The most obvious way of achieving the desired frame work would be to use 2-diazopropane as the carbene precursor. However, due to the lack of literature precedence in installing the desired functionality on furan type systems, alternative strategies were contemplated in case the core structure **1.72** failed to react with 2-diazopropane. Thus, the two chosen alternative diazo reagents are ethyl 2-diazopropanoate and dimethyl diazomalonate, which both fulfil the requirements in terms of the natural product carbon frame work. The two diazo reagents will be exemplified from literature procedures after reviewing the 2-diazopropane as the reagent when installing the desired cyclopropane ring with the desired *gem* dimethyl functionality.

### 1.3.5.1 Using 2-diazopropane

There are several examples in the literature of installing of a *gem* dimethyl cyclopropane ring on highly polarised alkenes.[141-144] One of these examples includes the synthesis of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors.[145] When using excess diazopropane and no catalyst, the desired product was afforded in 45-57 % yield depending on what substitiution groups,[145] R' and R'', were being used, as shown in Figure 3.4.

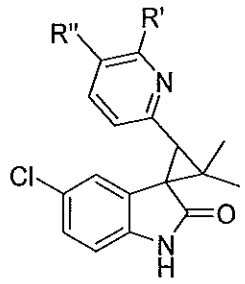
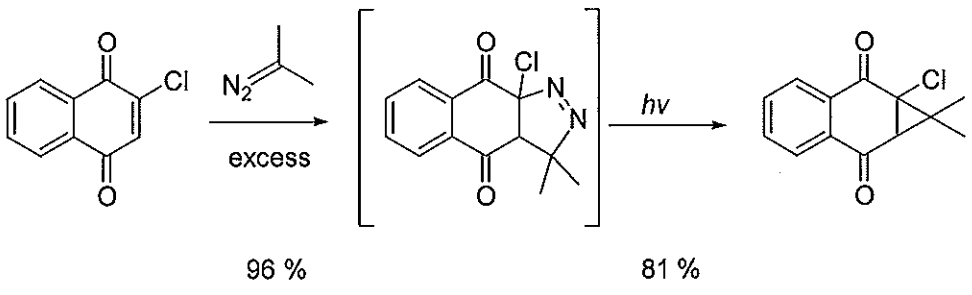



**Figure 3.4**

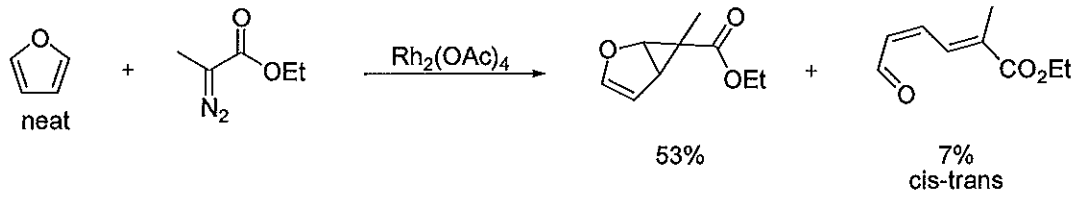
Another example can be shown when the addition of excess diazopropane to chloronaphthoquinones was investigated to give stable pyrazolines[146] as intermediates. The desired cyclopropane derivative was then achieved through photolytic treatment of the pyrazoline intermediate, thus no catalyst was also required in this case, as shown in Scheme 1.52.




**Scheme 1.52**

### 1.3.5.2 Using ethyl 2-diazopropanoate

Wenkert *et al.*[118-121,147] have reported on several occasions the reaction of furan/furan derivatives as substrates with ethyl 2-diazopropanoate as the carbene precursor in the presence of a metal catalyst. When the reaction was performed on a simple furan, the bicyclic isomer, with undetermined stereochemistry,[118] was isolated together with the *cis-trans* dienal isomer in a 53 % and 7 % yield respectively, after alumina based work up (Scheme 1.53).

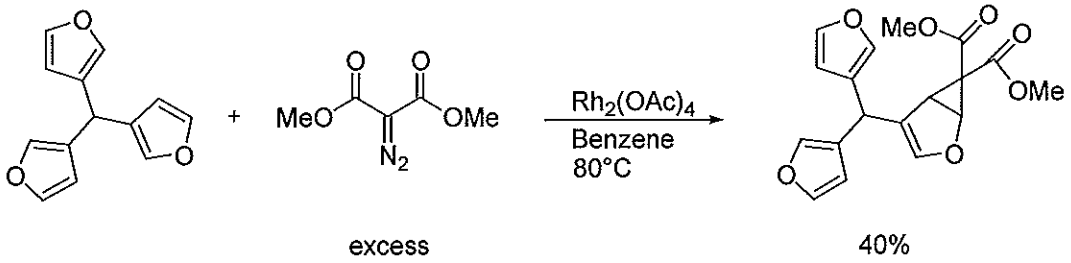



**Scheme 1.53**

Interestingly, if silica was used in the work up step, the *cis-trans* dienal was the only isolated product, as shown in Scheme 1.53, given in a 75 % yield..[118] This is in agreement with previous discussions.

### 1.3.5.3 Reaction of dimethyl diazomalonate with furans/substituted furans

The reaction of furan/furan derivatives and metal catalysed decompositions of dimethyl diazomalonate has been explored to some extent.[148-153] Depending on the reaction conditions and the substituents on the furan ring, the predominant reaction outcome proceeds through the unravelling of the furan ring to form different types of dienals, as products, in moderate to excellent yields.[149-153] However, Nair *et al.*[148] showed the possibility of installing a cyclopropane functionality in one of the three furan rings of *tris*-2-furylmethane, giving a yield of 40 % (Scheme 1.54).




**Scheme 1.54**

In this case, silica based adsorbent was used in the chromatography step to exclusively afford the product shown in the Scheme 1.54.

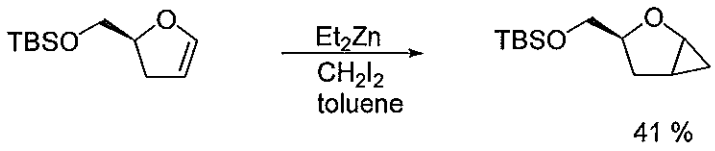
### 1.3.5.4 Summary

It has been demonstrated that ethyl 2-diazopropanoate[118] and dimethyl diazomalonate,[148] can give cyclopropanated products. However, in the case when using ethyl 2-diazopropanoate, it was found important to use alumina based adsorbents to be able to isolate the desired cyclopropanated product.[118] In contrast, the use of silica based adsorbents, yielded dienal type products similar to that obtained from the reaction of ethyl diazoacetate with furan, as substrate. Overall, successful installation of a cyclopropane ring functionality has been shown to be possible with both reagents when using the selected substrates, in moderate to good yields.

### 1.3.6 Other strategies of installing a cyclopropane ring functionality

The use of Simmons Smith type reactions[105] to install cyclopropane functionalities are frequently found in literature, even though few are found regarding substrates with conjugated systems. It would seem less likely then to be successful in the case

of using a furoquinolinone as the substrate. However, one example reported by Hoberg *et al.*,[154] can be shown where a furan dihydro type system was cyclopropanated by using a Simmon Smith type reaction (Scheme 1.55), giving a yield of 41 %.




**Scheme 1.55**

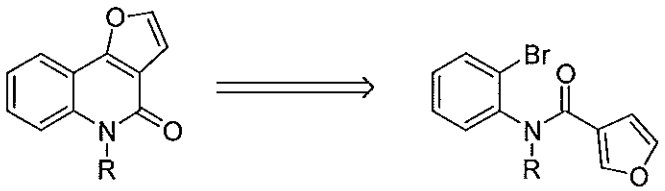
Other methods for constructing a *gem* dimethyl cyclopropane could be by installing a *gem* dihalo cyclopropane ring,[106] followed by conversion of the dihalo unit to a dimethyl unit.[155] This approach is less likely to be successful as there is no literature precedence of installing a *gem* dihalo cyclopropane on a furan type system.

# Chapter 2

## Synthesis of the furoquinolinone core structures

### 2.1 Novel synthesis strategy of the furoquinolinone core structure

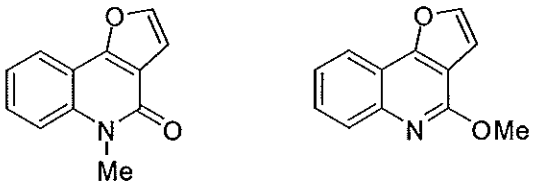
Having reviewed the present methods available for synthesising the core structure in Chapter 1, it was envisaged that the core structure could be assembled by using a novel approach. Considering Kuroda *et al.*'s[48] approach, the key step to access the furoquinolinone core structure would be through an analogues palladium catalysed intramolecular heck type coupling of a suitable precursor, as shown retrosynthetically in Scheme 2.1.




**Scheme 2.1**

Literature investigations showed that the cyclisation step in analogous structures[48,52,156] was only successful when the amide was tertiary. The reason being a tertiary amide gives the required conformation around the amide bond[156] in order for the cyclisation to occur. Hence, a tertiary amide was therefore most likely required for the cyclisation step to occur to form the furoquinolinone core structure.

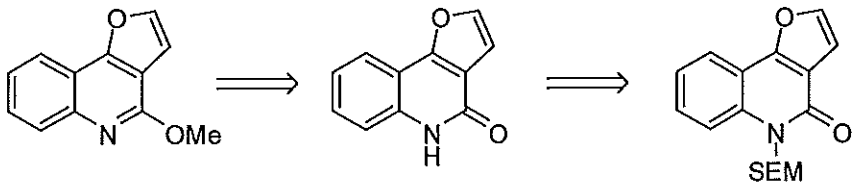
It was envisaged a methyl group on the nitrogen could be a simple and adequate protecting group to fulfil the requirements for the cyclisation to occur. However, a methyl group would be undesireable for the total synthesis of the natural product since it may be difficult to remove after the cyclisation step. Alternatively, protection of the carbonyl oxygen as an enol ether would allow for the continued synthesis of the natural product since it is easy to remove, but would probably not favour the cyclisation reaction due to the altered conformation around the amide bond (as discussed above). However, it was envisaged that the *N*-methyl substrate would serve as a model case for optimising the reaction conditions for the cyclisation, and also to be a well suited substrate in the cyclopropanation investigation in Chapter three. The *O*-methyl substrate could serve as a key substrate in the synthesis of the natural product, and also, as an analogue in the cyclopropanation investigation in Chapter three. This prompted us to synthesise the two substrates, the *N*-methyl (**1.30**) and the *O*-methyl (**2.01**) -furoquinolinone core structures, as shown in Figure 2.1




**1.30** **2.01**

**Figure 2.1**

In order to access the *O*-methyl core structure **2.01**, a removable protecting group on the amide nitrogen, prior to the cyclisation step was necessary. A trimethylsilylethoxymethyl (SEM) group was chosen due to its stability under the required conditions needed for the cyclisation to occur. After the cyclisation step, the *N*-SEM protecting group could be cleaved off and the furoquinolinone core structure in its secondary amide form (**1.72**) could then be converted to the *O*-methyl form (**2.01**) for further investigation, as shown retrosynthetically in Scheme 2.2. The conversion of the secondary amide **1.72** to the *O*-methyl substrate **2.01** has been shown previously by Grundon *et al.*[157] and Tuppy *et al.*[158]

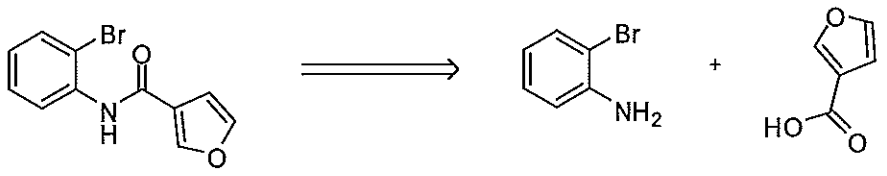



**2.01** **1.72** **2.02**

**Scheme 2.2**

In contrast to the *N*-SEM protected substrate (**2.02**), the *O*-methyl substrate (**2.01**) constitutes an imine form of the core structure. It was therefore desirable to investigate the reactivity of both the *N*-methyl (**1.30**) and the *O*-methyl (**2.01**) substrate towards a variety of reagents which will reflect the electronic properties of the two substrates, as will be discussed in Chapter three.

The precursor for the heck coupling reaction was envisaged to be accessed through an amide coupling of the corresponding commercially available 2-bromoaniline and 3-furoic acid, as shown retrosynthetically in Scheme 2.3.



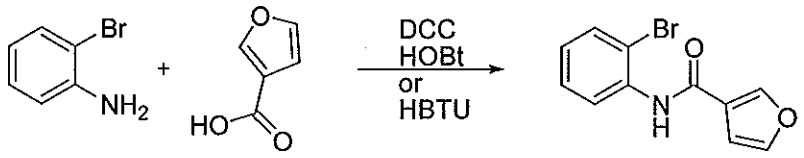

**2.03**

**Scheme 2.3**

## 2.2 Amide coupling using coupling reagents

Most commonly the bimolecular amide coupling of acids and amines can be performed by addition of a coupling reagent[53-55,57,58,156,159] e.g., DCC, EDC, HOBt or HBTU. Alternatively, amides are formed through treatment of the amine with the corresponding acid chloride under various temperatures.[52,59-61,160,161] Amines can also be converted directly to the amide form with the corresponding ester under mild conditions through pre-treatment of the amine with trimethylaluminium.[67-69,162,163]

In the synthesis of the amide coupled product, attempts were made to couple the commercially available starting materials 2-bromoaniline and 3-furoic acid by using DCC, HOBt or HBTU as a coupling reagent. However, only low yields of **2.03** were afforded in these cases, as shown in Scheme 2.4.



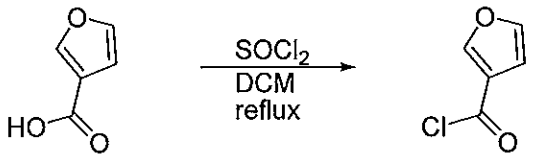

**2.03**

**Scheme 2.4**

The approach of using coupling reagents to facilitate the amide coupling was therefore discarded.

## 2.3 Amide coupling using an acid chloride

A second approach to synthesise **2.03** was by activating the 3-furoic acid by converting it to the corresponding acid chloride. After treatment of the 3-furoic acid with thionyl chloride[164] ($SOCl_2$) in DCM under reflux conditions for 2 h, the corresponding acid chloride was quantitatively afforded, as shown in Scheme 2.5.

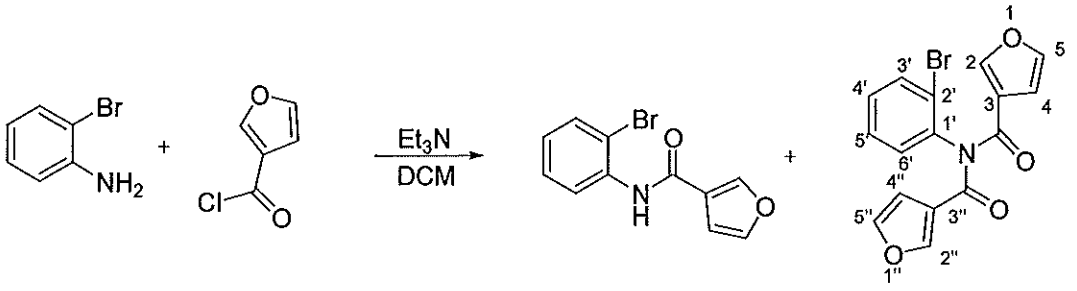



>95%

**Scheme 2.5**

The acid chloride was purified by bulb-to-bulb distillation[165] or used directly, after the solvent has been removed, in the amide coupling reactions. Initially, triethylamine was used as base to facilitate the amide coupling of the two starting

materials, as shown in Scheme 2.6. In this case two products were isolated where the desired product **2.03** was the major component (40 %), and a bis acylated product **2.04** (20-30 % depending on how much base used) as the minor side product.



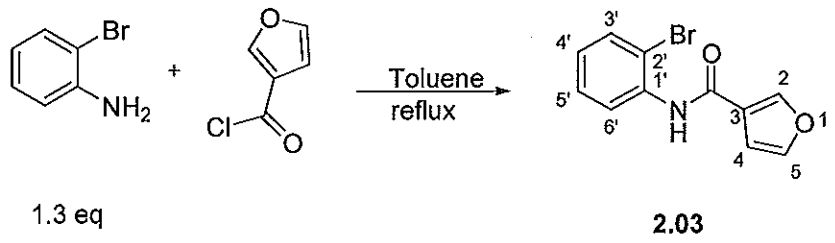

**2.03** **2.04**

**Scheme 2.6**

The $^{1}$H NMR of the bis acylation product **2.04** exhibited a complex spin coupling pattern of the benzene protons giving multiple signals at 7.70 – 7.78 and 7.26 - 7.40 ppm. The furan protons were coincident and resonated at 7.76, 7.35 and 6.54 ppm which corresponded to (H-2, H-2``), (H-5, H-5``) and (H-4, H-4``) respectively. The mass spectrum, which showed two pseudo molecular ion peaks indicative of a mono brominated compound at *m/z* 359 and 361 (1:1 ratio), and a high resolution mass spectrum, further supported the structure.

When the amount of base used was reduced from 3 to 0.5 molar equivalents, to minimise the formation of the side product **2.04**, exclusive formation of the amide coupled product **2.03** was observed, albeit, in low yield (30 %). By further optimisation, the best conditions were found to be by using the 2-bromoaniline in a slight excess under reflux conditions with the acid chloride in toluene. Thus, giving

the amide coupled product **2.03** in a 92 % yield with no trace of **2.04**, as shown in Scheme 2.7.




1.3 eq

**2.03**

**Scheme 2.7**

The $^{1}$H NMR of the amide coupled product **2.03** exhibited a broad singlet at 8.06 ppm which corresponds to the amide proton NH, and three signals at 8.10, 7.54 and 6.78 ppm assigned to the furan protons H-2, H-5 and H-4 respectively. Four distinct benzene ring protons resonated at 8.50, 7.37, 7.03 and 7.59 ppm corresponding to H-6`, H-5`, H-4` and H-3` respectively. The spin coupling pattern of the benzene ring protons indicated a typical *ortho* substitution where the H-6` to H-3` protons appeared as a doublet, triplet, triplet and a doublet respectively. The $^{13}$C NMR signals for the benzene carbons C-6` to C-3` resonated at 122.0, 128.8, 125.4 and 132.4 ppm respectively, while the two quaternary carbons C-2` and C-1` resonated at 113.6 and 135.8 ppm. The furan carbons C-5 to C-2 resonated at 144.5, 108.0, 123.3 and 145.6 ppm respectively. The mass spectrum, which showed a pseudo molecular ion peaks at *m/z* 266 and 268 (1:1 ratio), and a high resolution mass spectrum, supported the proposed structure. This structure was confirmed by X-ray crystallography (Figure 2.2).

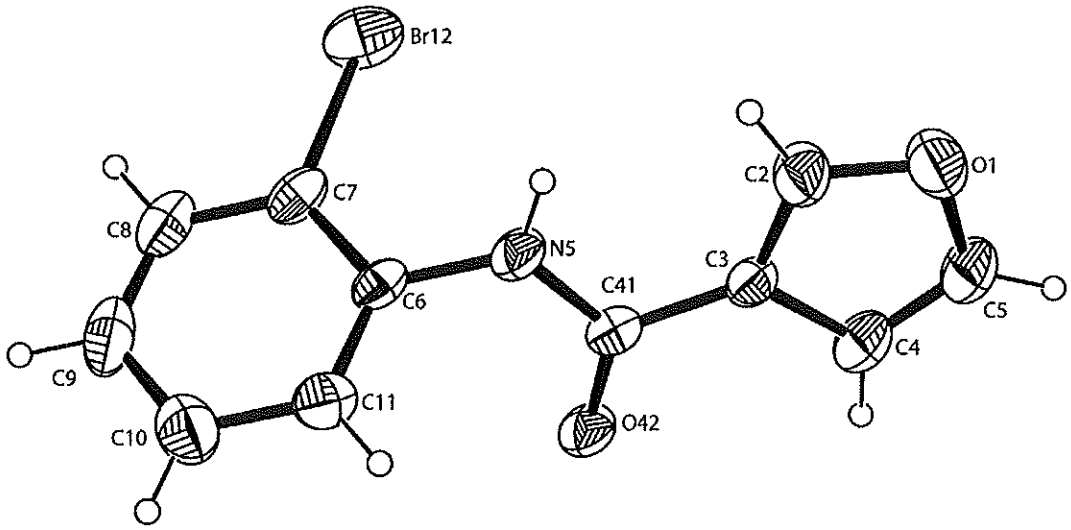
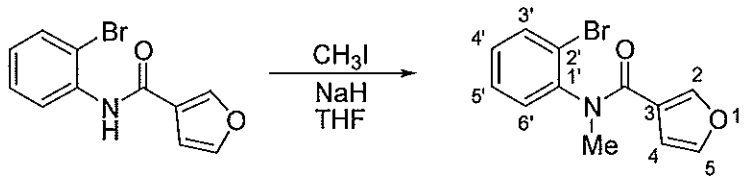



**Figure 2.2** ORTEP plot of product **2.03**, (30 % ellipsoids are shown)

The synthesis of the bromo-*N*-methyl precursor **2.05** was straight forward with no unexpected outcomes, and was afforded in a 95 % yield by treating **2.03** with sodium hydride and methyl iodide in THF as solvent, as shown in Scheme 2.8.




**2.03** **2.05**

**Scheme 2.8**

The $^{1}$H NMR spectral data of the desired product **2.05** exhibited four benzene protons which resonated at 7.70, 7.39 and 7.27-7.33 ppm as a doublet, triplet and a multiplet respectively. The furan protons resonated as three broad singlets at 6.89, 6.22 and 7.19 ppm corresponding to H-5, H-4 and H-2 respectively, and the introduced *N*-methyl group resonated as a singlet at 3.36 ppm. The $^{13}$C NMR signals for the benzene carbons resonated at 130.3, 129.2, 130.7 and 134.2 ppm (C-

6` to C-3` respectively). The two benzene quaternary carbons (C-2` and C-1`) now resonated at 124.0 and 143.2 ppm, and the furan carbons (C-5 to C-2 respectively) resonated at 142.4, 111.0, 121.9 and 145.3 ppm. The mass spectrum, which showed a pseudo molecular ion peaks at *m/z* 280 and 282 (1:1 ratio), and a high resolution mass spectrum, supported the proposed product **2.05**. The product was further confirmed by X-ray crystallography as shown in Figure 2.3.

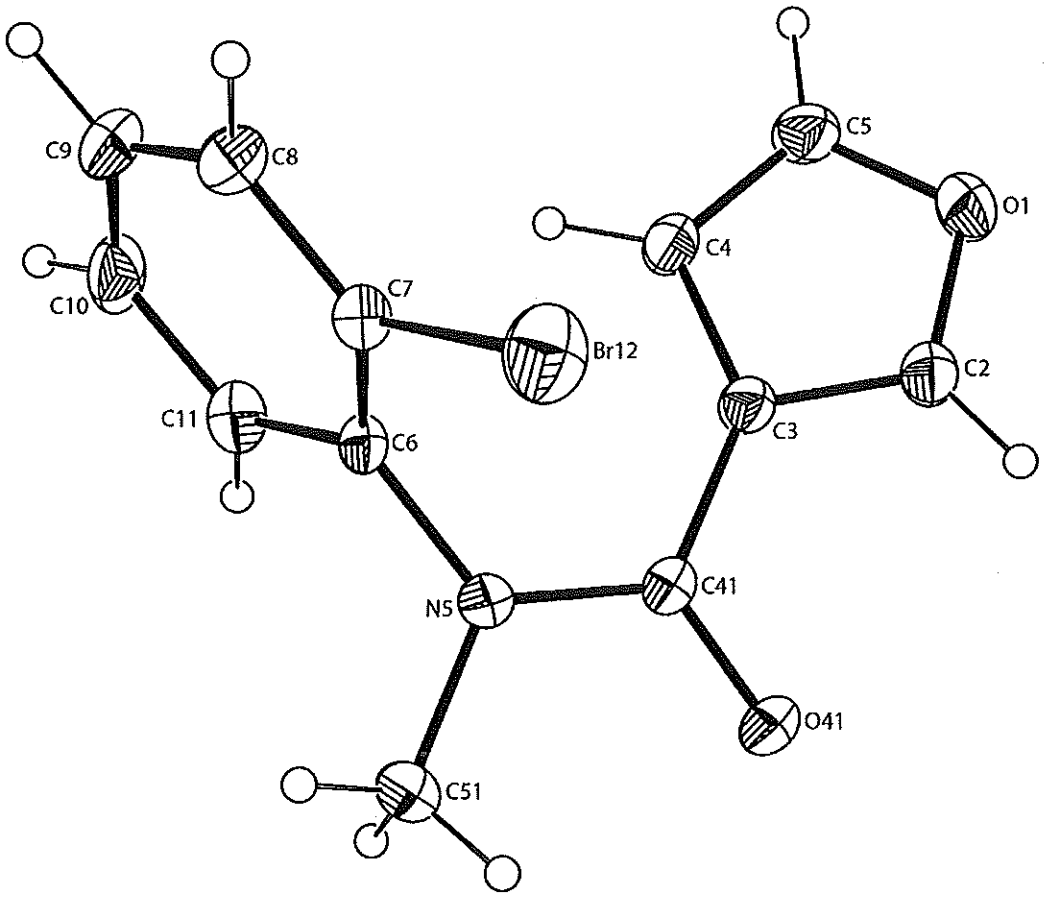
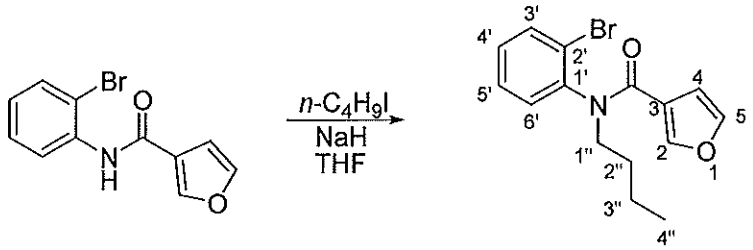



**Figure 2.3** ORTEP plot of product **2.05**, (30 % ellipsoids are shown)

## 2.4 The Heck coupling reaction, synthesis of 1.30

It was noted that Kuroda *et al.*[48] had used a butyl group in performing the cyclisation reaction. Our approach was to use a methyl group due to its simplicity in use. However, it was unknown if the butyl functionality as a protecting group would offer any advantage in performing the cyclisation step, and thus, the butyl protected derivative was synthesised for the preliminary investigation.

The bromo-*N*-butyl derivative **2.06** was afforded in a yield of 70 %, by treating **2.03** with excess sodium hydride and butyl iodide in THF as solvent, as shown in Scheme 2.9.




**2.03** **2.06**

**Scheme 2.9**

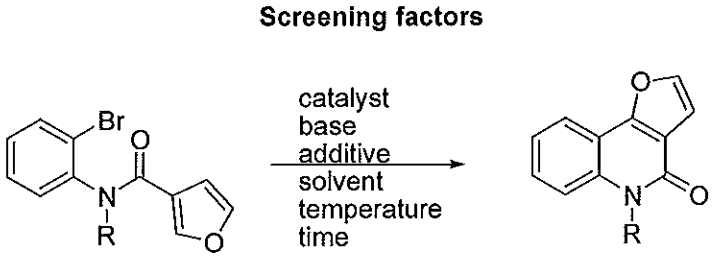
The $^{1}$H NMR of the bromo-*N*-butyl product **2.06** exhibited six distinct multiplet signals at 4.22, 3.37, 1.70, 1.63, 1.39 and 0.95 ppm corresponding to H-1a``, H-1b``, H-2a``, H-2b``, H-3` and H-4` respectively. The furan protons resonated at 7.17, 6.81 and 6.22 ppm corresponding to H-5, H-2 and H-4 respectively. Two protons at 7.70 and 7.40 ppm together with a multiplet at 7.30 ppm assigned to H-3`, H-5` and (H-6` and H-4`) respectively was observed. In the $^{13}$C NMR spectrum four additional carbons were apparent at 49.4, 29.8, 20.5 and 14.1 ppm owing to C-

1`` to C-4`` respectively. The mass spectrum, which showed a pseudo molecular ion peaks at *m/z* 322 and 324 (1:1 ratio), and elemental analysis, further supported the proposed structure.

As mentioned, the core structure **1.72** has been made by a bimolecular method (Glover *et al.* [47]) or can be envisaged to be made by unimolecular methods, such as Kuroda *et al.*,[48] where an amide linked imidazole group was used as the precursor (**1.71**) for the intramolecular heck type coupling (see Chapter 1). Palladium acetate was employed as catalyst together with sodium hydrogen carbonate and *n*-tetrabutylammonium chloride in DMA to give the desired cyclised product **1.70** in 83 % yield. Also, Glover *et al.*[47] investigated the bi molecular coupling of 1-bromo-2-nitrobenzene and ethyl-3-furoate by using palladium triphenylphosphine tetrakis as catalyst and potassium acetate in toluene to afford the furoquinolinone core structure **1.72** in a 80 % yield. As both reactions are heck type couplings in similar type of systems, it was deemed prudent to investigate both of the above conditions for the intramolecular cyclisation to afford the furoquinolinone core structure.

To furnish the furoquinolinone core structure, both **2.05** and **2.06** derivatives were employed as substrates. Initial attempts of the intramolecular heck type coupling using either Kuroda`s (see method C in the experimental section) or Glover`s (see method D in the experimental section) conditions were tried, however, only poor conversions were observed with either substrate which prompted us to investigate this reaction further. The substrates were screened with two catalysts (palladium acetate and palladium triphenylphosphine tetrakis), two solvents

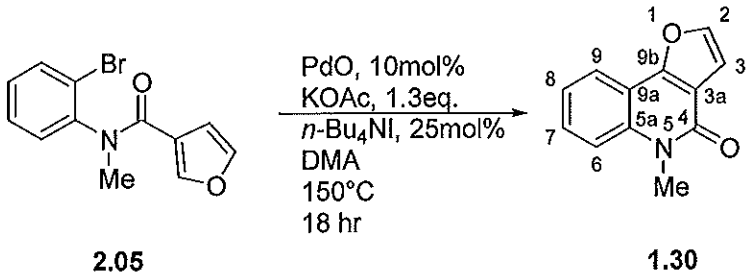
(dimethylacetamide, toluene), four bases (sodium bicarbonate, triethylamine, potassium hydroxide and potassium acetate), two temperatures (100 °C and 150 °C) and a variety of reaction times (10 min to 16 h) to find optimum conditions. To see the effect, most reactions were repeated with/without additive (*n*-butylammonium iodide or *n*-butylammonium chloride) present, as shown in Scheme 2.10.




**Scheme 2.10**

Heck couplings can require reaction times from 2 to 20 h to be completed.[47,48,166] It was thought that a microwave reactor could enhance the reaction and to give preliminary preferences for the screening factors since short runs are usually associated with microwave heating i.e., 10 min to 2 h. Initial indications showed more clean conversions of starting material to product when employing palladium acetate, as compared to palladium triphenylphosphine tetrakis, as catalyst. In summary, when reaction times were extended (i.e., overnight runs) under higher temperatures (150 °C) and by using palladium acetate as catalyst, additive (*n*-butylammonium iodide or *n*-butylammonium chloride), sodium bicarbonate or potassium acetate as base and DMA as solvent, the consumption of starting material was noticeably higher but still gave unsatisfactory yields (17 %, see Method C in the experimental section for an example). The **2.06** derivative

exhibited no advantage over **2.05** in the test runs of the cyclisation reaction. In addition, **2.05** involved a more efficient synthesis, which led to the sole use of **2.05**, and thus, the butyl protected derivative **2.06** was discarded from the investigation. The key to higher yields of the desired product **1.30** was found to be by using a more concentrated solution of the reaction mixture. Surprisingly, when using palladium oxide as catalyst, *n*-butylammonium iodide as additive, potassium acetate as base and DMA as solvent, the desired product **1.30** was achieved in 59 % yield (see Method B in the experimental section for an example), as shown in Scheme 2.11.




**2.05** **1.30**

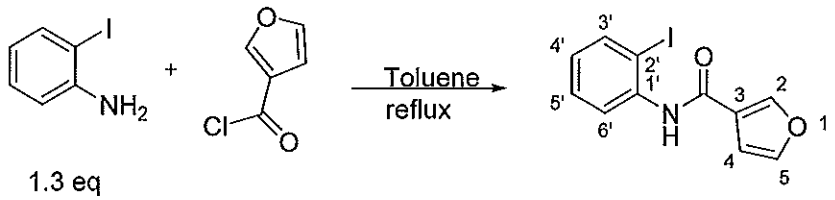
**Scheme 2.11**

The $^{1}$H NMR spectrum of the desired product **1.30** exhibited two furan protons and four distinct benzene protons. Signals at 7.64 and 7.09 ppm were assigned as the furan protons H-2 and H-3, respectively, and signals at 7.47, 7.57, 7.34 and 8.04 ppm were assigned as the benzene protons H-6, H-7, H-8 and H-9, respectively. Also, the *N*-methyl group resonated as a singlet at 3.80 ppm, as compared to 3.36 ppm of its precursor **2.05**. The $^{13}$C NMR spectrum exhibited four signals at 115.3, 129.8, 122.6 and 121.5 ppm assigned to the benzene carbons C-6 to C-9, together with two signals at 144.2 and 108.6 ppm assigned to the furan carbons C-2 and C-3. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 200, and

elemental analysis, supported the proposed structure. These results were in alignment with previous reported data[158] for the structure **1.30**.

As the increasing reactivity order is chloro, bromo to iodo -arenes in heck type couplings,[166] it was considered that the iodo-*N*-methylamide derivative **2.09** could potentially give better yields in the cyclisation reaction. The synthesis of **2.07** was undertaken by using the conditions already optimised for the synthesis of **2.03**.

When the 2-iodoaniline was treated with furoic acid chloride, the amide coupled product **2.07** was isolated in 93 % yield, as shown in Scheme 2.12.



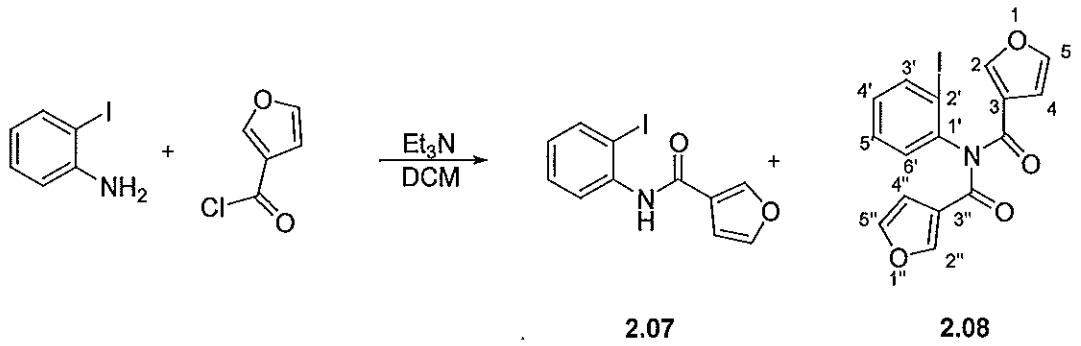

**2.07**

**Scheme 2.12**

The $^{1}H$ NMR of the amide product **2.07** exhibited a broad singlet at 7.90 ppm which corresponded to the amide proton NH, and three signals at 8.12, 7.54 and 6.82 ppm assigned to the furan protons H-2, H-5 and H-4, respectively. Four distinct signals of the benzene ring protons were apparent at 8.42, 7.40, 6.89 and 7.83 ppm corresponding to H-6` to H-3`, respectively. The spin coupling pattern of the benzene ring protons indicated a typical *ortho* substitution where the H-6` to H-3` protons appeared as a doublet, triplet, triplet and a doublet respectively. In the $^{13}C$ NMR spectrum the benzene carbons resonated at 139.0, 126.2, 129.7 and 121.9

ppm corresponding to C-3` to C-6` respectively, and with the furan carbons resonated at 144.5, 108.5, 123.5 and 145.6 ppm (C-5 to C-2 respectively). The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 314, and elemental analysis, supported the proposed structure.

Repeating the amide coupling reaction with the initial conditions, as in Scheme 2.6, but replacing 2-bromoaniline for 2-iodoaniline, similarly resulted in a mixture of the desired product **2.07** and the bis acylated product **2.08** in the same product ratio as previously observed, as shown in Scheme 2.13.



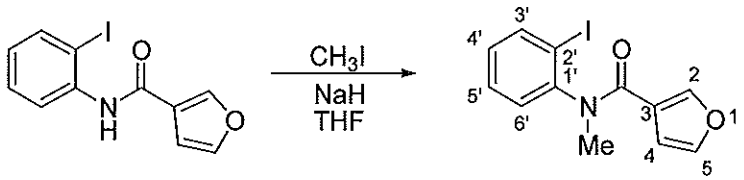

**2.07** **2.08**

**Scheme 2.13**

The $^{1}$H NMR spectrum for the bis acylated product **2.08** exhibited a different spin coupling pattern as compared to its bromo analogue. While the *ortho* substitution pattern of the benzene ring of the bromo analogue could not be distinguished due to overlap with the furan protons, the iodo analogue clearly showed a typical *ortho* substitution pattern. Thus, protons H-6` to H-3` appeared as a doublet, triplet, triplet and a doublet at 7.27, 7.41, 7.15 and 7.98 ppm, respectively. The furan protons exhibited three multiplets signals at 7.35, 6.55 and 7.73 ppm corresponding to (H-5, H-5`), (H-4, H-4`) and (H-2, H-2`), respectively. The mass spectrum,

which showed a pseudo molecular ion peak at *m/z* 408, and a high resolution mass spectrum, further supported the proposed structure.

As with the synthesis of the bromo-*N*-methyl analogue **2.05**, the methylation step to give the iodo-*N*-methyl amide precursor **2.09** was straight forward with no unexpected outcomes. **2.09** was afforded in a 95 % yield by treating the secondary amide **2.07** with an excess molar solution of sodium hydride and methyl iodide using THF as solvent, as shown in Scheme 2.14.




**2.07** **2.09**

**Scheme 2.14**

The $^{1}$H NMR spectrum for **2.09** was similar to its precursor with the major visual difference of the new introduced *N*-methyl group resonating as a singlet at 3.34 ppm, together with the absence of the former NH proton. Retention of the spin coupling pattern of the benzene protons was observed where the protons H-3` to H-6` appeared at 7.95, 7.13, 7.44 and 7.32 ppm, respectively. As with the analogue **2.05**, the furan protons of **2.09** appeared as three singlets shifted upfield, at 7.18, 6.22 and 6.82 ppm corresponding to protons H-2, H-4 and H-5 respectively, as compared to its precursor. In the $^{13}$C NMR spectrum the benzene carbons C-3` to C-6` resonated at 140.6, 130.4, 129.9 and 130.1 ppm, and with the furan carbons resonated at 145.5, 122.1, 111.2 and 142.4 ppm (C-2 to C-5 respectively). The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 328, and

elemental analysis, further supported the proposed structure. The structure of **2.09** was further confirmed by X-ray crystallography as shown in Figure 2.4.

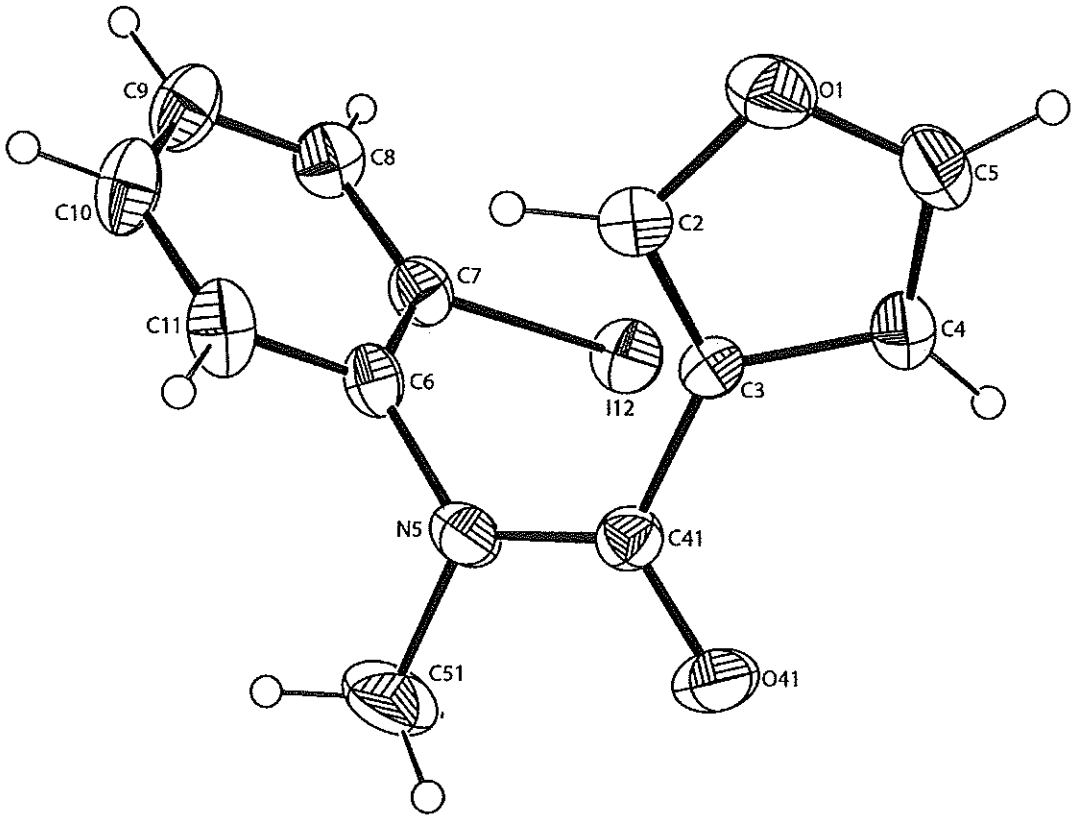



**Figure 2.4** ORTEP plot of product **2.09**, (30 % ellipsoids are shown)

When employing the **2.09** derivative as substrate for the cyclisation reaction under the same conditions used for **2.05**, but using a slightly more concentrated reaction mixture, even higher yields of the cyclised product **1.30** were observed. This prompted us to reinvestigate the conditions used by Kuroda *et al.*[48] and Glover *et al.*,[47] thus a final 12 reactions were performed by using **2.09** as substrate, as shown in Table 2.1.

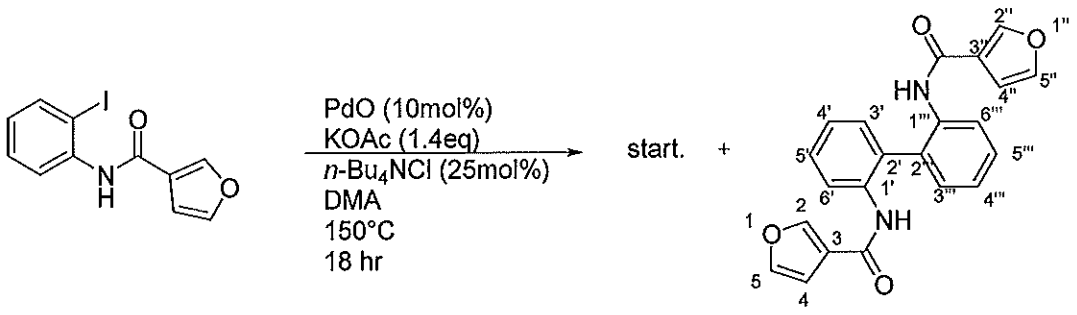
| Entry | Solvent | Catalyst | Base | additive | Temp (°C) | Time (h) | Yield (%) | Rec (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | DMA | $Pd(OAc)_2$ | $NaHCO_3$ | *n*-$Bu_4NCl$ | 150 | 18 | 83 | 0 |
| 2 | DMA | $Pd(PPh_3)_4$ | $NaHCO_3$ | *n*-$Bu_4NCl$ | 150 | 18 | 9 | 0 |
| 3 | DMA | PdO | $NaHCO_3$ | *n*-$Bu_4NCl$ | 150 | 18 | 10 | 0 |
| 4 | Toluene | $Pd(OAc)_2$ | $NaHCO_3$ | *n*-$Bu_4NCl$ | 100 | 18 | <5 | 90 |
| 5 | Toluene | $Pd(PPh_3)_4$ | $NaHCO_3$ | *n*-$Bu_4NCl$ | 100 | 18 | <5 | 68 |
| 6 | Toluene | PdO | $NaHCO_3$ | *n*-$Bu_4NCl$ | 100 | 18 | <5 | 90 |
| 7 | DMA | $Pd(OAc)_2$ | KOAc | *n*-$Bu_4NCl$ | 150 | 18 | 76 | 0 |
| 8 | DMA | $Pd(PPh_3)_4$ | KOAc | *n*-$Bu_4NCl$ | 150 | 18 | 64 | 0 |
| 9 | DMA | PdO | KOAc | *n*-$Bu_4NCl$ | 150 | 18 | 89 | 0 |
| 10 | Toluene | $Pd(OAc)_2$ | KOAc | *n*-$Bu_4NCl$ | 100 | 18 | 14 | 30 |
| 11 | Toluene | $Pd(PPh_3)_4$ | KOAc | *n*-$Bu_4NCl$ | 100 | 18 | 12 | 55 |
| 12 | Toluene | PdO | KOAc | *n*-$Bu_4NCl$ | 100 | 18 | 16 | 27 |

**Table 2.1**

The optimum conditions for the palladium catalysed cyclisation on the **2.09** derivative were found through a series of experiments where sequential changes were made to the catalyst, base and the solvent used (Table 2.1). The use of Kuroda *et al.*'s[48] best conditions in our system gave the furoquinolinone core structure **1.30** in 83 % yield (entry 1), however, if the catalyst was exchanged for palladium tetrakis or palladium oxide, the yield was dramatically reduced to 9 % and 10 % respectively. It was also noted that there was a poor recovery of starting material in these cases (entries 2 and 3). Performing the same reactions in a non polar solvent such as toluene gave only trace amounts of the cyclised product and an almost complete recovery of the starting material **2.09** (90, 68 and 90 % respectively) when all three types of catalysts were used (entries 4-6). Changing the base to potassium acetate gave good yields of the cyclisation product **1.30** (76, 64 and 89

% respectively) and complete consumption of the starting material **2.09**, with all of the catalysts when the reaction was run in DMA (entries 7-9 respectively). The best catalyst was interestingly found to be palladium oxide under these conditions, giving the furoquinolinone core structure **1.30** in 89 % yield (entry 9). Repeating the reactions using potassium acetate in toluene gave only slightly better yields of **1.30** (14, 12 and 16 % for entries 10-12 respectively) compared with the reactions using sodium hydrogen carbonate (entries 4-6 where all were <5 %), while the amount of starting material **2.09** recovered was significantly lower.

Having obtained the optimised conditions for the cyclisation to occur, attempts were made to cyclise the secondary amide **2.07** even though previous reports of attempts[48,49,156] had failed. Indeed, it was found that all attempts to perform the palladium catalysed cyclisation reaction using **2.07** as the starting material gave no indication of the furoquinolinone core structure **1.72**. Under prolonged reaction times, a biaryl coupled product was isolated in a yield of 18 % together with starting material being recovered, as shown in Scheme 2.15. This reinforced the importance of having a tertiary amide for the cyclisation to occur.




**2.07** **2.10**

**Scheme 2.15**

The $^{1}$H NMR of the biaryl coupled product **2.10** exhibited coincident signals for all furan and amide protons. The amide protons resonated as a coincident broad singlet

at 7.33 ppm, and the furan protons at 7.67, 7.27 and 6.22 ppm corresponding to (H-5, H-5``), (H-2, H-2``) and (H-4, H-4``) respectively. It was noted that the (H-5, H-5``) protons were more down field than the corresponding (H-2, H-2``) protons which is the opposite as compared to the starting material. The benzene protons exhibited complex splitting owing to a multiplet at 7.41-7.45 ppm (1 H) and 7.18-7.22 ppm (2 H), and an apparent doublet at 8.31 ppm (1 H). In the $^{13}C$ NMR spectrum, two coincident carbonyl carbons resonated at 161 ppm. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 373, and a high resolution mass spectrum, further supported the proposed biaryl coupled structure **2.10**.

To confirm the order of reactivity of halo arenes[166] in this study of palladium catalysed cyclisation reactions, the chloro-*N*-methyl derivative **2.12** was synthesised by adopting the optimised conditions found for the iodo and bromo derivatives. The structures proton and carbons were assigned (see experimental for the chloro-amide coupled product **2.11** and the chloro-*N*-mehtyl product **2.12**) and the derivative **2.12** was further confirmed by X-ray crystallography as shown in Figure 2.5.

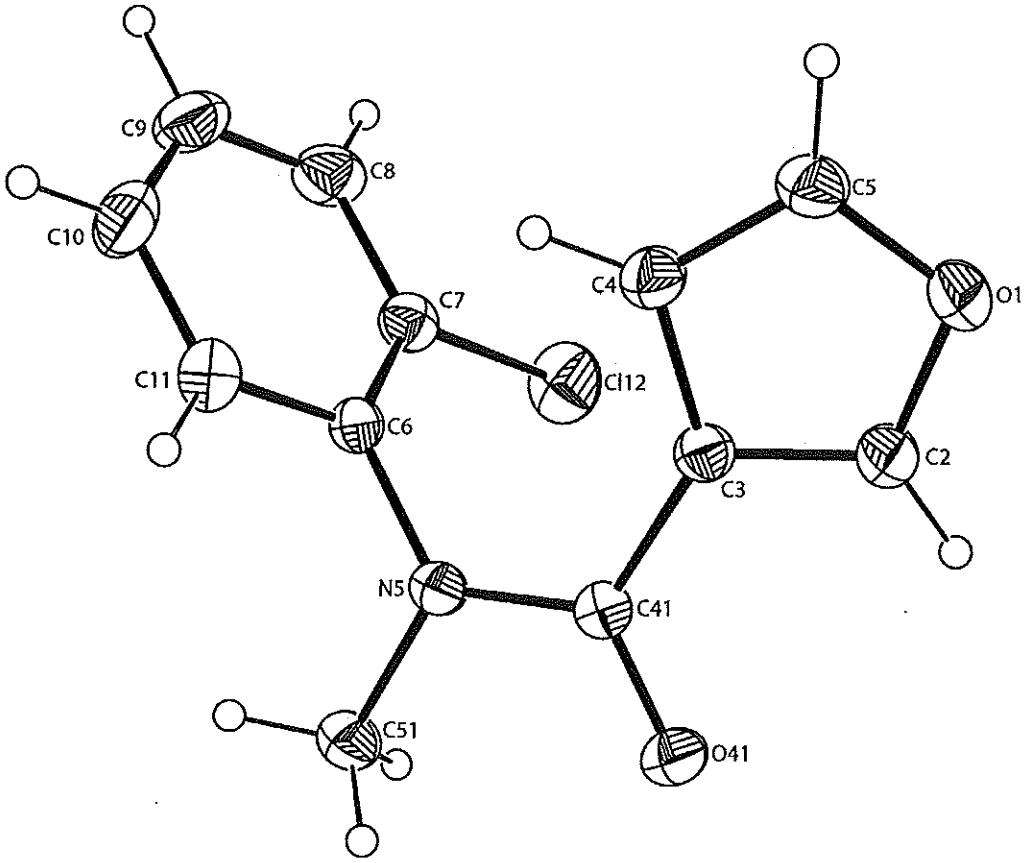
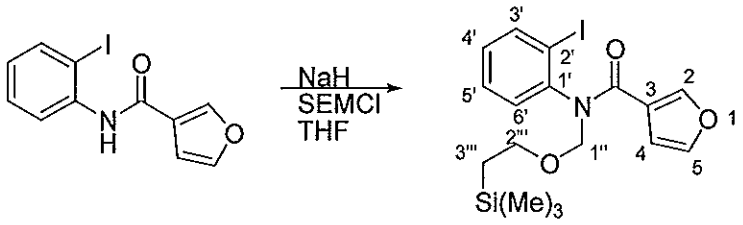



**Figure 2.5** ORTEP plot of product **2.12**, (30 % ellipsoids are shown)

After treatment of the chloro-*N*-methyl derivative **2.12** under the optimised conditions found for **2.09**, the desired cyclised key intermediate **1.30** was isolated in a 9 % yield. This result was in agreement with the previous reported statement[166] concerning the relative reactivity of aryl halides in heck type couplings.

## 2.5 Synthesis of the *O*-methyl key intermediate 2.01

To afford the *O*-methyl substrate **2.01**, the secondary amide **2.07** had to be protected with a removable protecting group. For this purpose a SEM (trimethylsilylethoxymethyl) group was chosen. The procedure of alkylating the secondary iodo-*N*-amide using the SEMCl reagent in THF proceeded as smooth as for the methyl alkylation in the synthesis of the iodo-*N*-methylamide derivative **2.09**. The *N*-SEM protected material **2.13** was afforded in a 95 % yield, with no unexpected outcomes, as shown in Scheme 2.16.



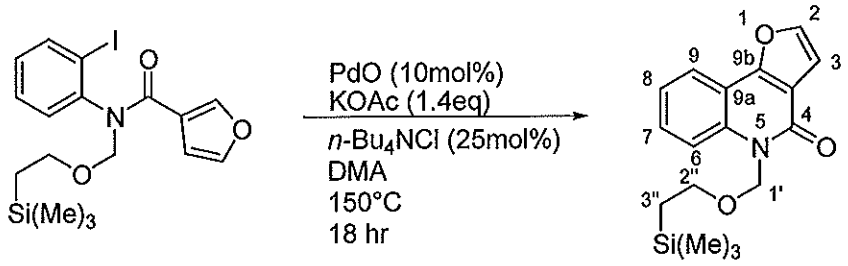

**2.07** **2.13**

**Scheme 2.16**

The $^{1}H$ NMR of the *N*-SEM protected product **2.13** exhibited similar splitting pattern as its precursor **2.07** in the aryl region. The introduced *N*-SEM protecting group gave rise, however, to a singlet at 0.03 ppm assigned to the trimethylsilyl group, and the two protons on carbon C-1`` were split to two signals at 5.82 and 4.57 ppm presumably due to steric constraints. Further, the two methylene groups H-2``` and H-3``` of the ethylene bridge, gave rise to two broad multiplet splittings at 3.76 and 0.99 ppm respectively. In the $^{13}C$ NMR the carbons C-1``, C-1``` and

C-2``` resonated at 77.3, 66.9 and 18.5 ppm together with the Si(Me$_3$) group at 0.03 ppm. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 444, and elemental analysis, further supported the molecular formula of $C_{17}H_{22}INO_3Si$.

When **2.13** was treated with the optimised cyclisation conditions, found for **2.09**, the desired *N*-SEM cyclised product **2.02** was isolated in 87 %, as shown in Scheme 2.17.



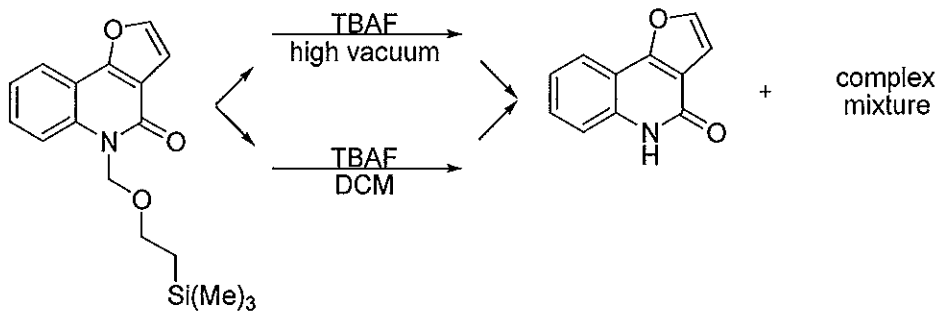

**2.13** **2.02**

**Scheme 2.17**

The $^1$H NMR of the *N*-SEM protected cyclised product **2.02** exhibited a broad singlet at 5.86 ppm assigned to the methylene group at carbon C-1`. The other two methylene groups at H-2`` and H-3`` resonated as two triplet signals at 3.74 and 0.96 ppm respectively, and, the trimethylsilyl group resonated at -0.022 ppm. The other features of the molecule exhibited similar spin coupling patterns as its precursor; the two furan protons resonated at 7.65 and 7.08 ppm corresponding to H-2 and H-3 respectively, and the benzene protons resonated at 7.71, 7.56, 7.34

and 8.01 ppm corresponding to H-6 to H-9 respectively appearing as a doublet, triplet, triplet and a doublet. The $^{13}C$ NMR spectrum remained similar to its precursor. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 316, and elemental analysis, further supported the molecular formula of $C_{17}H_{21}NO_3Si$.

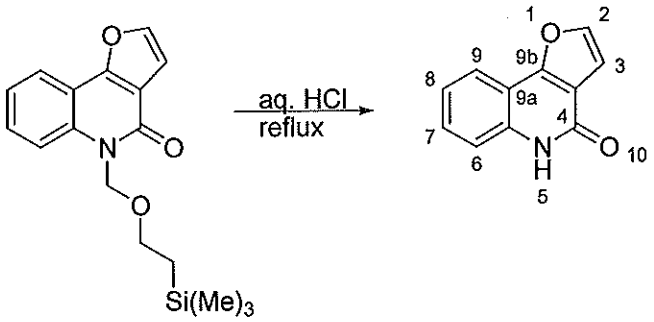
Initially, the cleavage of the *N*-SEM protecting group was attempted with the use of neat TBAF[167-171] (tetrabutylammonium fluoride) under high vacuum, but only a low yield of the furoquinolinone core structure **1.72** together with a complex mixture of unidentified products was observed when the crude mixture was analysed by $^1H$ NMR. Attempting the reaction using solvents, such as DCM, under different reaction times at ambient temperature also gave complex mixtures, as shown in Scheme 2.18.




**2.02** **1.72**

**Scheme 2.18**

Due to the lack of success in cleaving off the *N*-SEM protecting group, attention was focused on the use of aqueous acid. Several attempts were made with aqueous hydrochloric acid (Scheme 2.19) under reflux conditions,[172,173] and to a minor degree this seemed to be a successful approach. Varying reaction times and the molarity of the hydrochloric acid, the unprotected furoquinolinone core structure **1.72** was afforded in higher yields (36 %) but, still, this was overall an unsatisfactory yield, as shown in Scheme 2.19.



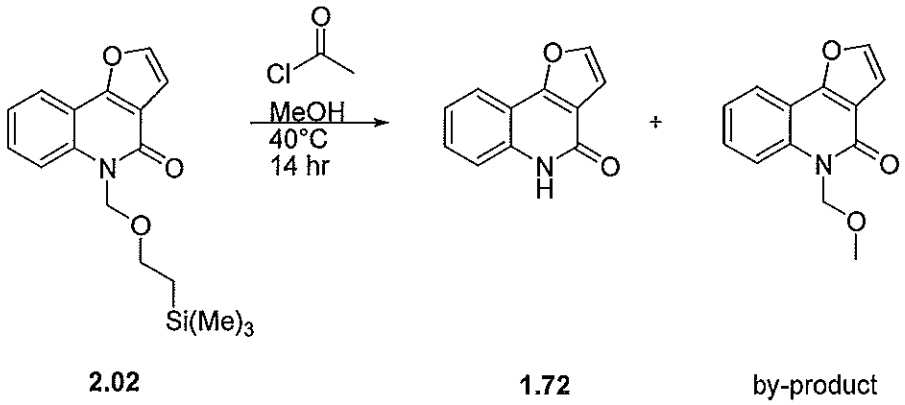

**2.02** **1.72**

**Scheme 2.19**

The $^{1}$H NMR of the desired deprotected furoquinolinone core structure **1.72** exhibited a broad peak at 11.73 ppm assigned to the amide proton. The two furan proton doublets resonated at 8.06 and 7.04 ppm corresponding to H-2 and H-3, respectively. This together with the mass spectrum, which showed a pseudo molecular ion peak at *m/z* 186, was in agreement with previous reports[174,175] and, thus, no further characterisation was needed.

Since product **1.72** could only be obtained but in low yields, it was necessary to optimise the reaction conditions. To facilitate the work up, attention was drawn to use dry hydrochloric acid which could be generated *in situ* (approximately a 3

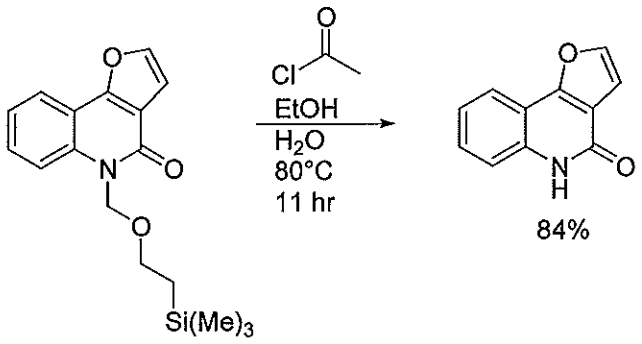
molar solution) by mixing acetyl chloride with methanol followed by addition of **2.02**. The deprotection reaction was improved and the desired product **1.72** could be isolated in moderate yields (50 %), together with a minor side product (14 %), as shown in Scheme 2.20.




**Scheme 2.20**

Analysis of the $^{1}H$ NMR and the mass spectral data of the minor component indicated the suggested structure as shown in Scheme 2.20. However, this minor side product was not further characterised.

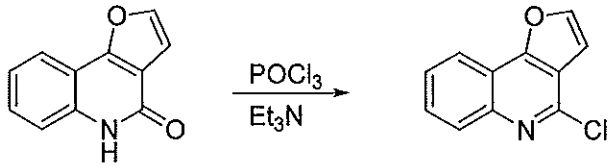
If higher concentrations of dry hydrochloric acid were used, such as 5 M, under slightly higher temperatures (55 °C), solely **1.72** was observed but in lower yields (48 %). Methanol was then substituted for ethanol to raise the boiling point and to find out if temperature would make a difference in terms of yields. When **2.02** was treated with a 5 M solution of hydrochloric acid in ethanol at 70 °C over two days, **1.72** was isolated in 75 %. By raising the temperature to 80 °C and the use of catalytic amounts of water, shorter reaction times were possible together with an improved yield to 84 % of **1.72**, as shown in Scheme 2.21.




**2.02** **1.72**

**Scheme 2.21**

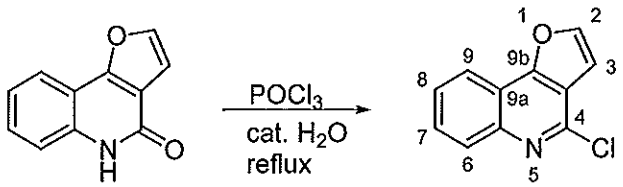
Finally, to achieve the *O*-methyl substrate **2.01**, the deprotected material **1.72** could be treated with base and phosphorusoxychloride ($POCl_3$) followed by a sodium methoxide solution to furnish the desired product. A literature precedence was found for converting the secondary amide **1.72** to its corresponding chloride by the treatment of phosphorusoxychloride (as solvent) and triethylamine as base.[175] When triethylamine was employed as base, good yields (77 %) of the chlorinated material was afforded as shown in Scheme 2.22.




**1.72** 77 %

**Scheme 2.22**

In the course of improving the yield of the chloro derivative, triethylamine was replaced with water. When using catalytic[158] amounts of water and raising the temperature to harsh refluxing conditions (135 °C), the desired product was isolated in 94 %, as shown in Scheme 2.23.

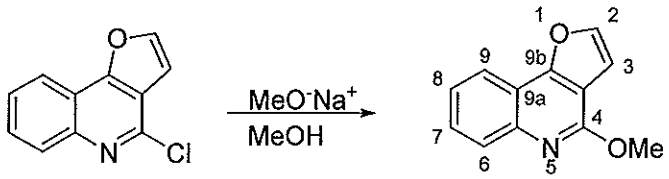



**1.72** 94%

**Scheme 2.23**

In the $^{1}$H NMR spectrum of the chlorinated material, the expected absence of the NH peak at 11.74 ppm was noted. The benzene protons exhibited a typical *ortho* substitution pattern with signals at 8.25, 7.73, 7.64 and 8.14 ppm corresponding to H-6 to H-9, and, the furan protons resonated as two doublets at 7.82 and 7.03 ppm corresponding to H-2 and H-3 respectively. The mass spectrum, which showed pseudo molecular ion peaks at *m/z* 204, 206 (3:1 ratio), further confirmed the proposed structure. Additionally, all spectroscopic data were in agreement with previous reported data[157,158,175] for this structure, thus, no further characterisation of the product was needed.

The chloride intermediate was then converted to the corresponding *O*-methyl substrate **2.01**[157] by the treatment of an excess molar solution of sodium methoxide in methanol at ambient temperature over night, giving the desired product **2.01** in a 80 % yield, as shown in Scheme 2.24.




**2.01**

**Scheme 2.24**

The major difference in the $^{1}$H NMR spectrum of **2.01** and its precursor, was the new introduced methyl group which resonated at 4.20 ppm. The other features were similar to its precursor in the spin coupling pattern; the four benzene protons exhibited a typical *ortho* substitution pattern and resonated at 7.95, 7.61, 7.46 and 8.15 ppm assigned to H-6 to H-9 respectively, and the two furan protons resonated at 7.72 and 6.95 ppm assigned to H-2 and H-3 as two doublets respectively. In the $^{13}$C NMR spectrum, coincident peaks at 157.68 and 157.64 were observed corresponding to carbon C-4 and C-9b respectively, also the *O*-methyl group resonated at 53.7 ppm. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 200, further confirmed the proposed structure. All spectroscopic data were in agreement with previous reported data[157,158] for compound **2.01**, thus no further characterisation of the product was needed.

## 2.6 Summary of Chapter 2

In summary, the synthesis of the furoquinolinone core structure, in either the *N*-methyl form **1.30** or the *O*-methyl form **2.01**, was achieved in excellent yields after optimisation. Surprisingly, palladium oxide was found to be the most efficient catalyst of all three catalysts screened for the intramolecular heck type coupling to

occur. By using palladium oxide together with potassium acetate as base, *n*-butylammonium chloride as additive and DMA as solvent, the furoquinolinone core structure **1.30** could be achieved in 89 % yield from precursors made over two steps nearly quantitatively.[†] Further, the *N*-SEM cyclised material **2.02** was afforded in an excellent yield of 87 %, which could be deprotected and converted to the *O*-methyl substrate **2.01** in a 63 % yield over three steps

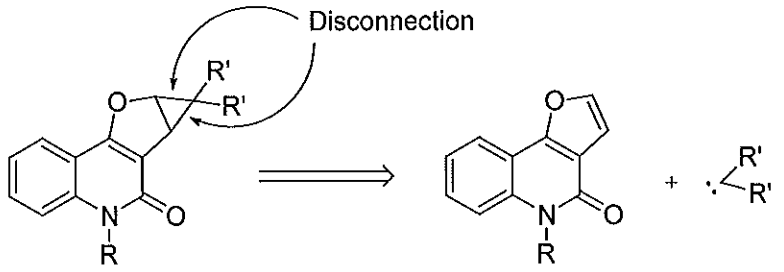
[†] It is acknowledged that Beccali *et al.* published a similar synthesis of the furoquinolinone core structure using the same strategy. However, their synthesis was published after this work had been already completed in our hands. For reference of Beccali *et al.*'s work see *Eur. J. Org. Chem.* **2005**, *10*, 2091-2096.

# Chapter 3

## Investigative chemistry of the furoquinolinone core structure

### 3.1 Potential synthesis of the furoquinolinone natural product frame work

Having achieved a new synthetic route to the furoquinolinone core structure, the final step to make the natural product was incorporation of a cyclopropane ring on the exocyclic double bond of the furan ring. From a retrosynthetic point of view, disconnection of two bonds gives the furoquinolinone core structure and a carbene precursor as shown in Scheme 3.1. Protection of the amide group would be required to avoid unwanted side reactions.[176]

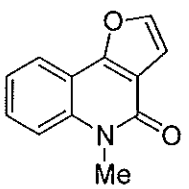



**Scheme 3.1**

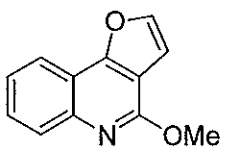
No literature precedent was found for installing a cyclopropane ring functionality with a *gem* dimethyl group on a furoquinolinone core, or even on a simple furan ring. However, to achieve the natural product **1.01**, emphasis had to be focused on carbene chemistry, and ultimately, the most direct method to install the desired *gem* dimethyl functionality, would be to employ 2-diazopropane as the carbene precursor. But, since there are no literature methods available, the investigation was expanded.

## 3.2 Investigative chemistry on two analogues of the furoquinolinone core structure

Two furoquinolinone analogues, **1.30** and **2.01**, were employed to extend the scope of the investigation (Figure 3.1). Both substrates have a free exocyclic double bond in the furan ring while the amide group is conveniently protected with a methyl group on either the nitrogen, **1.30**, or on the oxygen, **2.01**. As discussed previously in Chapter two, **2.01** is accessed through an optimised synthesis starting from the *N*-SEM protected structure **2.02**.



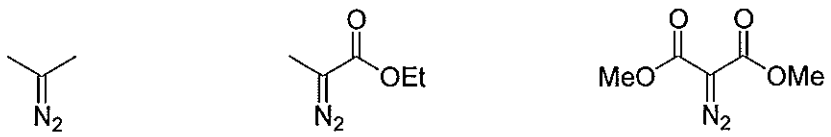

**1.30**




**2.02**

**Figure 3.1**

As mentioned in Chapter one, the use of two additional carbene precursors such as, ethyl 2-diazopropanoate and dimethyl diazomalonate, would not only provide the required carbon frame work for the natural product **1.01**, but also to a higher degree cover the reactivity spectrum of the two substrates, **1.30** and **2.01**. As shown in Figure 3.2, each one of the three diazo compounds reflects distinct electronic properties depending on what type of substituents adjacent to the carbene carbon are used. 2-Diazopropane is a non stabilised carbene precursor i.e., the carbene carbon is flanked by two methyl groups. Ethyl 2-diazopropanoate contains one EWG which stabilises the generated carbene, and dimethyl diazomalonate contains two EWG's further stabilising the generated carbene.



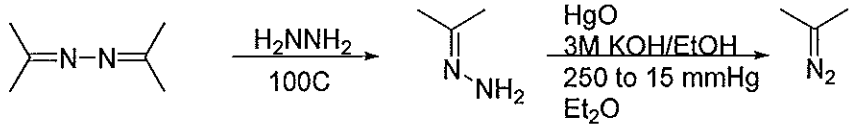

2-diazopropane ethyl 2-diazopropanoate dimethyl diazomalonate

**Figure 3.2**

This carbene chemistry investigation would not only provide a better understanding of reactivity of the two substrates **1.30** and **2.01**, but also, if a cyclopropane ring would successfully be installed by any of the two additional carbene precursors, a step closer to the natural product **1.01** has then been achieved. Ultimately, the use of 2-diazopropane as a carbene precursor would directly give the target functionality of concern i.e., a cyclopropane ring with a *gem* dimethyl group.

### 3.2.1 Preparation of Diazopropane

There are several available literature methods for the preparation of diazopropane,[177-179] however, one method in particular by Day *et al.*[180] has become frequently used and is a modified procedure from Staudinger *et al.*[177] The method involves treatment of the commercially available acetone azine with anhydrous hydrazine to give the acetone hydrazone. This freshly prepared acetone hydrazone is then oxidised by mercury oxide in the presence of ethanolic potassium hydroxide to furnish diazopropane. Upon subsequent distillation under reduced pressure, pure diazopropane is obtained as an approximately 2-3 molar ethereal solution, with the appearance of a deep red liquid, as shown in Scheme 3.2.




**Scheme 3.2**

As the half life of diazopropane is approximately 3 h at 0 °C,[181] it was necessary to use freshly prepared batches immediately. The use of diazopropane in cyclopropanating double bonds is most frequently performed without metal catalyst,[145,146,182] typically producing pyrazolines which can be rearranged photolytically or thermally to the desired cyclopropanes.[182]

### 3.2.2 Reaction of 1.30 and 2.01 with diazopropane

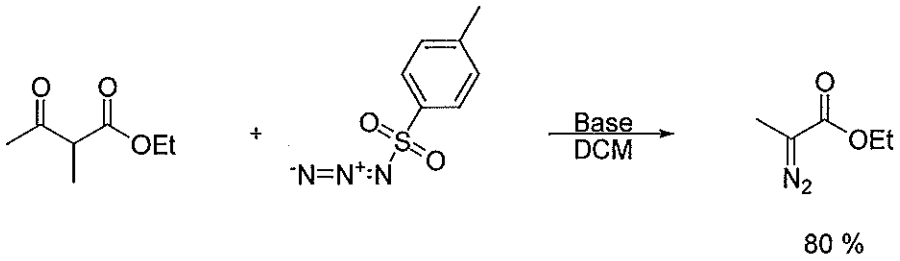
Initially, the ethereal solution of diazopropane was added in excess to a solution of substrate (**1.30** or **2.01**) in DCM at ambient temperature. After complete addition, the mixture became a pale reddish coloured liquid which dissipated after 6 h to

leave a colourless solution. It was evident from $^{1}H$ NMR analysis that only starting material was recovered from this reaction, since the characteristic furan protons was observed in the reaction mixture. To be complete, the reaction was attempted with altered reaction conditions, such as temperature and time, to see if at least a trace of product could be observed. After investigating three temperatures; -70 °C, 0 °C and 25 °C, and two reaction times; 5 h and 16 h, still no product was detected. As a last series of attempts, dirhodium tetraacetate was employed as a metal catalyst to facilitate the reaction, however, no change in outcome was observed. Thus, starting material was quantitatively recovered in all attempts.

No reactivity of the exocyclic furan double bond towards diazopropane was observed under any of the above described conditions. Hence, attempts to install a cyclopropane ring with a *gem* dimethyl functionality by using diazopropane as a carbene precursor, were therefore discarded. Other options to achieve the natural compound's frame work, such as stabilised carbenes, were contemplated.

### 3.2.3 Reaction of 1.30 with ethyl 2-diazopropanoate

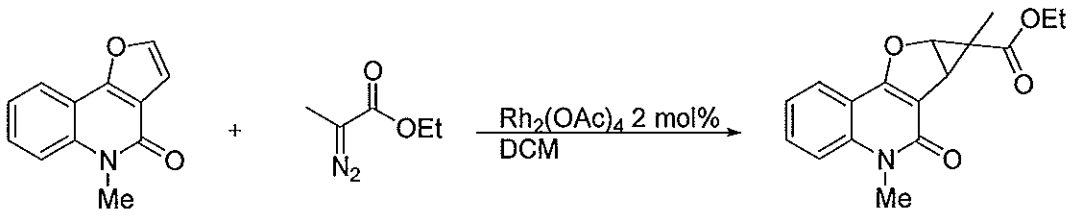
Previous reports of the preparation of ethyl 2-diazopropanoate[176,183,184] were used for the test reactions on the substrates **1.30** and **2.01**. To make the diazo compound, a diazo transfer reagent was required and, for convenience, tosyl azide was chosen. Tosyl azide was prepared by treatment of tosyl chloride with sodium azide according to Ghosh *et al.*[185] When ethyl-2-methyl acetoacetate was treated with tosyl azide in the presence of base, the desired diazo compound ethyl 2-diazopropanoate was afforded in 80 % yield, as shown in Scheme 3.3.




**Scheme 3.3**

The $^{1}H$ NMR spectrum of the diazo compound exhibited a singlet, triplet and a quartet at 1.97, 1.28 and 4.23 ppm, respectively. These results were in agreement with previous reported data[176] which further supported the proposed product.

When ethyl 2-diazopropanoate was reacted with **1.30**, the desired cyclopropanated product **3.01** was afforded, *albeit* in low to moderate yields, as presented in Table (entry 1[118] and 6[120]). This prompted us to optimise the conditions by varying the reaction factors such as; total reaction time, addition time of carbene and equivalents of carbene used, as shown in Table 3.1.



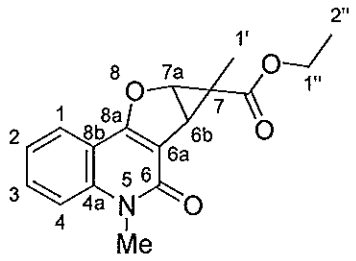

**1.30** **See table** **3.01**

| Entry | diazo | Time add. | Tot. time | Conver. |
|---|---|---|---|---|
| | eq | h | h | % |
| 1 | 3 | 18 | 19 | 16 |
| 2 | 3 | 1 | 19 | 32 |
| 3 | 9.5 | 3 | 16 | 30 |
| 4 | 7.5 | 1 | 16 | 40 |
| 5 | 7.5 | 1 | 16 | 35 |
| 6 | 2.5 | 3 | 3 | 35 |
| 7 | 3 | 1 | 1 | 45 |
| 8 | 3.2 | 1 | 1 | 68 |
| 9 | 3.2 | 1 | 1 | 81 |

**Table 3.1**

A prolonged addition time[118] of the carbene (entry 1) i.e., minimise the risk of dimerisation of the carbene, or a seven to nine fold excess of the carbene (entry 3 to 5) did not afford feasible yields of **3.01**. Extended total stirring times were not beneficial i.e., entry 2 vs entry 7. The optimal conditions (entry 9) were found to be by addition of the carbene over 1 h to a solution of **1.30** and catalyst, with a total stirring time of 2 h at ambient temperature. The crude mixture was then filtered through a short silica plug (EtOAc as eluent) to remove the rhodium catalyst. Wenkert *et al.*[118] found different products could be isolated depending on what adsorbent used in the purification step when using furan based systems. Ring opened products were favoured (dienal type isomers) when using silica and cyclopropanated products were favoured when using neutral alumina. However, in this case, no difference was observed by using either silica or neutral alumina in the purification step. A $^{1}$H NMR spectrum of the crude reaction mixture revealed a

conversion ratio, the relative NMR integral ratio of starting material and product (3.01/3.01 + 1.30), at best of 81 % (entry 9) of **3.01** but, surprisingly, only a 43 % isolated yield was afforded after chromatography. Reverse phase chromatography was required to separate the product from starting material, affording **3.01** as an off white solid.




**3.01**

The $^{1}$H NMR spectrum of **3.01** exhibited two protons at 3.50 and 5.18 ppm as a pair of doublets ($J$ = 6.0 Hz) assigned to H-6b and H-7a, and three additional signals at 0.93, 4.19 and 1.29 ppm assigned to H-1`, H-1``and H-2``, respectively. The major changes in the $^{13}$C NMR spectrum were apparent regarding the carbons C-7a and C-6b, now resonating at 72.8 and 34.4 ppm respectively, as compared to its precursor **1.30** (144.2 and 108.6 ppm, respectively) which indicated a saturated furan ring system. Analysis of the HMBC spectrum further confirmed the structure of **3.01** from $^{2}J$ and $^{3}J$ correlations observed from the protons H-6b, H-7a and H-1`, as shown in Table 3.2. Both protons H-6b and H-7a showed $^{3}J$ correlations to the carbonyl carbon of the ester group. Proton H-6b also correlated to the quaternary C-7 carbon which resonated at 20.2 ppm, a value that is in agreement for a quaternary carbon in a cyclopropane ring of a furan ring system.[121] Both H-7a and H-6b also correlated to carbon C-8a, which further confirmed the intact furan ring

system. The methyl protons at C-1` showed $^{3}J$ correlations to all three possible carbons (COOR, C-7a and C-6b) and a $^{2}J$ correlation to the quaternary carbon C-7, which all together strongly suggested the existence of a cyclopropane ring. The correlations observed from the HMBC spectrum, and the COSY spectrum which showed a strong correlation between proton H-6b and H-7a, together ruled out uncertainties concerning assignment of the proposed structure. Also, it was evident from the $^{1}$H NMR analysis that only one diastereoisomer of **3.01** was exclusively formed in the described reaction. Therefore a ROESY experiment was run to investigate the spacial correlations between the pertinent protons H-6b, H-7a and 1`. The ROESY spectrum showed no correlations from either H-6b or H-7a to any other proton, and the C-1` methyl protons are therefore not expected to be on the same face as the H-6b or H-7a protons. Thus, even though a lack of correlations does not necessarily confirm a stereochemical assignment, it is strongly suggested that the *exo*[139] diastereoisomer is the stereochemically favoured isomer in this reaction. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 300, and a high resolution mass spectrum, further supported the proposed structure.

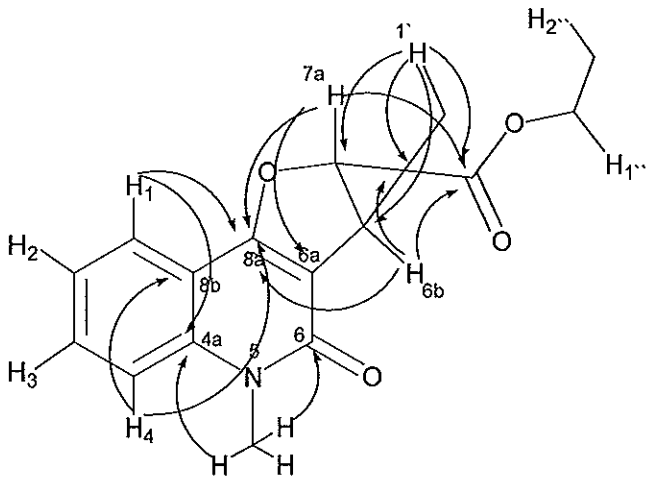
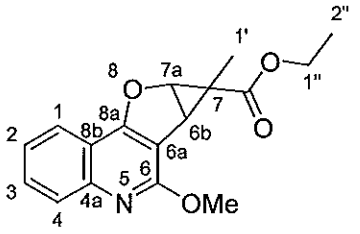



**Table 3.2** $^{1}$H (400 MHz), $^{13}$C (100 MHz) and HMBC NMR data for **3.01**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 1 | 122.8 | 7.77 (dd, *J* 7.6, 1.2 Hz, 1H) | C-3, C-4a, C-8b, C-8a C-6a, |
| 2 | 122.2 | 7.26 (dd, *J* 7.6, 1.2 Hz, 1H) | C-8b, C-4, C-1, C-3 |
| 3 | 131.5 | 7.61 (dd, *J* 7.6, 1.6 Hz, 1H) | C-1, C-4a |
| 4 | 115.0 | 7.41 (d, *J* 8.4 Hz, 1H) | C-2, C-8b, C-8a, C-3, C-4a |
| 4a | 140.6 | | |
| 6 | 161.1 | | |
| 6a | 110.3 | | |
| 6b | 34.4 | 3.50 (d, *J* 6.0 Hz, 1H) | C-7, COOR, C-8a |
| 7 | 20.2 | | |
| 7a | 72.8 | 5.18 (d, *J* 6.0 Hz, 1H) | C-6a, COOR, C-8a |
| 8a | 164.0 | | |
| 1` | 6.6 | 0.93 (s, 3H) | C-7, COOR, C-7a, C-6b |
| 1`` | 61.5 | 4.19 (q, *J* 7.2 Hz, 2H) | COOR, C-2`` |
| 2`` | 14.5 | 1.29 (t, *J* 7.2 Hz, 3H) | C-1`` |
| COOR | 173.3 | | |
| NMe | 29.6 | 3.73 (s, 3H) | C-4a, C-6 |

### 3.2.4 Reaction of 2.01 with ethyl 2-diazopropanoate

Similarly, when substrate **2.01** was treated under the optimised conditions as above described with ethyl 2-diazopropanaoate, the desired cyclopropanated product **3.02** was isolated in a 69 % yield. In this case, only normal phase chromatography was required to isolate the product, and in addition, no starting material could be observed when analysing the crude mixture by $^{1}$H NMR spectroscopy.




**3.02**

The $^{1}$H NMR spectrum of **3.02** exhibited two protons resonating at 3.48 and 5.25 ppm as a pair of doublets ($J$ = 5.6 Hz) assigned to H-6b and H-7a, and three additional signals at 0.86, 4.23 and 1.33 ppm assigned to H-1`, H-1`` and H-2``, respectively. The major visual changes in the $^{13}$C NMR spectrum were observed with respect to carbons, C-7a and C-6b, now resonating at 72.9 and 33.1 ppm, as compared to its precursor **2.01** (144.2 and 108.6 ppm respectively). By analogy with structure elucidation for product **3.01**, the analysis of the HMBC spectrum (for **3.02**) further confirmed the structure of **3.02** from $^{2}J$ and $^{3}J$ correlations observed as shown in Table 3.3. It was evident from the $^{1}$H NMR analysis that only one diastereoisomer of **3.02** was exclusively formed in the described reaction. Again, as for product **3.01**, the ROESY spectrum did not show any correlations from either H-6b or H-7a to any other proton, and the C-1` methyl protons are therefore not expected to be on the same face as the H-6b or H-7a protons. Thus,

again, it is strongly suggested that the *exo* diastereoisomer is the stereochemically favoured isomer in this reaction. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 300, and a high resolution mass spectrum, further supported the proposed structure.

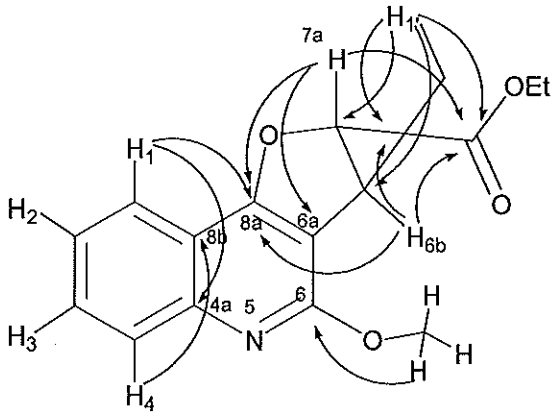


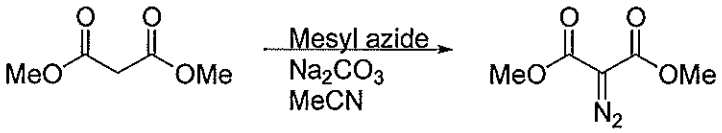

**Table 3.3** $^{1}$H (500 MHz), $^{13}$C (125 MHz) and HMBC NMR data for **3.02**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 1 | 127.5 | 7.86 (m, 2H, H-4 and H-1) | C-3, C-4a, C-8a |
| 2 | 124.0 | 7.36 (dd, *J* 6.8, 1.2 Hz, 1H) | C-8b, C-4 |
| 3 | 130.1 | 7.61 (dd, *J* 7.2, 1.6 Hz, 1H) | C-1, C-4a |
| 4 | 121.1 | 7.86 (m, 2H, H-4 and H-1) | C-2, C-8b |
| 4a | 147.4 | | |
| 6 | 160.4 | | |
| 6a | 106.5 | | |
| 6b | 33.1 | 3.48 (d, *J* 5.6 Hz, 1H) | C-7, COOR, C-8a |
| 7 | 20.1 | | |
| 7a | 72.9 | 5.25 (d, *J* 5.6 Hz, 1H) | C-6a, COOR, C-8a |
| 8a | 166.2 | | |
| 1` | 6.6 | 0.86 (s, 3H) | C-7, COOR, C-7a, C-6b |
| 1`` | 61.6 | 4.23 (q, *J* 6.0 Hz, 2H, H-1`` | COOR, C-2`` |
| 2`` | 14.5 | 1.33 ((t, *J* 6.0 Hz, 3H, H-2``) | C-1`` |
| COOR | 173.7 | | |
| OMe | 53.7 | 4.14 (s, 3H) | C-6 |

No unravelling of the furan ring was detected in either case analysed under the described cyclopropanation conditions with ethyl 2-diazopropanoate, as described.

### 3.2.5 Reaction of 1.30 with dimethyl diazomalonate

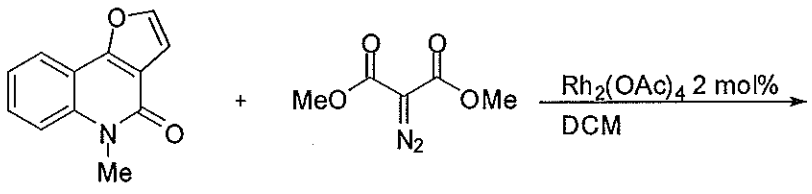
Dimethyl diazomalonate[186-188] was prepared by using literature methods, where the particular method chosen was easy and convenient.[186] This method involved treatment of dimethyl malonate with mesyl azide, as the diazo transfer reagent, and sodium carbonate as base in acetonitrile to furnish the desired diazo compound in a 70 % yield, as shown in Scheme 3.4.




**Scheme 3.4**

When a literature procedure[148] for cyclopropanation was adopted, using dimethyl diazomalonate and substrate **1.30**, only poor conversion of starting material to product was observed. Thus the reaction conditions optimised for ethyl 2-diazopropanoate as the carbene precursor, were then attempted. However, using these conditions with substrate **1.30** and dimethyl diazomalonate, resulted in low conversions of starting material i.e., the relative NMR integral ratio of starting material and product (product/product + starting material). Therefore different reaction factors such as time, addition time and temperature were investigated. As can be seen in Table 3.4, when prolonged addition times of the diazo reagent while

maintaining the temperature at 0 °C were applied, only starting material was recovered (entry 1). Repeating the reaction but at an increased temperature of 25 °C, only low conversions were observed (entry 2). An increase of concentration of carbene in the reaction mixture by shortening the addition rate from 12 to 3 h, again low conversion of starting material to product was observed (entry 3). However, after several attempts, when changing the total stirring time from 3 to 20 h and maintaining the total addition time of 3 h, total consumption of starting material was observed (entry 4).



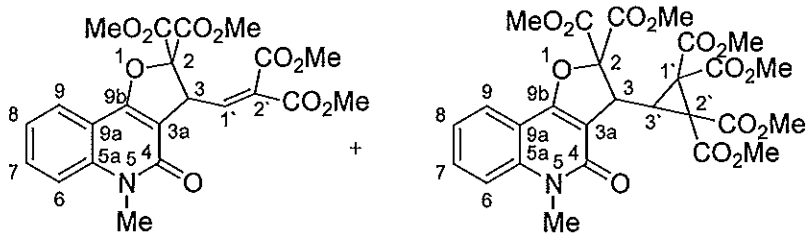

**1.30**

| Entry | diazo | Time add. | Tot. time | T | conver. |
|---|---|---|---|---|---|
| | eq | h | h | °C | % |
| 1 | 1 | 12 | 20 | 0 | 0 |
| 2 | 1 | 12 | 20 | 25 | <5 |
| 3 | 3 | 3 | 3 | 25 | <5 |
| 4 | 3.2 | 3 | 20 | 25 | 100 |

**Table 3.4**

The reaction mixtures (entry 4) were filtered through a short silica plug using EtOAc as eluent to obtain catalyst free mixtures. $^{1}$H NMR analysis of the mixtures revealed surprisingly no desired cyclopropanated product, or the potentially ring

opened material.[118] Two products, **3.03** and **3.04** in a ratio of 75:25, were isolated as a mixture with theoretically calculated yields of 55 and 18 %, respectively. Analytically pure samples of each product were obtained by means of flash- and reverse phase chromatography.




75 : 25

**3.03** ratio **3.04**

The mass spectrum of **3.03** showed a pseudo molecular ion peak at *m/z* 460, which supported the molecular formula $C_{22}H_{21}NO_{10}$. The major changes in the $^1$H NMR were the appearance of two doublet signals at 5.61 and 6.73 ppm ($J$ = 10.8 Hz) corresponding to two vicinal protons, and four additional OMe signals at (3.73 and 3.91) and (3.80 and 3.85) ppm, respectively. An APT NMR spectrum showed the presence of eleven quaternary carbons, where six were possibly carbonyls, several OMe signals and the NMe signal at 29.4 ppm. The HSQC spectrum showed six methine protons, where four where in the aromatic region, and several OMe groups. First, it was important to determine if the quinolinone moiety was intact. Since the protons in the aromatic area in the $^1$H NMR spectrum exhibited a typical *ortho* substitution pattern at 7.36, 7.62, 7.26 and 7.88 ppm (doublet, triplet, doublet and triplet respectively), it was indicative for an intact benzene ring. Also the NMe carbon resonated at 29.4 ppm which was in agreement with its precursor. The benzene moiety was confirmed through the $^3J$ correlations from the protons H-6 to

H-9 (Table 3.5), and the NMe correlations to carbons C-4, C-5a and C-6. Importantly the $^{3}J$ correlation from H-9 to carbon C-9b at 161.9 ppm was observed, which was indicative for an aromatic enol ether carbon, and thereby suggesting the existence of the quinolinone core structure. Next to investigate were the vicinal protons at 5.61 and 6.73 ppm with their corresponding $^{13}C$ carbon shifts at 46.7 and 142.3 ppm, respectively, which were assigned from correlations observed in a HSQC spectrum. The proton 5.61 ppm with its carbon at 46.2 ppm suggested to be in an allylic doubly position. In the HMBC spectrum the proton at 5.61 ppm correlated to carbons C-9b and C-3a which suggested it was α to the quinolinone ring and was assigned as H-3. A double bond was vicinal to C-3 since the vicinal proton at 6.73 ppm was attached to a double bond carbon at 142.3 ppm. Since this position (6.73 ppm) only correlated to carbon C-3a in the quinolinone ring, this was indicative of it being β to the quinolinone ring. The proton at 6.73 ppm also correlated to a quaternary double bond carbon at 131.4 ppm and two ester carbonyl carbons at 164.1 and 164.7 ppm. This data suggested that a 1,1-dicarboxylated double bond was present in the molecule. The downfield shift of the protonated double bond carbon (142.3 ppm) was consistent with it being β to the carbonyl groups. H-3 correlated to two different ester carbonyls (165.1 and 166.1 ppm) and an oxygenated quaternary carbon at 93.5 ppm. These correlations suggested that a *gem* dicarboxylated group was attached to a quaternary oxygen carbon which was vicinal to C-3. The molecular formula $C_{22}H_{21}NO_{10}$ from a high resolution mass spectrum indicated that there must be an ether linkage between C-9b and C-2. The chemical shift of C-2 is consistent with it being an ether carbon of a dihydrofuran ring system. This data supported the proposed structure shown in Table 3.5.

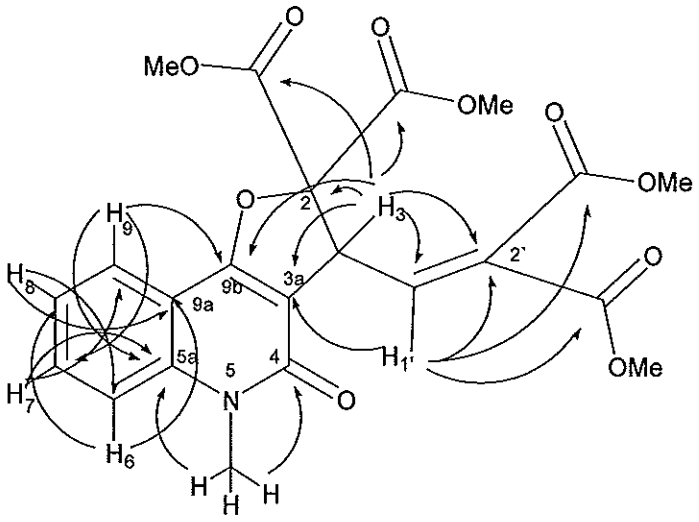



**Table 3.5** $^{1}$H (500 MHz), $^{13}$C (125 MHz) and HMBC NMR data for **3.03**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 2 | 93.5 | | |
| 3 | 46.7 | 5.61 (d, *J* 10.8 Hz, 1H) | (C-2, 2 x COOR), C-2, C-3a C-9b, C-1`, C-2` |
| 3a | 108.0 | | |
| 4 | 159.9 | | |
| 5a | 141.4 | | |
| 6 | 115.5 | 7.36 (d, *J* 8.4 Hz, 1H) | C-8, C-9a |
| 7 | 132.5 | 7.62 (app. t, *J* 7.8 Hz, 1H) | C-5a, C-9 |
| 8 | 122.5 | 7.26 (dd, *J* 7.2, 3.0 Hz, 1H) | C-6, C-9a |
| 9 | 124.0 | 7.88 (d, *J* 7.8 Hz, 1H) | C-5a, C-7, C-9b |
| 9a | 111.7 | | |
| 9b | 161.9 | | |
| 1` | 142.3 | 6.73 (d, *J* 10.8 Hz, 1H) | (C-2`, 2 x COOR), C-2`, |
| 2` | 131.4 | | C-3a |
| COOR (C-2) | 165.1 | | |
| | 166.1 | | |
| COOR (C-2`) | 164.1 | | |
| | 164.7 | | |
| NMe | 29.4 | 3.63 (s, 3H) | |

Structure **3.03** was confirmed by X-ray crystallography as shown in Figure 3.3.

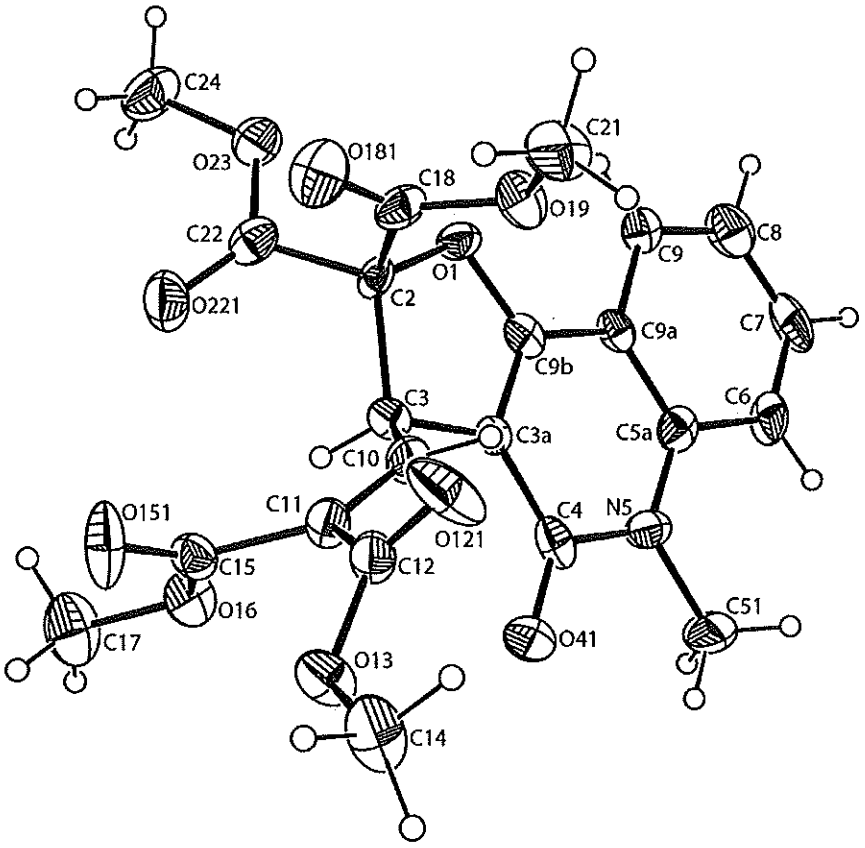
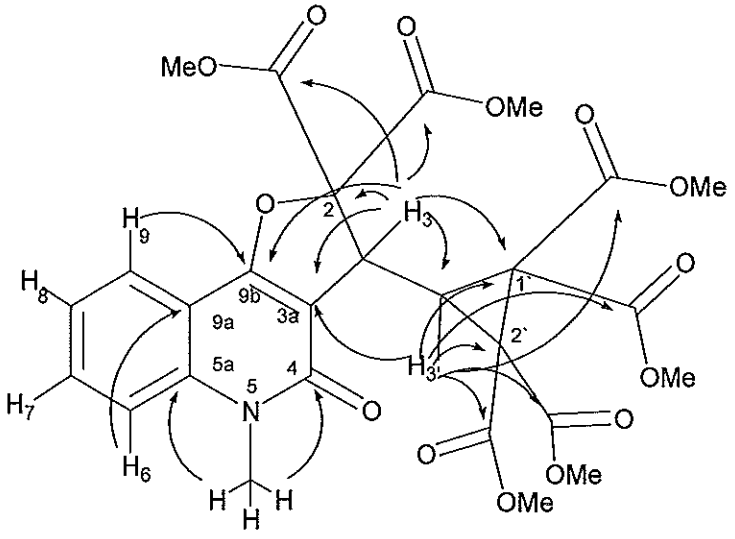



**Figure 3.3** ORTEP plot of product **3.03**, (30 % ellipsoids are shown)

The $^{1}$H NMR spectrum of the minor component **3.04**, exhibited two protons at 2.61 and 5.15 ppm as a pair of two doublets ($J$ = 11.0 Hz) assigned to H-3` and H-3 respectively, and one additional signal assigned to two OMe groups assigned to the third addition of dimethyl diazomalonate to the molecule. The major visual changes in the $^{13}$C NMR spectrum were, again, observed with respect to carbons C-2 and C-3 now resonating at 92.7 and 43.9 ppm, as compared to its precursor **1.30** (144.2 and 108.6 ppm respectively), and with two additional carbonyl carbon signals. Analysis of the HMBC spectrum further confirmed the structure of **3.04** from $^{2}J$ and $^{3}J$ correlations observed (from the protons H-3 and H-3` in particular),

as shown in Table 3.6. By analogy with the structure elucidation of **3.03**, similar correlations, now for protons H-3 and H-3`, were observed for **3.04**. The $^{13}C$ shifts of C-2 and C-3 were almost identical as for product **3.03**, again, indicative for a saturated furan ring system. The absence of the $^{13}C$ shifts at 142.3 and 108.0 ppm (being C-1` and C-2` in product **3.03**), and new peaks at 36.7, 45.3 and 43.7 ppm assigned to C-3`, C-1` and C-2`, suggested a saturated system. $^{3}J$ correlations from H-3` into all four ester carbonyls linked to C-1` and C-2`, where C-1` and C-2 being quaternary carbons, suggested a cyclopropane ring moiety. The $^{1}H$ shifts for (H-3 and H-3`) and the $^{13}C$ shifts for (C-2, C-3, C-3`, C-2` and C-1`), and the correlation between the two protons (H-3 and H-3`) in the COSY spectrum, further suggested the structure of **3.04**. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 590, and with a high resolution mass spectrum, further supported the proposed structure.



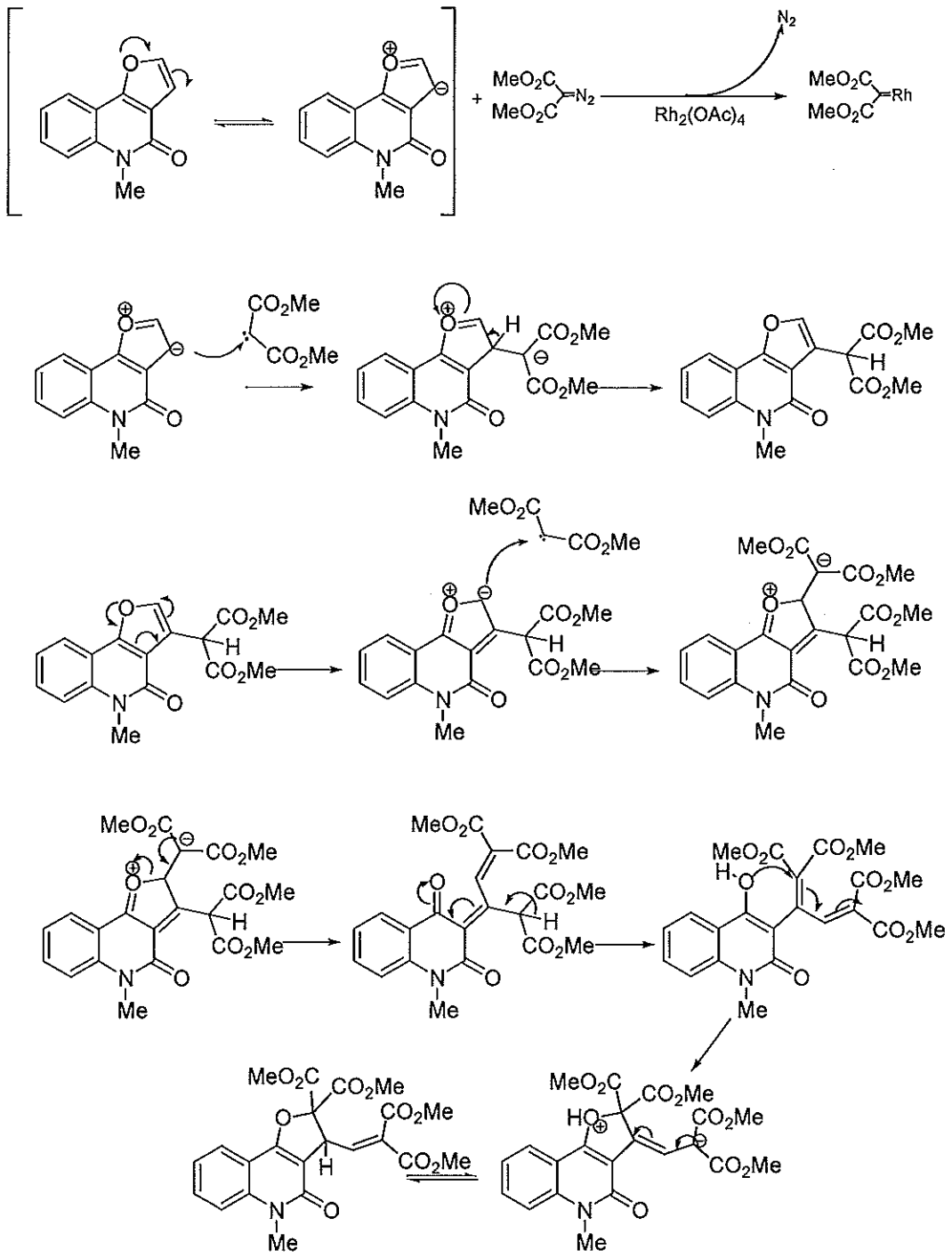

**3.04**

**Table 3.6** $^{1}H$ (500 MHz), $^{13}C$ (125 MHz) and HMBC NMR data for **3.04**

| Position | $^{13}C$ | $^{1}H$ (mult., *J*, int) | HMBC |
|---|---|---|---|
| 2 | 92. | | |
| 3 | 43.9 | 5.61 (d, *J* 11.0 Hz, 1H) | (C-2, 2 x COOR), C-2, C-3a C-9b, C-1`, C-2` |
| 3a | 108.8 | | |
| 4 | 160.1 | | |
| 5a | 141.4 | | |
| 6 | 114.7 | 7.37 (d, *J* 8.5 Hz, 1H) | C-8, C-9a |
| 7 | 132.1 | 7.63 (app t, *J* 7.5 Hz, 1H) | C-5a, C-9 |
| 8 | 122.1 | 7.28 (m, 1H, H-8) | C-6, C-9a |
| 9 | 123.8 | 7.88 (d, *J* 8.0 Hz, 1H) | C-5a, C-7, C-9b |
| 9a | 111.9 | | |
| 9b | 161.1 | | |
| 1` | 45.3 | | |
| 2` | 43.7 | | |
| 3` | 36.7 | 2.61 (d, *J* 11.0 Hz, 1H) | (C-1', 2 x COOR), C-1`, C-2`, (C-2`, 2 x COOR), C-3, C-3a, C-2 |
| COOR (C-2) | 167.5 | | |
| | 167.9 | | |
| COOR (C-1`) | 164.4 | | |
| | 166.0 | | |
| COOR (C-2`) | 166.2 | | |
| | 166.3 | | |
| NMe | 29.4 | 3.63 (s, 3H) | C-4, C-5a, C-6 |

Mechanistically it was believed, based on the two posssible resonance structures of the starting material **1.30** shown in Scheme 3.5, the negatively charged C-3 position reacts with one equivalent of carbene dimethyl malonate and forms, at first, an insertion product. The negatively charged resonance structure in C-2

position then reacts with a second equivalent of dimethyl diazomalonate, forming a presumable short lived transition intermediate which unravels the furan ring. This intermediate can then undergo ring closing, where the driving force is explained by re-installing the conjugation of the two six membered ring system, giving the double insertion product **3.03**, as shown in Scheme 3.5.



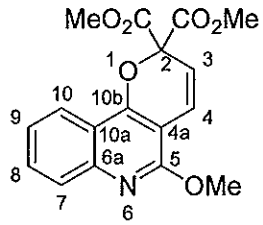
**Scheme 3.5**

By with an increasing concentration of product **3.03** being formed over time and an excess of diazo dimethylmalonate present in the reaction mixture, it is possible for **3.03** to react with a third aliquot of carbene malonate, giving rise to the second product **3.04**. No recovery of starting material was observed when analysing the

crude reaction mixture and, additionally, no reactivity elsewhere in the molecule was observed. Finally, attempts to selectively synthesise product **3.03** by using less diazo dimethylmalonate reagent under the same conditions, poor conversions, even though selective, were observed and mostly starting material was recovered.

### 3.2.6 Reaction of 2.01 with dimethyl diazomalonate

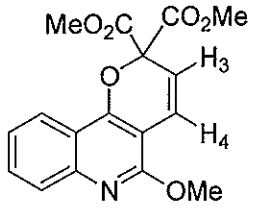
Treatment of the analogue substrate **2.01** with dimethyl diazolmalonate under the optimised conditions described for substrate **1.30**, gave one product, **3.05**, in a 38 % yield.



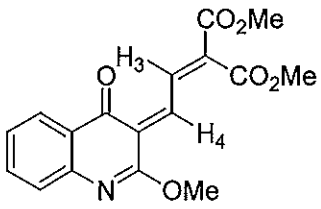

**3.05**

The $^{1}$H NMR spectrum of the isolated product **3.05** exhibited two proton signals at 6.05 and 6.97 ppm as a pair of two doublets ($J$ = 10 Hz) assigned to H-3 and H-4, and one signal at 3.86 assigned to the two OMe groups of the two ester groups linked to the C-2 carbon. The $^{13}$C NMR spectrum exhibited signals at 82.3, 116.9, 120.9, 101.4 and 155.4 ppm assigned to carbons (C-2 to C-4a) and C-10b, respectively. Analysis of the HMBC spectrum further confirmed the structure of **3.05** from $^{2}J$ and $^{3}J$ correlations observed (from the protons H-3 and H-4 in particular), as shown in Table 3.7. The H-3 proton correlated to C-2, C-4a and (2 x COOR), while the H-4 proton correlated to C-4a, C-10b, C-5. Thus, it is shown that

H-3 is connected to the ester carbonyls linked to C-2, and β to the quinoline ring since it shows only correlation to C-4a. In contrast, H-4 is α to the quinoline ring since it correlates to carbons C-4a, C-5 and C-10b. The connectivity from the two pertinent protons described (H-3 and H-4), supported the proposed pyrano type structure. However, by mass spectroscopy, either a pyrano type product or a ring opened diene was possible.




pyrano type product




diene form

The chemical shift of C-2 at 82.3 ppm was indicative of an oxygenated quaternary carbon while the chemical shift of C-10b at 155.4 ppm was indicative of an oxygenated aromatic quaternary carbon, thus favouring the pyrano structure over the ring opened diene. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 330, and with a high resolution mass spectrum, supported the proposed structure.

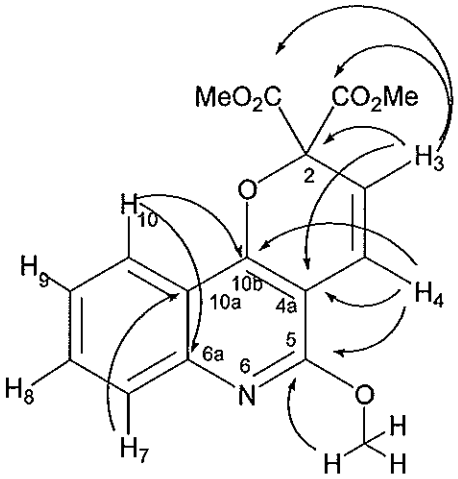



**Table 3.7** $^{1}$H (500 MHz), $^{13}$C (125 MHz) and HMBC NMR data for **3.05**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 2 | 82.3 | | |
| 3 | 116.9 | 6.05 (d, *J* 10.0 Hz, 1H) | C-2, C-4a, (C-2, 2 x COOR) |
| 4 | 120.9 | 6.97 (d, *J* 10.0 Hz, 1H) | C-4a, C-10b, C-5 |
| 4a | 101.4 | | |
| 5 | 158.7 | | |
| 6a | 147.2 | | |
| 7 | 127.2 | 7.77 (d, *J* 8.0 Hz, 1H) | C-8, C-9, C-10a |
| 8 | 130.7 | 7.62 (dd, *J* 7.0, 1.0 Hz, 1H) | C-6a, C-7, C-10 |
| 9 | 124.2 | 7.39 (dd, *J* 7.0, 1.0 Hz, 1H) | C-7, C-10a |
| 10 | 122.4 | 8.19 (d, *J* 8.0 Hz, 1H) | C-6a, C-8, C-10b |
| 10a | 117.7 | | |
| 10b | 155.4 | | |
| COOR (C-2) | 167.0 | | |
| COOMe | 53.86 | 3.86 (s, 2 x 3H) | C-2 |
| OMe (C-5) | 53.89 | 4.09 (s, 3H) | C-5 |

The suggested product was later determined by X-ray crystallography as shown in Figure 3.4.

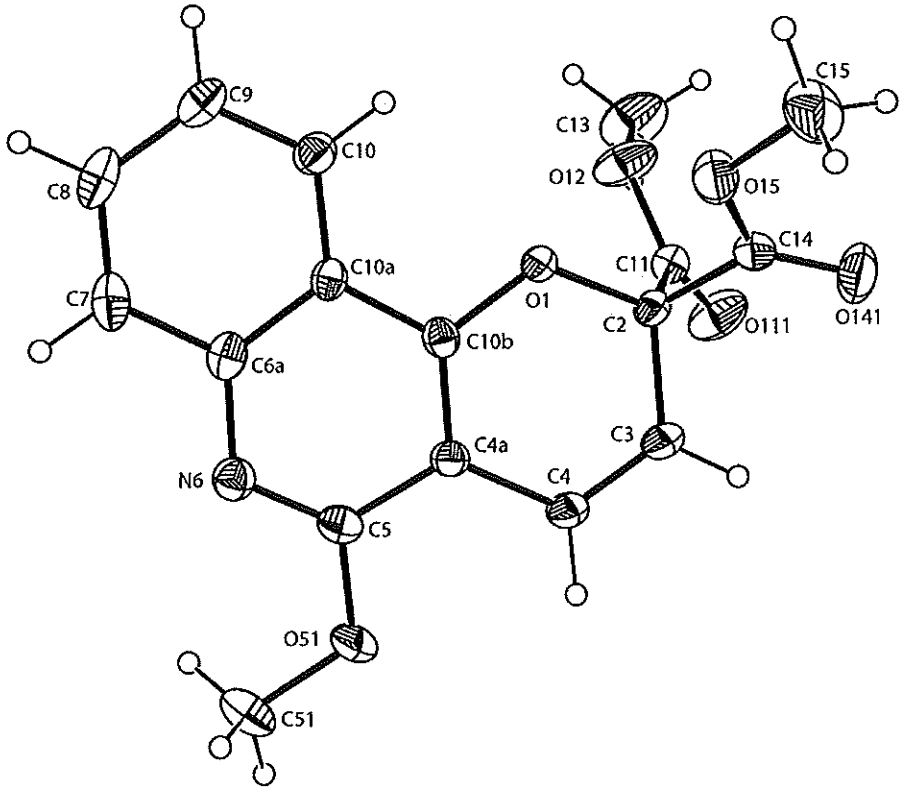



**Figure 3.4** ORTEP plot of product **3.05**, (30 % ellipsoids are shown)

As has been demonstrated, both alternative diazo reagents reacted to a high degree with substrates **1.30** and **2.01**. The reason for this observed high reactivity is most likely explained by the electron withdrawing effect of the substituents adjacent to the carbene centre, which in contrast, is lacking in the case of 2-diazopropane and therefore might serve as an explanation for the low reactivity. As 2-diazopropane would give the desired carbon frame work in one step, it was desirable to elaborate on what factor/moiety of the performed/used reactions/substrates that could be optimised/changed. Since both substrates, **1.30** and **2.01**, contain the desired carbon

framework of the natural product **1.01**, they cannot be compromised to any great extent. However, the reactivity of the exocyclic double of the furan ring could potentially be enhanced, if appropriate removable groups could be attached to the double bond.

## 3.3 A Synthetic approach of a third key intermediate

### 3.3.1 First approach

As low reactivity of 2-diazopropane with the susbstrates **1.30** and **2.01** was observed, a synthetic approach to a third key intermediate was contemplated and elaborated on to expand the investigation. It was thought that having an electron withdrawing group on either the C-2 or C-3 carbon of the furan ring in the key intermediate **1.30**, could further polarise the double bond (as compared to substrates **1.30** and **2.01**), and thus the reactivity of the double bond would then be altered. A methyl ester group was chosen to be linked on the C-3 carbon of the furan ring to give a third key ester intermediate, as shown in Figure 3.5.

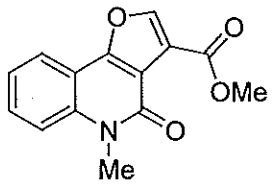
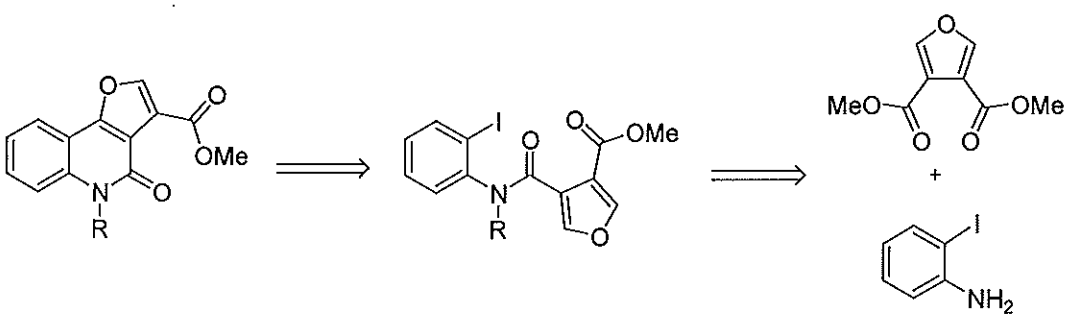



**Figure 3.5**

The synthesis of the third key intermediate was envisaged to be achieved by using the already developed methodology as for the *N*-methyl key intermediate **1.30**. Retrosynthetically, the disconnection of the C-C bond would give the amide

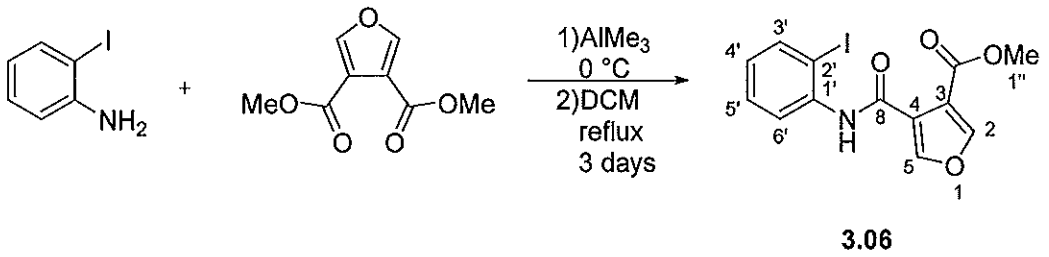
coupled product intermediate, followed by disconnection of the amide bond to give the iodoaniline and the dimethyl 3,4-furandicarboxylate as the two starting materials, as shown retrosynthetically in Scheme 3.6.



**Scheme 3.6**

### 3.3.1.1 Amide coupling

In this case, converting the furan ester derivative selectively to the corresponding acid chloride, was not considered as a useful synthetic approach. Instead, as described in the introduction in this Chapter, activating the amine with trimethyl aluminium[67-69,162,163] was thought to be the adequate method to use. Pre-treatment of 2-iodoaniline with an excess of trimethyl aluminium followed by addition of dimethyl 3,4-furandicarboxylate under reflux conditions, gave 44 % of the isolated amide coupled product **3.06** as shown in Scheme 3.7.



**3.06**

**Scheme 3.7**

The $^{1}$H NMR spectrum of the amide coupled compound **3.06** exhibited a broad singlet at 10.88 ppm which corresponded to the amide proton, and two signals at 8.28 and 8.13 ppm assigned to the furan protons H-5 and H-2, respectively. Four distinct signals of the benzene ring protons were apparent at 7.79, 7.38, 6.93 and 7.87 ppm corresponding to H-6` to H-3`, respectively. The spin coupling pattern of the benzene protons indicated a typical *ortho* substitution where the protons H-6` to H-3` appeared as a doublet, triplet, triplet and a doublet respectively. The $^{13}$C NMR spectrum exhibited the six benzene carbons C-1` to C-6` at 139.2, 93.6, 139.5, 127.5, 128.8 and 126.7 ppm respectively, and furan carbons C-2 to C-5 at 151.3, 115.4, 122.0 and 151.9 ppm respectively. Also the ester carbonyl and the methoxy group resonated at 165.2 and 52.9 ppm respectively. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 372, supported the proposed structure. This proposed structure was confirmed by X-ray crystallography as shown in Figure 3.6.

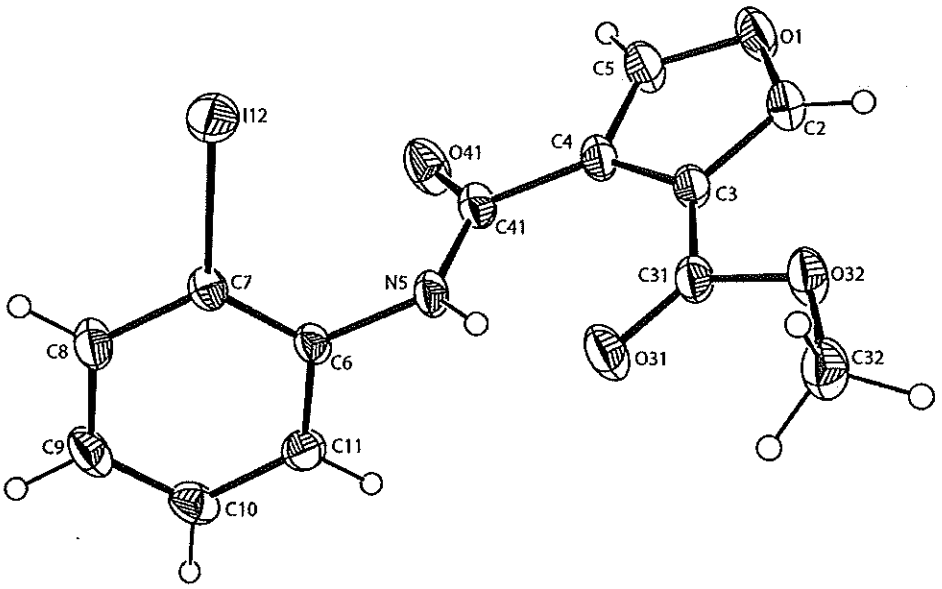
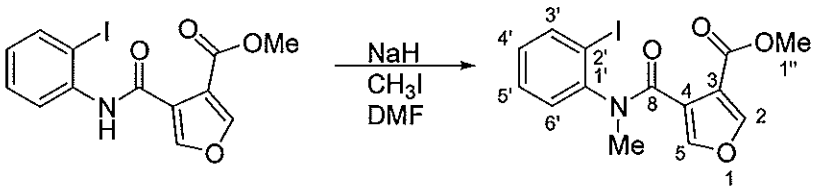



**Figure 3.6** ORTEP plot of product **3.06**, (30 % ellipsoids are shown)

The methylation step of **3.06** was straightforward by adopting the procedure developed for the iodo- and bromo derivatives as previously discussed. After treatment of the secondary **3.06** with an excess molar solution of both sodium hydride and methyl iodide using DMF as solvent, the desired iodo-*N*-methylamide-ester **3.07** was afforded in 96 %, as shown in Scheme 3.8.




**3.07**

**Scheme 3.8**

The $^{1}$H NMR spectrum of **3.07** exhibited two proton signals at 7.44 and 7.73 ppm corresponding to H-2 and H-5 together with OMe group at 3.87 ppm. The newly introduced methyl group protons resonated at 3.37 ppm. The benzene protons appeared as a triplet, multiplet and a doublet at 6.95, 7.26 and 7.81 ppm owing to protons H-4`, (H-5` and H-6`) and H-3`, respectively. An additional signal in the $^{13}$C NMR spectrum at 29.9 assigned to the *N*-methyl group, was the major difference as compared to the precursor. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 386, supported the proposed structure. This structure was confirmed by X-ray crystallography as shown in Figure 3.7.

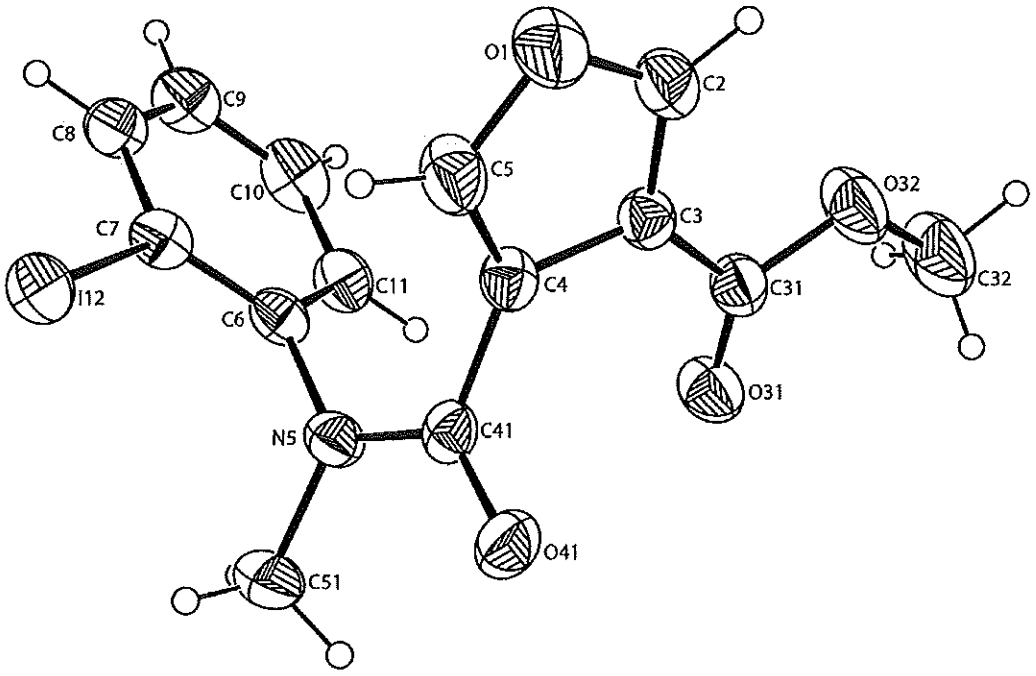
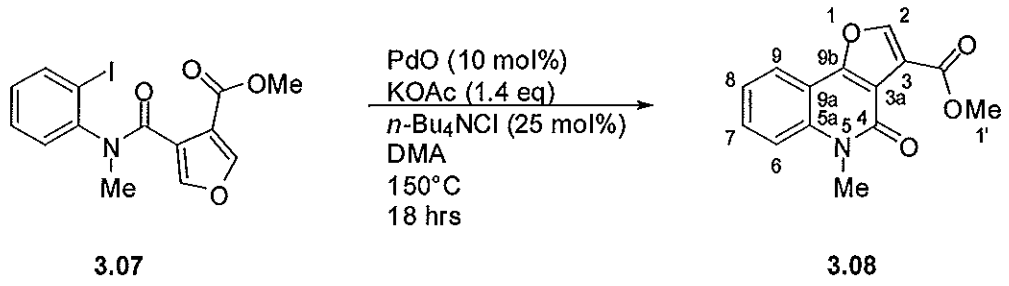



**Figure 3.7** ORTEP plot of product **3.07**, (30 % ellipsoids are shown)

### 3.3.1.2 The Heck coupling

Having prepared **3.07**, the next step was to cyclise it in order to afford the third key intermediate. After treatment of the **3.07** with the optimised conditions, as found for **2.09**, a low yield of the desired product **3.08** was obtained. Several attempts were undertaken, involving other catalysts such as palladium triphenylphosphine tetrakis and palladium acetate, to improve the yield, but all failed. The best isolated yield for **3.08** was 22 %, however not reproducible, as shown in Scheme 3.9.




**3.07** **3.08**

**Scheme 3.9**

The $^{1}$H NMR spectrum of the key ester intermediate **3.08** exhibited two singlet signals at 8.19 and 3.80 ppm assigned to proton H-2 and the OMe protons, respectively. A typical *ortho* substitution pattern of the benzene protons re-appeared at 7.46, 7.60, 7.33 and 8.02 ppm, corresponding to H-6 to H-9, respectively. The $^{13}$C NMR spectrum showed the same pattern as the other key intermediates synthesised with the major difference of a slightly lower field shift of the C-3 carbon (now at 118.6 ppm), due to the ester functionality linked to the C-3 carbon, which typically are around ~105 to 110 ppm for the other key intermediates **1.30** and **2.01**. The mass spectrum, which showed a pseudo molecular ion plus proton peak at *m/z* 258, supported the proposed structure. The suggested structure of product **3.08** was further confirmed by X-ray crystallography, as shown in Figure 3.8.

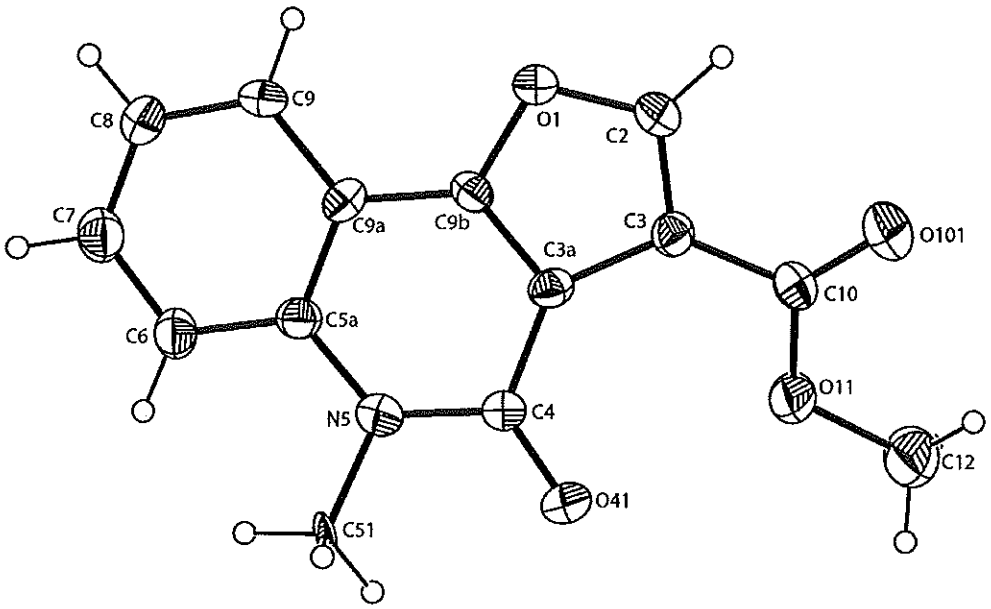
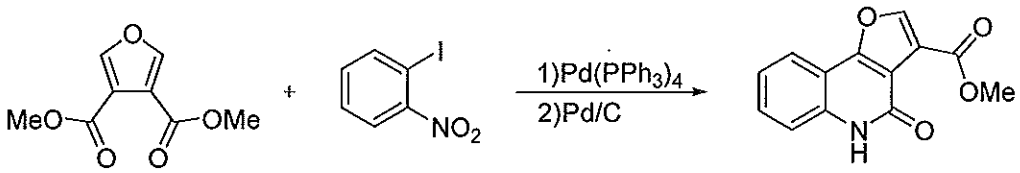



**Figure 3.8** ORTEP plot of product **3.08**, (30 % ellipsoids are shown)

Due to low yields and poor reproducibility of the palladium catalysed cyclisation reaction when using **3.07** as substrate, this synthetic approach was discarded and alternative methodologies were contemplated.

### 3.3.2 Second approach

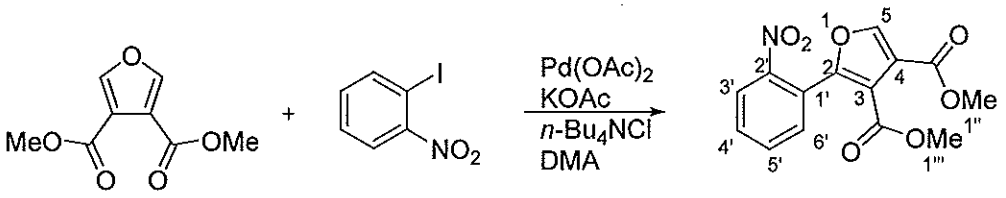
A direct method to achieve the secondary key-ester intermediate, could be by employing Glover *et al.*'s[47] methodology. The synthesis strategy would therefore first involve a palladium catalysed biaryl coupling using 1-iodo-2-nitrobenzene and dimethyl 3,4-furan-dicarboxylate (to give **3.09**), followed by reductive aminolysis to form a secondary amide key ester derivative **3.10**, as shown in Scheme 3.10.




**3.11**

**Scheme 3.10**

The biaryl coupling was initially attempted by using palladium triphenylphosphine tetrakis, however, a slightly higher yield of the desired coupled product was achieved by using palladium acetate or palladium oxide as catalyst, which gave the desired aryl coupled product **3.09** in 40 %, as shown in Scheme 3.11.




**3.09**

**Scheme 3.11**

The $^{1}H$ NMR spectrum of the bi aryl coupled product **3.09** exhibited a proton signal at 8.00 ppm assigned to H-5, and two OMe groups at 3.75 and 3.89 ppm respectively. The benzene protons, H-4` and H-5`, and H-3` appeared as a multiplet and a doublet at 7.63-7.73 and 8.10 ppm respectively. The $^{13}C$ NMR spectrum exhibited six benzene carbons at 123.9, 148.8, 124.9, 132.7, 133.0 and 131.2 ppm, together with the furan carbons at 147.7, 115.5, 119.7 and 153.1 ppm respectively. The C-3 and C-4 linked ester carbonyls resonated at 162.1 and 162.7 ppm while the respective methoxy groups C-1``` and C-1`` resonated at 52.4 and 52.3 ppm. The mass spectrum, which showed a pseudo molecular ion peak at 328 *m/z*, supported

the proposed structure. This structure was confirmed by X-ray crystallography as shown in Figure 3.9.

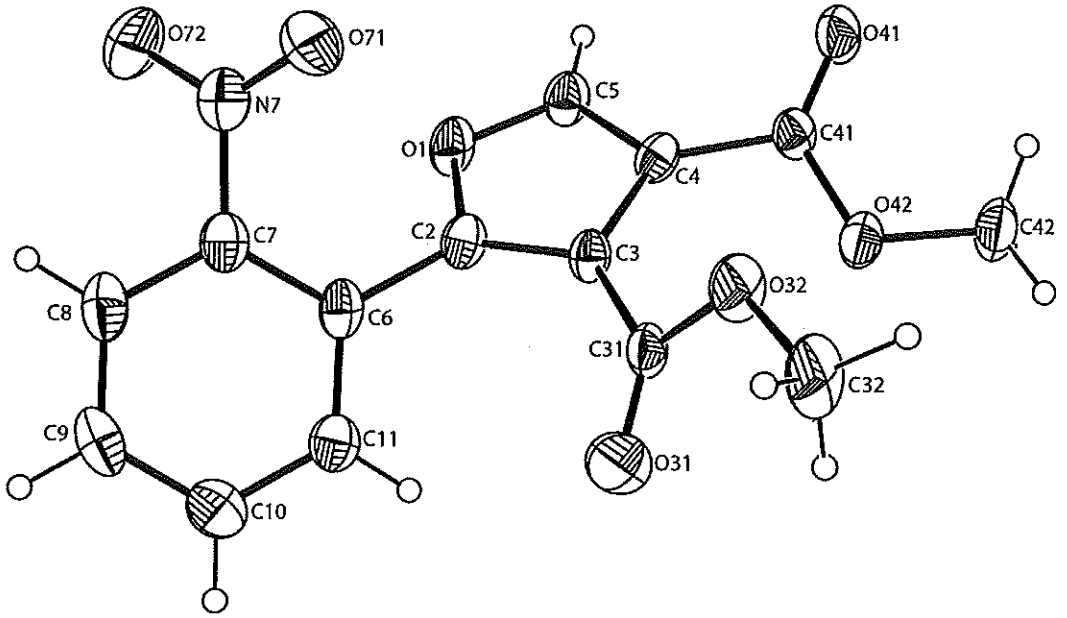
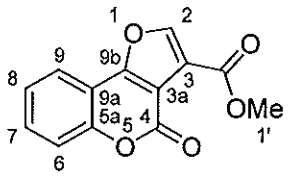



**Figure 3.9** ORTEP plot of product **3.09**, (30 % ellipsoids are shown)

A later compound was obtained eluting from the chromatography purification of the above reaction mixture. After extensive purification using reverse phase chromatography (HPLC), a pure sample of the minor product **3.10** was afforded and analysed.

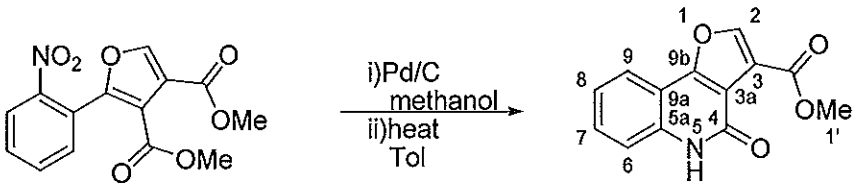



**3.10**

The $^{1}$H NMR spectrum of the chromene type product **3.10** exhibited a signal at 8.22 ppm and 3.97 ppm assigned to H-2 and the OMe protons, respectively. The

benzene protons exhibited a typical *ortho* substitution pattern at 7.38, 7.47, 7.58 and 7.90 ppm as a triplet, doublet, triplet and a doublet, assigned to H-8, H-6, H-7 and H-9, respectively. The $^{13}C$ NMR spectrum exhibited signals at 150.1 and 108.0 ppm corresponding to C-2 and C-3, and the benzene protons at 117.5, 131.9, 124.8 and 121.3 ppm assigned to C-6 to C-9, respectively. Also the carbonyl at C-4 and the methoxy group resonated at 155.8 and 52.7 ppm. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 245, and elemental analysis, supported the proposed structure.

The biaryl coupled product **3.09** was then treated[47] with palladium on activated carbon in MeOH followed by heating to reflux in toluene. However, after several low yielding attempts, the desired product **3.11** could not be optimised to give a better yield than 18 % as a pure product, shown in Scheme 3.12.




**3.11**

**Scheme 3.12**

The $^{1}H$ NMR spectrum of the desired NH-key-ester derivative **3.11** exhibited a typical *ortho* substitution pattern of the benzene protons at 7.49, 7.58, 7.33 and 8.00 ppm assigned to H-6 to H-9. Signals at 8.27, 4.00 and 10.87 ppm corresponded to proton H-2, the OMe group and the NH respectively. The $^{13}C$ NMR spectrum exhibited signals at 150.5 and 110.5 ppm assigned to C-2 and C-3,

and 119.1, 132.6, 125.7 and 121.2 ppm assigned to the corresponding benzene carbons C-6 to C-9, respectively. The mass spectrum, which showed a pseudo molecular ion peak at 244 *m/z*, and a high resolution mass spectrum, supported the proposed structure.

Attempts to go further with **3.11** i.e., selective methylation on the nitrogen, gave no promising results due to competing *O*-alkylation which in turn resulted in tedious purifications with no adequate separation. This, together with the overall low yielding reactions leading up to the **3.11**, led to discontinuation of this particular synthetic route in favour for alternative strategies.[47]

In summary of the attempts pursued to make the third key intermediate **3.08**, it was discovered that the palladium catalysed cyclisation step of **3.07** did not give yields as high as the analogues **2.09** and **2.13**. The reasons why low yields were obtained can only be speculative at this stage, but obviously had to do with the C-3 linked ester functionality. Also, by using an alternative synthetic strategy,[47] the secondary key ester derivative **3.11**, was synthesised, but only in a low yield. That together with the lack of selectivity in the following methylation step to achieve **3.08**, led to discontinuation of the attempts to synthesise the third desired key ester intermediate **3.08** as a whole.

## 3.4 Summary of the carbene investigation

When summarising the outcomes of the carbene chemistry investigation of the two substrates **1.30** and **2.01**, first of all, it is worth while emphasising the novelty of

the two rearrangement products **3.03** and **3.04** when using dimethyl diazomalonate as the carbene precursor. Insertion products of different kinds, as mentioned in Chapter one, are well known and utilised in syntheses, but through the numerous searches for rearrangement products, similar products to **3.03** and **3.04** have not been encountered. The structure of **3.03** was also confirmed by X-ray crystallography. A drawback though, were the unsuccessful attempts when using 2-diazopropane as the carbene precursor, which otherwise would have given the desired functionality in one step. However, the desired cyclopropanated products **3.01** and **3.02**, were achieved in moderate yields by using either substrate **1.30** or **2.01**, with ethyl 2-diazopropanoate as a carbene precursor. The latter proceeded with complete consumption of starting material.

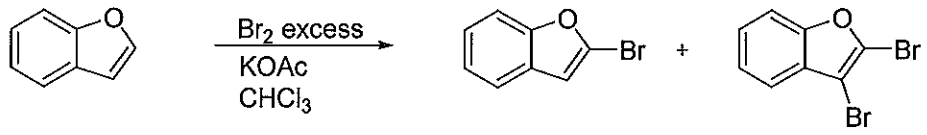
Finally, the substrates **1.30** and **2.01**, have demonstrated to be reactive towards stabilised carbenes under the described conditions with surprising outcomes, and inert to non stabilised carbenes such as 2-diazopropane. Thus, the choice of electrophile used had a tremendous effect on the degree of reactivity observed. These results opened an interest in expanding the types of electrophiles that could be used to further explore the reactivity of the substrates. Hence, this investigation was not considered as complete until electrophiles, other than carbenes, had been trialled with the selected substrates **1.30** and **2.01**.

## 3.5 Electrophilic Aromatic Substitution (EAS) reactions on 1.30 and 2.01

The fact that no previous investigation has been conducted regarding the reactivity of the furoquinolinone core structures, **1.30** or **2.01**, with electrophiles of any form, prompted us to take a step further and expand the already existing carbene investigation. Different electrophiles were contemplated, enabling the substrate to operate as a synthon for other investigations and/or production of other targets. Thus, in a broad sense, classical reactions such as bromination with elemental bromine, formylation using Vilsmeier Haak conditions and acetylation using aluminum trichloride, could serve this purpose and potentially give a better understanding of the two furoquinolinone core structures, **1.30** and **2.01**, in regards to chemical reactivity of the exocyclic double bond.

### 3.5.1 Bromination reactions on furan/substituted furans

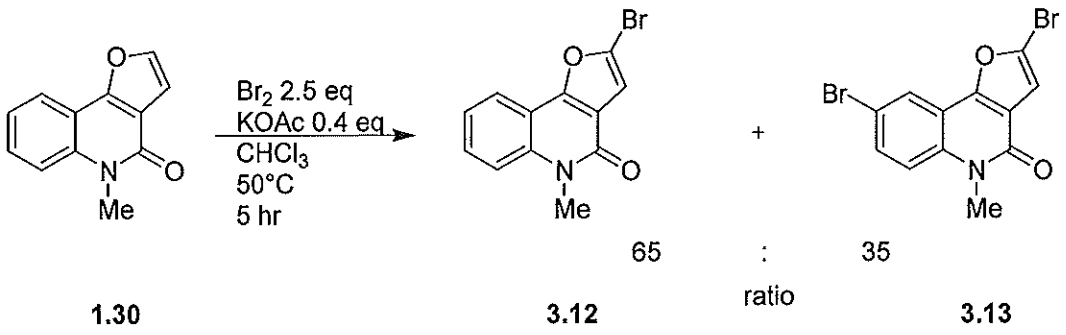
Available literature regarding bromination on furans/substituted furans is well established and comprises of several available methods.[148,189-192] Under electrophilic aromatic substitution conditions (EAS), simple furans are preferably brominated at C-2 over C-3, due to the resonance stabilised intermediate formed from the addition of the electrophile. In general, bromination of furans does not require lewis acids, however, procedures can interestingly be found utilising aluminium trichloride to facilitate the reaction with no apparent halogen scrambling.[192] Benzofurans have been subjected to typical bromination reaction conditions and showed the ability to be easily converted to the corresponding mono and *bis* halogenated forms,[190,191] as is shown in Scheme 3.13.




**Scheme 3.13**

### 3.5.2 Bromination reaction on substrate 1.30

Initial attempts to brominate the core structure **1.30** using the above described literature procedure[190,191] resulted in, after analysing the $^1$H NMR and mass spectral data, a mixture of two products, **3.12** and **3.13**, in a ratio of 65:35 respectively, as shown in Scheme 3.14.




**Scheme 3.14**

Thus, the reactivity was not only concentrated to the furan ring moiety in this case, but also in the benzene ring. However, these results were in agreement with regards to our previous calculations of the electron density of the structure **1.30.** Calculations, as depicted in Figure 3.10, suggested the highest electron density to be in the exocyclic double bond of the furan ring between the carbons C-2 and C-3, and to some minor degree in the actual benzene ring at carbons C-6 and C-8.

**Figure 3.10** Energy minimized structure of **1.30**[‡] (Spartan '04, V1.01, B3LYP/6-31G**). For clarity, the local ionization potential map has been adjusted to indicate only those regions most susceptible to electrophilic attack.

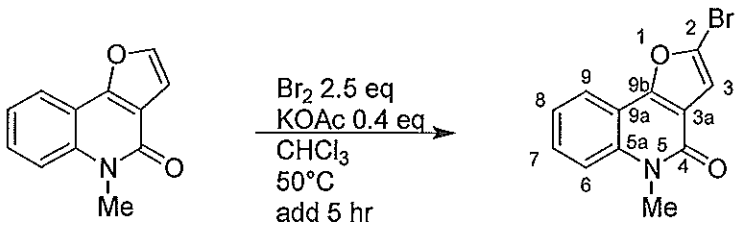
Hence, the outcome was in agreement with the calculated property for substrate **1.30**. Optimisation of this reaction with the aim to selectively afford a mono brominated product was desirable, and therefore changing the equivalents of bromine, base and time of addition of the bromine, was necessary, as shown in Table 3.8.

[‡] Calculation performed by Marc Campitelli, Research Fellow, Natural Product Discovery

| Entry | $Br_2$ | KOAc | Time add. | Tot. time | T | Product % |
|---|---|---|---|---|---|---|
| | eq | eq | h | h | °C | **3.12/3.13** |
| 1 | 2.5 | 0.25 | 0.1 | 15 | 50 | 65/35 |
| 2 | 1 | 0.25 | 0.1 | 24 | 50 | 60/40 |
| 3 | 0.5 | 0.25 | 5 | 5 | 50 | 95/5 |
| 4 | 0.5 | 0 | 5 | 5 | 50 | 100/0 |

**Table 3.8**

A negligible difference (entry 1 vs 2) in the ratio of **3.12** and **3.13** was observed when using 2.5 eq compared to 1 eq of bromine. Therefore the benzene moiety must be considered as being prone to undergoing reactions of this type quiet readily. When 0.5 eq of bromine were used with an addition over a period of 5 h, the base facilitated reaction still afforded **3.13**, even though it did so in low yields. By repeating the reaction but this time excluding base, the furan ring was exclusively and regio selectively mono brominated to give **3.12** in a yield of 94 %, as shown in Scheme 3.15.

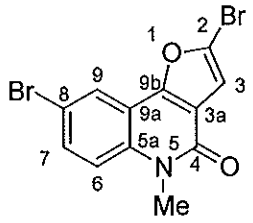



**1.30** **3.12**

**Scheme 3.15**

The $^{1}$H NMR spectrum of the isolated **3.12** product exhibited a proton signal at 7.00 ppm assigned to H-3, and a typical *ortho* substitution pattern of the benzene protons at 7.47, 7.59, 7.34 and 8.00 ppm assigned to protons H-6 to H-9 (as a doublet, triplet, triplet and a doublet, respectively). The $^{13}$C NMR spectrum exhibited signals at 125.8 and 110.2 ppm assigned to carbons C-2 and C-3, and signals at 115.3, 130.1, 122.8 and 121.3 ppm assigned to carbons C-6 to C-9, respectively. The ($^{1}$H and $^{13}$C) shift, and the HSQC spectrum for C-3, supported the bromination to have occurred at C-2. The mass spectrum, which showed a pseudo molecular ion peaks at *m/z* 278 and 280 (1:1), and a high resolution mass spectrum, further supported the proposed structure.

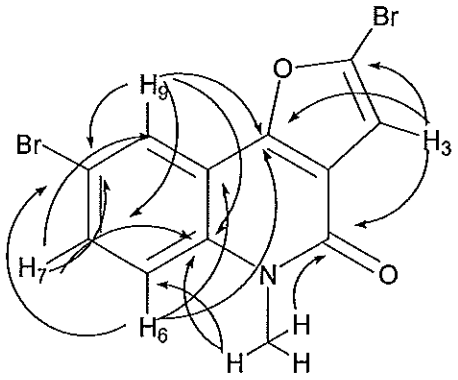
A pure sample of the *bis* brominated product **3.13** was afforded after reverse phase chromatography (HPLC).




**3.13**

The $^{1}$H NMR spectrum of the isolated *bis* brominated product **3.13** exhibited a proton signal at 7.01 ppm assigned to H-3. The benzene protons exhibited a complex splitting pattern and appeared as one doublet and two multiplets at 7.34, 7.66 and 8.12 ppm assigned to H-6, H-7 and H-9, respectively. The $^{13}$C NMR spectrum exhibited signals at 126.7 and 110.4 ppm assigned to carbons C-2 and C-3, and signals at 117.0, 132.8, 115.9 and 123.7 ppm assigned to carbons C-6 to C-9,

respectively. Analysis of the HMBC spectrum further confirmed the structure of **3.13** from $^{2}J$, $^{3}J$ and $^{4}J$ correlations observed from the protons H-3, NMe, H-6, H-7 and H-9, as shown in Table 3.9. The HMBC correlation of the NMe protons to C-6, the COSY correlation of H-6 to H-7, and $^{13}$C NMR shift of C-8 at 115.9 ppm, proposed the second bromination to have occurred at position C-8. The mass spectrum, which showed three pseudo molecular ion peaks at *m/z* 356, 358 and 360 (1:2:1), and elemental analysis, further supported the proposed structure.



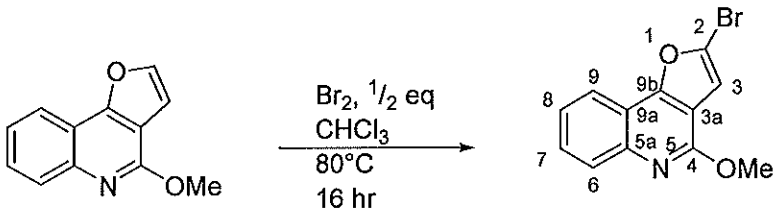

**3.13**

**Table 3.9.** $^{1}$H (500 MHz), $^{13}$C (125 MHz) and HMBC NMR data for **3.13**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 3 | 110.4 | 7.01 (s, 1H) | C-2, C-4, C-9b |
| 6 | 117.0 | 7.33 (d, *J* 8.8 Hz, 1H) | C-8, C-9a, C-9b |
| 7 | 132.8 | 7.66 (m, 1H) | C-5a, C-9, C-6 |
| 9 | 123.7 | 8.12 (m, 1H) | C-8, C-7, C-5a, C-9b |
| NMe | 29.9 | 3.77 (s, NMe) | C-4, C-5a, C-6 |

### 3.5.3 Bromination reaction on substrate 2.01

When the above optimised bromination conditions was used with substrate **2.01**, mostly starting material was recovered. Therefore, the temperature was raised to 80 °C and by monitoring the reaction with TLC, it was observed that all of the substrate was consumed after 16 h. After chromatography, the mono brominated product **3.14** could be isolated in a yield of 23 %, as shown in Scheme 3.16.




**2.01** **3.14**

**Scheme 3.16**

The $^1$H NMR spectrum of the mono brominated structure **3.14** exhibited as expected only one proton signal from the furan moiety at 6.89 ppm assigned to H-3. The benzene protons were slightly shifted upfield and remained exhibiting a typical *ortho* substitution pattern, as compared to its precursor. The mass spectrum, which showed two pseudo molecular ion peaks at *m/z* 278 and 280 (1:1 ratio), and a high resolution mass spectrum, further supported the structure.

Additionally, further elution in the above purification step gave a mixture of two other products. $^1$H NMR analysis of the mixture indicated two deprotected substrates in a ratio of 2:1 as shown in Figure 3.11. The major component indicated to be the secondary amide key intermediate **1.72**, and the minor component to be a C-2 brominated secondary amide key intermediate.

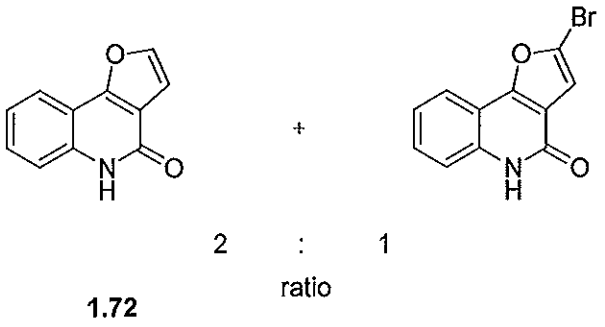



**Figure 3.11**

After several attempts at brominating the core structure **2.01** by altering time and temperature, no improved conditions were found which kept the methoxy protecting group intact.

### 3.5.4 Using other electrophilic reagents on 1.30 and 2.01

When treating substrate **1.30** under classical Vilsmeier Haak formylation conditions ($DMF/POCl_3$), low yields (30 %) of the desired product were observed and mostly starting material was recovered. When the same conditions were applied to substrate **2.01**, its precursor, the chloroquinoline derivative, was quantitatively isolated (100 %), as shown in Figure 3.12.

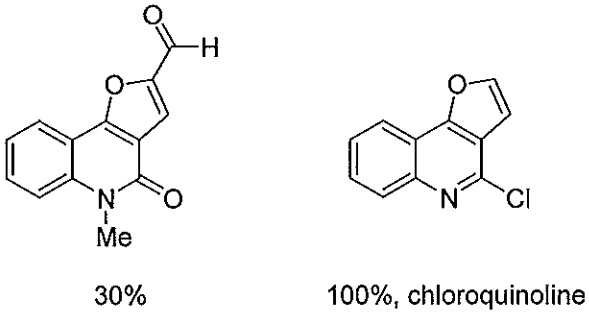



**Figure 3.12**

Poor conversions were observed when attempting acetylation reactions on substrate **1.30** under classical conditions, such as using acetyl chloride and aluminium trichloride, which gave a yield of the desired product below 15 %. Substrate **2.01** showed poor site selectivity under the acetylation conditions described, and its precursor was isolated (80 %) as similar to when treated under the Vilsmeier Haak formylation conditions.

## 3.6 Summary of Chapter 3

Out of all the reagents tested on substrate **1.30**, the best reactivity was shown in the bromination reaction when using elemental bromine as the reagent, giving a 94 % yield of product **3.12**, with exclusive regio selectivity after optimisation of the reaction conditions. However, not only the furan ring was reactive, but also the benzene ring was prone to bromination when using conditions adopted from literature procedures,[190,191] giving a mixture of **3.12** and **3.13**. Substrate **1.30** exhibited high reactivity towards the diazo reagents chosen (except for 2-diazopropane), with total consumption of starting material when using dimethyl diazomalonate, giving two interesting novel products **3.03** and **3.04** where the first structure was confirmed by X-ray crystallography. No cyclopropanated material was found when using dimethyl diazomalonate. However, when employing ethyl 2-diazopropanoate as the carbene precursor, an isolated yield of 43 % of the desired cyclopropanated product **3.01** was afforded, and can therefore be subjected to group manipulation to furnish the *gem* dimethyl functionality. When treating **1.30** with other electrophiles i.e., formylation and acetylation reagents, only low conversions to the desired products were observed.

Out of all the reagents tested, substrate **2.01** showed the highest reactivity towards diazo reagents (again with exception for 2-diazopropane), where total consumption of starting material was observed using either ethyl 2-diazopropanoate or dimethyl diazomalonate. When using ethyl 2-diazopropanoate as the electrophile, the desired cyclpropanated product **3.02** was isolated in a 69 % yield. Using dimethyl diazomalonate as the carbene precursor gave, to some extent surprisingly, a pyrano type product **3.05** in a 38 % yield, the structure of which was later confirmed by X-ray crystallography. When treating **2.01** with other electrophiles i.e., with classical formylation and acetylation reagents, high conversions back to the precursor, the chloroquinoline derivative, were observed in most cases. The mono brominated product **3.14** was synthesised and isolated after treatment with elemental bromine, but however, was only afforded in low yields.

In the first approach to make the third key intermediate **3.08**, low yields and poor reproducibility of the desired product was observed. Reasons for this can only be speculative but obviously had to do with the C-3 linked ester functionality. The second synthetic strategy to give **3.11** also showed to be low yielding. That, together with lack of selectivity in the methylation step to achieve **3.08**, led to discontinuation of the attempts to synthesise the third desired key ester intermediate **3.08** as a whole.

These results concluded the investigation of the two substrates **1.30** and **2.01**. It has been demonstrated that the area of the highest reactivity of key intermediates, **1.30** and **2.01**, is localised around the exocyclic double bond of the furan ring in both substrates. An additional site of reactivity of substrate **1.30**, was seen in the

benzene region to a minor degree, and for substrate **2.01**, in the methoxy protecting group site to a high degree.

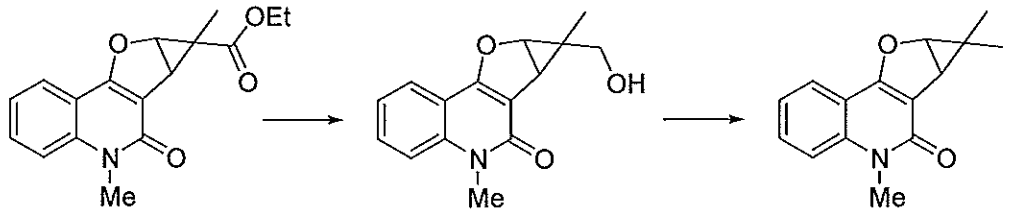
Most importantly, the cyclopropane ring moiety was successfully installed in both substrates (**1.30** and **2.01**) when using ethyl 2-diazopropanoate as the carbene precursor. Substrate **2.01** not only showed its high propensity to react and to install a cyclopropane ring, but also the ease of which the protecting group, OMe, was quantitatively removed under the described formylation (100 %) and acetylation (80 %) conditions to its corresponding haloquinoline precursor. Undoubtly, this can be of value at a later stage when the *gem* dimethyl functionality is installed.

# Chapter 4

## The cyclopropane ring with a gem dimethyl functionality

### 4.1 Synthetic strategy of installing the carbon frame work of the natural product 1.01

Having made the cyclopropane **3.01** by insertion of the generated carbene from ethyl 2-diazopropanoate into the exocyclic double bond of the furan ring in Chapter three, it was envisaged the ester functionality then could be reduced to the corresponding neopentyl alcohol **4.01**, and then deoxygenated to form the *gem* dimethyl functionality **4.02**, as shown in Scheme 4.1.

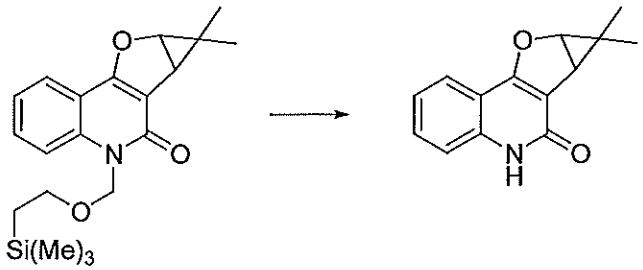



**3.01** **4.01** **4.02**

**Scheme 4.1**

Once the synthesis of the carbon frame work of the natural product is optimised by using the *N*-methyl derivative as a model case, the *N*-SEM protected derivative **4.03** could then provide access to the natural compound. Thus, the very last step

after installation of the *gem* dimethyl functionality would be to deprotect **4.03** to yield the natural product **1.01**, as shown in Scheme 4.2.

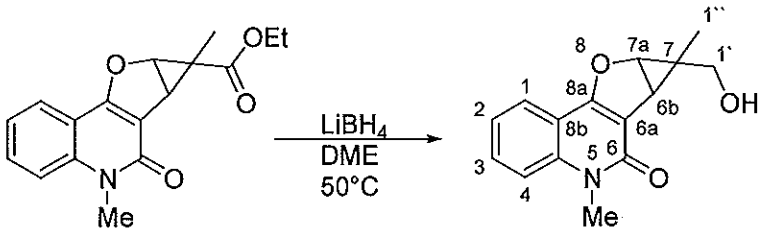



**4.03** **1.01**

**Scheme 4.2**

## 4.2 Reduction of the 3.01 ester to the alcohol

Literature procedures for reduction of cyclopropane esters have employed either sodium borohydride or DIBALH as the reducing reagent.[193,194] Adopting the first method on to substrate **3.01** resulted in tedious reaction times and low conversions to the desired product. However, when the more reactive reducing reagent lithium borohydride was employed in a six molar excess in dimethoxyethane with heating to 50 °C, the desired product **4.01** was afforded in a 93 % yield (Scheme 4.3).




**3.01** **4.01**

**Scheme 4.3**

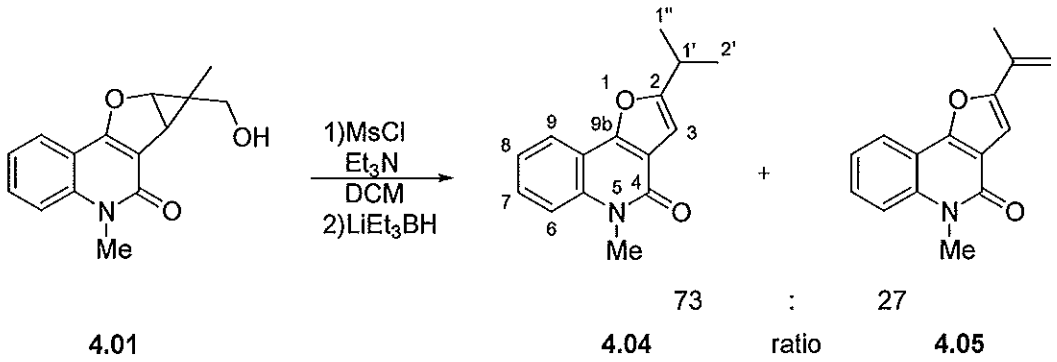
The $^{1}H$ and $^{13}C$ NMR spectrum of the neopentyl alcohol **4.01** exhibited a new methylene proton peak as a singlet at 3.59 ppm assigned to H-1` and its corresponding carbon C-1` at 67.4 ppm, respectively. The two furan protons H-7a and H-6b appeared slightly shifted upfield at 4.83 and 2.93 ppm respectively, and the corresponding carbons C-7a and C-6b at 71.6 and 28.8 ppm, respectively. The benzene protons exhibited a typical *ortho* substitution pattern and similar proton and carbon shifts to the precursor **3.01**. The absence of the ethyl ester moiety and the high resolution mass spectrum, further supported the proposed structure. All the proton and carbon shifts were assigned by analysis of correlations observed in the HMBC spectrum. The upfield shift of protons H-6b and H-7a in **4.01** relative to **3.01**, suggested that the methyl alcohol was on the same face as these protons, as the deshielding effect decreased due to reducing the ester to the corresponding alcohol functionality. Thus, the shift change observed of the pertinent protons (H-6b and H-7a) proposed the *exo* isomer was the diastereoisomer that was exclusively formed in the cyclopropanation reaction of substrate **1.30** with ethyl 2-diazopropanoate. Additionally, there were no signs of ring opened cyclopropane product.

## 4.3 Deoxygenation of the neopentyl alcohol 4.01

The next step in the synthesis of the natural product was to deoxygenate the neopentyl alcohol **4.01** to form the *gem* dimethyl functionality required for the natural product. In reviewing the literature regarding dehydroxylation reactions of alcohols, it was envisaged the alcohol functionality of **4.01** could be reduced by either first mesylation followed by *in situ* reduction,[194] or via direct methods.[195-205]

### 4.3.1 Mesylation of 4.01

A related example was found in the literature where a neopentyl alcohol off a cyclopropane ring functionality, was reduced to form the corresponding methyl.[194] It was first mesylated and then treated with a hydride source (superhydride) to reduce the, *in situ* formed, leaving group to afford the desired methyl group. Attempts to reduce the mesylated alcohol derivative (*in situ* formed), after treatment of **4.01** with mesyl chloride in DCM in the presence of triethylamine, by using superhydride ($LiEt_3BH$) as the reducing agent gave two products, **4.04** and **4.05**. The 2`,3`-saturated isomer **4.04** was the major component, and the 2,3-unsaturated isomer[206] of the natural product almeine[21] **4.05**, was the minor component, in a ratio of 73:27 respectively (Scheme 4.4).

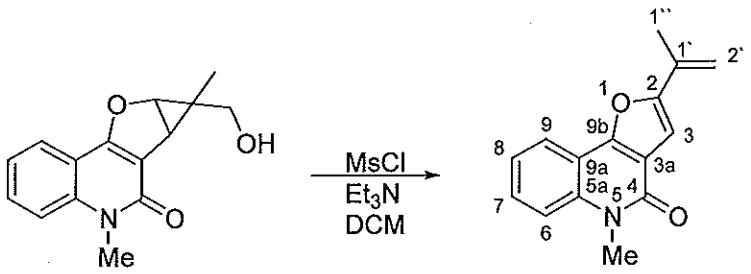



**Scheme 4.4**

The $^1H$ NMR spectrum of the 2`,3`-hydrated isomer **4.04** exhibited a six proton doublet at 1.39 ppm ($J = 4.0$ Hz) assigned to the two methyl groups on carbons C-2` and C-1``, and the furan proton at C-3 resonated as a singlet at 6.67 ppm. Another characteristic feature was a broad septet at 3.14 ppm assigned to proton H-1`. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 242,

supported the proposed structure which is in agreement with reported the data for compound **4.04**.[206-208]

To deduce whether the hydride source, or the generated mesylate derivative itself, was inducing the ring opening of the cyclopropane ring functionality, isolation of the mesylated intermediate was therefore required. Attempts to make and isolate the mesylate[194] resulted in exclusive formation of **4.05** in an 86 % yield (Scheme 4.5).




**4.01** **4.05**

**Scheme 4.5**

The $^{1}$H NMR spectrum of the rearrangement product **4.05** exhibited a new methyl peak at 2.14 ppm assigned to H-1``, and the two methylene protons which resonated at 5.19 and 5.80 ppm corresponding to H-2a` and H-2b`, respectively. The H-3 proton resonated at 6.92 ppm which is in agreement with expected values. The $^{13}$C NMR spectrum indicated that the C-2 and C-3 appeared at 156.7 and 104.5 ppm respectively. Carbons C-2`, C-1` and C-1`` resonated at 112.9, 133.3 and 19.5 ppm respectively. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 240, and analysis of the 2D NMR spectra obtained (Table 4.1), supported the proposed structure and was in agreement with reported data.[206]

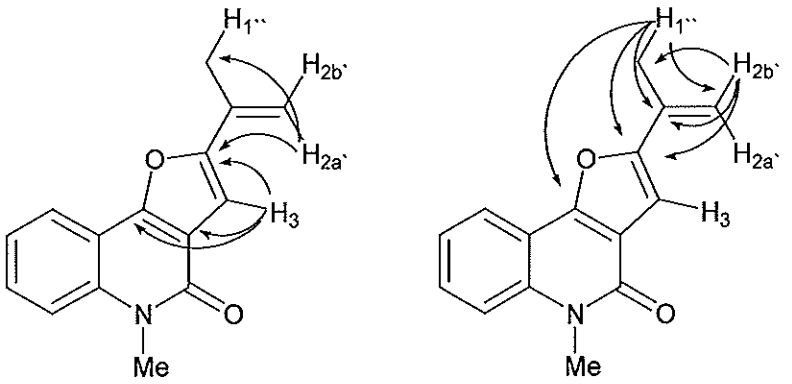



**Table 4.1** $^{1}H$ (400 MHz), $^{13}C$ (100 MHz) and HMBC NMR data for **4.05**

| Position | $^{13}C$ | $^{1}H$ (mult., *J*, int) | HMBC |
|---|---|---|---|
| 3 | 104.5 | 6.92 (s, 1H) | C-3a, C-9b, C-2 |
| 2a` | 112.9 | 5.20 (s, 1H) | C-1``, C-2 |
| 2b` | 112.9 | 5.80 (s, 1H) | C-1``, C-2, C-1` |
| 1`` | 19.5 | 2.14 (s, 3H) | C-2`, C-1`, C-9b, C-2 |

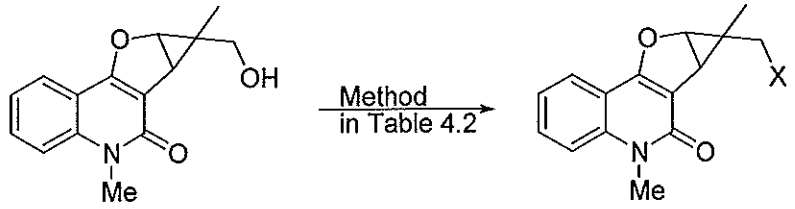
The method of using mesyl chloride and a hydride source, such as superhydride, in a one pot procedure, gave the ring-opened products **4.04** and **4.05** with no indication of the desired product. In attempts to isolate the mesylated alcohol intermediate, the ring-opened product **4.05** was exclusively formed, and thus, the hydride source could not be the sole reason for the ring opened products in the one pot procedure.

### 4.3.2 Halogenation of 4.01

The lack of success from the mesylation/reduction approach led us to focus on halogenating the neopentyl alcohol **4.01**. It was envisaged that if a halogenated compound was synthesised and isolated, it could then be reduced to the

corresponding methyl functionality. A range of available literature procedures were adopted and tried as shown in Table 4.2.

**Halogenation**




**4.01**

X=Cl, Br or I

| Method | Reagent |
|---|---|
| sulphur | $SOCl_2$[209] |
| phosphorus | $PBr_3$[210,211] $POCl_3$[212-214] |
| | $PCl_3$[215] DMPADC[216] |
| phosphine | $PPh_3$ and $CCl_4$[217-220] or $CBr_4$[221] |
| phosphite | $(PhO)_3P^+I^-Me$[222] |
| silicon | $(CH_3)_3SiCl$,[223] $(CH_3)_3SiI$[224,225] |
| | $PdCl_2$/ $(Et_3)_3SiH$[205] |
| succinimide | NCS[226] |

**Table 4.2**

Methods using sulphur or phosphorus reagents such as thionylchloride,[209] phosphorus oxychloride,[212-214] and *N*,*N*-dimethylphosphoramidic dichloride[216] (DMPADC) failed to indicate the presence of the desired product when the crude mixtures were analysed by mass spectrometry. Mostly starting material **4.01** was recovered together with minor amounts of the rearrangement product **4.05**. However, when employing phosphorous tribromide[210,211] at low temperatures (-40 °C or lower) using diethyl ether as solvent, a typical doublet (1:1 ratio) was

observed in the mass spectrum obtained from the reaction mixture. Even so, after chromatography only rearrangement product **4.05** was isolated in a 96 % yield (see experimental section method B). Methods including triphenylphosphine[217-220] as the activating reagent in neat carbon tetrachloride or carbon tetrabromide,[221] only afforded starting material. However, if heat was applied together with use of THF or acetonitrile as solvent and an excess of carbon tetrachloride, minor amounts of the rearrangement product **4.05** were observed when crude mixtures were analysed by $^{1}$H NMR spectroscopy. When using phosphite based reagents such as triphenylphosphite methiodide,[222] which has been shown to be useful for when halogenating neopentyl alcohols,[222] no product other than starting material **4.01** could be detected. When trimethylsilyl iodide[224,225] was used, a mixture of **4.05** and **4.04** was observed when analysed by $^{1}$H NMR spectroscopy. Other methods including silicon based reagents such as trimethylsilyl chloride[223] and triethylsilane/palladium chloride[205] using either DCM or diethyl ether as solvent, afforded no other products than starting material **4.01** when the crude mixtures were analysed by $^{1}$H NMR spectroscopy.

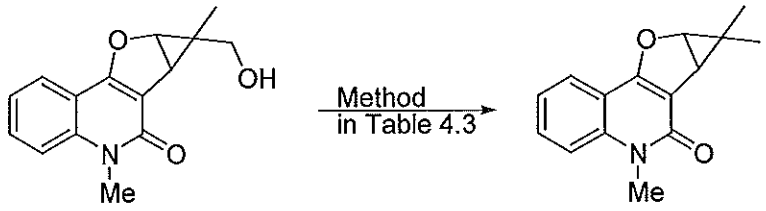
Conclusively, the desired halogenated product could not be synthesised via these procedures, but was nevertheless detected in some of the crude reaction mixtures when analysed by mass spectrometry. When isolation was attempted by flash chromatography only mixtures of starting material **4.01** and rearrangement product **4.05** were isolated. Either the detected halogenated product is too unstable, or, the reactions are too low yielding to be measured quantitatively. As there was some evidence of the halide being formed *in situ*, this prompted us to investigate the possibility of reducing the halogenated intermediate on formation via addition of a

hydride source. The previously conducted reactions involving phosphorous tribromide,[210,211] phosphine based reagents[217-221] and trimethylsilyl iodide[224,225] in Table 1, were therefore repeated with addition of a hydride source, such as super hydride ($LiEt_3BH$). However, the desired product was not obtained, and mixtures of starting material **4.01** and the rearrangement product **4.05** were recovered in most cases.

### 4.3.3 Direct reduction of 4.01

Attention was then focused on literature methods involving direct reduction of alcohols, or, activated alcohols with phosphorus based reagents, as shown in Table 4.3.

**Direct reduction**




**4.01** **4.02**

| Method | Reagent |
|---|---|
| silicon | $PdCl_2$/ $(Et_3)_3SiH$,[205]<br>$(Et_3)_3SiH$/TFA[204]<br>$(Ph)_2SiHCl/InCl_3$[203] |
| phosphite | $(PhO)_3P^+I^-Me$<br>$NaBH_3MeCN$[202] $PCl_3$[215] |
| Mitsunobu | $PPh_3$/DIAD/hydride[201] |
| Hendrickson | $PPh_3/Tf_2O$/hydride[200] |
| phosphorous | DMPADC[216]<br>TMPDA/Li/Naph.[195-199] |

**Table 4.3**

Methods including silicon based reagents such as, triethylsilane/palladium chloride,[205] triethylsilane/trifluoroacetic acid[204] and chlorodiphenyl silane/indium trichloride,[203] have previously been used for deoxygenations on similar alcohols to **4.01**. The method usinig triphenylphosphite methiodide together with a hydride source, in particular $NaBH_3MeCN$, has previously been used by Ishihara *et al.*,[202] in the course of deoxygenation of a neopentyl alcohol. Adopting these procedures to substrate **4.01** resulted in mixtures of rearrangement product **4.05** and starting material. Other methods to displace the alcohol **4.05** include Mitsunobu reaction which involves pre-activation by the use of triphenylphosphine together with DIAD, followed by addition of a suitable nucleophile. Even though it is known that direct reductions of alcohols are not observed[200] when employing classical mitsunobu conditions,[227] when the neopentyl system **4.01** was treated with triphenylphosphine, DIAD and $LiEt_3BH$ as the hydride source (instead of using an acid or sulphide as the nucleophile), no reaction occurred and starting material was recovered. This was not surprising. Conversely, it has been shown that alcohols can be deoxygenated via direct reduction by performing the closely related Hendrickson reaction,[200] which involves the use of triphenylphosphine together with $Tf_2O$ (to *in situ* generate the phosphonium anhydride reagent, POP) and a hydride source (such as $NaBH_4$). When employing these conditions with the neopentyl alcohol **4.01**, surprisingly, nothing but starting material **4.01** was recovered. It has been shown by others that phosphordiamidate type derivatives of neopentyl alcohols (*N*,*N*,*N*`,*N*`-tetramethylphosphordiamidate) can be deoxygenated in high yields under alkaline reductive conditions.[195-199] Thus, the phosphordiamidate derivative of this neopentyl system **4.01** was synthesised, however, as it proved to be unstable it had to be used immediately for reduction.

After several attempts at treating the phosphordiamidate derivative under reductive conditions (lithium and naphthalenide in THF),[195-199,216] only starting material **4.01** and rearrangement product **4.05** were observed.

### 4.3.4 Deoxygenation via Barton McCombie reduction

As the routes for installing the *gem* dimethyl functionality via mesylates, halogenation or by direct methods, were unsuccessful, the well known radical Barton McCombie deoxygenation of alcohols[228] was then contemplated. While it was noted that Barton McCombie type deoxygenation reactions on cyclopropane derivatives have previously been reported[229,230] with minor success, it was still considered worth the attempt. This reaction involves first the transformation of the alcohol to a corresponding *O*-alkyl thiocarbonyl derivative (various derivatives[231] can be made) which is then treated with a trialkyl tin hydride source to furnish the desired product in a radical fashion. In this case, the neopentyl alcohol **4.01** was converted to a xanthate ester,[232] by first *O*-alkylation with carbon disulfide followed by methylation with methyl iodide. This derivative was then used for the deoxygenation reaction by using tributyltin hydride, as the hydride source. However, no desired product was observed in any of the attempts, and mixtures of starting material **4.01** and the rearrangement product **4.05** were obtained.

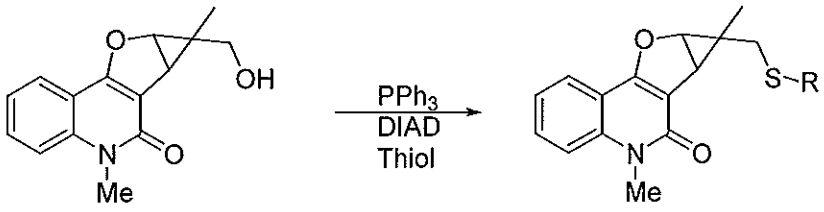
All together, these results demonstrated the difficulties encountered to reduce the neopentyl alcohol **4.01** via mesylation, halogenation, direct reduction or Barton McCombie type deoxygenation of **4.01**, and any further investigations using these methods were abandoned.

## 4.4 Mitsunobu displacement of the neopentyl alcohol

### 4.4.1 Using thioacetic acid

It became of interest to see if there was any possibility to alter **4.01** without rearrangement occurring. Mitsunobu type displacement[227] of the alcohol functionality of **4.01** with thioacetic acid[233] as nucleophile, was then attempted due to the use of mild reaction conditions (Scheme 4.6).

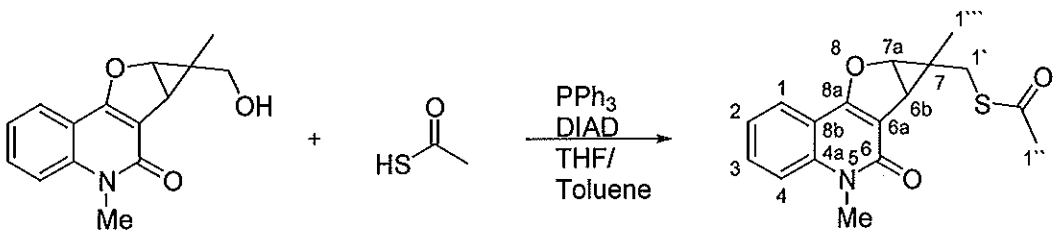
**Mitsunobu displacement**




**4.01**

**Scheme 4.6**

If the displacement was found to be successful, then there could be a possibility to cleave the sulphur ether bond to give the desired *gem* dimethyl under metal type reduction conditions.[233] To a pre-mixed solution of triphenylphosphine and DIAD (diisopropylazodicarboxylate) at -15 °C in toluene, was added a homogeneous solution of **4.01** and thioacetic acid in THF and toluene (1:1). The reaction mixture was allowed to warm up to RT and after 2 days stirring, the desired product **4.06** was isolated in a yield of 74 % (Scheme 4.7).




**4.01** **4.06**

**Scheme 4.7**

The $^{1}$H NMR spectrum of the thioester derivative **4.06** exhibited one new signal at 2.41 ppm assigned to the methyl protons at carbon C-1``. The methylene protons at carbon C-1` which resonated at (2.85 and 3.09 ppm, $J$ = 14.2 Hz) were assigned to H-1a` and H-1b`, and protons at (2.93 and 4.76 ppm, $J$ = 6.0 Hz) were assigned to H-6b and H-7a, where both set of pairs of protons were all shifted upfield as compared to **4.01**. In the $^{13}$C NMR spectrum, the C-1` and C-1`` resonated at 36.5 and 30.8 ppm and the thio ester carbonyl carbon at 195.7 ppm. The other proton and carbon signals were similar to **4.01**. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 316, and analysis of the 2D NMR spectra (Table 4.4), supported the proposed structure.

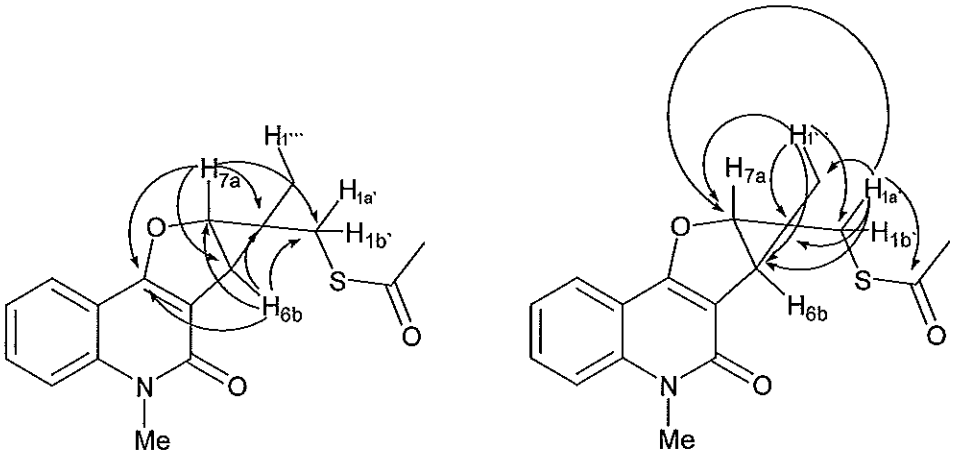


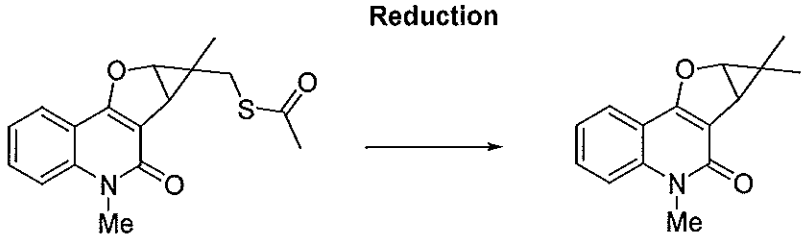

**Table 4.4** $^{1}$H (400 MHz), $^{13}$C (100 MHz) and HMBC NMR data for **4.06**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 6b | 32.1 | 2.93 (d, *J* 6.0 Hz, 1H) | C-1`, C-7, C-7a, C-8a |
| 7a | 72.6 | 4.76 (d, *J* 6.0 Hz, 1H) | C-1`, C-7, C-6b, C-8a |
| 1``` | 10.3 | 0.80 (s, 3H) | C-1`, C-7, C-7a, C-6b, |
| 1a` | 36.5 | 2.85 (d, *J* 14.2 Hz, 1H) | C-1```, C-7, C-7a, C-6b, S-C=O |
| 1b` | 36.5 | 3.09 (d, *J* 14.2 Hz, 1H) | C-1```, C-7, C-7a, C-6b, S-C=O |

**Table 4.4**

### 4.4.1.1 Reduction of the thioacetic acid derivative

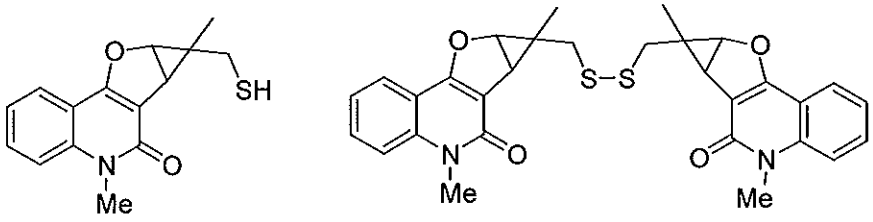
With the thioacetic acid derivative **4.06** in hand, it was envisaged that the sulphur ether bond could be reductively cleaved[233,234] to furnish the *gem* dimethyl functionality using known literature methods,[195-199,233,234] as shown in Scheme 4.8.




**4.06** **4.02**

**Scheme 4.8**

Employing methods using either Raney/Ni,[233] $LiAlH_4/CuCl_2/ZnCl_2$,[234] $Li/NH_3$[235] or Li/naphthalenide [195-199] with thioacetic acid derivative **4.06**, gave complex mixtures. The known rearrangement products, **4.04** and **4.05**, were detected in the crude mixtures by mass spectral and $^1H$ NMR spectroscopic analysis. The thiol **4.07**, resulting from reductive cleavage of the acetyl group, together with the disulfide **4.08**, were detected by analysis of the $^1H$ NMR spectrum and mass spectral data.

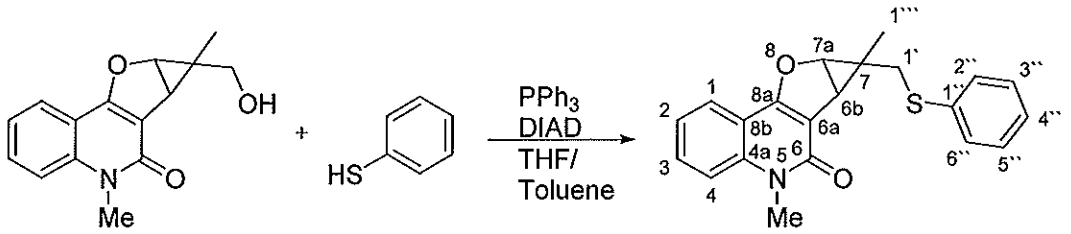



**4.07** **4.08**

Even though the attempts at reductive cleavage of the thioacetic acid derivative did not give the desired product, intact cyclopropane ring products **4.07** and **4.08** were indicated and this therefore suggested that other thio derivatives may be more successful.

### 4.4.2 Using thiobenzene

By introducing a bulky substituent, such as thiobenzene, it was hoped that sterically induced cleavage on the other side of the sulphur atom, could be obtained. Repeating the Mitsunobu reaction as described above using thio benzene as the nucleophile, gave the desired thiobenzene derivative **4.09** in an isolated yield of 65 % (Scheme 4.9).




**4.02** **4.09**

**Scheme 4.9**

The $^{1}$H NMR spectrum of the thiobenzene derivative **4.09**, exhibited signals of the methylene protons as two doublets ($J$ = 13.2 Hz) at 2.73 and 3.27 ppm assigned to H-1a` and H-1b`, respectively. The thiobenzene protons resonated at 7.44, 7.32 and 7.23 ppm assigned to protons (H-2`` and H-6``), (H-3`` and H-5``) and H-4``, respectively. In the $^{13}$C NMR spectrum the methylene carbon C-1` resonated at 42.9 ppm together with the thiobenzene carbons at 136.7, 130.6, 129.3 and 126.8 ppm assigned to C-1``, C-2``, C-3``, and C-4``, respectively. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 350, and analysis of the 2D NMR spectra (Table 4.5), supported the proposed structure.

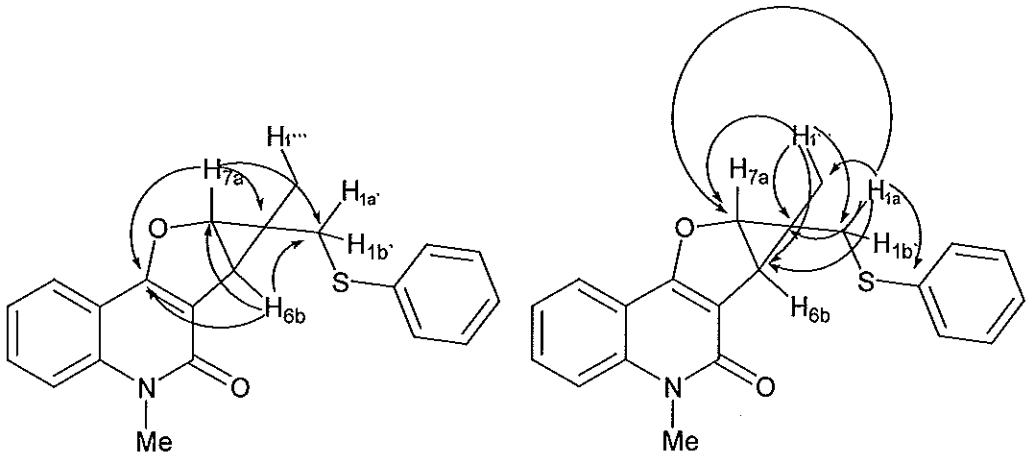



**Table 4.5** $^{1}$H (400 MHz), $^{13}$C (100 MHz) and HMBC NMR data for **4.09**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 6b | 31.7 | 3.50 (d, *J* 6.0 Hz, 1H) | C-1`, C-7a, C-8a |
| 7a | 72.5 | 5.18 (d, *J* 6.0 Hz, 1H) | C-1`, C-7, C-8a |
| 1``` | 10.3 | 0.93 (s, 3H) | C-7, C-6b, C-1`, C-7a |
| 1a` | 42.9 | 2.73 (d, *J* 13.2 Hz, 1H) | C-1```, C-7, C-6b, C-7a, C-1`` |
| 1b` | 42.9 | 3.27 (d, *J* 13.2 Hz, 1H) | C-1```, C-7, C-6b, C-7a, C-1`` |

This structure was further determined by X-ray crystallography to be in the *exo* configuration of the two possible diastereoisomeric forms, as shown in Figure 4.1. This confirmed the proposed stereochemistry from the NMR analysis regarding shift changes for protons H-6b and H-7a. The lack of the ester functionality in the neopentyl alcohol **4.01** is noted by the upfield shift of protons H-6b and H-7a as compared to **3.01**, thus implying the ester group was on the same side as the protons.

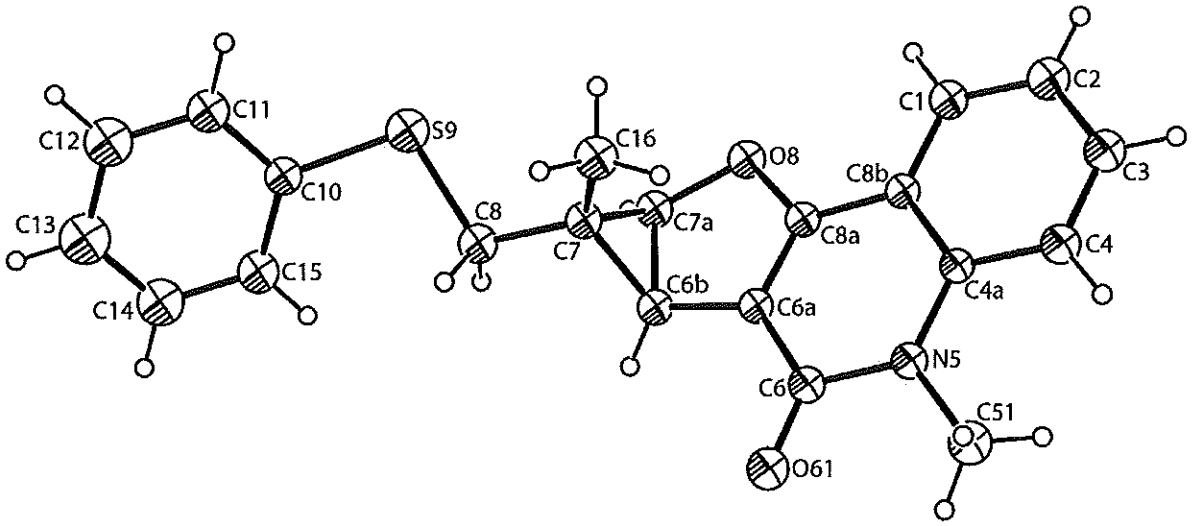



**Figure 4.1** ORTEP plot of product **4.09**, (30 % ellipsoids are shown)

### 4.4.4 Reduction of the thiobenzene derivative

Attempts at reductive cleavage of the thiobenzene **4.09** derivative using conditions employed for thioester **4.06**, resulted in complex mixtures of products. However, the desired product was not observed after analysis of the crude mixtures by either $^{1}$H NMR spectroscopic or mass spectral methods, and this approach was abandoned.

### 4.4.5 Summary of the Mitsunobu derivatives and the reductive cleavage attempts

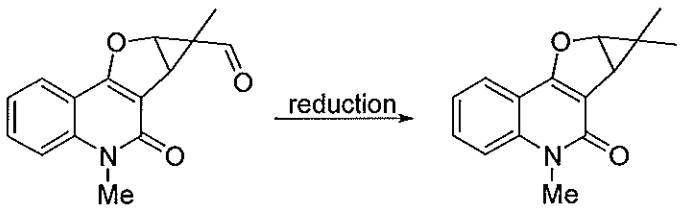
The alcohol **4.01** could be displaced under mitsunobu conditions to give high yields of the desired products **4.06** and **4.09** when using either thioacetic acid or thiobenzene as nucleophile without obtaining rearrangement products. When attempting reductive cleavage of the thioacetic acid derivative, complex mixtures were obtained. Minor products such as **4.07** and **4.08**, together with the

rearrangement products **4.04** and **4.05**, could be detected. Due to the cyclopropane ring in the thioester remaining intact during reduction, the more bulky thiobenzene derivative **4.09** was synthesised. It was hoped that a bulky benzene moiety would induce a cleavage of the C-S bond on the other side to that observed for the thioacetic acid derivative. However, only complex mixtures were obtained when attempting reductive cleavage. The stereochemistry of the thiobenzene derivative **4.09** was determined to be in the *exo* configuration by X-ray crystallography. Thus the installation of the cyclopropane ring system via reaction of ethyl 2-diazopropanoate with substrate **1.30**, gave exclusively the *exo* isomer of **3.01** as the product.

Thus, it has been shown that the furoquinolinone based neopentyl alcohol **4.01** is not easily converted to the corresponding *gem* dimethyl derivative via these methods. Therefore, in order to obtain the desired product, other strategies were considered.

## 4.5 Oxidation of the neopentyl alcohol 4.01 to the aldehyde

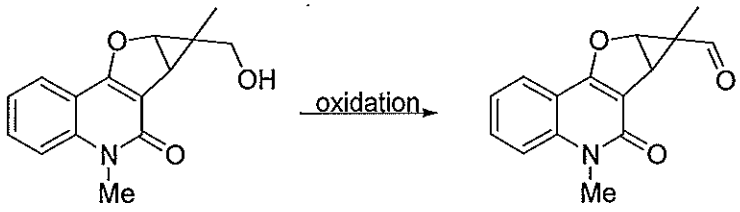
It was envisaged that an aldehyde in place of the alcohol moiety in **4.01**, may be reduced directly to afford the *gem* dimethyl functionality, as shown in Scheme 4.10.




**4.10** **4.02**

**Scheme 4.10**

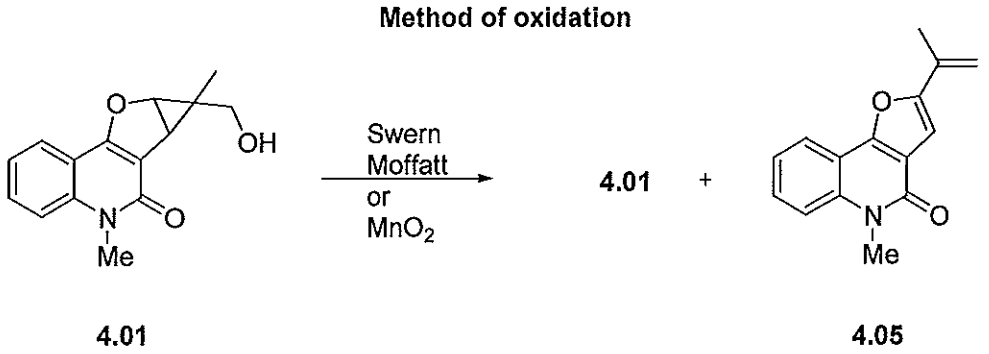
The neopentyl alcohol **4.01** could be oxidised to afford the corresponding aldehyde **4.10**, as shown in Scheme 4.11.




**4.01** **4.10**

**Scheme 4.11**

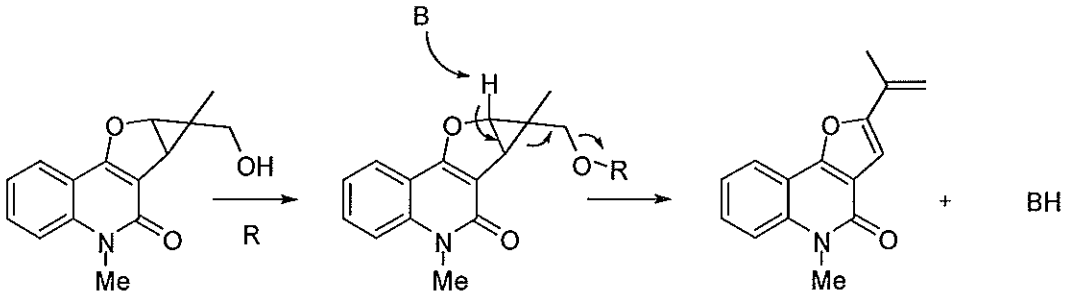
Methods such as that described by Swern,[236,237] Moffatt,[238,239] and the use of the reagent manganese oxide,[240,241] are known to selectively oxidise alcohols to the corresponding aldehyde or ketone, in the presence of other functional groups, under mild conditions. In the first two methods, the oxidative step is based on activation of the reagent DMSO at low temperatures. Typically, the activating reagent for Swern oxidations is oxalyl chloride, and DCC for Moffatt oxidations. Both procedures involve a relatively mild base, such as pyridine, to catalyse the reaction. However, after treatment of the neopentyl alcohol **4.01**, with any of the three methods just described, only the rearrangement product **4.05** was detected together with starting material **4.01**, as shown in Scheme 4.12.




**4.01** **4.05**

**Scheme 4.12**

It was believed that the cyclopropane ring opening was base facilitated when forming a good leaving group, GL, of the neopentyl alcohol functionality, and a mechanistic rationale was suggested as shown in Scheme 4.13.




O-R = GL e.g. mesylate etc

**Scheme 4.13**

To determine whether the addition of base was causing the rearrangement, a method that was not base promoted was required. The use of a Dess-Martin periodinane reagent[242-244] (DMP) was contemplated to circumvent the possibility of side reactions such as ring opening to occur. However, treatment of the alcohol **4.01** with the DMP reagent returned starting material together with a complex mixture. Several attempts at varying reaction conditions i.e., temperature,

concentrations of substrate and various loadings of the DMP reagent, were conducted but no indication of the desired product with the cyclopropane ring intact was observed.

## 4.6 Summary of Chapter 4

All the attempts to deoxygenate the alcohol **4.01** including halogenation, halogenation with *in situ* reduction, direct reduction using literature methods, displacing the alcohol under Mitsunobu conditions with thiols as nucleophiles and then reductive cleavage, and finally, oxidation of the alcohol **4.01** to the corresponding aldehyde, gave mostly starting material **4.01**, and ring opened products. Two isomers of the natural product almeine[21] **4.05** and **4.04** were isolated, and most commonly they were detected as minor by-products. However, in attempts to isolate the mesylated alcohol, or, the halogenated alcohol after treatment with phosphorous tribromide, high yields of the rearrangement product **4.05** were observed. Also, attempts at *in situ* deoxygenation of the mesylated alcohol, afforded the rearrangement product **4.04** as the major component. Displacing the alcohol moiety in **4.01** under Mitsunobu conditions with thiols, gave surprisingly high yields of the thio-derivatives **4.06** and **4.09**, where the stereochemistry of the cyclopropane ring was determined to be in the *exo* configuration due to obtained X-ray data from product **4.09**. Thus, the cyclopropanation reaction of ethyl 2-diazopropanoate with substrate **1.30** was exclusively giving the *exo* diastereoisomer of **4.01**. However, in attempts to reductively cleave the two thio-derivatives **4.06** and **4.09**, no desired product was observed. Finally, in attempts to oxidise **4.01** by using various reagents gave, in

one case, indication of a furan ring opened product, but mostly mixtures of starting material **4.01** and rearrangement product **4.05** were observed.

Attempts on the *O*-methyl derivative **2.01** were discounted, based upon its relative lack of stability in the presence of the reagents used as shown in Chapter 3. The *N*-SEM protected material **2.02** was not trialled as the electronic properties compared to the *N*-methyl derivative **1.30** were considered to be similar.

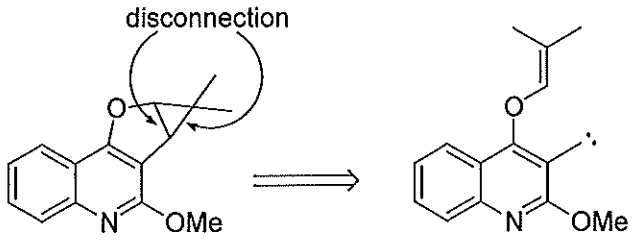
The propensity of the cyclopropane ring of the alcohol intermediate **4.01** to ring open has been demonstrated and, unfortunately, no method was found to circumvent the problem. This difficulty prompted us to elaborate on a new synthetic strategy to achieve the natural product, and this will be discussed in Chapter 5.

# Chapter 5

## Second approach of synthesising the natural product 1.01

### 5.1 New synthetic strategy of the natural product

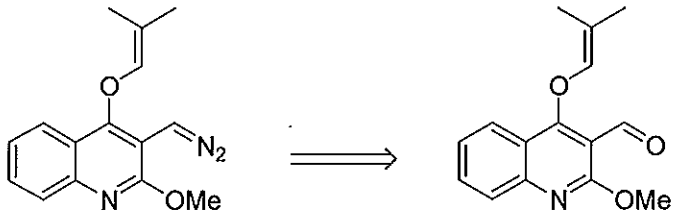
After experiencing the propensity of the cyclopropane ring to rearrange and give analogues of the already known natural product almeine,[21] a new synthetic strategy was developed. From a retrosynthetic point of view, disconnection of two bonds in **5.01** gives a vinyl ether with a tethered carbene precursor, as shown in Scheme 5.1.




**5.01**

**Scheme 5.1**

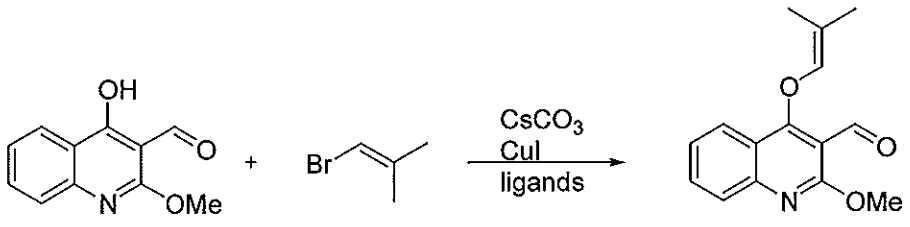
The retrosynthetic analysis depicted in Scheme 5.1 is novel in terms of performing an intramolecular tandem cyclisation/cyclopropanation reaction where a furan ring and a cyclopropane ring is formed. In this case, the carbene precursor of **5.02** in the C-3 position, could be generated from a corresponding aldehyde[245-247] **5.03**, as shown in Scheme 5.2.




**5.02** **5.03**

**Scheme 5.2**

Syntheses of vinyl ethers from alcohols have been reported in literature using various methods.[248-258] In narrowing the search for the synthesis of vinyl ethers from phenols, one protocol in particular, reported by Ma *et al.*,[148] became of interest. This method is an extended version of a copper iodide catalysed Ullmann type coupling, which promotes C-O bond formation in the presence of amino acids as ligands. It was envisaged the vinyl ether functionality could be installed via the above described method,[148] as shown in Scheme 5.3.

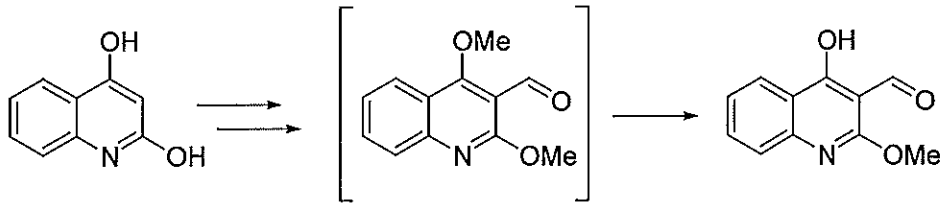



**5.04** **5.08** **5.03**

**Scheme 5.3**

Finally, the required alcohol precursor **5.04** could be synthesised via literature procedures[259-263] starting form the commercially available starting material 2,4-

dihydroxyquinoline, which can be dimethylated,[259] formylated[260-263] and finally selectively mono demethylated,[262] as shown in Scheme 5.4.




**5.07** **5.05** **5.04**

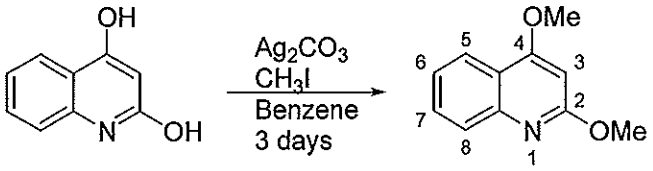
**Scheme 5.4**

## 5.2 Synthesis of the alcohol precursor 5.04 via literature procedures

The two methods available for the synthesis of 2,4-dimethoxyquinoline are either by condensation of aniline with malonic acid in the presence of phosphorus oxychloride followed by methoxylation,[264] or, by selective methylation of the commercially available 2,4-dihydroxyquinoline.[259] Since the second method is a one step procedure, it was favoured in this case.

It has been an acknowledged problem to selectively alkylate the *O*-position over the *N*-position, in systems where deprotonated ambident anions[265,266] are possible. Extensive studies have been made on the influence of base, electrophile and solvent on the regioselectivity of *N*- versus *O*-alkylation of the 2-pyridone moiety.[259] Morel *et al.*[259] optimised the conditions for regioselective *O*-alkylation when using 2,4-dihydroxyquinoline as substrate, silver carbonate as base, methyl iodide and benzene as solvent under ambient temperature for three days.[259] When the reaction

was attempted, as shown in Scheme 5.5, the desired product **5.06** was isolated in 51 %, which was appreciably less than the 71 % originally reported. Even after employing different batches of reagents and solvents, the yield was not able to be improved.



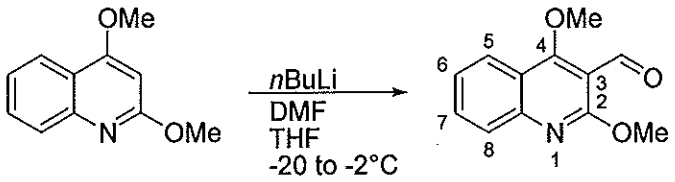

**5.06**

**Scheme 5.5**

The $^{1}$H NMR spectrum of the desired product **5.06** exhibited four distinct benzene signals, displaying a typical *ortho* substitution pattern at 8.05, 7.82, 7.61 and 7.34 ppm as a doublet, doublet, triplet and a triplet, corresponding to protons H-5, H-8, H-7 and H-6, respectively. The proton at C-3 position resonated at 6.23 ppm as a singlet, and the two OMe groups as two singlets at 4.08 and 4.00 ppm corresponding to positions C-2 and C-4 respectively. The mass spectrum, which showed a pseudo molecular ion peak at *m/z* 190, supported the proposed structure. These results were in agreement with previous reported data.[264,266]

The next step was to introduce a formyl group onto the C-3 position of the dimethoxyquinoline scaffold **5.06**.[260-263] When a solution of **5.06** in THF was treated with butyllithium, followed by addition of DMF, the desired formylated product could be isolated in a quantitative yield (97 %), as shown in Scheme 5.6. In this case, the procedure developed by Narasimhan *et al.*[262] was modified by using

THF instead of DEE as solvent, where the latter gave a slightly better yield than the reported procedure (94 %).[262]

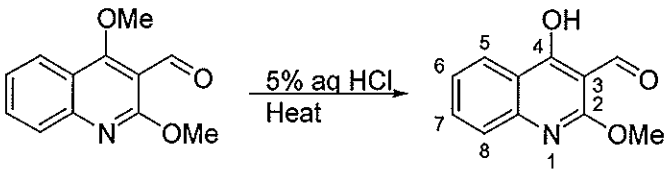



**5.06** **5.05**

**Scheme 5.6**

The $^{1}$H NMR spectrum of the desired product **5.05** exhibited four distinct benzene signals in a typical *ortho* substitution pattern at 8.15, 7.80, 7.72 and 7.41 ppm as a doublet, doublet, triplet and a triplet, corresponding to protons H-5, H-8, H-7 and H-6, respectively. The formyl proton at the C-3 position resonated at 10.53 ppm as a singlet, and the two OMe groups as a singlet at 4.15 ppm. This together with the mass spectrum, which showed a pseudo molecular ion peak at *m/z* 218, supported the proposed structure. These results were in agreement with previous reported data.[261,262,267]

Selective demethylation of the C-4 methoxy group to give **5.04**, was straightforward using literature methods.[262] Heating an aqueous hydrochloric acid solution of **5.05**, afforded the desired product **5.04** in 93 % yield, as shown in Scheme 5.7.




**5.05** **5.04**

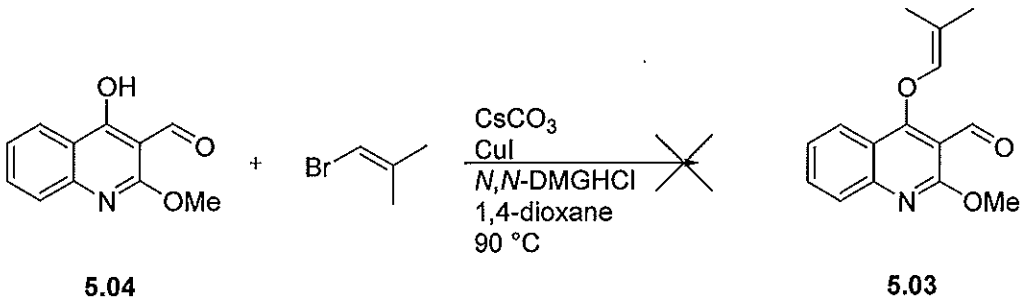
**Scheme 5.7**

The $^1$H NMR spectrum of the desired product **5.04** was visually different as when compared to its precursor **5.05**. The benzene protons resonated at 8.20, 7.72 and 7.38 ppm as a doublet and two multiplets, respectively. Lower polarity of the product **5.04** was observed by tlc analysis as by having a higher $R_f$ as compared to its precursor **5.05**. This was presumably due to the hydrogen bonding of the newly formed C-4 hydroxyl group with the formyl oxygen, and thereby creating a pseudo six membered ring system. The formyl proton signal was now further upfield at 10.28 ppm and the hydroxyl proton resonated as a broad singlet at 13.79 ppm. This together with the mass spectrum, which showed a pseudo molecular ion peak at *m/z* 204, supported the proposed structure. These results were in agreement with previous reported data.[262,267,268]

## 5.3 Alkylation with vinyl halides under Ullmann type C-O coupling

Up to this point, the chemistry has been conducted using literature procedures in order to install the two functionalities in the quinoline system i.e., the hydroxyl group at C-4, and the formyl group at C-3. The next step was to attempt the vinyl ether formation on the 4-hydroxylquinoline-3-carbaldehyde substrate, by adopting

procedures[248] successfully performed on similar systems. Initially, the conditions from Ma *et al.*[248] were adopted, as shown in Scheme 5.8.

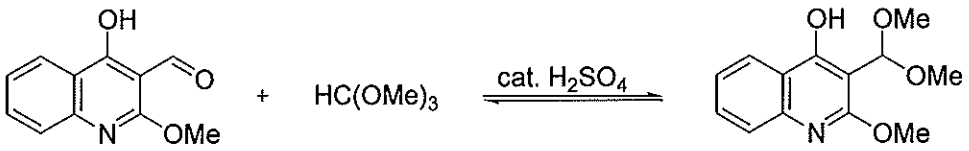



**5.04** **5.03**

**Scheme 5.8**

No desired product from the alkylation attempts was observed and therefore different reaction conditions were examined. Reaction factors such as base, equivalents of vinyl halide, solvent, temperature and time, were sequentially changed in order to improve the reaction. After many attempts, no indication of the desired product **5.03** was observed by either mass spectral or by $^1$H NMR analysis, and starting material was recovered in all cases.

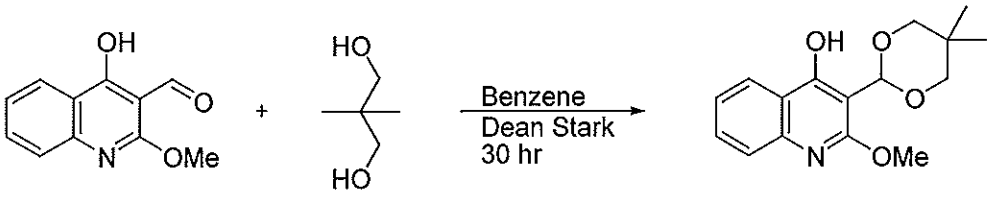
To rule out possible interfering factors related to the formyl group on the C-3 position, the formyl group was envisaged to be converted to the corresponding acetal group to alter the electronics, and, to prevent possible side reactions, such as decarbonylation.[269] At first, trimethyl orthoformate was initially used as the reagent in a series of attempts to install the acetal on **5.04**. However, due to the ease of **5.07** in aqueous medium to reverse back to **5.04**, as shown in Scheme 5.9, the desired product could not be efficiently isolated after aqueous work up, and hence, other reagents had to be used.




**5.04** **5.07**

**Scheme 5.9**

When **5.04** was treated under Dean-Stark conditions with an excess of the reagent, 2,2-dimethylpropane-1,3-diol, in benzene, the desired product **5.08** was isolated in a yield of 25 %, as shown in Scheme 5.10.



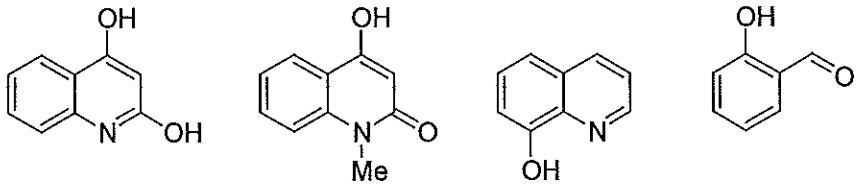

**5.04** **5.08**

**Scheme 5.10**

The $^{1}$H NMR spectrum of the hemi acetal protected intermediate **5.08** exhibited the hydroxyl proton signal at 9.74 ppm and the acetal proton at 5.94 ppm. The two acetal methylene protons resonated as two doublets at 3.71 and 3.82 ppm, and the two methyl groups as two singlets at 0.81 and 1.34 ppm, respectively. The benzene protons exhibited a typical *ortho* substitution pattern at 7.33, 7.59, 7.74 and 8.12 ppm corresponding to H-6, H-7, H-8 and H-5, respectively. This together with the mass spectrum, which showed a pseudo molecular ion peak at *m/z* 290, supported the proposed structure.

After treatment of the acetal derivative **5.08** under the vinyl halide alkylation conditions as described above, only starting material was observed when analysing the crude mixture by $^1$H NMR spectroscopy. This reaction was repeated unsuccessfully several times. Thus, it seemed less likely that the aldehyde was the interfering factor in the desired vinyl alkylation reaction.

To confirm the reported methodology[248] of vinyl alkylations with phenol type systems, the reaction using phenol as substrate was performed and the desired product was then observed in the $^1$H NMR spectra. To investigate why the reaction fails on **5.04**, other similar substrates such as 2,4-dihydroxyquinoline (**5.09**), 4-hydroxy-1-methylquinolinone (**5.10**), 8-hydroxyquinoline (**5.11**) and salicylaldehyde (**5.12**), were quantitatively assessed i.e., $^1$H NMR analysis of the crude from each test reaction.




**5.09** **5.10** **5.11** **5.12**

**Figure 5.1**

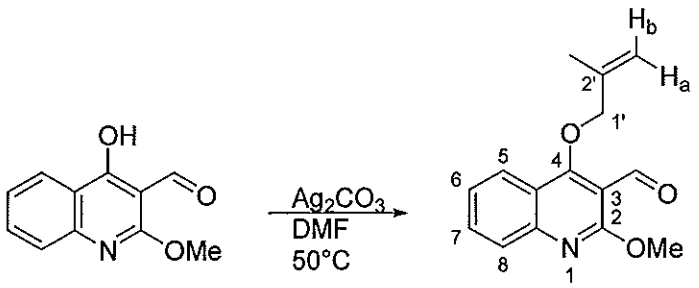
Having performed the test runs on the selected substrates, as shown in Figure 5.1, **5.11** and **5.12** were found to exhibit the desired characteristic vinylic proton signal, between 6 to 7 ppm, together with the typical *gem* dimethyl peak in the $^1$H NMR

spectra, as expected from a positive test run. The other two substrates, **5.09** and **5.10**, did not react under the same conditions. One striking difference between them is that **5.09** and **5.10** have a pyridone type moiety in the ring system. The lack of reactivity in the two substrates, **5.09** and **5.10**, might be explained by the electron withdrawing effect by the pyridone type moiety, which undermines the nucleophilic character of the oxygen anion.

These results concluded the investigation regarding alkylation with a vinyl halide using the modified Ullmann type C-O coupling conditions as reported.[148] The chosen substrate **5.04** proved not to be suitable for the desired reaction. Instead, focus was directed towards alkylation with an allyl halide to form an allyl ether, which then could be isomerised to the corresponding vinyl ether through various methods.[269-273]

## 5.4 Alkylation with allyl halides

For the synthesis of the natural product, an allyl bromide reagent was chosen as the alkylating group. After treatment of the substrate **5.04** with silver carbonate and 3-bromo-2-methylprop-1-ene, the allyl alkylated product **5.13** was isolated in a 64 % yield, as shown in Scheme 11.



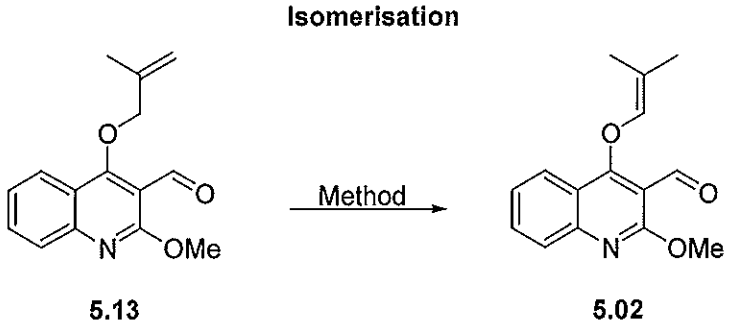

**5.04** **5.13**

**Scheme 11**

The $^{1}H$ NMR spectrum of the product **5.13** exhibited the expected methylene and the methyl protons, as two singlets at 4.66 and 1.90 ppm, respectively. The two vinylic protons, $H_a$ and $H_b$, appeared as two singlets at 5.06 and 5.17 ppm, respectively. The $^{13}C$ NMR of the alkyl group was well in agreement with the expected values, exhibiting carbon shifts at 80.7, 140.3, 19.7 and 114.7 ppm corresponding to C-1', C-2', C-Me and C=$CH_2$, respectively. Compared to the starting material **5.04** (10.28 ppm), the aldehyde proton in **5.13** was slightly shifted downfield to 10.51 ppm. Also, the benzene protons now exhibited a typical *ortho* substitution pattern at 8.15, 7.40, 7.71 and 7.80 ppm corresponding to H-5 to H-8 respectively. This together with the mass spectrum, which showed a pseudo molecular ion $[M+Na]^+$ peak at *m/z* 280, and a high resolution mass spectrum, supported the proposed structure.

### 5.4.1 Isomerisation attempts of the allyl ether substrate 5.13

Among several reagents used to isomerise allyl ethers, common ones were selected such as; $RuCl_2(PPh_3)_3$, the 1st and 2nd generation of Grubbs' catalyst, Pd/C and *t*-BuOK/DMSO, to investigate the reaction as shown in Scheme 12.




**5.13** **5.02**

**Scheme 12**

Ruthenium complexes have shown great success in isomerisations in a variety of substrates, and are at present the first choice[270,271] in this type of chemistry. They are generally seen as mild and stable reagents,[270] with the benefit that only catalytic amounts are required to produce high yields of the desired isomerised product.[274] It has also been demonstrated that isomerisations can be done in the presence of other sensitive functional groups, such as aldehydes,[271] which was a requirement for substrate **5.13**. However, after many attempts, none of the ruthenium based reagents was met with success in attempts of isomerising **5.13** to **5.02**, and mostly starting material was observed when the crude mixture was analysed by $^{1}$H NMR spectroscopy. In attempts to induce any change of outcome other than recovering starting material, either temperature was raised and/or extended reaction times were tried. However, mostly starting material together with minor amounts of complex mixtures was observed, and so, other reagents had to be used. Carless *et al.*[269] showed the possibility of inducing isomerisation of allyl- to the vinyl ether functionality in a variety of substrates by heating under reflux the substrate with palladium on activated carbon, in either benzene or toluene as solvent. Since this reaction had been successfully performed in the presence of sensitive functional

groups, such as aldehydes etc, this too, seemed to be a suitable method.[269] Adopting this protocol with **5.13** gave quantitatively the alcohol precursor **5.04**. Therefore, sequentially lowering the temperature in repeated experiments together with changing reaction times to prevent cleavage of the ether, resulted in an increase of recovery of starting material. At the lowest temperatures, starting material was quantitatively recovered. Finally the classic method using *t*-BuOK in dry DMSO[273] was investigated. This procedure requires highly moisture free reaction conditions, and includes a difficult work up to be successful.[270] However, even after extreme care had been taken in an effort of having moisture free conditions in the lab, mostly the cleaved product **5.04** was isolated together with a complex mixture.

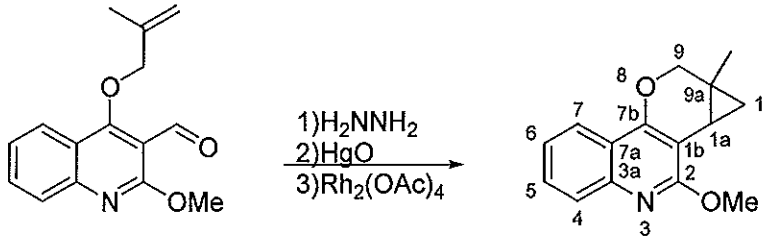
In conclusion, attempts at isomerisation of **5.13** using a large number of methods failed, indicating that it is not straightforward to isomerise the allyl ether **5.13** to the corresponding vinyl ether **5.03**. Consequently, more time and effort must be put into this reaction to find the required conditions, and hence, to gain access of the desired vinyl ether substrate **5.03**.

## 5.5 The tandem ringclosure/cyclopropanation reaction of 5.13

While the synthesis of the vinyl ether **5.03** was unsuccessful the question remained, would the tandem cyclisation/cyclopropane reaction work? Obviously, this could not be investigated on the desired substrate but could be investigated on the allyl derivative **5.13**. However, the outcome of using **5.13** as a substrate would be to give a pyran ring instead of a furan ring.

The tandem cyclisation/cyclopropanation reaction involves three steps; converting the aldehyde to the hydrazone, oxidise the hydrazone to the diazo compound, and finally induce carbene formation with the aid of dirhodium tetraacetate as the metal catalyst.

The available protocol from Ishii *et al.*,[245] was adopted to form the hydrazone from **5.13**. Initially, after the allyl ether **5.13** was treated with hydrazine mono-hydrate with heating, followed by aqueous work up and chromatography, the desired allyl ether hydrazone intermediate could not be isolated. Only an unknown side product was isolated. Previous reported observations by Holton *et al.*[247] suggested a dimerisation could have occurred. Prolonged contact of *in situ* formed hydrazones of this type with water/moisture, facilitates formation of dimerised products,[247] which fail to react further. However, the very speculative compound was not further characterised. In light of that, the excess hydrazine needed to be removed from the initial step, and therefore a quick work up to minimise exposure to water followed by concentrating was necessary. In the next step, the residue was then treated with an excess of mercury oxide, together with a catalytic amount of an ethanolic potassium hydroxide solution under cooled conditions, to furnish the diazo compound.[275] Attempts to isolate this intermediate, proved to be problematic and therefore the crude intermediate, after the solids were removed by filtration, was used in the next step. The resulting filtrate was immediately treated with catalytic amounts of dirhodium tetraacetate. This furnished the cyclised/cyclopropane ring product **5.14** in a 20 % yield, as shown in Scheme 5.13.




**5.14**

**Scheme 5.13**

The mass spectrum of **5.14** showed a pseudo molecular ion peak at *m/z* 242, which supported the molecular formula $C_{15}H_{15}NO_2$. The major changes in the $^1$H NMR were the appearance of three new multiplet signals at (1.07 and 1.17 ppm) and 2.12 ppm, together with two doublet signals at 3.87 and 4.45 ppm ($J$ = 13.6 Hz). The absence of the methylene group at 4.66 ppm, the two vinylic protons at 5.06 and 5.17 ppm, and the formyl proton at 10.51 ppm was also noted. The $^{13}$C NMR and HSQC spectra showed the presence of six quaternary carbons (where two were possibly carbonyls), five methine carbons (where four were in the aromatic region), two methylene carbons, one methyl (1.34 ppm) and one OMe signal (53.8 ppm). By analogy with structure elucidation of product **3.03**, it was important to first determine if the quinoline moiety was intact. Since the protons in the aromatic area in the $^1$H NMR spectrum exhibited a typical *ortho* substitution pattern at 7.77, 7.53, 7.32 and 7.94 ppm (doublet, triplet, triplet and doublet, respectively), it was indicative for an intact benzene ring. The benzene moiety was confirmed through the $^3J$ correlations from the protons H-4 to H-7 (Table 5.1), and the OMe correlations to carbon C-2. Importantly the $^3J$ correlation from H-7 to carbon C-7b at 155.1 ppm was observed, which was indicative for an aromatic enol ether carbon, and thereby suggesting the existence of the quinoline core structure. Next to investigate were the methine proton at 2.12 ppm with its carbon shift at 14.2

ppm. In the HMBC spectrum, the proton at 2.12 ppm correlated to C-1b and C-7b, indicative for being α to the quinoline ring. It also correlated to C-1 at 19.4 ppm and the methyl group at 20.3 ppm, indicative for a cyclisation to have occurred. The protons of the methylene group at 1.07 and 1.17 ppm correlated, in the HMBC spectrum, to C-1b, indicative for being β to the quinoline ring. They (protons at 1.07 and 1.17 ppm) also correlated to C-1a (quaternary), C-9 (methylene), C-9a (quaternary) and the methyl carbon. This data for the methylene protons at 1.07 and 1.17 ppm and with its observed carbon shift at 19.4 ppm suggested it to be part of a cyclopropane ring system. The methyl protons at 1.34 ppm correlated in the HMBC spectrum to C-1, C-1a, C-9 and C-9a. The $^{3}J$ correlation in particular to C-1a supported the existence of cyclopropane ring system. The correlation of the methylene protons at 3.87 and 4.45 ppm, in the HMBC spectrum, to C-1, C-1a, C-9a and the methyl group, suggested the existence of a cyclopropane ring. A COSY spectrum confirmed the expected correlations between H-1 and H-1a. Importantly, it was also noted that the methylene protons H-9 (at 3.87 and 4.45 ppm) correlated to C-7b which confirmed a dihydro pyrano type system. The supported molecular formula of $C_{15}H_{15}NO_2$ from a high resolution mass spectrum indicated that there must be an ether linkage between C-7b and C-9. This data supported the proposed structure shown in Table 5.1.

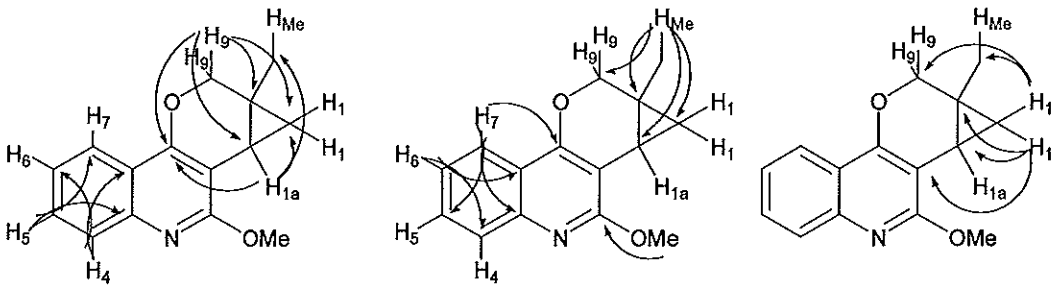



**Table 5.1** $^{1}$H (400 MHz), $^{13}$C (100 MHz) and HMBC NMR data for **5.14**

| Position | $^{13}$C | $^{1}$H (mult., *J*, int) | HMBC |
|---|---|---|---|
| 1 | 19.4 | 1.07 and 1.17 (m, 1H) | Me, C-9, C-9a, C-1a, C-1b |
| 1a | 14.2 | 2.12 (m, 1H) | Me, C-7b, C-2 |
| 1b | 108.5 | | |
| 2 | 161.4 | | |
| 3a | 144.8 | | |
| 4 | 127.1 | 7.77 (d, *J* 6.4 Hz, 1H) | C-6, C-7a |
| 5 | 128.8 | 7.53 (app t, *J* 6.2 Hz, 1H) | C-3a, C-7 |
| 6 | 123.4 | 7.32 (app t, *J* 6.0 Hz, 1H) | C-4, C-7a |
| 7 | 121.2 | 7.94 (d, *J* 6.8 Hz, 1H) | C-3a, C-5, C-7b |
| 7a | 119.1 | | |
| 7b | 155.1 | | |
| 9 | 68.0 | 3.87 and 4.45 (d, *J* 13.6 Hz, 2H) | C-1, C-1a, C-7b, C-9a |
| 9a | 23.7 | | |
| OMe | 53.8 | 4.14 (s, 3H) | C-2 |
| Me | 20.3 | 1.34 (s, 3H) | C-1, C-1a, C-9, C-9a |

## 5.6 Summary of Chapter 5

It has been shown through attempts at either alkylation **5.04** with the vinyl halide, or, isomerisation of the synthesised allyl ether **5.13**, that the synthesis of the natural product frame work by the new strategy was not a simple task. In both cases, there is enough evidence in literature to show that the desired reactions are possible to perform for similar structures. Although, substrate **5.04** was one of the selected compounds not suited for the desired reactions in a straightforward manner, we are confident that alternative conditions can be found to give the desired product. The overall synthetic strategy proved to be sound since the carbene insertion reaction afforded the desired cyclised product **5.14** for the model case **5.13**.

# Concluding Comments

The core structures **1.30** and **2.01** were achieved with excellent yields using the new synthetic strategy. Although it has been shown that 2-diazopropane is lacking in reactivity towards both of the furoquinolinone core structures, **1.30** and **2.01** under the conditions employed, the desired carbon scaffold was afforded when using ethyl 2-diazopropanoate as the carbene precursor with substrate **1.30.** Reduction of the ester functionality proceeded smoothly, however, the neopentyl alcohol **4.01** produced, did unfortunately not yield the desired *gem* dimethyl functionality under either reductive or oxidative conditions. This led to the new synthetic strategy, which incorporated first a vinyl alkylation followed by a novel tandem cyclisation/cyclopropanation reaction to furnish the desired *gem* dimethyl moiety. The new strategy turned out to be a non fruitful approach in terms of the vinyl alkylation step, but in contrast, a sound approach in terms of the novel tandem cyclisation/cyclopropanation reaction, yielding (for the model case **5.13**) the desired product **5.14.** In efforts to optimise the vinyl alkylation, five test substrates were qualitatively assessed. A common denominator of the observed test results was that the pyridone containing substrates did not react at all, while the non pyridone containing substrates did react and gave the desired vinyl ether.

The new method of synthesising the furoquinolinone core structure, in either the *N*-methyl (**1.30**) or the *O*-methyl (**2.01**) form, was successfully achieved. The Heck type coupling reaction afforded the key intermediate **1.30** in a 89 % yield, and the key intermediate **2.01** was afforded in a 63 % yield over three steps starting from the *N*-SEM protected material. Both substrates, **1.30** and **2.01**, showed high reactivity toward the diazo reagents ethyl 2-diazopropanoate and dimethyl

diazomalonate. The first reagent (ethyl 2-diazopropanoate) afforded the desired cyclopropanated frame work in both substrates in a 43 and a 69 % yield respectively. The other reagent (dimethyl diazomalonate) afforded two highly functionalised novel products, **3.03** and **3.04** with a theoretical calculated yield of 55 and 18 % respectively, when using **1.30** as substrate, and a pyrano type product **3.05** in a 38 % yield when using **2.01** as substrate. Products **3.03**, **3.04** and **3.05** were formed through complete consumption of starting material. The reactivity of the two substrates exocyclic double bond, **1.30** and **2.01**, was further investigated by the use of other electrophiles. When using **1.30**, the mono brominated material **3.12** was afforded in a 94 % yield after optimisation. Conversely, in the case of substrate **2.01**, the mono brominated material **3.14** was only able to be isolated in a 23 % yield. Both of these brominated materials can be envisaged to be potential synthons for other investigations or perhaps serve as intermediates in syntheses for other natural products in coming projects.

# Experimental

**General**

All reagents were purchased from commercial sources and were used without further purification. All solvents were available commercially dried or freshly dried and distilled prior to use. THF was freshly distilled from sodium benzophenone ketal. toluene, pyridine and DCM were distilled from calcium hydride and stored over activated 4Å sieves. Methanol was refluxed over magnesium and a catalytic quantity of iodine prior to distillation and storage over activated 3Å sieves. Reaction progress was monitored by TLC using Silica gel-60 $F_{254}$ plates with detection by short wave UV fluorescence ($\lambda = 254$ nm). Flash chromatography was conducted using Merk flash silica gel 60 (60–240 mesh).

NMR spectra were recorded on a Varian Unity 400 MHz, Varian Unity INOVA 500 MHz, or a Varian NMR System 600 MHz spectrometer with chemical shift values given in ppm (δ) using deuterated solvent as specified. $^{13}C$ NMR spectra were recorded at 100 MHz (on the Varian Unity 400 MHz) or at 125 MHz (Varian Unity INOVA 500 MHz) and referenced to either δ 77 ppm ($CDCl_3$) or δ 39.5 ppm (DMSO- $d_6$). Melting points were recorded on a GallenKamp Variable Temperature Apparatus by capillary method and are reported as uncorrected. Mass spectra were recorded on a Fisons VG platform II and a Waters Micromass ZQ4000 spectrometer employing a single quad dual source and using electrospray

as the ionisation technique in positive and negative ion modes. A waters HPLC system 600 (controller and pump) delivered isocratic streams for direct injections ($CH_3CN$–$H_2O$ eluents). Columns used for reverse phase purification were (Thermo, Betasil, $C_{18}$, particle size 5μm, dimension 150 x 21.2 mm; Hypersil, Hypersil BDS, $C_{18}$, particle size 5μm, dimension 250 x 10 mm; SUPELCO, Hypersil, $C_{18}$, particle size 5μm, dimension 250 x 4.6 mm; Thermo, BDS Hypersil, $C_{18}$, particle size 5μm, dimension 150 x 4.6 mm). High resolution electrospray ionisation mass spectra were recorded on a Bruker Daltonics 4.7T Fourier transform ion cyclotron resonance mass spectrometer (FTICRMS) fitted with an Apollo ESI source in positive ion or negative ion as stated. Elemental analyses were conducted by the University of Queensland Microanalytical service. X-ray diffraction data collection and data refinement was conducted on a Rigaku AF(C-7R diffractometer using MSC/AF7 Diffractometer Control Software. Data collections and refinements were performed by Prof. Peter Healy and Mr. Alan White at the Eskitis Institute and school of Biomolecular and Physical Sciences, Griffith University.

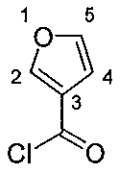
## Note on nomenclature

General naming preferences from IUPAC regarding furoquinonlinones and derivatives thereof were applied.

## Preparation and analytical data for compounds:

### Initial attempts of the amide coupling

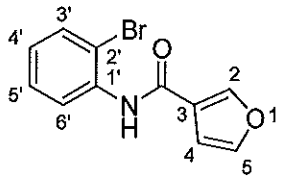
Methods for the initial attempts of synthesising the desired amide coupled product **2.03** using the reagents DCC, HOBt and HBTU, see standard literature methods.[53-55,57,58,156,159]




**Furan-3-carbonyl chloride**

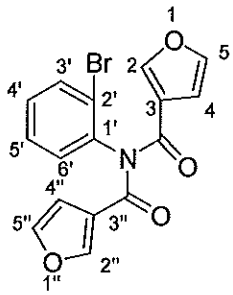
### Optimal conditions

To a solution of 3-furoic acid (5.00 g, 44.61 mmol) in DCM (100 mL), was added a solution of thionyl chloride (5.40 mL, 66.90 mmol) in DCM (40 mL) drop wise under a nitrogen atmosphere at 0 °C. After complete addition, the reaction mixture was allowed to stir for 1 h at 60 °C. The solvent and the excess thionyl chloride were removed by heating and the residue purified by short path distillation (120 °C/ 22 mbar) to afford 5.80 g of the desired product as a colourless liquid. Bp 162 °C (lit.[165] $bp_{50\ mmHg}$ 62-63 °C). $^1H$ NMR ($CDCl_3$, 500 MHz): δ 6.80 (d, *J* 1 Hz, 1H), 7.52 (d, *J* 1 Hz, 1H), 8.20 (s, 1H).



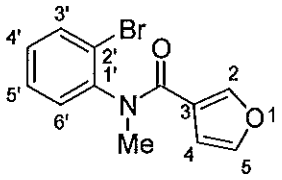

**_N_-(2-Bromophenyl)-3-furamide**

To a solution of 2-bromoaniline (313 mg, 1.82 mmol) in toluene (25 mL) was added 3-furoyl chloride (179 mg, 1.37 mmol) in one portion under a nitrogen atmosphere. The reaction mixture was heated under reflux for 15 h followed by concentrating the crude mixture under reduced pressure. Purification by flash chromatography (DCM:hexane/6:4) afforded 285 mg of **2.03** (92 %) as a white solid. Mp 68 °C. IR (KBr, $\nu_{max}$): 1666, 1590, 1514, 1426, 1316, 1158, 1024, 878, 814, 755 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 206.0 nm (42378), 247.2 nm (13411). $^{1}$H NMR ($CDCl_3$, 500 MHz): δ 6.78 (d, *J* 1.0 Hz, 1H, H-4), 7.03 (app t, *J* 7.5 Hz, 1H, H-4`), 7.38 (app t, *J* 7.5 Hz, 1H, H-5`), 7.54 (s, 1H, H-5), 7.59 (d, *J* 8.0 Hz, 1H, H-3`), 8.06 (s, 1H, NH), 8.10 (s, 1H, H-2), 8.50 (d, *J* 8.0 Hz, 1H, H-6`). $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 108.4 (C-4), 113.7 (C-2`), 122.0 (C-6`), 123.3 (C-3), 125.5 (C-4`), 128.8 (C-5`), 132.5 (C-3`), 135.8 (C-1`), 144.5 (C-5), 145.6 (C-2), 160.6 (C=O). MS (ESI): *m/z* 266, 268 (1:1) $[M+H]^+$. HRMS Calcd. for $C_{11}H_8BrNO_2$ $[M+H]^+$: 265.9811. Found: 265.9809.



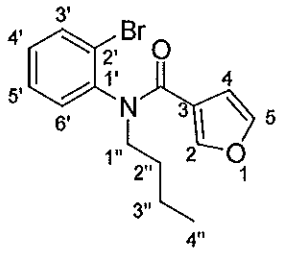
***N*-(2-Bromophenyl) -*N*-3-furoyl-3-furamide**

To a solution of 2-bromoaniline (922 mg, 5.36 mmol) and triethylamine (2.24 mL, 16.11 mmol) in DCM (8.90 mL) at 0 °C under a nitrogen atmosphere was added a solution of 3-furoyl chloride (700 mg, 5.36 mmol) in DCM (5 mL) dropwise with stirring. The reaction mixture was allowed to warm to RT. After 40 h of stirring the reaction mixture was diluted with EtOAc (100 mL), washed with 1M NaOH (2 x 30 mL), 1M HCl (2 x 30 mL), water (2 x 30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (EtOAc:hexane/3:7) afforded 400 mg of **2.04** (20 %) as an oil. IR (KBr, $\nu_{max}$): 3364, 3142, 3048, 2722, 2512, 2307, 1683, 1555, 1502, 1479, 1298, 1158, 1070, 1018, 872, 767, 592 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 205.2 nm (51531), 261.0 nm (12052). $^1$H NMR ($CDCl_3$, 400 MHz): δ 6.53 (m, 2H, H-4, 4`), 7.30 (m, 1H, H-6`), 7.35 (m, 2H, H-5, 5`), 7.37 (m, 1H, H-5`), 7.72 (dd, *J* 8.0, 1.2 Hz, 1H, H-3`), 7.75 (m, 2H, H-2, 2```). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 110.4 (C-4, 4``), 122.9 (C-3, 3``), 123.6 (C-2`), 129.1 (C-5`), 130.7 (C-6`), 131.5 (C-4`), 134.2 (C-3`), 138.9 (C-1`), 143.6 (C-5, 5``), 148.2 (C-2, 2``), 165.8 (2 x C=O). MS (ESI): *m/z* 359, 361 $[M+H]^+$, 381, 383 (1:1) $[M+Na]^+$. Anal. Calcd. for $C_{16}H_{10}BrNO_4$: C, 53.36; H, 2.80; N, 3.89 Found: C, 52.25; H, 2.71; N, 3.55. HRMS Calcd. for $C_{16}H_{10}BrNO_4Na$ $[M+Na]^+$: 381.9685. Found: 381.9698.



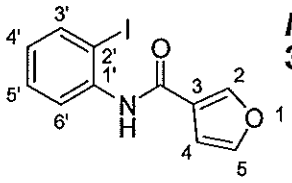

**_N_-(2-Bromophenyl)**
**-_N_-methylfuran**
**-3-carboxamide**

To a solution of **2.03** (798 mg, 3.0 mmol) and methyl iodide (852 mg, 6.0 mmol) in THF (30 mL) was added sodium hydride (216 mg, 9.0 mmol) portion wise at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to RT with stirring over night (18 h). After complete reaction time (monitored by TLC) the reaction mixture was quenched with water (40 mL) followed by extracting with EtOAc (100 mL). The organic phase was washed with 1M HCl (40 mL), 1M NaOH (40 mL), dried with MgSO4 and concentrated under reduced pressure. Purification by flash chromatography using (EtOAc:hexane/4:6) afforded 805 mg of **2.05** (95 %) as a white solid. Mp 89 °C. IR (KBr, $\nu_{max}$): 3498, 3110, 3048, 2932, 1636, 1496, 1479, 1421, 1386, 1304, 1146, 1018, 866, 755 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 209.6 nm (10125). $^{1}$H NMR ($CDCl_3$, 500 MHz): δ 3.36 (s, 3H, NMe), 6.22 (s, 1H, H-4), 6.89 (s, 1H, H-5), 7.19 (s, 1H, H-2), 7.28 (m, 1H, H-4`), 7.32 (m, 1H, H-6`), 7.39 (app t, *J* 7.25 Hz, 1H, H-5`), 7.70 (dd, *J* 7.5, 1.5 Hz, 1H, H-3`). $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 37.0 (NMe), 111.0 (C-4), 121.9 (C-3), 124.0 (C-2`), 129.2 (C-5`), 130.3 (C-6`), 130.7 (C-4`), 134.2 (C-3`), 142.4 (C-5), 143.2 (C-1`), 145.3 (C-2), 163.5 (C=O). MS (ESI): *m/z* 280, 282 (1:1) $[M+H]^+$. Anal. Calcd. for $C_{12}H_{10}BrNO_2$: C, 51.45; H, 3.60; N, 5.00 Found: C, 51.14; H, 3.49; N, 4.87.



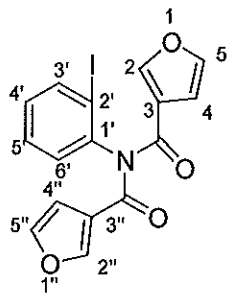

**_N_-(2-Bromophenyl) -_N_-butyl-3-furamide**

To a solution of **2.03** (664 mg, 2.5 mmol) and butyl iodide (92 mg, 5.0 mmol) in THF (30 mL) was added sodium hydride (200 mg, 5.0 mmol) portion wise under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to RT with stirring overnight (18 h) followed by quenching with water (20 mL). EtOAc (100 mL) was added and work up was done by washing the organic layer with 1M HCl (3 x 50 mL), 1M NaOH (3 x 50 mL), water (3 x 50 mL), drying with $MgSO_4$ and concentrating the organic layer under reduced pressure. Flash chromatography (EtOAc:hexane/7:3) afforded 560 mg of **2.06** (70 %) as a white solid. Mp 50 °C. IR (KBr, $\nu_{max}$): 3463, 2943, 2856, 1636, 1496, 1467, 1391, 1321, 1187, 1152, 1012, 866, 738 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 208.4 nm (25797). 1H NMR ($CDCl_3$, 500 MHz): δ 0.96 (t, *J* 8 Hz, 3H, H-4``), 1.39 (m, 2H, H-3``), 1.63 (m, 1H, H-2a``), 1.70 (m, 1H, H-2b``) 3.37 (m, 1H, H-1a``), 4.22 (m, 1H, H-1b``), 6.21 (s, 1H, H-4), 6.81 (s, 1H, H-2), 7.17 (s, 1H, H-5), 7.30 (m, 2H, H-4` and 6`), 7.40 (app t, *J* 7.25 Hz, 1H, H-5`), 7.71 (d, *J* 7.25 Hz, 1H, H-3`). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 14.1 (C-4``), 20.5 (C-3``), 29.8 (C-2``), 49.4 (C-1``), 111.1 (C-4), 122.3 (C-3), 124.6 (C-2`), 128.8 (C-5`), 130.2 (C-6`), 131.8 (C-4`), 134.3 (C-3`), 141.7 (C-1`), 142.3 (C-5), 145.2 (C-2), 163.1 (C=O). MS (ESI): *m/z* 322, 324 (1:1) $[M+H]^+$, 344, 346 (1:1) $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35. Found: C, 55.79; H, 4.93; N, 4.22.



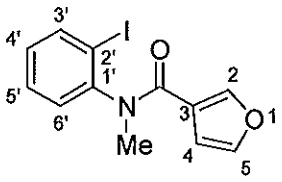

**N-(2-Iodophenyl)-3-furamide**

To a solution of iodoaniline (400 mg, 1.82 mmol) in toluene (25 mL) was added 3-furoyl chloride (119 mg, 0.91 mmol) in one portion under a nitrogen atmosphere. The reaction mixture was heated under reflux for 15 h followed by concentrating the crude mixture under reduced pressure. Purification by flash chromatography (DCM:hexane/6:4) afforded 285 mg of **2.07** (93 %) as a white solid. Mp 95-97 °C. IR (KBr, $\nu_{max}$): 3369, 3264, 3124, 3054, 2337, 1654, 1561, 1502, 1426, 1310, 1158, 1065, 1018, 866, 744 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 205.8 nm (21460), 225.0 nm (19732). $^1H$ NMR ($CDCl_3$, 500 MHz): δ 6.82 (d, *J* 1.0 Hz, 1H, H-4), 6.90 (app t, *J* 8.0 Hz, 1H, H-4`), 7.41 (app t, *J* 8.0 Hz, 1H, H-5`), 7.54 (s, 1H, H-5), 7.83 (d, *J* 8.0 Hz, 1H, H-3`), 7.90 (s, 1H, NH), 8.12 (s, 1H, H-2), 8.41 (d, *J* 8.0 Hz, 1H, H-6`). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 90.2 (C-2`), 108.5 (C-4), 121.9 (C-6`), 123.5 (C-3), 126.2 (C-4`), 129.7 (C-5`), 138.1 (C-1`), 139.0 (C-3`), 144.5 (C-5), 145.6 (C-2), 160.6 (C=O). MS (ESI): *m/z* 314 $[M+H]^+$, 187 $[M-I]^+$. Anal. Calcd. for $C_{11}H_8INO_2$: C, 42.20; H, 2.58; N, 4.47. Found: C, 42.03; H, 2.51; N, 4.35



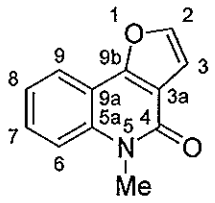
**_N_-(2-Iodophenyl)**
**-_N_-3-furoyl-3-furamide**

To a solution of 2-iodoaniline (12.1 g, 55.2 mmol) and triethylamine (23 mL, 165.0 mmol) in DCM (150 mL) was added a solution of 3-furoyl chloride (5.5 g, 42.5 mmol) in DCM (150 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to RT and was stirred for 44 h. The reaction mixture was then washed with 1M HCl (3 x 50 mL), 1M NaOH (3 x 50 mL) and water (3 x 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (DCM:hexane/6:4) afforded 251 mg of **2.08** (20 %) as an oil. IR (KBr, $\nu_{max}$): 3585, 3136, 3054, 2354, 1689, 1561, 1502, 1461, 1298, 1170, 1070, 1006, 872, 744 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 210.2 nm (25754), 220.0 nm (21767). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 6.56 (m, 2H, H-4, 4``), 7.14 (dd, *J* 7.6, 2.0 Hz, 1H, H-4`), 7.28 (dd, *J* 8.0, 2.0 Hz, 1H, H-6`), 7.36 (m, 2H, H-5, 5``), 7.41 (dd, *J* 8.0, 2.0 Hz, 1H, H-5`), 7.75 (m, 2H, H-2, 2``), 7.99 (dd, *J* 8.0, 1.8 Hz, 1H, H-3`). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 100.2 (C-2`), 110.9 (C-4, 4``), 123.1 (C-3, 3``), 130.0 (C-5`), 130.8 (C-4`), 131.3 (C-6`), 140.4 (C-3`), 142.1 (C-1`), 143.7 (C-5, 5``), 148.6 (C-2, 2``), 165.8 (2 x C=O). MS (ESI): *m/z* 408 $[M+H]^+$, 430 $[M+Na]^+$. HRMS Calcd. for $C_{16}H_{11}INO_4$ $[M+H]^+$: 407.9727. Found: 407.9746.




**_N_-(2-Iodophenyl) -_N_-methyl-3-furamide**

To a solution of the **2.07** (2.0 g, 6.4 mmol) and iodomethane (1.8 g, 12.8 mmol) in dry THF (70 mL) was added sodium hydride (383 mg, 16.0 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to RT and was stirred for 18 h followed by diluting with EtOAc (200 mL). The crude was then extracted with water (200 mL), 1M NaOH (2 x 200 mL), 1M HCl (2 x 200 mL), dried with $MgSO_4$ and concentrated under reduced pressure to afford 2.08 g of **2.09** (95 %) as a white solid. Mp 80-82 °C. IR (KBr, $\nu_{max}$): 3440, 3135, 2917, 1631 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 204.6 nm (13460), 226.2 nm (10716). $^1$H NMR ($CDCl_3$, 500 MHz): δ 3.34 (s, 3H, NMe), 6.22 (s, 1H, H-4), 6.82 (s, 1H, H-5), 7.14 (app t, *J* 7.5 Hz, 1H, H-4`), 7.19 (s, 1H, H-2), 7.32 (d, *J* 7.25 Hz, 1H, H-6`), 7.44 (app t, *J* 8.0 Hz, 1H, H-5`), 7.95 (d, *J* 7.5 Hz, 1H, H-3`). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 37.2 (NMe), 100.2 (C-2`), 111.2 (C-4), 122.1 (C-3), 129.9 (C-5`), 130.1 (C-6`), 130.4 (C-4`), 140.6 (C-3`), 142.4 (C-5), 145.5 (C-2), 146.5 (C-1`), 163.2 (C=O). MS (ESI): *m/z* 328 $[M+H]^+$, 350 $[M+Na]^+$ Anal. Calcd. for $C_{12}H_{10}INO_2$: C, 44.06; H, 3.08; N, 4.28. Found: C, 43.88; H, 3.04; N, 4.14.




**5-Methylfuro[3,2-*c*] quinolin-4(5*H*)-one**

**Method A**

A mixture of **2.09** (612 mg, 1.87 mmol), KOAc (257 mg, 2.62 mmol), *n*-$Bu_4NCl$ (138 mg, 0.50 mmol), PdO (23 mg, 0.19 mmol) in DMA (3.67 mL) under a nitrogen atmosphere was heated to 150 °C for 18 h followed by concentrating the crude mixture under reduced pressure. Purification by flash chromatography (EtOAc:hexane/3:7) afforded 373 mg of the cyclised product **1.30** (89 %) as a pink solid. Mp 126-128 °C. IR (KBr, $\nu_{max}$): 3579, 1660, 1257, 738 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 228.8 nm (82846), 285.2 nm (15376), 319.2 nm (19621), 332.2 nm (18589). $^1$H NMR ($CDCl_3$, 500 MHz): δ 3.81 (s, 3H, NMe), 7.10 (d, *J* 1.8 Hz, 1H, H-3), 7.33 (app t, *J* 8.0 Hz, 1H, H-8), 7.48 (d, *J* 8.5 Hz, 1H, H-6), 7.58 (app t, *J* 8.5 Hz, 1H, H-7), 7.64 (d, *J* 1.8 Hz, 1H, H-2), 8.04 (dd, *J* 8.0, 1.8 Hz, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 29.7 (NMe), 108.6 (C-3), 113.5 (C-9a), 115.3 (C-6), 115.6 (C-3a), 121.5 (C-9), 122.6 (C-8), 129.8 (C-7), 138.4 (C-5a), 144.2 (C-2), 155.4 (C-9b), 159.7 (C=O). MS (ESI): *m/z* 200 $[M+H]^+$. Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.14; H, 4.53; N, 6.86.

**Method B**

A mixture of **2.05** (40 mg, 0.142 mmol), KOAc (18 mg, 0.185 mmol), *n*-$Bu_4NI$ (13 mg, 0.035 mmol), PdO (17 mg, 0.014 mmol) in DMA (0.3 mL) under a nitrogen atmosphere was heated to 150 °C for 15 h followed by concentrating the crude

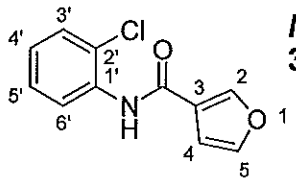
mixture under reduced pressure. Purification by flash chromatography (EtOAc:hexane/3:7) afforded 17 mg of the cyclised product **1.30** (59 %) as a pink solid. See method A for data.

**Method C**

A mixture of **2.05** (50 mg, 0.180 mmol), $NaHCO_3$ (20 mg, 0.233 mmol), *n*-$Bu_4NI$ (7 mg, 0.018 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol) in DMA (5 mL, the volume was not given in the reference and so initially 5 mL was used) under a nitrogen atmosphere was heated to 150 °C for 15 h followed by concentrating the crude mixture under reduced pressure. Purification by flash chromatography (EtOAc:hexane/3:7) afforded 6 mg of the cyclised product **1.30** (17 %) as a pink solid. See method A for data.

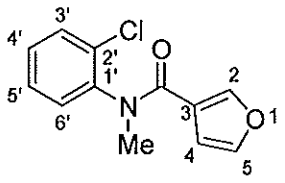
**Method D**

A mixture of **2.05** (560, 2.0 mmol), 0.29 g of potassium KOAc (292 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (120 mg, 0.1 mmol) toluene (3.6 mL) was heated at reflux under a nitrogen atmosphere for 16 hours. The mixture was cooled to room temperature, filtered through celite, and rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by flash chromatography (EtOAc:hexane/3:7) to afford **1.30** (<5 %). See method A for data.



**N-(2-Chlorophenyl)-3-furamide**

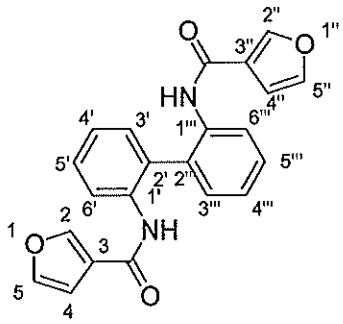
To a solution of iodoaniline (800 mg, 6.27 mmol) in toluene (50 mL) was added 3-furoyl chloride (400 mg, 3.06 mmol) in one portion under a nitrogen atmosphere. The reaction mixture was allowed to reflux for 15 h followed by concentrating the crude mixture under reduced pressure. Purification by flash chromatography (DCM:hexane/6:4) afforded 643 mg of **2.11** (84 %) as a white solid. Mp 72 °C. IR (KBr, $\nu_{max}$): 3280, 2360, 1654 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 245 nm (8444). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 6.76 (m, 1H, H-4), 7.08 (app t, *J* 8.0 Hz, 1H, H-4`), 7.32 (app t, 7.5 Hz, 1H, H-5`), 7.40 (app d, *J* 8.1 Hz, 1H, H-3`), 7.52 (m, 1H, H-5), 8.09 (s, 1H, H-2), 8.50 (app d, *J* 8.5 Hz, 1H, H-6`). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 108 (C-4), 121.8 (C-6`), 122.9 (C-2`), 123.3 (C-3), 124.9 (C-4`), 128.1 (C-5`), 129.2 (C-3`), 134.7 (C-1`), 144.5 (C-5), 145.6 (C-2), 160.6 (C=O). MS (ESI): *m/z* 222, 224 (3:1) $[M+H]^+$, 244, 246 (3:1) $[M+Na]^+$. HRMS Calcd. for $C_{11}H_8ClNO_2$ $[M+H]^+$: 222.0316. Found: 222.0315.



**N-(2-Chlorophenyl) -N-methyl-3-furamide**

To a solution of **2.11** (500 mg, 2.26 mmol) and iodomethane (640 mg, 4.51 mmol) in dry THF (20 mL) was added sodium hydride (225 mg, 5.64 mmol) under a

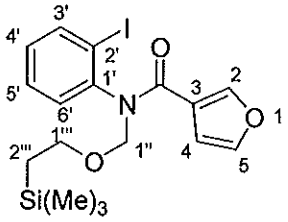
nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to RT and was stirred for 18 h followed by diluting with EtOAc (200 mL). The crude was then extracted with water (200 mL), 1M NaOH (2 x 200 mL), 1M HCl (2 x 200 mL), dried with $MgSO_4$ and concentrated under reduced pressure to afford 528 mg of **2.12** (99 %) as a white solid. Mp 89 °C. IR (KBr, $\nu_{max}$): 3137, 3113, 1625 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: none. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.36 (s, 3H, NMe), 6.20 (s, 1H, H-4), 6.91 (s, 1H, H-5), 7.18 (s, 1H, H-2), 7.30-7.39 (m, 3H, H-4`, 5`, 6`), 7.51 (app d, *J* 7.9 Hz, 1H, H-3`). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 36.9 (NMe), 110.9 (C-4), 121.9 (C-3), 128.4 (C-3`), 130.0 (C-5`), 130.6 (C-4`), 131.0 (C-6`), 133.6 (C-2`), 141.6 (C-1`), 142.4 (C-2), 145.2 (C-5), 163.6 (C=O). MS (ESI): *m/z* 236, 238 (3:1) $[M+H]^+$, 258, 260 (3:1) $[M+Na]^+$. HRMS Calcd. for $C_{12}H_{10}ClNO_2Na$ $[M+Na]^+$: 258.0292. Found: 258.0286.




**N,N`-Biphenyl-2,2'-diyldi(3-furamide)**

A mixture of **2.07** (50 mg, 0.160 mmol), KOAc (20 mg, 0.210 mmol), *n*-$Bu_4NI$ (15 mg, 0.040 mmol), PdO (2 mg, 0.016 mmol) in DMA (0.3 mL) was microwaved at 150 °C (300 watts) for 30 min. The reaction mixture was then heated, using an oil bath, to 150 °C for 15 h followed by filtering through celite with EtOAc (20 mL), and concentrated under reduced pressure. Purification by flash chromatography

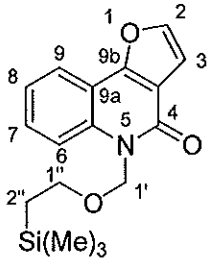
(EtOAc:hexane/3:7) afforded 11 mg of **2.10** (18 %) as an orange solid. Mp 164 °C. IR (KBr, $\nu_{max}$): 3264, 3133, 2361, 2332, 1654, 1576, 1523 and 1502 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 206.0 nm (7745). $^1H$ NMR ($CDCl_3$, 500 MHz): δ 6.22 (d, *J* 1.0 Hz, 2H, H-4, 4``), 7.19 (m, 2H, H-5`, 5```), 7.21 (m, 2H, H-6`, 6```), 7.26 (s, 2H, H-5, 5``), 7.33 (br s, 2H, NH), 7.43 (m, 2H, H-4`, 4```), 7.67 (d, *J* 1.0 Hz, 2H, H-2, 2``), 8.31 (d, *J* 8.5 Hz, 2H, H-3`, 3```). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 108.2 (C-4, 4``), 122.7 (C-6`,6```), 122.9 (C-3, 3``), 125.3 (C-3`, 3```), 128.4 (C-2`, 2```), 130.1 (C-4`, 4```), 130.5 (C-5`, 5```), 135.8 (C-1`, 1```), 144.3 (C-5, 5```), 145.4 (C-2, 2``), 161.0 (2 x C=O). MS (ESI): *m/z* 373 $[M+H]^+$, 395 $[M+Na]^+$. HRMS Calcd. for $C_{22}H_{16}N_2O_4Na$ $[M+Na]^+$: 395.1002. Found: 395.1006.




**N-(2-Iodophenyl)-N-((2-(trimethylsilyl)ethoxy)methyl)furan-3-carboxamide**

(2-(Chloromethoxy)ethyl)trimethylsilane (1.49 mL, 8.42 mmol) was added dropwise to a solution of the **2.07** (635 mg, 2.03 mmol) and sodium hydride (202 mg, 8.42 mmol) in THF (20 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to stir for 11 h (mean while slowly warming up to RT) and was then quenched by adding water (20 mL). The reaction mixture was extracted with EtOAc (3 x 50 mL), washing the combined organic layers with 1M NaOH (30 mL), 1M HCl (30 mL) and brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (EtOAc:hexane/1:9) afforded 855

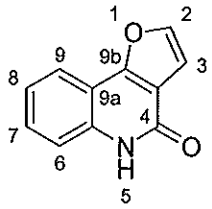
mg of **2.13** (95 %) as an oil. IR (KBr, $\nu_{max}$): 2946, 2921, 2357, 2324, 1655, 1581 and 1471 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 206.0 nm (14577), 226.2 nm (10829). $^1H$ NMR ($CDCl_3$, 500 MHz): δ 0.03 (s, 9H, $SiMe_3$), 0.99 (m, *J* 10 Hz, 2H, H-2```), 3.77 (app d, *J* 5 Hz, 2H, H-1```), 4.57 (d, *J* 10.5 Hz, 1H, H-1``), 5.81 (d, *J* 9 Hz, 1H, H-1b``), 6.28 (s, 1H, H-4), 6.73 (s, 1H, H-5), 7.16 (app t, *J* 7.5 Hz, 1H, H-4`), 7.20 (s, 1H, H-2), 7.37 (d, *J* 8.0 Hz, 1H, H-6`), 7.45 (app t, *J* 8.0 Hz, 1H, H-5`), 7.96 (d, *J* 8.0 Hz, 1H, H-3`). $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 0.0 ($SiMe_3$), 18.5 (C-2```), 66.9 (C-1```), 77.3 (C-1``), 101.4 (C-2`), 111.4 (C-4), 121.9 (C-3), 129.7 (C-5`), 130.9 (C-4`), 132.0 (C-6`), 140.4 (C-3`), 142.5 (C-5), 143.8 (C-1`), 145.9 (C-2), 163.7 (C=O). MS (ESI): *m/z* 445 $[M+H]^+$, 467 $[M+Na]^+$, 910 $[2M+Na]^+$. Anal. Calcd. for $C_{17}H_{22}INO_3Si$: C, 46.05; H, 5.00; N, 3.16. Found: C, 46.09; H, 5.01; N, 3.02.




**5-((2-(Trimethylsilyl) ethoxy)methyl)furo [3,2-*c*]quinolin-4(5*H*)-one**

A mixtue of **2.13** (90.0 mg, 0.20 mmol), KOAc (26.0 mg, 0.26 mmol), *n*-$Bu_4NCl$ (11.0 mg, 0.04 mmol) and PdO (2.5 mg, 0.02 mmol) was stirred in DMA (0.4 mL) at 150 °C under a nitrogen atmosphere for 18 h. The crude mixture was then concentrated under reduced pressure followed by flash chromatography (EtOAc:hexane/15:85) to afford 55 mg of **2.02** (87 %) as a slightly yellowish solid. Mp 61-62 °C. IR (KBr, $\nu_{max}$): 3158, 3133, 2949, 2900, 1662, 1584 and 1499 $cm^{-1}$.

UV (MeOH) $\lambda_{max}(\varepsilon)$: 227 nm (38358), 276 nm (7485), 286 nm (8934), 316 nm (9261), 331 nm (9435). $^1$H NMR ($CDCl_3$, 500 MHz): δ -0.022 (s, 9H, H-$SiMe_3$), 0.96 (t, *J* 8.5, 7.5 Hz, 2H, H-2``), 3.74 (t, *J* 8.5, 8 Hz, 2H, H-1``), 5.86 (s, 2H, H-1`), 7.08 (s, 1H, H-3), 7.35 (app t, *J* 7.5 Hz, 1H, H-8), 7.56 (app t, *J* 8.0 Hz, 1H, H-7), 7.65 (s, 1H, H-2), 7.72 (d, *J* 8.0 Hz, 1H, H-6), 8.02 (d, *J* 8.1 Hz, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 0.0 ($SiMe_3$), 18.4 (C-2``), 66.6 (C-1``), 71.7 (C-1`), 108.8 (C-3), 113.7 (C-3a), 115.1 (C-9a), 116.8 (C-6), 121.3 (C-9), 123.1 (C-8), 129.8 (C-2), 137.9 (C-5a), 144.3 (C-7), 156.1 (C-9b), 160.2 (C=O). MS (ESI): *m/z* 316 $[M+H]^+$, 338 $[M+Na]^+$. Anal. Calcd. for $C_{17}H_{21}NO_3Si$: C, 64.73; H, 6.71; N, 4.44. Found: C, 64.76; H, 6.70; N, 4.45.




**Furo[3,2-*c*]quinolin-4(5*H*)-one**

**Initial attempts**

In the initial attempts, TBAF[167-171] was used either neat or in solution to cleave the *N*-SEM-protecting group to give **1.72**. These are standard literature methods and are only referenced.

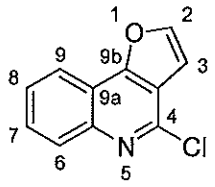
**General methods using aqueous hydrochloric acid**

A solution of **2.02** (100 mg, 0.5 mmol) in either 5 % aq HCl in MeOH (50 mL) or 3 M aq HCl in EtOH (50 mL) was heated under reflux until all starting material was consumed (TLC). After cooling to ambient temperature, the mixture was

neutralized with $NaHCO_3$ and extracted with EtOAc (3 X 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to give a residue which was flash chromatografied (EtOAc:hexane/1:1) to give the desired product **1.72** in 18 mg (19 %) or 33 mg (36 %) (see optimal conditions for data).

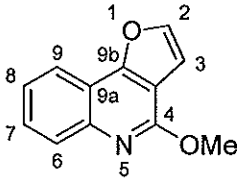
**Optimal conditions using dry HCl**

To a pre-mixed solution of acetyl chloride (43 mL), ethanol (73 mL) and water (5 mL), was added **2.02** (1.82 g, 5.77 mmol) at RT with stirring. After all substrate was dissolved, the reaction flask was fitted with a reflux condenser and heated to 80°C for 11 h, and the reaction mixture was then concentrated under reduced pressure. Purification by flash chromatography (EtOAc:hexane/1:1) afforded 0.90 g of **1.72** (84 %) as an off white solid. $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 7.04 (d, *J* 2.0 Hz, 1H, H-3), 7.25 (app t, *J* 7.4 Hz, 1H, H-8), 7.47 (app d, *J* 7.4 Hz, 1H, H-7), 7.53 (app t, *J* 7.4 Hz, 1H, H-9) 7.88 (d, *J* 7.4 Hz, 1H, H-6), 8.06 (d, *J* 2.0 Hz, 1H, H-2), 11.73 ( br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 108.4, 111.9, 116.2, 116.7, 120.8, 122.9, 130.1, 137.7, 146.1, 156.1, 159.5. MS (ESI): *m/z* 185 $[M+H]^+$. The spectral data were in agreement with previous reported data for this compound.[174,175]




**4-Chlorofuro[3,2-*c*] quinoline**

A mixture of **1.72** (0.87 g, 4.7 mmol), phosphorusoxychloride (10.0 mL) and water (0.5 mL) was refluxed at 135 °C for 4 h. The cold reaction mixture was quenched by adding water (10 mL) and with 25% ammonia. The aqueous layer was extracted with DCM (3 x 150 mL) and EtOAc (3 x 150 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure to afford 0.90 g of the desired 4-chlorofuro[3,2-*c*]quinoline (94 %). $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.03 (d, *J* 2.2 Hz, 1H, H-3), 7.64 (m, 1H, H-8), 7.73 (m, 1H, H-7), 7.82 (d, *J* 2.2 Hz, 1H, H-2), 8.14 (dd, *J* 8.0, 2.0 Hz, 1H, H-9), 8.25 (dd, *J* 7.4, 2.0 Hz, 1H, H-6). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 106.3, 116.6, 119.8, 120.1, 127.2, 128.8, 129.2, 144.3, 145.0, 145.2, 156.4. MS (ESI): *m/z* 204 $[M+H]^+$. The spectral data were in agreement with previous reported data for this compound.[157,158,175]



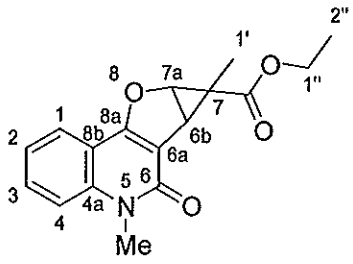

**4-Methoxyfuro[3,2-*c*] quinoline**

A mixture of the 4-chlorofuro[3,2-*c*]quinoline (125 mg, 0.49 mmol) and a methanolic solution of sodium methoxide (approximately 1.2 M, generated from 230 mg sodium in 10 mL of methanol) at RT under nitrogen atmosphere, was stirred until all starting material was consumed (monitored by TLC). The reaction

mixture was extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (EtOAc:hexane/0 to 2.5:100 to 97.5) afforded 100 mg of the **2.01** (80 %). $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.20 (s, 3H, OMe), 6.95 (m, 1H, H-3), 7.46 (app t, *J* 7.2 Hz, 1H, H-8), 7.61 (app t, *J* 7.2 Hz, 1H, H-7), 7.72 (m, 1H, H-2), 7.95 (app d, *J* 7.2 Hz, 1H, H-6), 8.15 (app d, *J* 7.2 Hz, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 53.7 (OMe), 105.4 (C-3), 111.4 (C-3a), 116.0 (C-9a), 120.1 (C-9), 124.4 (C-8), 127.7 (C-6), 128.6 (C-7), 144.3 (C-1), 144.5 (C-5a), 157.64 (C-9b), 157.68 (C-4). MS (ESI): *m/z* 200 $[M+H]^+$. The spectral data were in agreement with previous reported data for this compound.[157,158]

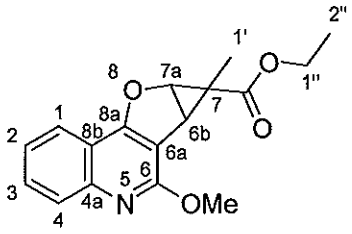
**General method for cyclopropanation attempts when using diazopropane**

To a solution of substrate, **1.30** or **2.01**, (50 mg, 0.25 mmol) in DCM (10 mL) with/without dirhodium tetraacetate (2.49 mg, 2 mol%) at -70 °C, 0 °C or RT, was added an excess of freshly made diazopropane[180] in ether. The reaction mixture was allowed to stir for either 5 hr or 16 hr followed by concentrating the mixture under reduced pressure. The residue was filtered through a silica plug using EtOAc as eluent and concentrated under reduced pressure. The resulting residue was analysed by NMR and mass spectrometry.



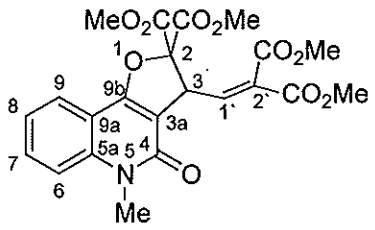

**Ethyl 5,7-dimethyl-6-oxo-5,6b,7,7a -tetrahydro-6*H*-cyclopropa[4,5] furo[3,2-*c*]quinoline-7-carboxylate**

To a solution of **1.30** (482 mg, 2.41 mmol) and dirhodium tetraacetate (24 mg, 0.05 mmol, 2 mol%) in DCM (15 mL) under a nitrogen atmosphere was added a solution of ethyl 2-diazopropanoate (988 mg, 7.71 mmol, 3.2 eq) in DCM (5 mL) over 1 h period followed by 1 h stirring at ambient temperature. The crude reaction mixture was then filtered through a short silica plug using EtOAc as eluent (3 x 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Reverse phase flash chromatography (MeOH:$H_2O$/7:3) afforded 314 mg of **3.01** as a white solid (43 %). Mp 141-142 °C. IR (KBr, $\nu_{max}$): 3081, 2974, 2929, 1716, 1659, 1593 and 1569 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 224 (25226), 298 (3488), 324 (3880) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.93 (s, 3H, H-1`), 1.29 (t, *J* 7.2 Hz, 3H, H-2``), 3.50 (d, *J* 5.6 Hz, 1H, H-6b), 3.73 (s, 3H, NMe), 4.19 (q, *J* 7.2 Hz, 2H, H-1``), 5.18 (d, *J* 5.6 Hz, 1H, H-7a), 7.26 (dd, *J* 7.6, 1.2 Hz, 1H, H-2), 7.41 (d, *J* 8.4 Hz, 1H, H-4), 7.61 (dd, *J* 7.6, 1.6 Hz, 1H, H-3), 7.77 (dd, *J* 7.6, 1.2 Hz, 1H, H-1). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 6.6 (C-1`), 14.5 (C-2``), 20.2 (C-7), 29.6 (NMe), 34.4 (C-6b), 61.5 (C-1``), 72.8 (C-7a), 110.3 (C-6a), 111.8 (C-8b), 115.0 (C-4), 122.2 (C-2), 122.8 (C-1), 131.5 (C-3), 140.6 (C-4a), 161.1 (C-6), 164.0 (C-8a), 173.3 (COOR). MS (ESI): *m/z* 300 $[M+H]^+$, 322 $[M+Na]^+$. HRMS Calcd. for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$: 322.1049. Found: 322.1041.




**Ethyl 6-methoxy-7-methyl-7,7a -dihydro-6b*H*-cyclopropa[4,5] furo[3,2-*c*]quinoline-7-carboxylate**

To a solution of **2.01** (100 mg, 0.50 mmol) and dirhodium tetraacetate (5 mg, 0.01 mmol, 2 mol%) in DCM (3.1 mL) under a nitrogen atmosphere was added a solution of ethyl 2-diazopropanoate (209 mg, 1.60 mmol, 3.2 eq) in DCM (1 mL) over 1 h period followed by 1 h stirring at ambient temperature. The crude reaction mixture was then filtered through a short silica plug using EtOAc as eluent (2 x 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (EtOAc:hexane/5:95) afforded 103 mg of **3.02** as a white solid (69 %). Mp 105 °C. IR (KBr, $\nu_{max}$): 2979, 2949, 2938, 2899, 1707, 1637, 1604 and 1576 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 234 (52189), 320 nm (22709) nm. $^1H$ NMR ($CDCl_3$, 500 MHz): δ 0.86 (s, 3H, H-1`), 1.33 (t, *J* 6.0 Hz, 3H, H-2``), 3.48 (d, *J* 5.6 Hz, 1H, H-6b), 4.14 (s, 3H, OMe), 4.23 (q, *J* 6.0 Hz, 2H, H-1``), 5.25 (d, *J* 5.6 Hz, 1H, H-7a), 7.36 (dd, *J* 6.8, 1.2 Hz, 1H, H-2), 7.61 (dd, *J* 7.2, 1.6 Hz, 1H, H-3), 7.86 (m, 2H, H-4 and H-1). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 6.6 (C-1`), 14.5 (C-2``), 20.1 (C-7), 33.1 (C-6b), 53.7 (OMe), 61.6 (C-1``), 72.9 (C-7a), 106.5 (C-6a), 114.6 (C-8b), 121.1 (C-4), 124.0 (C-2), 127.5 (C-1), 130.1 (C-3), 147.4 (C-4a), 160.4 (C-6), 166.2 (C-8a), 173.7 (COOR). MS (ESI): *m/z* 300 $[M+H]^+$, 322 $[M+Na]^+$. HRMS Calcd. for $C_{17}H_{18}NO_4$ $[M+H]^+$: 300.1230. Found: 300.1221.

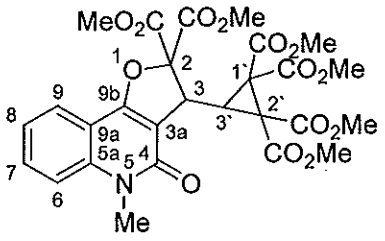



**Dimethyl 3-(3-methoxy-2-(methoxycarbonyl)-3-oxoprop-1-enyl)-5-methyl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2,2(3*H*)-dicarboxylate**

To a solution of **1.30** (100 mg, 0.50 mmol) and dirhodium tetraacetate (5 mg, 0.01 mmol, 2 mol%) in DCM (2.5 mL) under a nitrogen atmosphere was added a solution of dimethyl diazomalonate (293 mg, 1.85 mmol, 3.7 eq) in DCM (0.5 mL) over 3 h period followed by 17 h stirring at ambient temperature (monitored by tlc). The crude was then filtered through a short silica plug using EtOAc as eluent (2 x 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. $^1$H NMR analysis of the crude mixture indicated **3.03** and **3.04** in the ratio of 75:25 which gave a theoretical yield of 55 and 18 % respectivley. A pre-purification by flash chromatography (EtOAc:hexane/1:1) afforded 180 mg of a transparent oil as a mixture of the two products. Reverse phase chromatography (HPLC, MeOH:$H_2O$/7:3) afforded an analytically pure sample of each product.

**3.03**: Mp 179 °C. IR (KBr, $\nu_{max}$): 3464, 3003, 2954, 1744, 1670, 1633, 1593 and 1437 cm$^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 226 (12355), 283 (1738), 292 (1922) nm. $^1$H NMR ($CDCl_3$, 600 MHz): δ 3.63 (s, 3H, NMe), 3.73 and 3.91 (2 x s, 2 x OMe, C-2`), 3.80 and 3.85 (2 x s, 2 x OMe, C-2), 5.61 (d, *J* 10.8 Hz, 1H, H-3), 6.73 (d, *J* 10.8 Hz, 1H, H-1`), 7.26 (dd, *J* 7.2, 3.0 Hz, 1H, H-8), 7.36 (d, *J* 8.4 Hz, 1H, H-6), 7.62 (app. t, *J* 7.8 Hz, 1H, H-7), 7.88 (d, *J* 7.8 Hz, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 29.4 (C-5), 46.7 (C-3), 52.8 and 53.1 (C-2`, 2 x OMe), 53.7 and 54.2 (C-2, 2 x OMe), 93.5 (C-2), 108.0 (C-2`), 111.7 (C-9a), 115.0 (C-6), 122.5 (C-8), 124.0 (C-9), 131.4 (C-3a), 132.5 (C-7), 141.4 (C-5a), 142.3 (C-1`), 159.9 (C-4), 161.9

(C-9b), 164.1 and 164.7 (C-2`, 2 x COOR), 165.1 and 166.1 (C-2, 2 x COOR) MS (ESI): *m/z* 460 $[M+H]^+$, 482 $[M+Na]^+$. HRMS Calcd. for $C_{22}H_{22}NO_{10}$ $[M+H]^+$: 460.1238. Found: 460.1252.

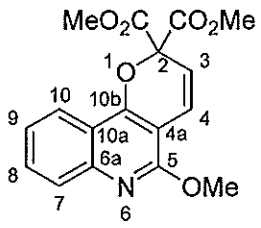


**Tetramethyl 3-(2,2-bis(methoxycarbonyl) -5-methyl-4-oxo-2,3,4,5-tetrahydrofuro [3,2-c]quinolin-3-yl)cyclopropane -1,1,2,2-tetracarboxylate**

**3.04**: Mp 199 °C. IR (KBr, $\nu_{max}$): 3460, 3007, 2954, 1752, 1666, 1638 and 1433 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 229 (14802), 279 (2944), 290 (2931), 326 (2379) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 2.61 (d, *J* 11.0 Hz, 1H, H-3`), 3.66 (s, 3H, NMe), 3.73, 3.82, 3.87 and 3.95 (4 x s, 4 x OMe), 3.78 (s, 2 x OMe), 5.15 (d, *J* 11.0 Hz, 1H, H-3), 7.28 (m, 1H, H-8), 7.37 (d, *J* 8.5 Hz, 1H, H-6), 7.63 (app t, *J* 7.5 Hz, 1H, H-7), 7.88 (d, *J* 8.0 Hz, 1H, H-9). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 29.6 (C-5), 36.7 (C-3`), 43.7 (C-2`), 43.9 (C-3), 45.3 (C-1`), 53.0, 53.2, 53.5, 53.6, 53.7 and 53.9 (6 x OMe), 92.7 (C-2), 108.9 (C-3a), 111.9 (C-9a), 114.7 (C-6), 122.1 (C-8), 123.8 (C-9), 132.1 (C-7), 141.4 (C-5a), 160.1 (C-4), 161.1 (C-9b), 164.4 and 166.0 (C-1`, 2 x COOR), 166.2 and 166.3 (C-2`, 2 x COOR), 167.5 and 167.9 (C-2, 2 x COOR). (ESI): *m/z* 590 $[M+H]^+$, 612 $[M+Na]^+$. HRMS Calcd. for $C_{27}H_{28}NO_{14}$ $[M+H]^+$: 590.1504. Found: 590.1495.

**Attempt to selectively synthesise 3.03**

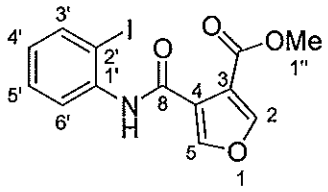
To a solution of **1.30** (100 mg, 0.50 mmol) and dirhodium tetraacetate (5 mg, 0.01 mmol, 2 mol%) in DCM (2.5 mL) under a nitrogen atmosphere was added a solution of dimethyl diazomalonate (79 mg, 0.50 mmol, 1 eq) in DCM (0.5 mL) over 3 h period followed by 17 h stirring at ambient temperature (monitored by TLC). The crude was then filtered through a short silica plug using EtOAc as eluent (2 x 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Analysis of the crude mixture revealed formation of the product **3.03** to be less than 5 % according to the $^1$H NMR integrals, and starting material could be recovered in 90 %.




**Dimethyl 5-methoxy-2*H*-pyrano [3,2-*c*]quinoline-2,2-dicarboxylate**

To a solution of **1.30** (100 mg, 0.5 mmol) and dirhodium tetraacetate (4.95 mg, 0.01 mmol, 2 mol%) in DCM (2.5 mL) under nitrogen atmosphere, was added a solution of dimethyl diazomalonate (293 mg, 1.85 mmol, 3.7 eq) in DCM (0.5 mL) over 3 h period followed by 17 h stirring at ambient temperature (monitored by tlc). The crude reaction mixture was then filtered through a short silica plug using EtOAc as eluent (2 x 20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (EtOAc:hexane/1:9) afforded 63 mg of **3.05** as a white solid (38 %). Mp 85-86 °C. IR (KBr, $\nu_{max}$): 3101, 3015, 2954, 1761, 1740, 1642, 1605, 1569, 1507, 1475 cm$^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 229 (4083), 254 (2936), 263 (2520), 317 (982) nm. $^1$H NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 2 x 3H, 2 x COO<u>Me</u>), 4.09 (s,

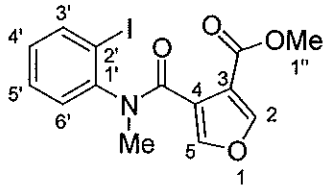
3H, OMe), 6.05 (d, *J* 10.0 Hz, 1H, H-3), 6.97 (d, *J* 10.0 Hz, 1H, H-4), 7.39 (dd, *J* 7.0, 1.0 Hz, 1H, H-9), 7.62 (dd, *J* 7.0, 1.0 Hz, 1H, H-8), 7.77 (d, *J* 8.0 Hz, 1H, H-7), 8.19 (d, *J* 8.0 Hz, 1H, H-10). $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 53.86 (C-2, 2 x COOMe), 53.89 (C-5, OMe), 101.4 (C-4a), 82.3 (C-2), 116.9 (C-3), 117.7 (C-10a), 120.9 (C-4), 122.4 (C-10), 124.2 (C-9), 127.2 (C-7), 130.7 (C-8), 147.2 (C-6a), 155.4 (C-10b), 158.7 (C-5), 167.0 (C-2, 2 x COOR). MS (ESI): *m/z* 330 $[M+H]^+$, 352 $[M+Na]^+$, 298 $[M-CH_3O]^+$. HRMS Calcd. for $C_{17}H_{16}NO_6$ $[M+H]^+$: 330.0972. Found 330.0960.




**Methyl 4-{[(2-iodophenyl) amino]carbonyl}-3-furoate**

To a pre-stirred solution (30 min at 0 °C) of 2-iodoaniline (2.4 g, 10.8 mmol) and trimethylaluminium (8.14 mL, 16.3 mmol) in DCM (60 mL), was added dimethyl 3,4-furandicarboxylate (5.0 g, 27.1 mmol; pre-dissolved in minimum volume of dry DCM). The mixture was allowed to reach RT and was then treated under reflux conditions for 48 h, where upon it was quenched carefully with aqueous 1M HCl until no further bubbles appeared. After the mixture was concentrated under reduced pressure, it was then redissolved in EtOAc (30 mL) and filtered through a celite plug and again, concentrated under reduced pressure. Flash chromatography (EtOAc:DCM:hexane/5:20:75) afforded 1.8 g of **3.06** (44 %) as an off white solid. Mp 140-141 °C. IR (KBr, $\nu_{max}$): 3183, 3117, 3028, 1699, 1659, 1565 and 1536 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 226.0 (8457) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 3.95 (s,

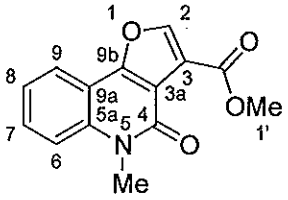
3H, H-1``), 6.93 (app t, *J* 8.0 Hz, 1H, H-4`), 7.38 (app t, *J* 8.8 Hz, 1H, H-5`), 7.80 (dd, *J* 8.0, 1.6 Hz, 1H, H-6`), 7.87 (dd, *J* 8.0, 1.2 Hz, 1H, H-3`), 8.13 (m, 1H, H-2), 8.28 (m, *J* 7.2 Hz, 1H, H-5). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 52.9 (C-1``), 93.6 (C-2`), 115.4 (C-3), 122.0 (C-4), 126.7 (C-6`), 127.5 (C-4`), 128.8 (C-5`), 139.2 (C-1`), 139.5 (C-3`), 151.3 (C-2), 151.9 (C-5), 159.8 (C=O), 165.2 (C-3, C=O). MS (ESI): *m/z* 372 $[M+H]^+$, 378 $[M+Li]^+$. HRMS Calcd. for $C_{13}H_{10}INO_4Na$ $[M+Na]^+$: 393.9546. Found: 393.9532.




**Methyl 4-{[(2-iodophenyl) (methyl)amino]carbonyl} -3-furoate**

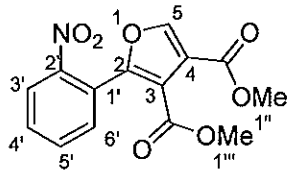
To a solution of **3.06** (100 mg, 0.27 mmol) and iodomethane (168 µL, 2.70 mmol) in DMF (3 mL), was added sodium hydride (20 mg, 0.50 mmol) portionwise at RT under nitrogen atmosphere. The mixture was stirred for 3 h at ambient temperature, quenched with water (10 mL) and then extracted with EtOAc (2 x 10 mL) to afford 100 mg of **3.07** (96 %) as an off white solid. Mp 108 °C. IR (KBr, $\nu_{max}$): 2361, 1732 and 1646 cm$^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 223 (9629) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 3.37 (s, 3H, NMe), 3.87 (s, 3H, H-1``), 6.95 (app t, *J* 7.2 Hz, 1H, H-4`), 7.22-7.30 (m, 2H, H-6` and H-5`), 7.44 (d, *J* 1.6 Hz, 1H, H-2), 7.73 (d, *J* 1.6 Hz, 1H, H-5), 7.81 (dd, *J* 8.0, 1.6 Hz, 1H, H-3`). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 29.9 (NMe), 52.1 (C-1``), 99.8 (C-5), 118.2 (C-3), 121.5 (C-4), 129.5 (C-6` or 5`), 129.7 (C-6` or 5`), 129.9 (C-4`), 140.1 (C-3`), 141.5 (C-2), 147.7 (C-5), 162.7 (COOR),

163.6 (C=O). MS (ESI): *m/z* 386 $[M+H]^+$, 408 $[M+Na]^+$. HRMS Calcd. for $C_{14}H_{12}INO_4Na$ $[M+Na]^+$: 407.9703. Found: 407.9694.



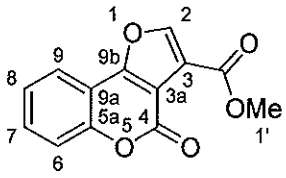

**Methyl 5-methyl-4-oxo -4,5-dihydrofuro [3,2-*c*]quinoline -3-carboxylate**

A mixture of **3.07** (100.0 mg, 0.260 mmol), KOAc (35.0 mg, 0.360 mmol), *n*-$Bu_4NCl$ (18.0 mg, 0.065 mmol), PdO (3.2 mg, 0.026 mmol) in *N*,*N*-DMA (1.3 mL) under a nitrogen atmosphere was heated to 150 °C for 18 h followed by concentrating the crude mixture under reduced pressure. Purification by flash chromatography (EtOAc:hexane/1:1) afforded 15 mg of **3.08** (22 %) as an off white solid. Mp 89-90 °C. IR (KBr, $\nu_{max}$): 3151, 3070, 2956, 1714, 1661, 1570 and 1542 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 225 (7718) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.49 (s, 3H, NMe), 3.80 (s, 3H, H-1`), 7.33 (m, 1H, H-8), 7.46 (d, *J* 8.4 Hz, 1H, H-6), 7.60 (m, 1H, H-7), 8.02 (m, 1H, H-9), 8.19 (s, 1H, H-2). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 29.8 (C-10), 52.5 (C-1`), 112.2 (C-9a), 112.4 (C-3a), 115.2 (C-6), 118.6 (C-3), 121.7 (C-9), 122.6 (C-8), 130.7 (C-7), 138.9 (C-5a), 149.5 (C-2), 156.9 (C-9b), 158.0 (COOR), 162.4 (C-4). MS (ESI): *m/z* 258 $[M+H]^+$, 280 $[M+Na]^+$. HRMS Calcd. for $C_{14}H_{11}NO_4$ $[M+H]^+$: 258.0760. Found: 258.0759.



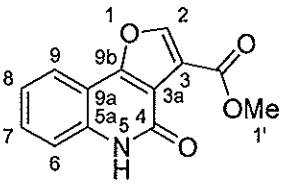
**Dimethyl 2-(2-nitrophenyl) furan-3,4-dicarboxylate**

A mixture of iodo-2-nitrobenzene (2.0 g, 8.0 mmol), dimethyl 3,4-furan-dicarboxylate (4.4 g, 24.0 mmol), potassium acetate (1.2 g, 12.0 mmol), *n*-tetrabutylammonium chloride (560 mg, 2.0 mmol) and palladium acetate (180 mg, 0.8 mmol) in DMA (12 mL) under a nitrogen atmosphere, was heated to 150 °C for 24 h. The mixture was then concentrated and filtered through celite and the residual washed with EtOAc. The filtrate was then concentrated with silica and purified by flash chromatography (EtOAc:hexane/1:9) to afford 990 mg of **3.09** (40 %) as a yellow solid. Mp 83-84 °C. IR (KBr, $\nu_{max}$): 3427, 3138, 2958, 1716, 1528 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 246.0 (8740) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.75 (s, 3H, H-1```), 3.89 (s, 3H, H-1``), 7.63-7.73 (m, 3H, H-4`, H-5` and H-6`), 8.00 (s, 1H, H-5), 8.10 (m, 1H, H-3`). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 52.3 (C-1``), 52.4 (C-1```), 115.5 (C-3), 119.7 (C-4), 123.9 (C-1`), 124.9 (C-3`), 131.2 (C-6`), 132.7 (C-4`), 133.0 (C-5`), 147.7 (C-2), 148.8 (C-2`), 153.1 (C-5), 162.1 (C-3, COOR), 162.7 (C-4, COOR). MS (ESI): *m/z* 328 $[M+Na]^+$. HRMS Calcd. for $C_{14}H_{11}NO_7Na$ $[M+Na]^+$: 328.0427. Found: 328.0424.



**Methyl 4-oxo-4*H*-furo[3,2-c] chromene-3-carboxylate**

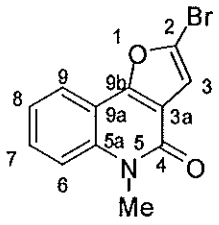
Further elution from the above purification afforded 40 mg of the crude product **3.10** (2 %). This residual was further purified with HPLC (MeOH:$H_2O$/8:2) to give an analytically pure sample as a thin film. IR (KBr, $\nu_{max}$): cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 272 (2976), 284 (3053), 310 (2827) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 3.97 (s, 3H, H-1`), 7.38 (app t, *J* 7.6 Hz, 1H, H-8), 7.47 (app d, *J* 7.6 Hz, 1H, H-6), 7.58 (dd, *J* 7.6, 1.6 Hz, 1H, H-7), 7.90 (dd, *J* 7.6, 1.2 Hz, 1H, H-9), 8.22 (s, 1H, H-2). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 52.7 (C-1`), 108.0 (C-3), 112.2 (C-9a), 117.5 (C-6), 118.6 (C-3a), 121.3 (C-9), 124.8 (C-8), 131.9 (C-7), 150.1 (C-2), 153.2 (C-5a), 155.8 (C-4), 159.5 (C-9b), 161.5 (COOR). MS (ESI): *m/z* 245 $[M+H]^+$, 267 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_8O_5$: C, 63.94; H, 3.30. Found: C, 63.48; H, 2.98. HRMS Calcd. for $C_{13}H_8O_5$ $[M+H]^+$: 245.0444. Found: 245.0437.



**Methyl 4-oxo-4,5-dihydrofuro [3,2-*c*]quinoline-3-carboxylate**

To a solution of **3.11** (990 mg, 3.25 mmol) in MeOH (40 mL) under nitrogen atmosphere, was added palladium on activated carbon (99 mg). The reaction flask was purged with hydrogen gas and the mixture was stirred for 2 h and then filtered through celite and solvents removed under reduced pressure. To the residue was

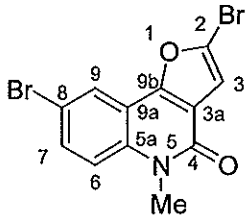
added toluene (40 mL), and the resultant mixture was refluxed for 1.5 h. After cooling, the title compound **3.11** precipitated and was collected by filtration and dried to afford 147 mg (18 %) as an off white solid. Mp 251 °C. IR (KBr, $\nu_{max}$): 3154, 3011, 2954, 2889, 2844, 1753, 1675 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 230 (19543), 262 (6932), 282 (5337), 320 (5561) nm. $^{1}H$ NMR ($CDCl_3$, 500 MHz): δ 4.00 (s, 3H, OMe), 7.33 (app t, *J* 8.0 Hz, 1H, H-8), 7.49 (d, *J* 8.0 Hz, 1H, H-6), 7.58 (app t, *J* 8.0 Hz, 1H, H-7), 8.00 (d, *J* 8.0 Hz, 1H, H-9), 8.27 (s, 1H, H-2). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 53.5 (OMe), 110.5 (C-3), 112.5 (C-9a), 117.8 (C-3a), 119.1 (C-6), 121.2 (C-9), 125.7 (C-8), 132.6 (C-7), 150.5 (C-2), 159 (C-9b), 160.3 (C-4), 163.5 (COOR). MS (ESI): *m/z* 244 $[M+H]^+$, 266 $[M+Na]^+$. HRMS Calcd. for $C_{13}H_9NO_4$ $[M+H]^+$: 244.0604. Found: 244.0592.




**2-Bromo-5-methylfuro[3,2-*c*] quinolin-4(5*H*)-one**

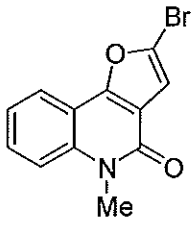
To a solution of **1.30** (500 mg, 2.50 mmol) in chloroform (4 mL) and KOAc (60 mg, 0.10 mmol) at 50 °C under a nitrogen atmosphere, was added bromine (320 μL, 6.25 mmol) over a period of 5 min. The reaction mixture was stirred for 15 h followed by addition of 5 % aqueous solution of $NaHSO_3$ to quench the reaction. The organic layer was washed with a 5 % sodium bicarbonate solution (2 x 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure to afford 720 mg of a mixture of **3.12** and **3.13**. Reverse phase chromatography (HPLC, MeOH:$H_2O$/8:2) afforded an analytically pure sample of each product:

**3.12**: Mp 186 °C. IR (KBr, $\nu_{max}$): 3126, 1661, 1589 and 1503 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 234 (15634), 281 (7557), 292 (7685), 323 (7712) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 3.80 (s, 3H, NMe), 7.00 (s, 1H, H-3), 7.34 (dd, *J* 7.2, 1.2 Hz, 1H, H-8), 7.47 (d, *J* 8.8 Hz, 1H, H-6), 7.59 (ddd, *J* 7.2, 1.6, 1.2 Hz, 1H, H-7), 8.00 (dd, *J* 7.6, 1.6 Hz, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 29.8 (C-10), 110.2 (C-3), 112.5 (C-9a), 115.3 (C-6), 117.4 (C-3a), 121.3 (C-9), 122.8 (C-8), 125.8 (C-2), 130.1 (C-7), 138.1 (C-5a), 156.3 (C-9b), 158.3 (C=O). MS (ESI): *m/z* 278, 280 (1:1 ratio) $[M+H]^+$, 300, 302 (1:1 ratio) $[M+Na]^+$. HRMS Calcd. for $C_{12}H_9BrNO_2$: 277.9811. Found: 277.9809. Anal. Calcd. for $C_{12}H_9BrNO_2$: C, 51.83; H, 2.90; N, 5.04. Found: C, 51.24; H, 2.90; N, 4.66.




**2,8-Dibromo-5-methylfuro [3,2-*c*]quinolin-4(5*H*)-one**

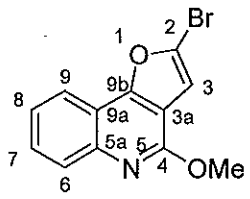
**3.13**: Mp 204 °C. IR (KBr, $\nu_{max}$): 3134, 1663, 1581, 1561, 1491 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 245 (18975), 285 (3472), 295 (4018), 333 (4032) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H, NMe), 7.01 (s, 1H, H-3), 7.34 (d, *J* 8.8 Hz, 1H, H-6), 7.66 (m, 1H, H-7), 8.12 (m, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 29.9 (C-10), 110.4 (C-3), 113.8 (C-9a), 115.9 (C-8), 117.0 (C-6), 118.2 (C-3a), 123.7 (C-9), 126.7 (C-2), 132.8 (C-7), 136.9 (C-5a), 154.8 (C-9b), 157.9 (C-4). MS (ESI): *m/z* 356, 358, 360 (1:2:1 ratio) $[M+H]^+$. Anal. Calcd. for $C_{12}H_7Br_2NO_2$: C, 40.37; H, 1.98; N, 3.92. Found: C, 39.80; H, 1.98; N, 3.48. HRMS Calcd. for $C_{12}H_7Br_2NO_2$ $[M+H]^+$: 355.8916. Found: 355.8901.




**2-Bromo-5-methylfuro [3,2-*c*]quinolin-4(5*H*)-one**

*To selectively synthesise 3.12:*

To a solution of **1.30** (200 mg, 1.0 mmol) in chloroform (4 mL) at 50 °C under a nitrogen atmosphere, was added a solution of bromine (25 μL, 0.5 mmol) in chloroform (1 mL) over a period of 5 h. The reaction mixture was then quenched with a 5 % aqueous solution of $NaHSO_3$. The organic layer was then washed with a 5 % solution of $NaHCO_3$ (2 x 20 mL) and water (2 x 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure to afford 261 mg of the desired mono brominated product **3.12** (94 %). See above for data.

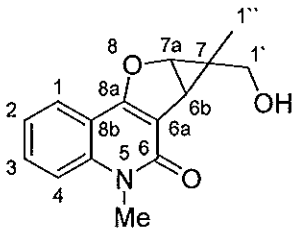



**2-Bromo-4-methoxyfuro [3,2-*c*]quinoline**

To a solution of **2.01** (100 mg, 0.5 mmol) in DCE (3 mL) at 80 °C under a nitrogen atmosphere, was added a solution of bromine (12.5 μL, 0.25 mmol) in DCE (0.5 mL) over a period of 5 min. The reaction mixture was stirred for 15 h followed by addition of 5 % aqueous solution of $NaHSO_3$ to quench the reaction. The organic layer was then washed with 5 % $NaHCO_3$ (2 x 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (EtOAc:hexane/10-

50:90-50) afforded 32 mg of the desired mono brominated product **3.14** (23 %). Mp 121-122 °C. IR (KBr, $\nu_{max}$): 3130, 2366, 1646, 1601, 1532, 1507, 1483 cm-1. UV (MeOH) $\lambda_{max}(\varepsilon)$: 242 (20659), 266 (4245), 276 (4250), 284 (2946) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.19 (s, 3H, OMe), 6.89 (s, 1H, H-3), 7.47 (dd, *J* 8.4, 1.2 Hz, 1H, H-8), 7.62 (dd, *J* 8.4, 1.2 Hz, 1H, H-7), 7.95 (d, *J* 8.4 Hz, 1H, H-6), 8.11 (m, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 53.8 (OMe), 107.3 (C-3), 113.0 (C-3a), 115.0 (C-9a), 120.0 (C-9), 124.7 (C-8), 126.5 (C-2), 127.8 (C-6), 128.9 (C-7), 144.2 (C-5a), 156.2 (C-4), 158.4 (C-9b). MS (ESI): *m/z* 278, 280 (1:1 ratio) $[M+H]^+$. HRMS Calcd. for $C_{12}H_8BrNO_2$ $[M+H]^+$: 277.9811. Found: 277.9804.

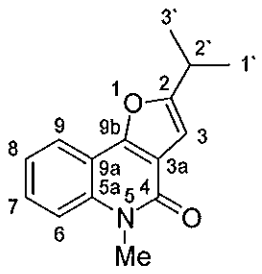
General method for formylation under Vilsmeier Haak conditions, and acetylation using acetyl chloride and aluminium trichloride, of compounds **2.01** and **1.30** see ref.[276] and ref.[277] respectively.




**7-(Hydroxymethyl)-5,7-dimethyl -5,6b,7,7a-tetrahydro-6*H*-cyclopropa [4,5]furo[3,2-*c*]quinolin-6-one**

To a solution of **3.01** (160 mg, 0.54 mmol) in dry dimethoxyethane (20 mL) at ambient temperature under nitrogen atmosphere, was added lithium borohydride (1.44 mL, 3.21 mmol). After addition the reaction mixture was stirred for 18 h and then heated to 50 °C for 1 h followed by quenching and washing with water (2 x 30 mL), the organic layer was dried with $MgSO_4$ and concentrated under reduced

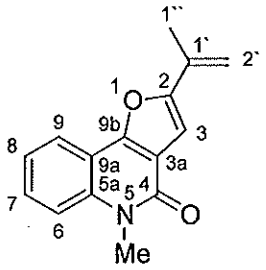
pressure. Purification of the residual using a short silica plug (MeOH:EtOAc/5:95) afforded 128 mg of the desired alcohol **4.01** (93 %). Mp 169-170 °C. IR (KBr, $\nu_{max}$): 3350, 3309, 2921, 2905, 2831, 1646, 1622, and 1585 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 225 (29434), 323 (7604), 337 (6677) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.88 (s, 3H, H-1``), 2.93 (d, *J* 6.0 Hz, 1H, H-6b), 3.59 (s, 2H, H-1`), 3.76 (s, 3H, NMe), 4.83 (d, *J* 6.0 Hz, 1H, H-7a), 7.28 (ddd, *J* 7.2, 1.6, 0.8 Hz, 1H, H-2), 7.43 (d, *J* 8.8 Hz, 1H, H-4), 7.61 (ddd, *J* 8.8, 1.6, 1.2 Hz, 1H, H-3), 7.77 (dd, *J* 8.0, 1.2 Hz, 1H, H-1). $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 8.7 (C-1``), 19.4 (C-7), 28.8 (C-6b), 29.8 (NMe), 67.4 (C-1`), 71.6 (C-7a), 110.4 (C-6a), 112.4 (C-8b), 115.1 (C-4), 122.5 (C-2), 122.8 (C-1), 131.4 (C-3), 140.1 (C-4a), 161.8 (C-6), 164.3 (C-8a). MS (ESI): *m/z* 258 $[M+H]^+$, 280 $[M+Na]^+$. HRMS Calcd. for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$: 280.0944. Found: 280.0932.




**2-Isopropyl-5-methylfuro [3,2-*c*]quinolin-4(5*H*)-one**

To a solution of **4.01** (120 mg, 0.47 mmol) and mesyl chloride (54.5 µL, 0.70 mmol) in DCM (4 mL) at 0 °C under a nitrogen atmosphere, was added triethylamine (130 µL, 0.94 mmol). The reaction mixture was stirred for 30 min and then lithium triethylborohydride (609 µL, 0.61 mmol, 1 M solution in THF) was added with continued stirring for 2 h followed by concentrating the solution under reduced pressure. Purification of the residual by flash chromatography (acetone:hexane/1:3) afforded a mixture of two products **4.04** and **4.05** (ratio of

73:17), in a total yield of 70 mg. Data for **4.04**, $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.38 and 1.39 (d, *J* 4.0 Hz, 6H, H-2` and H-1``), 3.14 (br sep, *J* 7.2 Hz, 1H, H-1`), 3.80 (s, 3H, NMe), 6.67 (s, 1H, H-3), 7.31 (app t, *J* 7.2 Hz, 1H, H-8), 7.45 (d, *J* 8.4 Hz, 1H, H-6), 7.56 (m, 1H, H-7), 8.00 (dd, *J* 8.0, 1.6 Hz, 1H, H-9). MS (ESI): *m/z* 242 $[M+H]^+$, 264 $[M+Na]^+$. The data were in agreement with previous reported data for this compound.[206-208]




**2-Isopropenyl-5-methylfuro [3,2-*c*]quinolin-4(5*H*)-one**

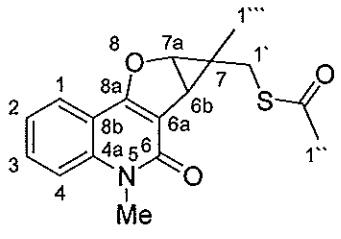
**Method A**

To a solution of **4.01** (20 mg, 0.077 mmol) and mesyl chloride (9 μL, 0.116 mmol) in dry DCM (1 mL) at 0 °C under nitrogen atmosphere, was slowly added pyridine (12.6 μL, 0.154 mmol). The reaction mixture was allowed to reach room temperature over a period of 4 h and was then quenched and washed with water (2 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residual by flash chromatography (EtOAc:hexane/3:7) afforded 16 mg of the ring opened product **4.05** (86 %). Mp 135-136 °C. IR (KBr, $\nu_{max}$): 3109, 1663, 1585, 1438 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 210 (29855), 245 (23749), 305 (13271) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H, H-1``), 3.80 (s, 3H, NMe), 5.19 (s, 1H, H-2a`), 5.80 (s, 1H, H-2b`), 6.92 (s, 1H, H-3), 7.32 (app

t, *J* 7.2 Hz, 1H, H-8), 7.46 (d, *J* 8.4 Hz, 1H, H-6), 7.56 (ddd, *J* 8.4, 7.2, 1.2 Hz, 1H, H-7), 8.05 (dd, *J* 8.0, 1.6 Hz, 1H, H-9). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 19.5 (C-1``), 29.7 (NMe), 104.5 (C-3), 112.9 (C-2`), 113.3 (C-9a), 115.3 (C-6), 117.1 (C-3a), 121.5 (C-9), 122.5 (C-8), 129.7 (C-7), 132.5 (C-1`), 138.6 (C-5a), 154.7 (C-9b), 156.7 (C-2), 159.6 (C=O). MS (ESI): *m/z* 240 $[M+H]^+$, 262 $[M+Na]^+$. HRMS Calcd. for $C_{15}H_{13}NO_2$ $[M+H]^+$: 240.1019. Found: 240.1014. The data were in agreement with previous reported data for this compound.[206]

**Method B**

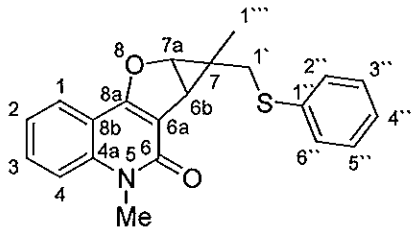
To a solution of **4.01** (0.010 mg, 0.038 mmol) in diethyl ether (1 mL) at -40 °C under a nitrogen atmosphere, was slowly added phosphorous tribromide (2 x 6 µL, 0.078 mmol). After complete addition the reaction mixture was allowed to slowly warm to room temperature with continued stirring for 24 h, then concentrated under reduced pressure. Purification of the residual by flash chromatography (EtOAc:hexane/1:1) afforded 9 mg of **4.05** (96 %).




**S-[(5,7-Dimethyl-6-oxo-5,6b,7,7a-tetrahydro-6*H*-cyclopropa[4,5] furo[3,2-*c*]quinolin-7-yl)methyl] ethanethioate**

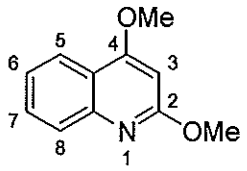
To a solution of DIAD (321 µL, 1.63 mmol) in dry toluene (2 mL) under a nitrogen atmosphere at -15 °C was added triphenylphosphine (426 mg, 1.63 mmol). After 15 min a solution of **4.01** (120 mg, 0.47 mmol) and thioacetic acid (100 µL, 1.4 mmol)

in dry toluene (1 mL) and THF (3 mL), was added over a period of 5 min via syringe and stirring continued at -15 °C for another 30 min. The temperature was then allowed to warm to rt with continued stirring for 48 h. The reaction mixture was then concentrated, diluted with DCM (3 mL) and mixed with silica (30 mg). Purification of the silica mixed residual by flash chromatography (EtOAc:hexane/2:8) afforded 108 mg of the desired thio acetic acid derivative **4.06** (74 %). Mp 166-167 °C. IR (KBr, $\nu_{max}$): 3056, 2978, 2950, 2921, 1683, 1650 and 1593 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 225 (37340), 305 (5731), 324 (6987) nm. $^{1}H$ NMR ($CDCl_3$, 400 MHz): δ 0.80 (s, 3H, H-1```), 2.41 (s, 3H, H-1``), 2.85 (d, *J* 14.1 Hz, 1H, H-1a`), 2.93 (d, 6.1 *J* Hz, 1H, H-6b), 3.09 (d, *J* 14.1 Hz, 1H, H-1b`), 3.73 (s, 3H, NMe), 4.76 (d, *J* 6.1 Hz, 1H, H-7a), 7.23 (dd, *J* 7.2, 1.0 Hz, 1H, H-2), 7.40 (d, *J* 8.8 Hz, 1H, H-4), 7.59 (dd, *J* 7.6, 1.6 Hz, 1H, H-3), 7.73 (m, *J* 8.0 Hz, 1H, H-1). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 10.3 (C-1```), 18.1 (C-7), 29.6 (NMe), 30.8 (C-1``), 32.1 (C-6b), 36.5 (C-1`), 72.6 (C-7a), 110.6 (C-6a), 112.1 (C-8b), 114.9 (C-4), 122.2 (C-2), 122.7 (C-1), 131.2 (C-3), 140.3 (C-4a), 161.3 (C-6), 163.9 (C-8a), 195.7 (S-C=O). MS (ESI): *m/z* 316 $[M+H]^+$, 338 $[M+Na]^+$. Anal. Calcd. for: C, 64.74 ; H, 5.43 ; N, 4.44 . Found: C, 63.61 ; H, 5.43 ; N, 4.37. HRMS Calcd. for $C_{17}H_{17}NO_3S$ $[M+H]^+$: 316.1001. Found: 316.1007.




**5,7-Dimethyl-7-[(phenylsulfanyl) methyl]-5,6b,7,7a-tetrahydro-6*H*-cyclopropa[4,5]furo[3,2-*c*]quinolin-6-one**

To a solution of DIAD (1.069 mL, 4.67 mmol) in dry toluene (7 mL) under nitrogen atmosphere at -15 °C, was added triphenylphosphine (1.42 g, 4.67 mmol). After 15 min a solution of **4.01** (400 mg, 1.57 mmol) and thiophenol (477 µL, 4.67 mmol) in dry toluene (3.5 mL) and THF (10 mL), was added over a period of 5 min via syringe and stirring continued at -15 °C for another 30 min. The temperature was then allowed to warm to room temperature with continued stirring for 48 h. Then the reaction mixture was concentrated, diluted with DCM (3 mL) and mixed with silica (70 mg). Purification of the silica mixed residual by flash chromatography (EtOAc:hexane/2:8) afforded 353 mg of the desired thio benzene derivative **4.09** (65 %). Mp 144-145 °C. IR (KBr, $\nu_{max}$): 3040, 1655, 1638, 1593 and 1565 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 224 (20489), 325 (3631) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.92 (s, 3H, H-1```), 2.73 (d, *J* 13.2 Hz, 1H, H-1a`) 2.91 (d, *J* 6.0 Hz, 1H, H-6b), 3.27 (d, *J* 13.2 Hz, 1H, H-1b`), 3.73 (s, 3H, NMe), 4.65 (d, *J* 6.0 Hz, 1H, H-7a), 7.23 (m, 1H, H-4``), 7.24 (m, 1H, H-2), 7.32 (app t, *J* 7.2 Hz, 2H, H-3``), 7.39 (d, *J* 8.4 Hz, 1H, H-4), 7.44 (m, 2H, H-2``), 7.58 (dd, *J* 7.2, 1.6 Hz, 1H, H-3), 7.72 (dd, *J* 8.2, 1.6 Hz, 1H, H-1). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 10.3 (C-1```), 17.5 (C-7), 29.6 (NMe), 31.7 (C-6b), 42.9 (C-1`), 72.5 (C-7a), 110.7 (C-6a), 112.2 (C-8b), 114.9 (C-4), 122.1 (C-2), 122.7 (C-1), 126.8 (C-4``), 129.3 (C-3``), 130.6 (C-2``), 131.2 (C-3), 136.7 (C-1``), 140.3 (C-4a), 161.5 (C-6), 163.8 (C-8a). MS (ESI): *m/z* 350 $[M+H]^+$, 372 $[M+Na]^+$. HRMS Calcd. for $C_{21}H_{19}NO_2SNa$ $[M+Na]^+$: 372.1028. Found: 372.1021.



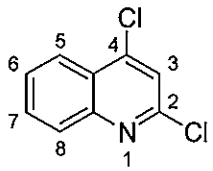

**2,4-Dimethoxyquinoline**

**Method A**[259]

To a suspension of 2,4-dihydroxyquinoline (2.58 g, 16 mmol) in anhydrous benzene (80 mL) was added silver carbonate (8.80 g, 32 mmol) under a nitrogen atmosphere. The resulting slurry was stirred for 5 min to give a yellowish suspension followed by slow addition of methyl iodide (4.00 mL, 64 mmol), and then, continued stirring for three days in the dark at ambient temperature. The mixture was then filtered through Celite and the remaining solid were washed with EtOAc (5 x 20 mL). After concentrating under reduced pressure, flash chromatography (EtOAc:hexane/5:95) afforded 1.54 g of the desired product **5a** (51 %). Mp 80-81 °C (lit.[266] 81-82 °C). $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.00 (s, 3H, C-4 OMe), 4.08 (s, 3H, C-2 OMe), 6.23 (s, 1H, H-3), 7.34 (app t, *J* 6.8 Hz, 1H, H-6), 7.61 (app t, *J* 6.8 Hz, 1H, H-7), 7.82 (d, *J* 8.8 Hz, 1H, H-8), 8.05 (dd, *J* 8.4, 1.6 Hz, 1H, H-5). MS (ESI): *m/z* 190 $[M+H]^+$. The spectral data were in agreement with previous reported data for this compound.[264,266]

**Method B**[20] (in two steps)

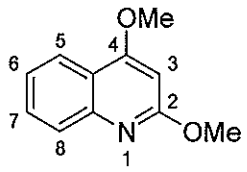
Step 1




**2,4-Dichloroquinoline**

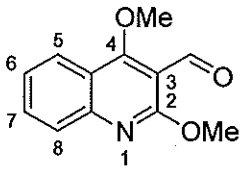
A mixture of aniline (6.70 g, 72 mmol) and malonic acid (11.70 g, 112 mmol) was heated under reflux in phosphorus oxychloride (60 mL), with stirring, for 5 h. The mixture was cooled, poured into crushed ice with vigorous stirring and then made alkaline with 5 M sodium hydroxide. Filtration gave the crude product as a brown solid. A 4 h continuous soxhlet extraction with hexane followed by concentrating under reduced pressure afforded a pale yellow powder. Flash chromatography (EtOAc:hexane/5:95) afforded 5.16 g of the desired product (36 %). Mp 66-67 °C (lit.[278] 66 °C). $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.52 (s, 3H, H-3), 8.21 (m, 1H, H-5), 8.04 (m, 1H, H-8), 7.80 (dd, *J* 9.2, 1.6 Hz, 1H, H-7), 7.66 (dd, *J* 9.6, 1.6 Hz, 1H, H-6). MS (ESI): *m/z* 197 $[M+H]^+$. The data were in agreement with previous reported data for this compound.[264]

Step 2



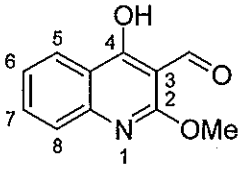

**2,4-Dimethoxyquinoline**

Dichloroquinoline (5.16 g, 26.06 mmol was heated under reflux in a methanolic sodium methoxide solution (from 4.1 g, 176 mmol Na in 95 mL MeOH) for 24 h. The reaction mixture was cooled and poured into ice-cold water, and the resulting white precipitate was filtered off, yielding 4.80 g of the desired product **5.06** (97%).




**2,4-Dimethoxyquinoline -3-carbaldehyde**

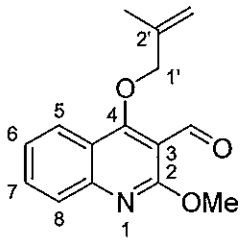
To a solution of **5.06** (525 mg, 2.78 mmol) in THF (28 mL) under nitrogen atmosphere at -20 °C, was added *n*-butyllithium (4.78 mL, 3.61 mmol) over a period of 10 min. The reaction mixture was then allowed to warm to -2 °C and was stirred at that temperature for 2 h, followed by re-cooling to -20 °C again and then DMF in THF (2 mL) was added to the red metallation mixture over a period of 10 min. The reaction mixture was then allowed to warm to -10 °C and was stirred at that temperature for another 2 h. The resulting colourless mixture was then quenched with water (10 mL), extracted with DEE (3 x 50 mL), the combined organic layers were dried with $Na_2SO_4$ and finally concentrated under reduced pressure. Flash chromatography (EtOAc:hexane/5:95) afforded 585 mg of the desired product **5.05** (97 %). Mp 82 °C (lit.[261] 82 °C). $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.15 (s, 2 x OMe), 7.41 (m, 1H, H-6), 7.72 (m, 1H, H-7), 7.80 (d, *J* 8.4 Hz, 1H, H-8), 8.15 (dd, *J* 8.4, 1.2 Hz, 1H-5). MS (ESI): *m/z* 218 $[M+H]^+$. The data were in agreement with previous reported data.[261,262,267]




**4-Hydroxy-2-methoxyquinoline -3-carbaldehyde**

**5.05** (450 mg, 2.07 mmol) was dissolved in 5 % aqueous hydrochloric acid (50 mL) by heating. The solution was allowed to stand at RT for 10 min and then

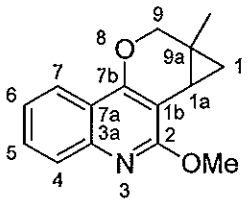
diluted with water (100 mL), neutralised with aqueous sodium carbonate and extracted with DEE (3 x 100 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated under reduced pressure to afford 392 mg of the desired product **5.04** (93 %). Mp 105 °C (lit.[262] 105 °C). $^1$H NMR ($CDCl_3$, 400 MHz): δ 4.13 (s, OMe), 7.38 (m, 1H), 7.72 (m, 2H), 8.20 (d, *J* 8.0 Hz, 1H), 10.28 (s, 1H, CHO), 13.78 (br s, OH). MS (ESI): *m/z* 204 $[M+H]^+$, 226 $[M+Na]^+$. The data were in agreement with previous reported data.[262,267,268]




**2-Methoxy-4-[(2-methylprop-2-en-1-yl)oxy] quinoline-3-carbaldehyde**

To a pre-mixed solution of **5.04** (35 mg, 0.17 mmol) and silver carbonate (143 mg, 0.52 mmol) in DMF (3.5 mL) at ambient temperature under a nitrogen atmosphere, was added 3-bromo-2-methylprop-1-ene (52 µL, 0.52 mmol). The reaction mixture was stirred at 50 °C for 12 h, cooled and was then filtered through Celite using ethyl acetate as eluent (2 x 10 mL). The organic layer was washed with water (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give 42 mg of the crude product. Flash chromatography (EtOAc:hexane/3:97) afforded 28 mg of the desired product **5.03** (64 %). Mp 67 °C. IR (KBr, $\nu_{max}$): 3077, 2978, 2950, 2901, 1683, 1618, 1597, 1569 and 1499 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 236 (33268), 296 (11735) nm. $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.90 (s, Me), 4.15 (s, OMe), 4.66 (s,

2H, H-1'), 5.06 and 5.17 (2 x s, 2 x 1H, C=$\underline{C}H_2$), 7.40 (app t, *J* 7.2 Hz, 1H, H-6), 7.71 (app t, 7.2 Hz, 1H, H-7), 7.80 (d, *J* 8.4 Hz, 1H, H-8), 8.15 (dd, *J* 8.4, 1.6 Hz, 1H, H-5), 10.51 (s, 1H, CHO). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 19.7 (Me), 54.4 (OMe), 80.7 (C-1'), 110.4 (C-3), 114.7 (C=$\underline{C}H_2$), 121.1 (C-4a), 124.1 (C-5), 124.6 (C-6), 127.1 (C-8), 132.7 (C-7), 140.3 (C-2'), 148.6 (C-8a), 162.2 (C-2), 167.0 (C-4), 188.8 (C-3, CHO). MS (ESI): *m/z* 280 $[M+Na]^+$, 229 $[M-CHO]^+$, 217 $[M-C_3H_5]^+$, 201 $[M-C_3H_5O]^+$. HRMS Calcd. for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$: 280.0944. Found: 280.0933.




**2-Methoxy-9a-methyl-1,1a,9,9a -tetrahydrocyclopropa[4,5]pyrano [3,2-*c*]quinoline**

To a solution of **5.03** (151 mg, 0.59 mmol) in DCE (1.5 mL), was added hydrazine monohydrate (1.5 mL, excess). After the reaction mixture was stirred at 65 °C for 1 h and 25 min, it was cooled, diluted with DCM (7 mL) and washed with water (5 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. To a stirred solution of the crude mixture and mercury oxide (4.62 mmol, 1 g) in DCM (5 mL), was added 15 drops of an approximately 3M ethanolic solution of potassium hydroxide. The reaction was then stirred in the dark keeping the temperature at -5 °C for 4 h and then 45 min at RT, The reaction mixture was then filtered through celite and the residues washed with DCM (7 mL). Dirhodium tetraacetate (8 mg, 0.018 mmol) was then added to the combined filtrate and the reaction mixture stirred in the dark keeping the temperature at -1 °C

for 10 min and then at ambient temperature for 14 h. The reaction mixture was then concentrated together with silica (100 mg) under reduced pressure. Flash chromatography (EtOAc:hexane/2:98) afforded 28 mg of the desired product (20 %). An analytically pure sample was obtained by re-dissolving in a minimum amount of DMSO, and performing flash chromatography with reverse phase silica (MeOH:$H_2O$/8:2) which afforded 10 mg of the desired product **5.14** (7 %) as a thin film. IR (KBr, $\nu_{max}$): 3068, 2950, 2868, 2361, 2341, 1626, 1610, 1577, 1507 and 1471 $cm^{-1}$. UV (MeOH) $\lambda_{max}(\varepsilon)$: 234 (13576), 279 (4189), 320 (3853) nm. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.07 and 1.17 (2 x m, 2 x 1H, $CH_2$, H-1), 1.34 (s, Me), 2.12 (m, 1H, CH, H-1a), 3.87 and 4.45 (2 x d, *J* 13.6 Hz, 2 x 1H, H-9), 4.14 (s, OMe), 7.32 (app t, *J* 6.0 Hz, 1H, H-6), 7.53 (app t, *J* 6.2 Hz, 1H, H-5), 7.77 (d, *J* 6.4 Hz, 1H, H-4), 7.94 (d, *J* 6.8 Hz, 1H, H-7). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 14.2 (C-1a), 19.4 (C-1), 20.3 (Me), 23.7 (C-9a), 53.8 (OMe), 68.0 (C-9), 108.5 (C-1b), 119.1 (C-7a), 121.2 (C-7), 123.4 (C-6), 127.1 (C-4), 128.8 (C-5), 144.8 (C-3a), 155.1 (C-7b), 161.4 (C-2). MS (ESI): *m/z* 242 $[M+H]^+$. HRMS Calcd. for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.1175. Found: 242.1168.

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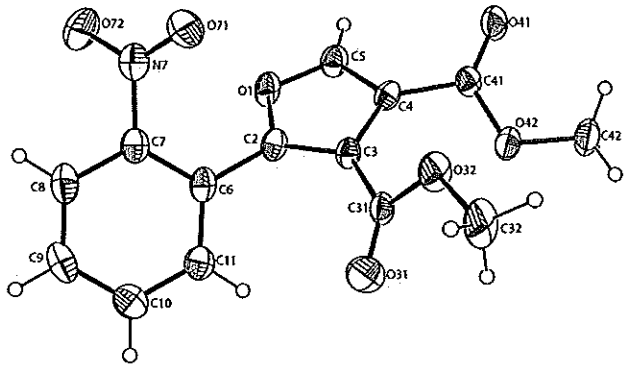
# Appendix

## Crystal structures



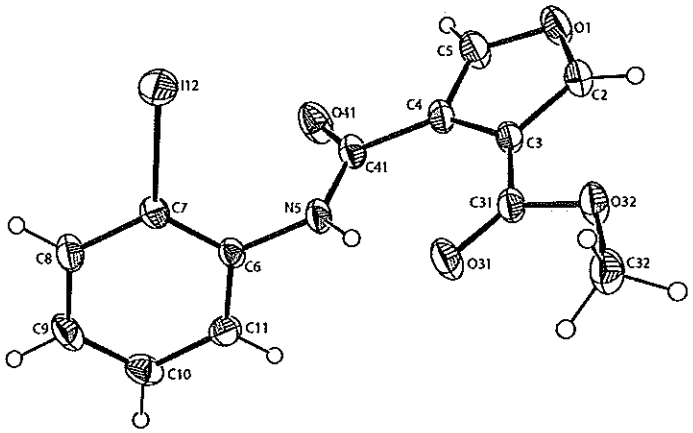

Product **3.09**

*Crystal data*

| | |
|---|---|
| $C_{14}H_{11}NO_7$ | $V$ = 693 (3) Å$^3$ |
| $M_r$ = 305.24 | $Z$ = 2 |
| Triclinic, $P\bar{1}$ | $D_x$ = 1.462 Mg m$^{-3}$ |
| $a$ = 9.000 (13) Å | Mo $K\alpha$ |
| $b$ = 10.60 (3) Å | μ = 0.12 mm$^{-1}$ |
| $c$ = 7.949 (19) Å | $T$ = 295.1 K |
| α = 108.48 (18)° | Prismatic, yellow |
| β = 101.03 (15)° | 0.40 × 0.30 × 0.20 mm |
| γ = 96.59 (16)° | |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int}$ = 0.069 |
| ω–2θ scans | $\theta_{max}$ = 27.6° |
| Absorption correction: none | 3 standard reflections |
| 3747 measured reflections | every 0 reflections |
| 3663 independent reflections | intensity decay: 0.00% |
| 1663 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **3.06**
I-NH-ester

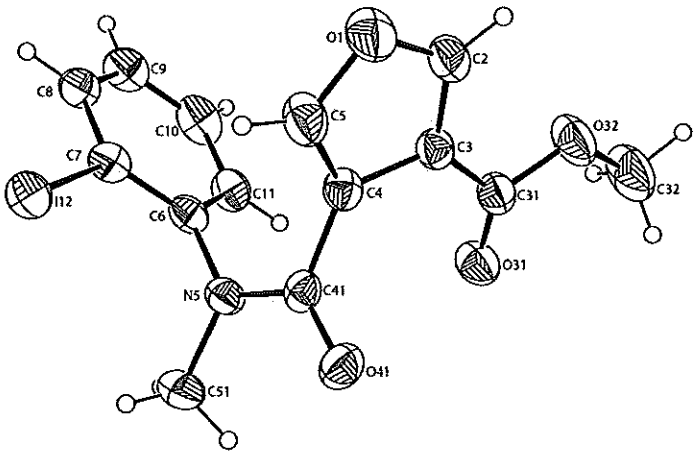
**862rq68_18.17.1**

*Crystal data*

| | |
|---|---|
| $C_{13}H_{10}INO_4$ | $Z = 4$ |
| $M_r = 371.13$ | $D_x = 1.900$ Mg m$^{-3}$ |
| Monoclinic, $P2_1/n$ | Mo $K\alpha$ |
| $a = 14.8888$ (18) Å | $\mu = 2.48$ mm$^{-1}$ |
| $b = 10.473$ (2) Å | $T = 295.1$ K |
| $c = 8.5425$ (11) Å | Block, colorless |
| $\beta = 103.122$ (10)° | 0.60 × 0.50 × 0.34 mm |
| $V = 1297.2$ (3) Å$^3$ | |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int} = 0.081$ |
| ω–2θ scans | $\theta_{max} = 27.5°$ |
| Absorption correction: none | 3 standard reflections |
| 3396 measured reflections | every 0 reflections |
| 3315 independent reflections | intensity decay: 0.00% |
| 2557 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **3.07**
I-NMe-ester

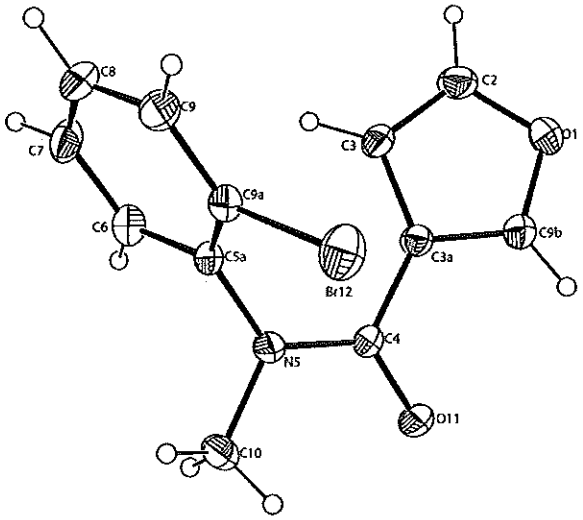
**864rq69m_18.19.1**

*Crystal data*

| | |
|---|---|
| $C_{14}H_{12}INO_4$ | $Z = 16$ |
| $M_r = 385.16$ | $D_x = 1.750$ Mg m$^{-3}$ |
| Orthorhombic, *Ccce* | Mo *K*α |
| $a = 17.732\ (3)$ Å | $\mu = 2.20$ mm$^{-1}$ |
| $b = 22.904\ (4)$ Å | $T = 295.1$ K |
| $c = 14.3942\ (15)$ Å | Block, colorless |
| $V = 5846.0\ (15)$ Å$^3$ | 0.50 × 0.25 × 0.25 mm |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int} = 0.020$ |
| ω scans | $\theta_{max} = 27.5°$ |
| Absorption correction: none | 3 standard reflections |
| 4231 measured reflections | every 0 reflections |
| 4129 independent reflections | intensity decay: 0.00% |
| 2221 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **2.05**
Br-NMe-

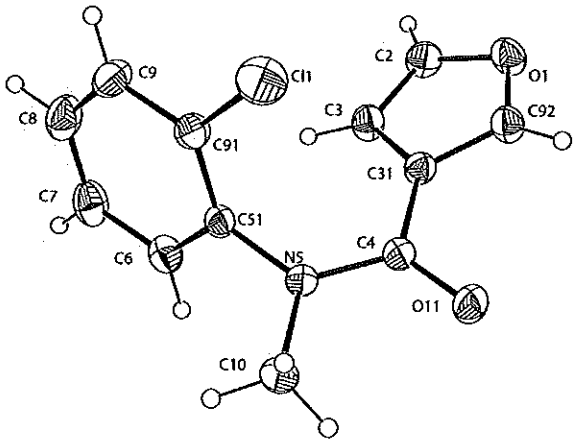
**869rq71_NPS00**
**3**

*Crystal data*

| | |
|---|---|
| $C_{12}H_{10}BrNO_2$ | $V$ = 563.97 (19) Å$^3$ |
| $M_r$ = 280.12 | $Z$ = 2 |
| Triclinic, $P\bar{1}$ | $D_x$ = 1.649 Mg m$^{-3}$ |
| $a$ = 8.0393 (17) Å | Mo $K\alpha$ |
| $b$ = 10.4484 (15) Å | μ = 3.64 mm$^{-1}$ |
| $c$ = 7.8743 (18) Å | $T$ = 295.1 K |
| α = 97.543 (15)° | Prismatic, colorless |
| β = 116.278 (15)° | 0.35 × 0.30 × 0.30 mm |
| γ = 101.134 (15)° | |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int}$ = 0.037 |
| ω–2θ scans | $\theta_{max}$ = 27.5° |
| Absorption correction: none | 3 standard reflections |
| 3038 measured reflections | every 0 reflections |
| 2966 independent reflections | intensity decay: 0.00% |
| 2214 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **2.12**
Cl-NMe_

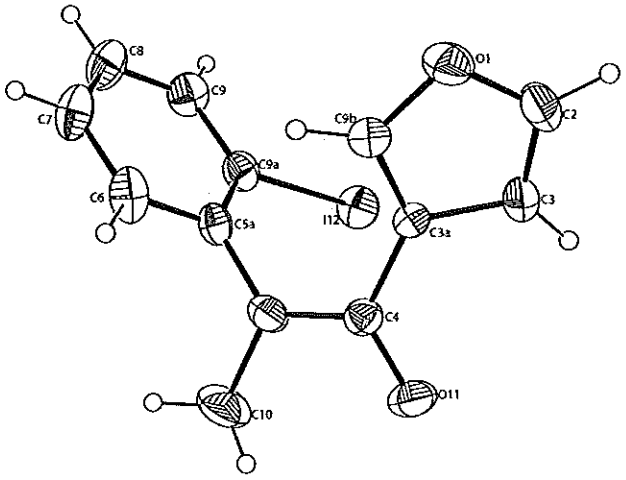
**874rq73_NPS0035)**

*Crystal data*

| | |
|---|---|
| $C_{12}H_{10}ClNO_2$ | $V$ = 551.1 (2) Å$^3$ |
| $M_r$ = 235.67 | $Z$ = 2 |
| Triclinic, $P\bar{1}$ | $D_x$ = 1.420 Mg m$^{-3}$ |
| $a$ = 7.8594 (19) Å | Mo $K\alpha$ |
| $b$ = 7.928 (3) Å | μ = 0.33 mm$^{-1}$ |
| $c$ = 10.2771 (18) Å | $T$ = 295.1 K |
| α = 99.115 (19)° | Prismatic, colorless |
| β = 98.504 (16)° | 0.60 × 0.40 × 0.30 mm |
| γ = 115.97 (2)° | |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int}$ = 0.011 |
| ω–2θ scans | $\theta_{max}$ = 27.5° |
| Absorption correction: none | 3 standard reflections |
| 2969 measured reflections | every 0 reflections |
| 2900 independent reflections | intensity decay: 0.00% |
| 2136 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **2.09**
I-NMe

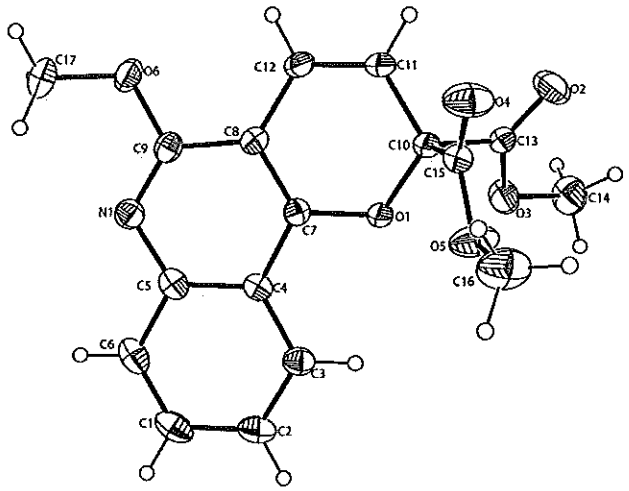
**875rq74_NPS00**
**7**

*Crystal data*

| | |
|---|---|
| $C_{12}H_{10}INO_2$ | $Z = 8$ |
| $M_r = 327.12$ | $D_x = 1.789$ Mg m$^{-3}$ |
| Monoclinic, $P2_1/n$ | Mo $K\alpha$ |
| $a = 16.299\ (9)$ Å | $\mu = 2.62$ mm$^{-1}$ |
| $b = 11.618\ (3)$ Å | $T = 295.1$ K |
| $c = 16.297\ (8)$ Å | Prismatic, yellow |
| $\beta = 51.91\ (3)°$ | 0.40 × 0.40 × 0.25 mm |
| $V = 2428.6\ (18)$ Å$^3$ | |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int} = 0.069$ |
| ω–2θ scans | $\theta_{max} = 25.0°$ |
| Absorption correction: none | 3 standard reflections |
| 5465 measured reflections | every 0 reflections |
| 5339 independent reflections | intensity decay: 0.00% |
| 3197 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **3.05**
Malonate pyrano

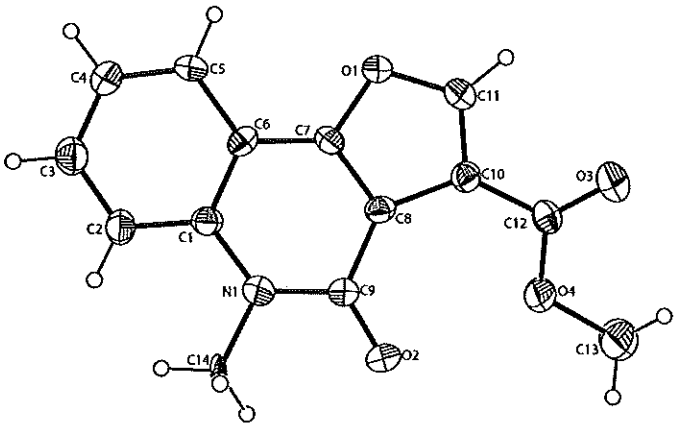
**903rq77_7.103.**
**1**

*Crystal data*

| | |
|---|---|
| $C_{17}H_{15}NO_6$ | $V$ = 773.7 (3) Å$^3$ |
| $M_r$ = 329.31 | $Z$ = 2 |
| Triclinic, $P\bar{1}$ | $D_x$ = 1.413 Mg m$^{-3}$ |
| $a$ = 9.2823 (17) Å | Mo $K\alpha$ |
| $b$ = 11.062 (2) Å | μ = 0.11 mm$^{-1}$ |
| $c$ = 7.968 (3) Å | $T$ = 295.1 K |
| α = 106.91 (2)° | Block, colorless |
| β = 97.049 (19)° | 0.40 × 0.25 × 0.20 mm |
| γ = 83.008 (16)° | |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int}$ = 0.016 |
| ω–2θ scans | $\theta_{max}$ = 25.0° |
| Absorption correction: none | 3 standard reflections |
| 3268 measured reflections | every 0 reflections |
| 3196 independent reflections | intensity decay: 0.00% |
| 1854 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **3.08**
NMe-key ester

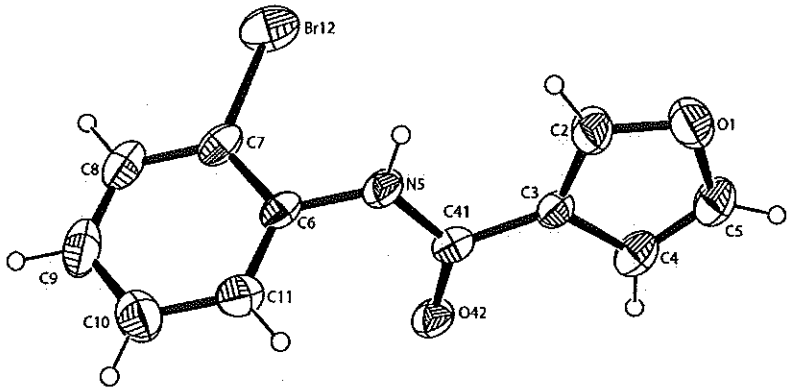
**906rq78_7.101.1**

*Crystal data*

| | |
|---|---|
| $C_{14}H_{11}NO_4$ | $Z = 8$ |
| $M_r = 257.25$ | $D_x = 1.412$ Mg m$^{-3}$ |
| Orthorhombic, *Pbca* | Mo *Kα* |
| $a = 17.104\ (4)$ Å | $\mu = 0.11$ mm$^{-1}$ |
| $b = 22.727\ (4)$ Å | $T = 295.1$ K |
| $c = 6.2263\ (15)$ Å | Block, yellow |
| $V = 2420.4\ (9)$ Å$^3$ | 0.30 × 0.20 × 0.20 mm |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int} = 0.029$ |
| ω scans | $\theta_{max} = 25.0°$ |
| Absorption correction: none | 3 standard reflections |
| 2788 measured reflections | every 0 reflections |
| 2713 independent reflections | intensity decay: 0.00% |
| 963 reflections with $F^2 > 2.0\sigma(F^2)$ | |




Product **2.03**
Br-NH

**909rq79_1.66.1**

*Crystal data*

| | |
|---|---|
| $C_{11}H_8BrNO_2$ | $V$ = 1073.6 (4) Å$^3$ |
| $M_r$ = 266.09 | $Z$ = 4 |
| Triclinic, $P\bar{1}$ | $D_x$ = 1.646 Mg m$^{-3}$ |
| $a$ = 10.1861 (16) Å | Mo $K\alpha$ |
| $b$ = 11.613 (3) Å | μ = 3.82 mm$^{-1}$ |
| $c$ = 9.7866 (17) Å | $T$ = 295.1 K |
| α = 104.791 (17)° | Block, yellow |
| β = 98.755 (14)° | 0.40 × 0.25 × 0.20 mm |
| γ = 101.046 (18)° | |

*Data collection*

| | |
|---|---|
| Rigaku AFC7R diffractometer | $R_{int}$ = 0.038 |
| ω–2θ scans | $\theta_{max}$ = 25.0° |
| Absorption correction: none | 3 standard reflections |
| 4476 measured reflections | every 0 reflections |
| 4380 independent reflections | intensity decay: 0.00% |
| 2190 reflections with $F^2 > 2.0\sigma(F^2)$ | |

Data collection: WinAFC; cell refinement: WinAFC; data reduction: *CrystalStructure*; program(s) used to solve structure: *SIR92*; program(s) used to refine structure: *SHELXL*; molecular graphics: ; software used to prepare material for publication: *CrystalStructure* 3.7.0.

Rigaku/MSC and Rigaku Corporation. (2004). *CrystalStructure* 3.7.0. Single Crystal Structure Analysis Software. Rigaku/MSC, 9009 New Trails Drive, The Woodlands, TX, USA 77381-5209. Rigaku, 3-9-12 Akishima, Tokyo 196-8666, Japan.

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