PHD

Synthesis and evaluation of narciclasine analogues

Judd, Katie

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Synthesis and Evaluation of Narciclasine Analogues

Katie Elizabeth Judd
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This research has been carried out under the supervision of Dr Lorenzo Caggiano

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Date..........................................................
ABSTRACT

Narciclasine was isolated from the common daffodil in 1967 and was shown to exhibit potent and selective anti-cancer activity. However, current synthetic routes are generally long and low yielding, hampering its progress as a clinical candidate. This project aims to synthesise bioactive analogues using a short, elegant and scalable synthesis.

A one-pot procedure has been developed whereby a carboxylic acid is converted to an isocyanate using a modified Curtius rearrangement, which is then captured by a tethered electron-rich aromatic ring in a Lewis-acid mediated intramolecular Friedel-Crafts acylation. This methodology was then applied to produce a series of dihydroisoquinolinones as simplified AB-ring analogues in 73-90 % yields. Interestingly, the cyclisation of 3,4,5-(trimethoxyphenyl)propionic acid proceeds with selective demethylation at the 8-position when BF$_3$·OEt$_2$ is employed as the Lewis acid. To mimic the sp$^2$ centre at the 10b position of narciclasine, the analogues were oxidised using palladium on activated carbon in 39-89 % yields.

This synthetic methodology has been applied to the synthesis of the more complex ABC-ring analogues. Acetophenones were readily converted to β-ketoesters, which were then condensed with methyl vinyl ketone using a Robinson annulation reaction to generate modified Hagemann’s esters. Reduction followed by saponification of this ester provided the corresponding acid for cyclisation using the Curtius rearrangement and Friedel-Crafts acylation. Three analogues have been synthesised using this approach in 6 steps and overall yields of 10-18 %.

These analogues have been evaluated against HT29 colon cancer cell lines, showing a range of activities from 715 μM to 15 μM, with patterns in the structure-activity relationship that mirror those in the natural products.

The prenyl and chroman groups are medicinally important functional groups found in a number of natural products. During our investigations, a mild method of prenylating an aromatic ring using Bi(OTf)$_3$ as a catalyst was discovered. The procedure was optimised and applied to a range of aryl rings to identify the scope and limitations of the reaction. It was also found that applying the same procedure to phenols gave chromans as the products. This reaction was applied to the synthesis of the natural product 2-(3-methyl-2-butenyl)-3,4,5-trimethoxyphenol, in 34 % overall yield.
I would like to take this opportunity to thank everyone that has made this project possible and contributed to my life in Bath over the last 3 ½ years.

Firstly on the technical front, I must say a massive thank you to Dr Pauline Wood for all her work on the biology in this project, without her support this would not have been a medicinal chemistry project. Also, thank you to Dr Tim Woodman and Dr Anneke Lubben for their support with NMR and Mass Spectrometry; and to Dr Mary Mahon for the lovely X-ray crystal structures in Section 3.

Thank you to the University of Bath for funding the project.

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I started in Bath as the only member of the Caggiano group and during my PhD saw the group grow each year. Thank you to Gemma Tunbridge who has been there almost from the start and who has been a great friend both in the lab and out of
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I would like to express by deepest gratitude and appreciation to Dr Lorenzo Caggiano for allowing me to complete my PhD under his supervision. Thank you for all your support, encouragement, patience and guidance; which has allowed me to grow as a chemist and a person during the last 3 ½ years. Thank you for all the pearls of chemistry wisdom, they will not be forgotten. Your enthusiasm for chemistry has been truly inspiring.

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PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS


ORAL PRESENTATIONS

22\textsuperscript{nd} April 2010: “From Daffodils to Drugs: Synthesis and Evaluation of Narciclasine Analogues” - Oral presentation at RSC Bioorganic Group Postgraduate Symposium

POSTER PRESENTATIONS


Jan 2009: “New applications of robust chemistry in the synthesis of tetrahydroisoquinolines and dihydroisoquinolones” - Poster presentation at RSC Organic Division Regional Meeting, South of England. I also presented with another group member on behalf of our supervisor in an adjoining lecture theatre.

Sept 2008: “New applications of robust chemistry in the synthesis of tetrahydroisoquinolines and dihydroisoquinolones” - Poster presentation at RSC Heterocyclic and Synthesis Group, 23\textsuperscript{rd} Postgraduate Heterocyclic Symposium.
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<td>Å</td>
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<tr>
<td>Boc</td>
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</tr>
<tr>
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<td>Diphenylphosphoryl azide</td>
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<tr>
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<tr>
<td>Ns</td>
<td>4-Nitrophenylsulfonyl</td>
</tr>
<tr>
<td>o-</td>
<td>ortho-</td>
</tr>
<tr>
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<tr>
<td>p-</td>
<td>para-</td>
</tr>
<tr>
<td>Pd/C</td>
<td>Palladium on activated carbon</td>
</tr>
<tr>
<td>PE</td>
<td>40-60 °C petroleum ether</td>
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<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>pK&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Acidity constant</td>
</tr>
<tr>
<td>Abbreviation</td>
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1. INTRODUCTION

1.1. NARCICLASINE; SYNTHESIS AND BIOLOGICAL ACTIVITY

1.1.1. Isolation

The Amaryllidaceae family of plants have long been known to have medicinal properties and there are reports of their use throughout history in treating a number of ailments including cancer. A review by Hartwell found that many of the plants in the family have been used in civilisations across the world and throughout history to treat symptoms of what we now know as cancer.¹ In particular, oil isolated from the bulbs of the plants from the Narcissus genus has been used as a treatment by Hippocrates in Ancient Greece and Pliny the Elder in Ancient Rome. Commonly, the plants of the Narcissus genus are known as the daffodil. In herbal medicine, Culpeper describes daffodils being used to treat a range of ailments from healing wounds to treating fevers.² Daffodils have also been found to have a negative effect on the length of vase life of cut flowers.³

![Daffodils at University of Bath](image1)

Figure 1: Daffodils at University of Bath

Narciclasine has since been discovered to be the compound responsible for these effects. Ceriotti initially described narciclasine as “A potent antimitotic
substance which was isolated from several varieties of *Narcissus* bulbs” in 1967. In the following year, the group published 1 as what they believed to be the structure of narciclasine (Figure 2). Meanwhile, Okamoto et al. had isolated lycoricidinol from the bulbs of *Lycoris radiate* and published its structure as 2 along with initial growth inhibition studies. After a chemical study and X-ray crystallography, narciclasine and lycoricidinol were identified as the same substance and the structure was assigned with absolute stereochemistry as 3.

![Figure 2: Debated structures of narciclasine](image)

To date, narciclasine has been isolated from many different plants of the Amaryllidaceae family, but it is found in the bulbs of all species of *Narcissus* genus at 30-200 mg/kg depending on the variety of plant. This yield from the natural sources is not sufficient to progress narciclasine as a clinical candidate. However, there have been many investigations into the biological activity and chemical synthesis of narciclasine and its analogues.

### 1.1.2. Biological Activity

Narciclasine’s anticancer properties were first described in 1967 by Ceriotti when he tested the substance *in vivo* in mice on sarcoma 180 cells, observing an antimitotic activity at high doses. Okamoto et al. also studied narciclasine and its anticancer effects in Ehrlich carcinoma and observed a significant drop in cell viability after treatment with 100 µg of narciclasine over 30 days. Mondon and Krohn published the first structure-activity relationship study in 1975. They found that in HeLa (cervical cancer) and HEPH (laryngeal cancer) cell lines that narciclasine was toxic in concentrations of >0.1 µg/mL and showed an effect between 0.025-0.1
µg/mL. Since then, narcicasine has been shown to have a number of mechanisms of action for its anti-cancer activity.

In 1975, Vazquez et al. published a series of letters investigating the ribosomal mechanism of action of narcicasine in yeast. They found narcicasine blocks peptide synthesis by interacting with the 60S ribosome subunit, preventing the tRNA at the A site of the ribosome binding to the peptidyl-transferase centre so the next amino acid in the sequence cannot be attached to the growing peptide chain (Figure 3).¹¹ This was proved by studying strains of yeast ribosomes with a mutation in the peptidyl-transferase centre and these strains showed resistance to narcicasine.¹²

![Diagram of ribosome with A and P sites and tRNA](image)

**Figure 3: Role of the ribosome in protein synthesis**

Kiss et al. have shown that narcicasine can induce apoptosis selectively in cancer cells, but not in normal cells.¹³ They found that the mechanism for apoptosis is dependent on the type of cancer cell, but in both types of cell apoptosis goes via the death receptor pathway (Figure 4). The cascade begins with the narcicasine-promoted activation of death receptors FAS and DR4, followed by formation of the Death Inducing Signalling Complex (DISC). Procaspase-8 is recruited to DISC and activated to give caspase-8 and it is from here that the two types of cell differ. In type I cells, such as the PC-3 prostate cancer cells, a high concentration of caspase-8 is recruited and activated which in turn directly recruits the effector caspases to
trigger apoptosis.\textsuperscript{14} In type II cells, such as MCF-7 breast cancer cells, the recruitment of caspase-8 is low, so further amplification of this signal is required to initiate the effector caspases. This amplification occurs through the mitochondria, affecting the potential of the outer mitochondrial membrane,\textsuperscript{15} thus allowing the release of cytochrome c, which forms part of the apoptosome. This structure then activates the effector caspases, triggering apoptosis.\textsuperscript{16}

![Apoptosis pathways in MCF-7 and PC-3 cells, representing type II and type I cells\textsuperscript{13}]

These observations nicely complement observations made on pancratistatin, a closely related analogue of narciclasine, which has also found to selectively induce apoptosis in cancer cells\textsuperscript{17,18} and leukaemia.\textsuperscript{19} There are also no signs of DNA damage caused by pancratistatin in either cancer cells or normal cells. Matching Kiss’ observations on effects of narciclasine on MCF-7 breast carcinoma, pancratistatin has shown to affect the mitochondrial membrane potential in SHSY-
SY neuroblastoma cells, making the outer membrane more permeable and so allowing the release of cytochrome c.\textsuperscript{17} However this may be a downstream effect of activation of caspase-3,\textsuperscript{18} a protein which is also related to the activation of caspase-8.\textsuperscript{20}

Ingrassia and Lefranc have also performed an in-depth study of narciclasine and various analogues.\textsuperscript{21} They found that narciclasine impairs cell proliferation and cell migration in cancer cell lines to a greater extent than in normal cell lines (Figure 5). The natural product displays activity in cell lines that are both resistant (e.g. U373 glioblastoma cells) and sensitive (e.g. PC-3 prostate cancer cells) to apoptosis as it works through non-apoptotic mechanisms. These include promoting actin polymerisation, which in turn rigidifies the actin cytoskeleton, impairing growth and movement of the cancer cells (Figure 6).

![Figure 5: Results from scratch wound healing assays of human PC-3, U373 and Ccd-25-Lu normal human lung fibroblasts](image1)

![Figure 6: Effects of narciclasine on actin polymerisation in PC-3, U373 and Ccd-25-Lu cells (F-actin shown in green and G-actin shown in red)\textsuperscript{21}](image2)
This work in the U373 glioblastoma cells has been extended to glioblastomas GL19 and Hs683 and into xenograft models. The investigation found that narciclasine decreases the rate of mitosis by increasing the time between cell division. It decreases cell migration and an increase in fibrillary actin is observed. This effect is due to the activation of Rho, a family of proteins which are key regulators of the actin cytoskeleton (Figure 7). This has the effect of activating its downstream substrates ROCK-1 and LIMK-1 by phosphorylation. Activated LIMK-1 then phosphorylates the Serine3 on cofilin, rendering it inactive. Cofilin is an actin-severing protein, so its inactivation means that the growing actin filaments are not depolymerised, leading to extensive filament formation and cell rigidity, rendering the cell immobile. Although to date, only glioblastoma cells have been investigated for this effect, narciclasine could prove to be effective in other metastasising cell lines, such as breast cancers.

![Diagram of Rho activation leading to increase fibrillary actin within the cell](image)

**Figure 7:** Mechanism of Rho activation leading to increase fibrillary actin within the cell
Despite the many modes of action of narciclasine and its congener pancreatistatin, the compounds display a selective anti-cancer activity, whilst showing little effect on normal human cell lines. This gives a strong advantage over many other chemotherapies which have toxicity issues associated with them.

1.1.3. Structure-Activity Relationship

During the numerous investigations on narciclasine, a large number of analogues have been accessed by either isolation from natural sources or synthesised as part of SAR studies or total synthesis attempts. Many of these compounds have been tested for their anti-cancer activity allowing the formation of a structure activity relationship. Narciclasine can be described as a phenanthridinone with a tricyclic core structure consisting of an aromatic, polyoxygenated A-ring, a lactam B-ring and a polyhydroxylated C-ring (Figure 8).

![Figure 8: Nomenclature and numbering for the structure of narciclasine](image)

The A-ring in narciclasine 3 has a 7-hydroxy-8,9-methylenedioxy substitution pattern (Figure 9). 7-Deoxynarciclasine 4, also a natural product shows a 10-fold decrease in mean GI$_{50}$ of 145 nM compared to narciclasine’s 15.5 nM in the NCI 60 cell line screen. A decrease in activity is also seen when comparing 7-hydroxy-\textit{trans}-dihydrornarciclasine 5 and 7-deoxy-\textit{trans}-dihydrornarciclasine 6 with GI$_{50}$ values of 12.6 nM and 67.6 nM, although the difference is not so pronounced.\textsuperscript{24}
Hudlicky *et al.* have synthesised a number of analogues of the related compound pancratistatin 7 with changes made to the A-ring (Figure 10). The 9-methoxy analogue 8 had an average GI<sub>50</sub> value of 3.7 µg/mL across 6 solid tumour cell lines and a leukaemia cell line<sup>25</sup>, a 100-fold reduction in activity when compared to pancratistatin’s activity of 0.034 µg/mL in the same cell lines. This means that in general there is a 10-fold loss in activity with the removal of each subsequent oxygen group. Hudlicky also synthesised analogue 9 where the A-ring was replaced with an indole, with the reasoning that the NH would mimic the hydroxyl and the aromatic ring would mimic the lipophilic methylenedioxy substituent<sup>26</sup>. The compound was approximately 100-fold less active than pancratistatin in P388 leukaemia and inactive against the 3 human cancer cell lines that were tested showing that despite the modelling comparing the two compounds, they do behave differently in a cellular environment.
The B-ring in both narciclasine and pancratistatin is a δ-lactam. Reduction of this lactam to a cyclic amine has a detrimental effect on activity. Pettit et al. synthesised amines 10 and 11 by reduction of the corresponding amides.27 The amines and their HCl salts were evaluated against a panel of human cancer cell lines and displayed growth inhibition values of >1 µg/mL compared with those of corresponding amides of <0.15 µg/mL.

![Figure 11: Cyclic amine analogues of lycoridine and dihydrolycoridine](image)

Chapleur et al. have investigated changes to the B-ring, synthesising lactone analogues of narciclasine 12 which were found to be inactive (Figure 12).28 They also synthesised a series of seco-analogues 13 where the A and C-rings were not connected between the 10a and 10b positions and again these were found to be devoid of activity.29

![Figure 12: Chapleur's B-ring analogues](image)

Arylcyclitol analogues have also been reported by Kornienko et al. where the B-ring has been removed completely (Figure 13).30 These have also shown to be completely inactive, complementing Chapleur’s findings that the B-ring needs to remain intact with an amide NH for biological activity.
Narciclasine 3 has an sp\(^2\) centre at the 10b position and a stereogenic centre at the 4a position which is in the R-configuration. Analogues of narciclasine with changes to the ring junction have been isolated from natural sources and tested in the NCI 60 cell line screen (Figure 14).\(^{24}\) When the ring junction was a double bond between the 4a and 10b positions in 14, the activity was reduced significantly to 1180 nM. Changing the 10b position to an R-configured sp\(^3\) centre to give 5 with a trans-geometry at the ring junction had little effect on the activity with a slight increase from 15.5 nM to 12.6 nM. However, when the 10b position was an S-configured sp\(^3\) centre, giving 15 with a cis-geometry at the ring junction there was a large loss in activity to 380 nM.
The C-ring in narciclasine can be described as an amino-inositol ring. Many analogues of narciclasine have been isolated or synthesised with changes made in the C-ring. A number of analogues have been made in the *trans*-dihydrolycoricidine series, testing how many hydroxyl groups are needed for activity (Figure 15). The mono-alcohol 16 displayed only a moderate activity against P388 murine leukaemia of 40.1 µg/mL, whereas the diols proved to be more active in the same cell line. The 3,4-diol 17 had an ED$_{50}$ of 1.39 µg/mL, but the most active analogue was the 2,3-diol 18 with an ED$_{50}$ of 0.45 µg/mL. This is much less active than pancratistatin (ED$_{50}$ = 0.039 µg/mL) or narciclasine (ED$_{50}$ = 0.0012 µg/mL) in the same cell line; however, a direct comparison should not be drawn as the analogues do not contain the 7-hydroxyl group. The 2,4-diol 19 was not tested against P388 leukaemia, but has been shown to be inactive against MCF-7 breast cancer cells.

![Figure 15: C-ring analogues in the dihydrolycoricidine series](image)

Hudlicky *et al.* have synthesised the C1 homologue of 7-deoxypancratistatin 20, which showed between 2 and 20 fold loss of activity depending on the cell line when compared to *trans*-dihydrolycoricidine 6 which bears no substituent at the C1 position (Figure 16).
Kornienko et al. have also investigated modifications on the C-ring by opening the ring and contracting the ring to a furan (Figure 17). All three compounds 21, 22 and 23 showed at 10-12 fold loss in activity in HeLa and MCF-7 cells when compared to narciclasine. The cyclic system is more rigid in the natural product, holding the hydroxyls group in a favourable conformation compared to the acyclic analogues.

A series of 28 analogues based on 24 were synthesized and tested by Ingrassia and Lefranc (Figure 18). They found that protection of all the heteroatoms resulted in a reduction in activity; and in particular, the loss of the NH upon protection of the amide always resulted in a complete loss of activity. The hydroxyl at the C2 position was not sensitive to protection and a range of substituents were attached here without any affect on the activity. The 7-hydroxyl group proved to be much more sensitive, especially towards alkyl substituents, although acyl and sugar substituents were tolerated more. Acetal protection of the 3,4-diol was also tolerated. The only changes in the C-ring that gave comparable
activities to narciclasine were the C2-hydroxyl esters, but this was not surprising as it was found on closer inspection that these decomposed in the biological media to give narciclasine.

![Diagram of narciclasine structure]

Figure 18: General structure and substituents of synthesised analogues of narciclasine

In summary for biological activity, the A-ring needs to be a poly-oxygenated aryl ring, the B-ring must be a lactam, with the 4a position in the \( R \)-configuration and the 10b position either being \( sp^2 \) or in the \( R \)-configuration. The C-ring should be cyclised and contain a minimum of three hydroxyl groups.

### 1.1.4. Pro-drug Synthesis

A major problem with advancing narciclasine or its analogues as clinical candidates has been the poor solubility of the compounds; pancratistatin has a solubility of only 53 µg/mL. To overcome this, pro-drugs have been investigated. Work has mostly been performed on pancratistatin 7 rather than narciclasine 3, but the ideas can be applied to both compounds. Pancratistatin has 5 free hydroxyl groups and these provide the perfect handles to make pro-drugs. Synthesis of phosphate esters has been the most investigated method of making pancratistatin and narciclasine more soluble.

The sodium 7-O-phosphate 25 has a greatly improved aqueous solubility of 20 mg/mL at 25 °C and showed comparable activities against a panel of cancer cell lines when compared to pancratistatin (Figure 19). Other counterions were also investigated and showed a range of solubility and activity values.
A number of 4-O-phosphate esters of pancratistatin 26 and 3,4-O-cyclic phosphate esters of narciclasine 27 and pancratistatin 28 have also been synthesised and tested against a panel of cancer cell lines (Figure 20).\textsuperscript{36} Generally, the phosphates showed a 10-fold reduction in activity when compared to the parent compounds but this was dependant on the cell line and the counterion used. The solubility of these compounds has not been assessed quantitatively as the increase in solubility had previously been demonstrated with 25. The improved solubility of sodium pancratistatin 3,4-O-cyclic phosphate 28 has allowed \textit{in-vivo} studies to be performed in Human colon tumour xenograft models. At 100 mg/kg, 28 gave an increase in tumour necrosis and a disruption in mitochondrial membrane potential was also observed, complementing the \textit{in-vitro} observations.\textsuperscript{37}

Phenstatin 29 is the 1-benzoyl adduct of pancratistatin and displays up to a 300-fold increase in activity across a panel of 6 cell lines when compared to pancratistatin and up to an 80-fold increase when compared to narciclasine across the same cell lines (Figure 21).\textsuperscript{36,38} However, as the solubility of phenstatin has not been
determined, it is not known whether this increase is due purely to improvements in solubility or due to improved potency.

![Chemical Structure](image)

**Figure 21: Phenstatin 29**

1.1.5. Synthetic Attempts

Since 1997 there have been four syntheses of narciclasine, each taking a different approach.

Rigby *et al.* published the first total synthesis of narciclasine 3 in 1997 in 22 steps and 0.3 \% overall yield (Scheme 1). In this approach, the A-ring originated from 2,3-dihydroxybenzaldehyde 30 and the C-ring is synthesised from methyl cyclohex-3-ene carboxylate 33. The two portions were connected by capturing the isocyanate 32 with the aryl lithium carbanion 35 to give the amide 36 in 52 \% yield. Then a photochemical cyclisation formed the bond between the 10a and 10b positions in 46 \%. The C-ring was manipulated to install the hydroxyl substituents and finally deprotection revealed the natural product 3.
Although Rigby reported the first total synthesis, the step count and overall yield was poor. This was addressed in 1999 when two different syntheses were published by Hudlicky and Keck.

Hudlicky has a great interest in enzymatic dihydroxylation, which was used as a key step together with a Diels-Alder reaction in the synthesis of the C-ring. The A-ring originated from o-vanillin and was transformed in four steps into the borate coupling partner for a Suzuki reaction with the C-ring bromide 41. A modified Bischler-Napieralski reaction formed the B-ring lactam 44 in 40%. Finally
deprotection revealed narciclasine 3 in a much improved 14 steps from \(o\)-vanillin but a poorer overall 0.13 % yield (Scheme 2).\(^{40}\)

Keck et al. used a radical cyclisation as the key step in his synthesis to form the C-ring (Scheme 3).\(^{41}\) His approach employed a Sonogashira coupling of alkyne 47 and aryl iodide 50 to provide the precursor 51 for the radical cyclisation in 89 % yield. After the radical cyclisation, the AC-ring intermediate 52 was isolated in an excellent 88 %. A number of transformations were then required to cyclise the B-ring, remove the thioether installed during the radical reaction and deprotect the hydroxyl groups to reveal the natural product 3 in 14 steps and a much improved 13 % overall yield.
Yan et al. published the most recent synthesis of narciclasine in 2002, a 9 step route in a 19% overall yield, making it the most efficient synthesis of the natural product to date (Scheme 4). This synthesis used the same disconnections as Rigby et al., but instead the A-ring is tethered to the C-ring by an N-alkylation to afford amine 56, then the A/C-ring junction was formed by the ring opening of an epoxide to give the tricyclic compound 57. An oxidation step afforded the amide 58.
and further manipulations gave the natural product 3. As with Hudlicky’s synthesis, the oxygenation pattern in the C-ring is set early on before the cyclisation of the B-ring.

Despite the improvements to the synthesis of narciclasine, the step counts and yields are still less than desirable for taking the natural product forward as a clinical candidate. These approaches have targeted the natural product for academic interest and to develop new chemical reactions; however, they are not ideal for use in creating libraries of compounds to further investigate structure-activity relationships. To efficiently build libraries of biologically active analogues, an efficient synthesis
of a late-stage intermediate is required, which can then be easily functionalised to give a diverse set of compounds. Developing a route based on this approach should enhance the appeal of the compound as a clinical candidate.

1.2. PROPOSED SYNTHESIS OF ANALOGUES

The initial target of the synthesis will be the tricyclic late stage intermediate 63. This intermediate can be made from simple commercially available starting materials and there is scope for it to be easily functionalised at several of stages within the synthesis to generate diverse libraries of compounds.

Scheme 5: Proposed synthesis of ABC-ring analogues

The synthesis will begin with the condensation of an acetophenone 59 to generate a β-ketoester 60 (Scheme 5). There are many acetophenones commercially available, allowing different substitution patterns to be investigated on the A-ring. There are two available routes from the β-ketoester to the tricyclic core 63. In route A, the acid generated from saponification of the β-ketoester will undergo a Curtius rearrangement and intramolecular Friedel-Crafts acylation to give the AB-ring
lactam 61. This will be followed by a Robinson annulation with a vinyl ketone to install the C-ring. Route B will use the same reactions but applied in the opposite order, so the β-ketoester will be condensed with a vinyl ketone in a Robinson annulation to give a modified Hagemann’s ester 62. After saponification of the ester, the acid will then undergo a Curtius rearrangement and intermolecular Friedel-Craft acylation to give the B-ring lactam 63. The Robinson annihilations will be optimised using methyl vinyl ketone (MVK), however a range of vinyl ketones can be used to install functional groups at the C1 and C4 positions of the phenanthridone core.

Once the intermediate 63 has been synthesised, a range of methods are available to decorate the C-ring further with different functional groups. For example, the ketone can undergo Rubottom oxidation to install a hydroxyl group at the C3-position (Scheme 6a). Enolate chemistry can be used to install a number of functional groups at the C3 position (Scheme 6b). The ketone can also be reduced to the alcohol using a Luche reduction (Scheme 6c) and the hydroxyl group substituted by different nucleophiles to give variation at the C2 position (Scheme 6d).

Scheme 6: Possible methods to further functionalise the C-ring
1.3. THE CURTIUS REARRANGEMENT

The Curtius rearrangement is the thermal decomposition of an acyl azide, generated from a carboxylic acid, to an isocyanate with the loss of nitrogen. The isocyanate can then be trapped with a range of nucleophiles to afford various groups such as amines, amides, carbamates or ureas (Scheme 7).

\[
\begin{align*}
\text{acyl azide} & \quad \text{isocyanate} \\
R\text{COOH} & \quad R\text{N}_3 & \quad R\text{NC}O & \quad R\text{NHX}R^1 \\
\text{X} = \text{C, O, N}
\end{align*}
\]

Scheme 7: The Curtius rearrangement

Curtius first described the rearrangement of acyl azides in 1890,\(^4\) and in the following years published a number of papers investigating the reaction.\(^4\) There have been a number of reviews into the rearrangement, experimental procedures and its applications,\(^4\),\(^5\),\(^6\) including the comprehensive review of the first 50 years of the reaction by Smith.\(^7\)

There are several methods of accessing the acyl azide from the carboxylic acid, as there are many ways of activating the carboxylic acid towards nucleophilic substitution including three commonly used methods (Scheme 8). The acid can be converted to the acid chloride using oxalyl chloride,\(^8\) or thionyl chloride.\(^9\) Alternatively, the acid can be activated as the mixed anhydride using a chloroformate, as described by Weinstock.\(^10\) This approach has been taken by Ohta and Kimoto in their synthesis of lycoricidine,\(^11\) where they used ethyl chloroformate in the presence of base to form the mixed anhydride. In both of these methods, an external source of azide is added to the reaction to form the acyl azide and an aqueous wash is performed before the reaction is heated to promote the rearrangement. The third method of activating the acid is to use diphenylphosphoryl azide (DPPA) to generate the phosphoryl ester. The use of DPPA for the Curtius rearrangement was first reported in the synthesis of urethanes by Yamada \textit{et al.}\(^5\) They also commented on the ease of the experimental procedure as DPPA acts to both activate the acid and provide a source of azide and that the reaction proceeds without racemisation of existing stereocentres.
Scheme 8: Three commonly used methods of activating the carboxylic acid

The rearrangement of the acyl azide is normally induced thermally; however photolytic,\textsuperscript{55} protic acid\textsuperscript{56} and Lewis acid \textsuperscript{57} catalysed methods have also been reported. The mechanism for the rearrangement could follow two possible mechanisms (Figure 22). In the concerted mechanism, the loss of nitrogen and the migration of the R-group occur at the same time. Alternatively, initial elimination of nitrogen leads to an electron deficient nitrene intermediate which then rearranges to give the isocyanate. There is much debate over the mechanism, but under thermal conditions, it is most likely to proceed via the concerted mechanism, as the nitrene intermediate was not trapped in investigations by Hauser \textit{et al.}\textsuperscript{58} and Lowowski \textit{et al.}\textsuperscript{59,60}

**Concerted Mechanism:**

![Concerted Mechanism Diagram](image)

**Step-wise Mechanism:**

![Step-wise Mechanism Diagram](image)

Figure 22: Two mechanisms of isocyanate formation

A number of products can be generated from the isocyanate by adding different nucleophiles to the reaction mixture (Scheme 9).
The free amine can be accessed by adding aqueous acid or base to the isocyanate, as initially the carbamic acid is formed which decomposes with the loss of carbon dioxide to reveal the amine. The reaction can be performed using an alcohol as the solvent, which traps the isocyanate once it is formed to give a carbamate. In particular, $t$-BuOH can be used as the nucleophile, giving a Boc-protected amine as the product. This is an approach which has been taken in the synthesis of pancratistatin; Kim et al. used a Curtius rearrangement to transform a carboxylic acid on the C-ring to a methyl carbamate. The aryl ring was then reacted with the carbamate in a Bischler-Napieralski reaction to give the B-ring lactam (Scheme 10).

A number of carbon-based nucleophiles have also been described giving amide products. Padwa et al. reported the addition of Grignard reagents to an isocyanate to form a series of 2-amidofurans. In Trost’s synthesis of pancratistatin, an isocyanate was trapped by a tethered aryl lithium to give the B-ring lactam, and
Electron rich aromatic rings have been used as nucleophiles, although the addition is often promoted by Lewis acids. Boron trichloride has been used by Piccolo et al. to catalyse the ortho-acylation of a phenol with an isocyanate.\textsuperscript{66} AlCl\textsubscript{3} has also been described to catalyse the addition to an isocyanate (Scheme 11). Hanessian et al. used AlCl\textsubscript{3} to catalyse the addition of a tethered aromatic ring to an isocyanate \textbf{71} to form tetrahydroisoquinolinones \textbf{72} in good yields.\textsuperscript{67} Afarinkia et al. also used AlCl\textsubscript{3} in their synthesis of phenanthridones to catalyse the addition of the aryl A-ring to the isocyanate on the C-ring giving the B-ring lactam \textbf{75}.\textsuperscript{68}

\begin{center}
\textbf{Scheme 11: AlCl\textsubscript{3}-catalysed intramolecular addition of a tethered aryl ring to an isocyanate}
\end{center}

BF\textsubscript{3}·OEt\textsubscript{2} is a commonly used Lewis acid and has been employed to the promote addition of an aryl ring to an isocyanate. Hilton et al. successfully acylated
indoles using *tert*-butylisocyanate catalysed by BF$_3$·OEt$_2$ to afford 2-amidoindoles 77 (Scheme 12).$^{69}$ Ohta and Kimoto treated the isocyanate 79 with BF$_3$·OEt$_2$ to promote the cyclisation to the lactam 80 in their synthesis of lycoricidine.$^{53}$ Finally and possibly most interestingly in the synthesis of narciclasine analogues, Tőke *et al.* used BF$_3$·OEt$_2$ to promote addition to an isocyanate and cyclisation to give the tricyclic core 82.$^{70}$ However, they also noted that when the substrate contained a methoxy-group at the 7-position, BF$_3$·OEt$_2$ also promoted selective demethylation to give the substitution pattern seen in the A-ring of narciclasine.

**Hilton *et. al.*$^{69}$**

![Hilton Scheme](image)

**Ohta and Kimoto$^{53}$**

![Ohta Scheme](image)

**Tőke *et. al.*$^{70}$**

![Tőke Scheme](image)

Reagents and conditions: i) t-BuNCO, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, 0 °C; ii) BF$_3$·OEt$_2$; iii) 1:1 BF$_3$·OEt$_2$:Et$_2$O, 0 °C, 2 hrs

**Scheme 12: Examples of BF$_3$·OEt$_2$ catalysed addition of aryl rings to isocyanates**
The examples of Afarinkia et al., Töke et al. and Ohta and Kimoto are of particular interest to this project due to their use in the synthesis of narciclasine analogues. Afarinkia et al. accessed the carboxylic acid precursor in only 3 steps, giving only a 4-step synthesis of the tricyclic core structure. Töke et al. generated the isocyanates from the corresponding carboxylic acids; however, they do not report the route they used to make the carboxylic acids. Ohta and Kimoto synthesised the tricyclic core in 4 steps from a benzaldehyde and then manipulated the C-ring to incorporate the hydroxyl groups. These examples prove that the Curtius rearrangement is a viable method of cyclising the B-ring, however they have not been investigated further as a synthetically practical and high yielding reaction in the synthesis of narciclasine analogues.

1.4. THE ROBINSON ANNULATION

The Robinson annulation was discovered by Robert Robinson in 1935 whilst he was working on the synthesis of sterol derivatives. He found that the sodium enolate of cyclohexenone reacted with methyl styryl ketone to give cyclohexenone (Scheme 13).

![Scheme 13: Reaction of cyclohexanone and methyl styryl ketone using sodamide](image)

Reviews by Gawley and Jung discuss the mechanism and applications of the Robinson annulation, showing how the reaction has become a staple of the chemists’ toolbox. The reaction has been used in the synthesis of many natural products to build the carbon skeleton, including milbemycin, tanabalin, aspidospermidine and codeine (Figure 23).
The Robinson annulation proceeds via a Michael addition followed by an intramolecular aldol cyclisation, as shown by the mechanism in Scheme 48. Typically the reaction is performed by making a sodium enolate 92 using either NaOH or NaOMe/NaOEt and treating it with a Michael acceptor such as methyl vinyl ketone. The product of the conjugate addition is also an enolate 93 which can isomerise to give enolate 94 and then react nucleophilically with the ketone in an intramolecular aldol reaction to form a 6 membered ring 95. Finally, dehydration installs the double bond to give conjugated cyclohexenone 97.72

Scheme 14: Mechanism of the Robinson annulation72
An aprotic variation using the strong base LDA in THF was reported in 1983 to give a regioselective annulation of dihydrocarvone 98 with ethyl vinyl ketone (EVK) to give the bicyclic enone 101 (Scheme 15).\textsuperscript{79} The regioselectivity arises from the formation of the thermodynamic enolate 99, which reacts with the EVK selectively at the axial position to give the intermediate 100 in the thermodynamically favourable chair conformation.

![Scheme 15: Aprotic variation of the Robinson annulation using LDA](image)

Reagents and conditions: i) LDA, EVK, THF, -78 °C; ii) KOH, EtOH, heat, 1 hr.

In addition to the one-pot annulation procedure, the transformation has been performed in two steps, isolating the Michael adduct prior to cyclisation. This approach has allowed stereochemical control to be applied at either stage. In the synthesis of Saudin,\textsuperscript{80} a chiral enamine 103 was formed to direct the Michael addition, before the cyclisation step took place, giving the 6-membered ring 105 in 87 % yield and 95 % e.e. (Scheme 16).

![Scheme 16: Stereoselective Michael addition and annulation in the synthesis of Saudin\textsuperscript{80}](image)

Reagents and conditions: i) a) EVK, toluene, 50 °C; b) aq HCl; ii) pyrrolidine, AcOH, toluene
Christoffers et al. also carried out work on asymmetric copper-catalysed Michael additions, where the products can then be cyclised in a Robinson annulation. In work similar to the approach used in the synthesis of Saudin, chiral amines were investigated to direct the Michael addition, giving chiral products in modest to good enantioselectivity.\textsuperscript{81} The conditions were then applied in the synthesis of indoles (Scheme 17).\textsuperscript{82}

\begin{align*}
\text{Et}_2\text{N}^+\text{O} & \rightarrow \text{H}_2\text{O} \\
\text{NH} & \rightarrow \text{HCl} \\
\end{align*}

Reagents and conditions: i) a) Cu(OAc)\textsubscript{2}·H\textsubscript{2}O, MVK, acetone, 23 °C; b) HCl/H\textsubscript{2}O; ii) Pyrrolidine/AcOH

\textbf{Scheme 17: Christoffers’ application of his copper-catalysed, stereoselective Michael addition and Robinson annulation in the synthesis of indoles.}\textsuperscript{82}

The mechanism, scope and limitations and some applications of chiral imines and enamines in the asymmetric Michael addition have been reviewed by d’Angelo.\textsuperscript{83}

Once the chiral Michael adduct has been synthesised, there are a number of methods reported in the literature for promoting the cyclisation. The use of p-TsOH in toluene heated at reflux was reported by Liu et al. to induce the annulation of ketone \textbf{112} to afford enone \textbf{113} (Scheme 18).\textsuperscript{84}
As shown in the examples of the enamine catalysed Michael addition, pyrrolidine and piperidine can also be used to perform the annulation. In 1956, Plenninger et al. demonstrated that enone 116 could be formed by the cyclisation of Michael adduct 115 using piperidinium acetate.\textsuperscript{85} Golding et al. developed the conditions in 1972 when synthesising Hagemann’s ester 118 from 117 using pyrrolidine and acetic acid (Scheme 19).\textsuperscript{86}

\begin{equation}
\begin{array}{c}
\text{R}^2 \text{CO}_2\text{R}^1 \\
\text{CO} \\
\text{O} \\
\end{array} \xrightarrow{\text{piperidinium acetate}^{85} \text{ or pyrrolidinium acetate}^{86}} 
\begin{array}{c}
\text{R}^1 \text{CO}_2\text{R}^2 \\
\text{CO} \\
\text{O} \\
\end{array}
\end{equation}

115: \text{R}^1 = \text{Et}, \text{R}^2 = \text{Me} \\
117: \text{R}^1 = \text{Et}, \text{R}^2 = \text{H} \\
116: \text{R}^1 = \text{Et}, \text{R}^2 = \text{Me} \\
118: \text{R}^1 = \text{Et}, \text{R}^2 = \text{H} \\
\text{(Hagemann's ester)}

Scheme 19: Cyclisation of Michael adducts using piperidinium acetate or pyrrolidinium acetate

The method has since been used in the synthesis of a number of natural products or medicinally active compounds, including Saudin,\textsuperscript{80} Hagemann’s ester 118 \textsuperscript{87} and fluorenones.\textsuperscript{88}

Related to these conditions is the Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction, a stereoselective variant of the Robinson annulation which used a proline catalyst to promote the cyclisation of a pro-chiral triketone 119 to give a
chiral bicyclic product 121 (Scheme 20). The reaction was described almost simultaneously by Eder, Sauer and Wiechert in 1971\textsuperscript{89} and by Hajos and Parrish in 1974.\textsuperscript{90}

![Scheme 20: Hajos-Parrish's cyclisation of triketone 119 using a proline catalyst\textsuperscript{90}](image)

Reagents and conditions: i) (S)-Proline, DMF; ii) \(p\)-TsOH, benzene, reflux

The mechanism for the reaction has attracted much debate, with at least four different models of the transition state in the reaction. However, the widely accepted explanation for the stereoselectivity was proposed by Houk \textit{et al.} after examining experimental evidence and computational modelling.\textsuperscript{91}

![Figure 24: Houk's transition state model for the stereoselectivity in the annulation\textsuperscript{91}](image)

The use of amino acid catalysts for this reaction has been briefly reviewed by Jarvo and Miller.\textsuperscript{92} Other amino acids have been investigated for the catalysis of this reaction. Phenylalanine\textsuperscript{93,94,95} and proline derivatives containing substitution on the heterocyclic ring\textsuperscript{91,96} have also been employed for the cyclisation of a range of substrates. Davies \textit{et al.} have investigated \(\beta\)-amino acids as chiral catalysts for the
transformation and found that (1R,2S)-cispentacin 124 catalysed the HPESW reaction with comparable or higher enantioselectivity to (S)-proline.\(^{97}\)

![Scheme 21: Daviess' use of (1R,2S)-cispentacin 124 to catalyse the cyclisation of (S)-121.\(^{97}\)](image)

There have also been efforts to access bicyclic ketones by performing the Michael addition and aldol cyclisation in one step using proline catalysis. Barbas III \textit{et al.} found that using (S)-proline in DMSO, ketone 127 can be synthesised in 49% yield and 76% e.e. (Scheme 22).\(^{98}\) This research prompted Swaminathan \textit{et al.} to publish their work on the same substrate, where 127 was isolated after a separate dehydration step in 68% yield and 63% e.e.\(^{99}\)

\begin{align*}
\text{Barbas III:}^{98} & \quad \text{O} & \text{O} \\
\text{126} & \quad \text{i}) & \quad 49\% \\
\quad & \quad & \quad \text{127} \\
\quad & \quad & \quad \text{76%} \ \text{ee} \\
\text{Swaminathan:}^{99} & \quad \text{O} & \text{O} \\
\text{126} & \quad \text{ii}) & \quad 68\% \\
\quad & \quad & \quad \text{127} \\
\quad & \quad & \quad \text{63%} \ \text{ee} \\
\end{align*}

Reagents and conditions: i) (S)-Proline, DMSO, 89 hrs; ii) a) (S)-Proline, DMSO, 145 hrs, b) \(p\)-TsOH, benzene, reflux.

\textbf{Scheme 22: One-step synthesis of 127 using (S)-proline catalysis}
This literature provides the basis for the work in this project on the Robinson annulation, showing the route to be viable. Although the synthesis will initially be performed racemically, these reports show that a stereoselective synthesis may also be achieved.

1.5. AIMS

The aim of this project is to synthesise simplified analogues of narciclasine, via a late stage intermediate, which retain biological activity, using a short synthetic sequence that can be applied on a larger scale.

Initially, a series of simplified AB-ring analogues will be generated to develop the conditions for the Curtius rearrangement and intramolecular Friedel-Crafts acylation. These compounds will also be tested for their anti-cancer activity.

Then a route to the ABC-ring analogues will be developed, which will use a Robinson annulation to generate the C-ring and incorporate the Curtius rearrangement and intramolecular Friedel-Crafts acylation reaction optimised on the AB-ring analogues. This route will be used to produce a series of ABC-ring analogues which will also be evaluated for their biological activity in cancer cell lines.

The theme of the group is the efficient synthesis of biologically active compounds using known and new methodologies. In view of this, interesting or unexpected results will also be investigated with the aim of developing new reactions that will be useful to the synthetic and medicinal chemist.
2. SYNTHESIS AND EVALUATION OF AB-RING ANALOGUES

2.1. SYNTHESIS OF AB-RING ANALOGUES USING THE CURTIUS REARRANGEMENT

2.1.1. 3,4-Dihydroisoquinolin-1-ones

Narciclasine and pancratistatin contain a 3,4-dihydroisoquinolinone as their AB-ring. As previously discussed in Section 1.2 (p. 20), it was envisaged that this motif would be formed in a one-pot procedure from a dihydrocinnamic acid 128 through a Curtius rearrangement to generate an isocyanate 129, followed by a Lewis acid mediated intramolecular Friedel-Crafts acylation (Scheme 23)

Scheme 23: Dihydroisoquinolinone formation via the isocyanate

Two different methods were investigated for the Curtius rearrangement. Following the step-wise procedure reported by Ohta and Kimoto, the hydrocinnamic acid was first treated with ethyl chloroformate in the presence of a base to generate the corresponding mixed anhydride 131, which upon reaction with sodium azide afforded the acyl azide 132. The by-products were removed by extraction and heated in toluene to afford the isocyanate 129, then a Lewis acid was added to promote the cyclisation to give the lactam 130.
Scheme 24: Step-wise method of making an isocyanate using EtOCOCl to activate the acid

Diphenylphosphoryl azide (DPPA) was also used to generate the isocyanate in a one-pot procedure. This is a dual functional reagent, comprising of a phosphoryl group to activate the acid as the phosphoryl ester 133 and the azide group to make the acyl azide precursor 132 for the Curtius rearrangement (Scheme 25). The acid 128 was heated with DPPA at 90 °C for 1 hr before the solvent was removed and the isocyanate 129 treated with a Lewis acid to furnish the isoquinolinone 130.

Scheme 25: Mechanism for DPPA mediated azide formation

When hydrocinnamic acid 134 was treated with DPPA and Et$_3$N in toluene at 90 °C without the addition of a Lewis acid, the desired cyclised material was not observed; instead the symmetrical urea 138 was isolated in a 64 % yield (Scheme 26). The mechanism for urea formation involves a molecule of water. The isocyanate is hydrolysed to give the carbamic acid 136 which undergoes decarboxylation to furnish amine 137. The urea 138 is then generated by nucleophilic addition of the amine to isocyanate 135. However, it is not known whether this was formed in the
reaction or upon aqueous workup as the reaction was performed under anhydrous conditions.

![Scheme 26: Mechanism of urea formation](image)

However, the formation of the urea 138 demonstrates that the isocyanate is formed during the reaction and that the subsequent ring closing step proves to be problematic. Addition of Lewis acids BF$_3$·OEt$_2$, AlCl$_3$ and ZnCl$_2$ were investigated to promote cyclisation; however, these gave either the urea or a mixture of compounds which could not be separated by column chromatography. It was found that increasing the temperature of the BF$_3$·OEt$_2$ mediated step to 80 °C promoted some cyclisation; however, the dihydroisoquinolinone 139 was isolated in only 5 % yield (Scheme 27).

![Scheme 27: Cyclisation of dihydrocinnamic acid 134](image)

Reagents and conditions: a) DPPA, Et$_3$N, toluene, 90 °C; b) BF$_3$·OEt$_2$; c) 2M NaOH/EtOAc, 60 °C

It was shown that the Thorpe-Ingold effect can have a positive effect on the
outcome of the reaction. The Thorpe-Ingold effect is the increase in the rate of a ring-forming reaction due the presence of substituents on the ring.\textsuperscript{100} Using an AlCl\textsubscript{3}-catalysed Michael addition of benzene to 3-methylbut-2-enoic acid \textbf{140}, 3,3-dimethyl-3-phenylpropionic acid \textbf{141} was synthesised in 99 % yield. The acid was then subjected to the stepwise reaction conditions, performing the BF\textsubscript{3}\cdot\text{OEt}\textsubscript{2} mediated cyclisation at room temperature, to give the 4,4-dimethylisoquinolinone \textbf{142} in 8 % yield (Scheme 28).

\[ \text{Reagents and conditions: i) AlCl}_3, \text{benzene; ii) a) EtOCOCl, Et}_3\text{N, acetone/H}_2\text{O; b) NaN}_3, \text{acetone/H}_2\text{O; c) toluene, 90 }^\circ\text{C; d) BF}_3\cdot\text{OEt}_2 } \]

\textbf{Scheme 28: The Thorpe-Ingold effect increases the rate of cyclisation}

An unsubstituted aryl group is a poor nucleophile due to the lack of electron-donating substituents on the ring. Substrates with electron-rich, oxygenated aryl rings were investigated as they would be better nucleophiles and because narciclasine contains an oxygenated A-ring. 3-(3,4-Methylenedioxyphenyl)propionic acid \textbf{143} was subjected to three different sets of conditions for the rearrangement and cyclisation. When the step-wise conditions were applied and BF\textsubscript{3}\cdot\text{OEt}\textsubscript{2} was used to promote the cyclisation, the isoquinolinone \textbf{144} was isolated in 63 % yield. Using the step-wise conditions and AlCl\textsubscript{3} as the Lewis acid afforded \textbf{144} in 67 % yield. When the reaction was performed using DPPA the lactam \textbf{144} was isolated in 81% yield (Scheme 29). Only regioisomer \textbf{144} was formed in the reactions and isomer \textbf{145} was not observed. This was proved with the \textsuperscript{1}H NMR spectra where the aromatic region contained only two singlets at 6.64 ppm and 7.49 ppm. Two doublets with a coupling constant of around 8 Hz would be expected for regioisomer \textbf{145}. 

\[ \text{3-(3,4-Methylenedioxyphenyl)propionic acid } \textbf{143} \]
Scheme 29: Cyclisation of 3-(3,4-methylenedioxyphenyl)propionic acid 143

3,4-(Dimethoxyphenyl)propionic acid 146 was also investigated as a substrate for the reaction; however using the DPPA reaction conditions, lactam 147 was isolated in only 55 % yield. Heating the BF$_3$·OEt$_2$ mediated cyclisation step at 50 °C increased the yield to 76 % (Scheme 30).

Scheme 30: Cyclisation of 3-(3,4-methylenedioxyphenyl)propionic acid 146

As narciclasine contains a trioxygenated A ring, the cyclisation of (3,4,5-trimethoxyphenyl)propionic acid 148 was investigated. When the acid was submitted to the step-wise set of conditions, using BF$_3$·OEt$_2$ as the Lewis acid, the $^1$H NMR spectrum of the product showed the loss of a methyl group, however the site of demethylation could not be determined. Regioselective demethylation by BF$_3$·OEt$_2$ has been reported in similar systems and was discussed in Section 1.3 (p. 26). As the product was a thermally stable and highly crystalline solid, an X-ray crystal structure was obtained to determine the site of demethylation (Figure 25).

### Reagents and conditions

- **Scheme 29**: i) EtOCCl$_2$, Et$_3$N, acetone/H$_2$O; b) Na$_2$O$_4$, acetone/H$_2$O; c) toluene, 90 °C; d) BF$_3$·OEt$_2$; ii) EtOCCl$_2$, Et$_3$N, acetone/H$_2$O; b) Na$_2$O$_4$, acetone/H$_2$O; c) toluene, 90 °C; d) AlCl$_3$; iii) DPPA, Et$_3$N, toluene, 90 °C; b) BF$_3$·OEt$_2$; c) 2M NaOH, EtOAc, 50 °C.

- **Scheme 30**: a) DPPA, Et$_3$N, toluene, 90 °C; b) BF$_3$·OEt$_2$, r.t. or 50 °C; c) 2 M NaOH, EtOAc, 50 °C.
The structure shows the demethylated product coordinated to boron difluoride through the phenol and carbonyl groups. Presumably, as the boron trifluoride coordinates to the product, there is loss of a fluoride ion which can act as a nucleophile to perform the demethylation, allowing the resulting phenol to bind more strongly to the boron to give the thermally stable adduct 148 (Scheme 31).

Scheme 31: Proposed mechanism of selective demethylation of the 8-methoxy group

The trimethoxy-product 150 was not observed and the BF$_2$-adduct was isolated in an unoptimised 21 % yield (Scheme 32). Nicolau et al. reported similar chelate structures and described their hydrolysis using refluxing methanol/water or THF/water.$^{101}$ The dissociation of 148 was achieved using 2M NaOH and EtOAc at 50 °C and the free phenol 151 was isolated in an unoptimised 24 % yield from the propionic acid 149.
Scheme 32: Cyclisation and demethylation of 3-(3,4,5-trimethoxyphenyl)propionic acid 149 using the unoptimised stepwise procedure

When the rearrangement and cyclisation of (3,4,5-trimethoxyphenyl)propionic acid 149 was attempted using DPPA, lactam 151 was isolated in 73 % yield on a 5 mmol scale, but only in 52 % yield on a 25 mmol scale. After optimisation, the BF$_2$-adduct 148 could be isolated in 62 % yield on a 25 mmol scale without column chromatography. Subsequent hydrolysis was performed using 2M NaOH and EtOAc, giving lactam 151 in an 85-92 % yield on a 5 mmol scale.

Reagents and conditions: i) a) EtOCOCl, Et$_3$N, acetone/H$_2$O; b) NaN$_3$, acetone/H$_2$O; c) toluene, 90 ºC; d) BF$_3$·OEt$_2$; ii) 2M NaOH, EtOAc, 50 ºC (151 only)

Scheme 33: Synthesis of 8,9-dimethoxy-7-hydroxy-3,4-dihydroisoquinolinone 151

Reagents and conditions: i) a) DPPA, Et$_3$N, toluene, 90 ºC; b) BF$_3$·OEt$_2$; ii) a) DPPA, Et$_3$N, toluene, 90 ºC; b) BF$_3$·OEt$_2$; c) 2M NaOH, EtOAc, 50 ºC; iii) 2M NaOH, EtOAc, 50 ºC.
2.1.2. Indole Analogues

Hudlicky et al. proposed that in pancratistatin the A-ring could be substituted for an indole where the NH mimics the hydroxyl group. Indole is an electron rich aromatic ring that can capture an isocyanate, as demonstrated by Hilton et al., a range of indole carboxylic acids were investigated as substrates for the reaction.

![Figure 26: Pancratistatin 7 and Hudlicky's indole analogue 9](image)

Indole-3-propionic acid 152 was treated with DPPA and Et$_3$N in toluene at 90 °C, followed by cyclisation mediated by BF$_3$·OEt$_2$ to afford carbolinone 153 in 87 % yield which is a natural product isolated from an Indonesian sponge. When AlCl$_3$ was employed as the Lewis acid, the lactam was isolated in 153 in 79 % (Scheme 34).

![Scheme 34: Cyclisation of indole-3-propionic acid 152](image)

The mechanism for the Curtius rearrangement is the same as that for the oxygenated aryl ring analogues. However, the cyclisation step proceeds with more complexity due to the electronics of the indole ring (Scheme 35). In indole, the lone pair on the nitrogen atom is involved in the aromaticity of the ring, so can be
delocalised onto the 3-position, making this the most nucleophilic position within the ring. This means that the isocyanate is trapped by the 3-position to give a spirocyclic intermediate 155, which must undergo a migration and deprotonation to restore aromaticity to the indole. This spirocyclic intermediate has been described previously in related systems with substitution at the 2-position, which prevented migration and allowed the compounds to be isolated and characterised.\textsuperscript{103} Only a 1,2-acyl migration was observed, the product of a 1,2-alkyl migration was never isolated. This is because as the group migrates, a positive charge develops at the 3-position and this will be affected by the remaining adjacent group. An adjacent acyl group is electron withdrawing so would destabilise the cation, whereas an adjacent alkyl group is slightly electron-donating so will act to stabilise the positive charge. This leads to migration of the acyl group, giving carbolinone 153 as the product.

The structure was determined by 2D $^1$H NMR experiments and X-ray crystallography, where the N-H and carbonyl can be seen on the same side of the
molecule, indicating a 1,2-acyl migration. The crystal structure also showed the ribbon-like arrangement of molecules formed by hydrogen bonding.

Figure 27: X-ray crystal structures of carbolinone 153

The $N$-methylated analogues were also synthesised. Following the methylation procedure reported by Compernolle using iodomethane in the presence of KOH, followed by base hydrolysis of the ester, $N$-methylindole-3-propionic acid 159 was synthesised in 87 % yield (Scheme 36). The acid 159 was then subjected to the optimised reaction conditions to afford the carbolinone in 87 % from indole-3-propionic acid 160.

![Scheme 36: Synthesis of methylated carbolinone 160](image)

Reagents and conditions: i) a) MeI, KOH, acetone; b) KOH, water reflux; ii) a) DPPA, Et$_3$N, toluene, 90 °C; b) BF$_3$·OEt$_2$; c) 2M NaOH, EtOAc, 50 °C.

The $N,N$-dimethylcarbolinone 160 was synthesised by methylation of carbolinone 153. Using iodomethane and KOH as described by Compernolle resulted in the methylation of only the indole to give 160 in 69 % yield, whereas the use of NaH as the base as reported by Hamann$^{105}$ gave the dimethyl-analogue 161 in 55 % yield (Scheme 37).
Other chain lengths linking the indole and the carboxylic acid were also investigated. When the reaction conditions were applied to indole-3-carboxylic acid and indole-3-acetic acid, mixtures of products inseparable by column chromatography were observed. This is possibly due to the mechanism of the reaction, where the substrates must proceed via 3- and 4-membered ring spirocyclic structures, which are thermodynamically unfavourable.

Azepinones are 7-membered ring homologues of the carbolinones and have been shown to be interesting as anti-mitotic compounds which inhibit tubulin polymerisation by Dodd et al.\textsuperscript{106} and Joseph et al.\textsuperscript{107}

The commercially available indole-3-butyric acid 162 was submitted to the optimised cyclisation conditions and the product 163 was isolated in only 40 % yield (Scheme 38). The yield was increased to 68 % and 90 % when the BF\(_3\)-OEt\(_2\) mediated cyclisation was performed at 50 °C and 80 °C respectively. Presumably, the elevated temperatures aid the energetically unfavourable ring expansion from the 6-membered spirolactam to the 7-membered azepinone.
The methylated derivatives were also synthesised to probe the role of the acidic protons in the molecule. Surprisingly, when indole-3-butyric acid 162 was subjected to the conditions previously used for the methylation of indole-3-propionic acid 152 as reported by Compernolle, only the starting material was recovered. However, methylation of the indole nitrogen and the ester was achieved using t-BuOK and iodomethane in DMF as reported by Perregaard, to give ester 164 in 73% yield. The ester was then hydrolysed in aqueous KOH to provide the crude acid 165 which was cyclised at 50 °C to give 166 in 85% yield from the ester 164 (Scheme 39).

Reagents and conditions: i) t-BuOK, DMF, 5 mins; ii) KOH, H2O; iii) DPPA, Et3N, toluene, 90 °C; b) BF3·OEt2, 50 °C; c) 2M NaOH/EtOAc, 50 °C.

Scheme 39: Synthesis of mono-methylated azepinone derivative 166

The dimethylated analogue 167 was also synthesised in 86% yield by the dimethylation of azepinone 163 using NaH and iodomethane in THF (Scheme 40).

Scheme 40: Methylation of azepinone 163
2.2. SYNTHESIS OF AB-RING ANALOGUES BY THE DEHYDROGENATION OF LACTAMS

2.2.1. Dehydrogenation of Lactams using DDQ

To emulate the sp\(^2\) centre at the 10b position of narcilasine, the oxidation of the previously synthesised AB-ring analogues was investigated. There are a number of reported methods of performing the oxidation and one of the approaches that was explored was the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Chang et al.\(^{110}\)

\[
\begin{align*}
\text{Br} & \quad \text{N} \quad \text{Bn} \\
\text{168} & \quad \text{70\%} \\
\text{Br} & \quad \text{N} \quad \text{Bn} \\
\text{169}
\end{align*}
\]

Bracher et al.\(^{111}\) and Islam et al.\(^{112}\)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \quad \text{H} \quad \text{NH} \\
\text{170} & \quad \text{43 - 61\%} \\
\text{Cl} & \quad \text{Cl} \quad \text{H} \quad \text{NH} \\
\text{Bauerine C} \\
\text{171}
\end{align*}
\]

Reagents and conditions: i) DDQ, THF or dioxane, reflux.

Scheme 41: Examples of DDQ mediated dehydrogenation

DDQ has been described extensively in the literature for performing dehydrogenations at benzylic positions and a review of its reactions was published in 1967.\(^{109}\) Since then, DDQ in dioxane or THF heated at reflux has been reported for the oxidation of dihydroisoquinolinones 168,\(^{110}\) in the synthesis of Bauerines A, B and C 171\(^{111,112}\) and in the synthesis of carbolines\(^{113}\) (Scheme 41).
Following the literature precedent, the methylenedioxy-derivative 144 was treated with 4 eq. DDQ in dioxane heated at reflux (Scheme 42). After 4 hrs, $^1$H NMR analysis of the crude material showed a 2:1 mixture of starting material to product 172. Increasing the reaction time to 22 hrs increased the conversion to 75 % by $^1$H NMR; however, the isolated yield of 172 was only 37 % (Table 1, entry 1). Portion-wise addition of DDQ to the reaction mixture did not increase the yield and isoquinolinone 172 was isolated in only 31 % yield after the addition of 4 eq. DDQ in three portions over 32 hrs.

Table 1: Oxidative aromatisation of lactam rings using DDQ

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>eq. DDQ</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="144" /></td>
<td><img src="image" alt="172" /></td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="147" /></td>
<td><img src="image" alt="173" /></td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="151" /></td>
<td><img src="image" alt="174" /></td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="153" /></td>
<td><img src="image" alt="175" /></td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="160" /></td>
<td><img src="image" alt="176" /></td>
<td>4</td>
<td>22</td>
</tr>
</tbody>
</table>

* a: Performed using 3 eq. DDQ for 1 hr
The remaining analogues were oxidised using 4 eq. DDQ added in one portion (Table 1). The dimethoxy derivative 173 was isolated in 31% yield (Entry 2). When the 6,7-dimethoxy-8-hydroxy analogue 151 was subjected to the reaction conditions, full conversion was not achieved and the oxidised product 174 could not be separated from the starting material by column chromatography (Entry 3). A mixture of products resulting from the conjugate addition of the substrate to DDQ was also observed. The carbolinone 175 was isolated in 25% yield (Entry 4); however the oxidation of N-methylcarbolinone 160 led to demethylation. Altering the reaction conditions to 3 eq. DDQ for only 1 hr gave the desired N-methylcarbolinone 176 in 20% yield (Entry 5). These conditions were also applied to the carbolinone 153 to give the oxidised product 175 in 58% yield (Entry 4).

The driving force for this transformation is the formation of an extended aromatic system, so unsurprisingly the azepinones could not be oxidised using these conditions and in these cases unchanged starting material was recovered.

Due to the poor yields of these reactions, alternative methods of performing the oxidation were investigated. Following literature reported by Snider,114 and Ciganek,115 MnO₂ and Ag₂O were briefly investigated as oxidants, however only the starting material was recovered from the reactions.

2.2.2. Dehydrogenation of Lactams using Palladium on Carbon

Palladium on carbon (Pd/C) is typically used as a hydrogen transfer agent in the presence of hydrogen gas for the reduction of double bonds, but it has also been described in the formation of double bonds in the absence of hydrogen. The oxidation of dihydroisoquinolinones has been reported by Hutchinson,116 and Bracher described the dehydrogenation of carbolinones.117

Following the procedure reported by Dufour,118 the 6,7-methylenedioxy-derivative 144 was oxidised using 7 mol% Pd/C in xylene heated at reflux and after 24 hrs, the catalyst was removed by filtration and the product 172 was isolated in 53% yield (Table 2, entry 1a). Using the same procedure, the dimethoxy analogue 147
was oxidised in to afford isoquinolinone 173 in 61 % yield (Entry 2a) and the 8-hydroxy derivative 174 was isolated in 51 % yield (Entry 3a). Dehydrogenation of the carbolinones 153 and 160 was also achieved in 39 % in 60 % yields respectively (Entries 4 and 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Thermal yield (%)</th>
<th>Microwave yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image]</td>
<td>![Image]</td>
<td>54&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>172</td>
<td>42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>67&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>![Image]</td>
<td>![Image]</td>
<td>61&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>147</td>
<td>173</td>
<td>87&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>![Image]</td>
<td>![Image]</td>
<td>51&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>151</td>
<td>174</td>
<td>49&lt;sup&gt;b&lt;/sup&gt;</td>
<td>38&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>![Image]</td>
<td>![Image]</td>
<td>39&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>![Image]</td>
<td>![Image]</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>: achieved using 7 mol% Pd/C and the catalyst was removed by filtration through celite.
<sup>b</sup>: achieved using 33 mol% Pd/C and the catalyst was removed by filtration through celite.
<sup>c</sup>: achieved using 15 mol% Pd/C and the catalyst was removed by column chromatography.
<sup>d</sup>: performed by Gemma Tunbridge

The reactions were found to be capricious and starting material was often recovered when the reactions were repeated. Increasing the amount of Pd/C used to 33 mol% did not improve the reliability or yield of the reactions. The oxidation of the 6,7-methylenedioxy derivative 144 was performed on an 8 mmol scale using 33 mol% Pd/C and the product 172 was isolated in 42 % yield (Entry 1b). Oxidation of the 8-hydroxy derivative 151 on a 5.95 mmol scale was achieved to give the product 174 in 49 % yield (Entry 3b).
$^1$H NMR analysis of the reaction mixtures showed clean conversion of the starting materials to products, implying that the poor yields were due to problems in the purification of the products. Changing the method of removing the catalyst from filtration through celite to column chromatography generally increased the yields in the reactions. Using 15 mol% Pd/C, the methylenedioxy derivative 172 was isolated in 67 % yield and the dimethoxy derivative 173 was isolated in 87 % yield (Entries 1c and 2c).

Different solvents, including EtOH, EtOAc, $t$-BuOH and AcOH, were also examined as for the dehydrogenation; however, the products were not observed and the starting materials reclaimed. Cyclohexene has been described in the literature as an additive to dehydrogenation reactions as it acts as a hydrogen sink, removing the hydrogen taken from the lactam ring by its reduction to cyclohexane.$^{116}$ This had no effect on the reaction and only the starting materials were isolated.

Microwave technology has provided the greatest amount of success with these reactions, allowing temperatures of up to 200 °C to be reached and the reaction times to be reduced dramatically whilst achieving high yields. After 1 hr at 200 °C, 6,7-dimethoxy-8-hydroxyisoquinolinone 151 was oxidised to give 174 in 80 % yield; and after only ½ hr, carbolinone 175 was isolated in an 89 % yield. The reactions conditions have since been repeated within the group using the dimethoxy analogue 147, affording 173 in an excellent yield of 98 %!

The oxidation of the $N,N$-dimethyl analogue 161 was not performed, however the carbolinone 177 was synthesised by methylation of carbolinone 175 using iodomethane and NaH in 54 %.

![Scheme 43: Methylation of carbolinone 175](image)
2.3. **BIOLOGICAL EVALUATION**

The compounds have all been tested in an MTS cell proliferation assay using human HT29 colon cancer cells with a 72 hr exposure time. The compounds were tested twice and an average taken.

The AB-ring analogues did not possess potent anti-cancer activity (Figure 28). In the series of dihydroisquinolinones, the methylenedioxy and dimethoxy derivatives 144 and 147 were found to be inactive and the 8-hydroxy analogue 151 displayed a weak activity of 386 µM. The series of isoquinolinones 172, 173 and 174 were more active with IC₅₀ values of 398 µM to 71 µM and the 8-hydroxy analogue 174 was the most active compound in the series. Despite the weak activity, the trends in the potency of these compounds do mirror those in the natural product discussed in Section 1.1.3 (p. 7). The presence of the 8-hydroxyl group increases the activity and the oxidation of the C4 position to an sp² centre also increases the activity. Interestingly, the methylenedioxy analogue 172 is less active than the dimethoxy analogue 173, implying that the substitution pattern on the A-ring of narciclasine may not be optimal for activity.

![Chemical structures](image)

*Figure 28: Biological activity of the isoquinolinones*

In addition to these results, two of the compounds have biological data reported in the literature. The dimethoxy-derivative 147 shows some anti-tumour
promoting activity, and its oxidised analogue 173 has been shown to be a weak inhibitor of TNF-α, a protein involved in inflammation and apoptosis.

The indole analogues 153, 160, 161, 175, 176 and 177 were also found to be only mildly active in HT29 cells with IC$_{50}$ values of 260 µM to 86 µM (Figure 29). As with the isoquinolinones, oxidation of the lactam ring increases the activity of the analogues. However, there is not a definite pattern for the effect of N-methylation on activity, as within the unoxidised series 153 is the least active analogue yet its oxidised 175 counterpart is the most active within its series. This may be due to the compounds having an effect at more than one target within the cell. For example, carbolinones have been found to be inhibitors of MK2, a kinase involved in the inflammatory response and apoptosis.

Figure 29: Biological activity of carbolinones

In addition to Hudlicky’s use of the indole moiety as a substitute for the oxygenated aryl ring in narciclasine analogues, carbolinones are interesting medicinal compounds in their own right. Carbolinone 153 has been tested for its anti-leishmaniasis activity, but was found to be inactive. Its oxidised analogue 175 has been found to be inactive against HeLa cells.

The azepinone analogues 163, 166 and 167 were less active than the carbolinones, displaying activities of 120 µM, 302 µM and 373 µM respectively.
(Figure 30). However, the structure-activity relationship is much easier to see; N-methylation drastically reduces activity implying that these protons are important for interactions with the target.

![Figure 30: Biological activity of azepinones](image)

Azepines have been described by Dodd et al.\textsuperscript{106} and Joseph et al.\textsuperscript{107} as inhibitors of tubulin polymerisation, so these compounds could possibly act by this mechanism either instead, or in addition to, the mechanisms by which narciclason works. A method of investigating this would be to submit the compounds to a tubulin-binding assay, whereby the amount of tubulin polymerisation or depolymerisation is assessed by measuring changes in turbidity of the assay mixture.

2.4. SYNTHESIS OF PRO-DRUGS

As previously discussed in the introduction, narciclason and its congeners suffer from poor solubility so pro-drugs have been synthesised to improve their in vivo properties. The synthesis of a series of pro-drugs was undertaken in this project to investigate if their use could improve the physical properties and activity of the AB-ring analogues. The approach taken in this project was the use of carbamates and carbonates to mask the amide and phenol groups. As shown by the X-ray crystal structure of the carbolinone 174 (Figure 27), the lactams are able to form a series of hydrogen bonds which must be broken in order to dissolve the compound. Formation of the pro-drugs removes the hydrogen bond donors, preventing the number of bonds the product can form and aiding solubility. The lipophilicity of the phenol 174 has been increased by the synthesis of its pro-drugs (Figure 31),\textsuperscript{123} but remains below 5; the limits of Lipinski’s Rules for absorption of drugs in-vivo.\textsuperscript{124} Only the most active
6,7-dimethoxy-8-hydroxyisoquinolinone 174 was used in the first instance as a proof of principle.

![Chemical structures](image)

**Figure 31: Partition coefficients of the parent compound 174 and the pro-drugs 178 and 179**

Ethyl and benzyl carbamates and carbonates were synthesised using the corresponding chloroformate and NaH in THF in 12-41 % yields (Scheme 44). The poor yields may partly be due to the instability of the carbonate. The ethyl and benzyl carbonates 180 and 181 were found to hydrolyse on standing to give the carbamates 178 and 179.

![Synthesis scheme](image)

**Scheme 44: Synthesis of ethyl and benzyl pro-drugs**

As with the previously synthesised analogues, the pro-drugs were tested in an MTS cell proliferation assay using human HT29 colon cancer cells with a 72 hr exposure time (Table 3). The activities of the compounds were found to be
comparable to that of the parent compound, showing that the addition of carbamate and carbonate groups to the compound did not have a deleterious effect on activity.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>174</td>
<td>71</td>
</tr>
<tr>
<td>178</td>
<td>83</td>
</tr>
<tr>
<td>179</td>
<td>95</td>
</tr>
</tbody>
</table>

It was not known what the active species was within the assay, or at what point, if at all, the carbamate groups were hydrolysed. To evaluate this, the benzyl pro-drug 179 was incubated in the assay medium for 72 hrs, to mimic the assay conditions without the cells present. Aliquots of the media were taken at intervals and analysed by mass spectroscopy for the degradation of the pro-drug and appearance of the parent compound. The mass spectra showed the pro-drug to remain intact throughout the 72 hrs, without the appearance of the parent compound 174. This shows that the pro-drug must be entering the cell, where it is either then hydrolysed to give the active compound or it stays intact and shows cytotoxicity itself.

2.5. CONCLUSIONS AND FUTURE WORK

A one-pot method to synthesise a series of AB-ring analogues of narciclasine from their corresponding carboxylic acids has been developed and optimised, using a modified Curtius rearrangement and Lewis-acid catalysed intramolecular Friedel-Crafts alkylation. Using this procedure, twelve analogues have been synthesised in moderate to good yields. This procedure can now be applied in the synthesis of the more complex ABC-ring analogues.

The 6-membered ring analogues were all oxidised to give their fully aromatic counterparts which mimic the sp² position in narciclasine. Although DDQ was able to perform the oxidation of most of the analogues, the yields were generally poor and the procedure was not successful on all of the analogues. There was more success using palladium on carbon, especially when the reactions were performed in a microwave and in future this procedure should be used for the dehydrogenation of dihydroisoquinolinones and carbolinones.
These analogues have been tested against HT29 colon cancer cells and were found to be poor to moderately cytotoxic. Despite these activities, these compounds are privileged structures which have been reported to be active against a range of targets when incorporated into larger molecules (Figure 32). The oxidised electron rich aromatic motif is found in the cytotoxic topoisomerase I inhibitor NSC 314622 182 developed by Cushman. 125 4-Aryl-1-isoquinolinone derivatives 183 have been found to inhibit phosphodiesterase 5, a target in the treatment of cardiovascular diseases. 126 Carbolinones, such as 184, have also found to be glutamate receptor (mGluR) antagonists. 127 A series of carbolinones including 185 have been investigated as potent inhibitors of MK2, a kinase involved inflammation, cell proliferation and apoptosis. 121

Figure 32: Examples of AB-ring analogues incorporated into larger, bioactive molecules

To extend the work on the carbolinone series, preliminary experiments were performed into the Friedel-Crafts acylation of 153 at the 5-position using acetyl chloride and AlCl$_3$. Unfortunately, despite following literature precedent, 128 the compounds were not isolated during these initial investigations. However, further optimisation could provide a route to these medicinally interesting compounds.
In addition it has been found that triketone 186 is a caspase-3 inhibitor so is an inhibitor of apoptosis.\textsuperscript{129} Ruthenium tetroxide, generated by the oxidation of ruthenium dioxide by sodium periodate, has been described for the oxidation of 3,4-dihydroisoquinolinones to the corresponding triketones.\textsuperscript{130} In preliminary investigations, following this protocol, the oxidation of the methylenedioxy analogue 144 and its Boc-protected derivative 187 was investigated, however the corresponding triketones 188 and 189 were not observed.

**Scheme 45: Triketone 186 and the attempted oxidation of dihydroisoquinolinones**

The benzyl and ethyl carbamate pro-drugs 178 and 179 have been prepared and evaluated using the HT29 colon carcinoma cell line and displayed only a small reduction in activity when compared to the parent compound. As the carbonate groups on the phenol in 180 and 181 were unstable under ambient conditions, other functional groups can be investigated to make use of this handle (Figure 33). Carbamates 190 can be synthesised using carbamoyl chlorides in the presence of strong base. Esters 191 can also be investigated as groups which are stable in ambient conditions, but susceptible to hydrolysis within the body. Within studies on narciclasine, the 1-phenyl ester was found to be active, however the 7-phenyl ester was not prepared. Phosphate esters 192, similar to those of narciclasine discussed in section 1.1.4 (p. 14) can also be investigated.

**Figure 33: Examples of possible pro-drugs that could be investigated**
3. SYNTHESIS AND EVALUATION OF ABC-RING ANALOGUES

3.1. SYNTHESIS OF THE DIMETHOXY-ANALOGUE

3.1.1. Synthesis of the β-Ketoester

For the synthesis of the tricyclic core, the dimethoxy-substituted analogue was chosen as the model system as it simplifies the cyclisation of the B-ring in comparison to the trimethoxy-derivative which undergoes selective demethylation. The cost and availability of the starting acetophenone favoured the use of dimethoxyacetophenone over methylenedioxyacetophenone. The optimised synthetic route would then be applied to the synthesis of other analogues.

![Scheme 46: Synthesis of β-ketoester 194](image)

Reagents and conditions: 1.5 eq NaH, diethyl carbonate, 80 °C.

The first step in the synthesis was a Claisen condensation of 3,4-dimethoxyacetophenone 193 with diethyl carbonate (Scheme 46). Following the procedure reported by Jung et al.,131 on a 10 mmol scale using sodium hydride as the base at 80 °C, the β-ketoester 194 was isolated in 97 % yield. The reaction has been repeated on a 50 mmol scale with a yield of 96 %, demonstrating the consistency and scalability in the reaction. Condensation of the β-ketoester with another molecule of the carbonate was not observed.

Following the proposed synthesis discussed in Section 1.2 (p. 20), there were two possible routes that could be taken from the β-ketoester to form the tricyclic core structure.
3.1.2. Route A

Following Route A, saponification of the β-ketoester was attempted, to provide the carboxylic acid for the Curtius rearrangement. Herbert et al. reported the saponification of ethyl ester 194 using aqueous KOH and isolated the resulting acid 196 in 82 % yield. However, in our hands acid 196 could not be isolated, instead only ketone 193, the product from decarboxylation was isolated (Scheme 47).

![Scheme 47: Saponification and decarboxylation of β-ketoester](image)

Treatment of β-ketoester 194 with KOH in EtOH gave the potassium carboxylate 195 in 84 % yield after filtration from the reaction mixture. As the free acid could not be isolated, the potassium carboxylate was subjected to the rearrangement and cyclisation conditions optimised with the AB-ring analogues (Section 1.2.1.), however the product was not isolated. As gas evolution had not been observed, it was believed that the isocyanate was not formed due to poor solubility of the potassium salt in toluene. In an attempt to solubilise the carboxylate 195, 18-crown-6 was added to the reaction mixture to chelate to the potassium ion; however, the cyclised product was still not observed. Instead, the corresponding ethyl ester was isolated in 33 % yield, indicating that some of carboxylate had been activated, but residual ethanol from the saponification had acted as the nucleophile instead of the azide. The remainder of the mass could not be identified.

These experiments indicated that the cyclisation in route A would require further investigation and since the alternative route was more successful, further work on Route A was not performed.
3.1.3. Route B

The first step in route B is the reaction of the β-ketoester 60 with methyl vinyl ketone (MVK) in a Robinson annulation to give a modified Hagemann’s ester 63. As previously discussed in the introduction; the mechanism proceeds via a Michael addition to the MVK, followed by an intramolecular aldol condensation to give the cyclohexenone (Scheme 48).

![Scheme 48: Simplified mechanism of the Robinson annulation](image)

There are many examples of Robinson annulations in the literature, providing confidence in the approach. Using NaOH in MeOH, as reported by Ziegler,$^{133}$ Umbezawa$^{134}$ and Turnbull,$^{135}$ followed by acidification with sulfuric acid and heating to 70 °C gave a number of compounds, most of which could not be identified. However, two compounds were identified as the acetophenone 193 in 4 % yield and cyclised material 198 in 17 % yield (Scheme 49).

![Scheme 49: Reaction of β-ketoester 194 with NaOH as the base](image)

The appearance of these compounds is due to hydrolysis of the ester group and subsequent decarboxylation. As previously described in Route A; the acidic work-up results in decarboxylation of the β-ketoacid 194 when hydrolysis occurs before the Robinson annulation resulting in acetophenone 193. When hydrolysis
occurs in the cyclised material 199, the extended conjugated system proves a route for decarboxylation under basic conditions as the ketone acts as an electron sink (Scheme 50). This observation has been reported Counsell et al. in their synthesis of androstenedione analogues.\(^{136}\)

![Scheme 50: Mechanism of decarboxylation in cyclised material](image)

As the cause of the saponification was due to the hydroxide, other bases were investigated. Sodium methoxide in methanol has been reported in similar systems by Kitahara in the synthesis of tanabalin 87,\(^{75}\) and MaGee in the synthesis of decahydroisoquinolines 201 (Scheme 51).\(^{137}\)

**Scheme 50: Mechanism of decarboxylation in cyclised material**

**Scheme 51: Kitahara’s\(^ {75}\) and MaGee’s\(^ {137}\) examples of NaOMe/MeOH mediated Robinson annulations**
To prevent the formation of a mixture of the ethyl and methyl esters, sodium ethoxide in ethanol was used instead. Following a procedure reported by Aubé, the β-ketoester 194 was treated with the MVK and NaOEt in EtOH, at 70 °C as reported and at room temperature. However, the main product from both reactions was the decarboxylated ketone 198. Ethanol was used directly without distillation, so residual water could have led to de-esterification. The reactions were repeated with a preformed solution of NaOEt in EtOH under anhydrous conditions and after heating at both 50 °C and 90 °C, the main product isolated from the reaction was the β-ketoester 194, with a small amount of the acetophenone 193. This shows that in the absence of water de-esterification does not occur, but that NaOEt is still not a suitable base for the transformation. This may be because the enolate formed by the deprotonation of a β-ketoester can chelate a sodium ion, stabilising the negative charge and rendering it a poor nucleophile (Figure 34). A solution to this would be to use a base with a larger cation that is unable to coordinate so strongly to the enolate.

![Figure 34: Chelation of sodium ion](image)

Potassium carbonate was investigated as a non-nucleophilic base, with a larger counterion to avoid the problems of saponification and chelation. There is some literature precedent for the use of K₂CO₃, using alcohols as the solvent. Alcohols are nucleophilic and generally hygroscopic, so to avoid the use of a nucleophilic solvent or the possible introduction of water, anhydrous acetonitrile was employed instead (Scheme 52).
Using 2.5 eq. of the base and MVK for 18 hrs at room temperature gave two products; the mono-addition product 202 in 72 % yield and the bis-addition product 203 in 9 % yield (Table 4, entry 1). Increasing temperature and reaction time were investigated to promote cyclisation to the modified Hagemann’s ester 204 (Table 4, entries 2-4). However any cyclised material observed had also undergone a second Michael addition. As there are three sets of acidic protons in the cyclohexenone adjacent to a carbonyl group, there are three possible sites for this second addition to occur leading to three possible regioisomers, but the structure of the product could not be deduced by spectroscopic methods. Interestingly, the Michael addition product 202 can be formed in good yield under mild conditions (Entry 5).

Table 4: Optimisation of the reaction of β-ketoester 194 and MVK with K$_2$CO$_3$ in acetonitrile

<table>
<thead>
<tr>
<th>Entry</th>
<th>K$_2$CO$_3$ (eq)</th>
<th>MVK (eq)</th>
<th>Time (hrs)</th>
<th>Temp (°C)</th>
<th>Yield 202 (%)</th>
<th>Yield 203 (%)</th>
<th>Yield 204 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>2.5</td>
<td>18</td>
<td>r.t.</td>
<td>72</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>2.5</td>
<td>24</td>
<td>50</td>
<td>11</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>1.5</td>
<td>24</td>
<td>50</td>
<td>34</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
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<tr>
<td>5</td>
<td>1.1</td>
<td>1.1</td>
<td>2.5</td>
<td>0-rt</td>
<td>97</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Dehydration of the cyclised material 204 under acidic conditions was performed to install the double bond (Scheme 53). Conditions similar to those reported by Jørgensen\textsuperscript{96} utilising 4M HCl in dioxane yielded 66 % of the dehydrated product 205 and 20 % starting material. When \( p \)-TsOH in refluxing toluene was employed, as described by Agami,\textsuperscript{93} only the dehydrated product 205 was isolated in a 72 % yield. The site of the second Michael addition could still not be deduced by spectroscopic methods, but the absence of an alkenyl proton in the \( ^1 \)H NMR spectrum implied that the second Michael addition did not occur adjacent to the ester group.

\[
\text{Reagents and conditions: i) 4M HCl, dioxane; ii) \( p \)-TsOH, toluene}
\]

Scheme 53: Dehydration of alcohol 204 to give one of three possible regioisomers 205a, b or c

Due to the success of the mild Michael addition reaction conditions it was decided to approach the annulation as a two step process. There was literature precedent for performing the cyclisation and dehydration in one step from the Michael addition product 202 in acidic conditions including the use of pyrrolidine or piperidine and acetic acid as described by Golding\textsuperscript{86} and Christoffers.\textsuperscript{82} Following the conditions reported by Boeckman,\textsuperscript{80} ester 202 was heated in toluene in refluxing
conditions with 3 eq. pyrrolidine and 4 eq. of acetic acid for 24 hrs, giving the desired cyclised product 206 in only 16 % yield (Table 5, entry 1). In addition aniline 207 was also isolated in a 25 % yield, presumably generated by the condensation with pyrrolidine and subsequent oxidation to give the aromatic ring (Scheme 54).

Scheme 54: Cyclisation of Michael addition product 202 using pyrrolidine and acetic acid

Formation of similar aniline products has been described by Padwa where a cyclisation of a Michael addition product was carried out in the presence of an excess of pyrrolidine and catalytic p-TsOH acid in refluxing toluene.139 To avoid the formation of the aniline, different conditions were investigated (Table 5).

Table 5: Optimisation of pyrrolidinium acetate promoted cyclisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrolidine (eq)</th>
<th>AcOH (eq)</th>
<th>Time (hrs)</th>
<th>Temp (°C)</th>
<th>Yield 206 (%)</th>
<th>Yield 207 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>4</td>
<td>24</td>
<td>Reflux</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>0.95</td>
<td>1.5</td>
<td>80</td>
<td>65a</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>0.95</td>
<td>2.5</td>
<td>80</td>
<td>52</td>
<td>-</td>
</tr>
</tbody>
</table>

*a* isolated as a mixture of starting material 202 and product 206 in a 15:85 ratio.

Following the conditions reported by Nour, the reaction was performed using a substoichiometric amount of pyrrolidine and AcOH at 80 °C and the aniline was not observed (Table 5, entries 2 and 3). However, full conversion of the starting material to product was not achieved when the reaction was stirred for only 1.5 hrs (Entry 2). Full conversion of the starting material to the product was essential as the
compounds could not be separated by column chromatography and this was achieved in 2.5 hrs (Entry 3).

As lowering the temperature from reflux to 80 °C resulted in an increase in yield, further increases in yield may be achieved by reducing the temperature further but increasing the reaction time. This method holds promise in also providing an enantioselective route to the cyclohexenone by using chiral secondary amines or proline derivatives; an approach which has been used by Jørgensen et al. in the enantiomeric synthesis of cyclohexenones.96

![Scheme 55: p-TsOH catalysed cyclisation of 202](image)

Liu84 and Agami93 have reported the use of p-TsOH in toluene to affect the cyclisation and dehydration (Scheme 55). Initially 10 mol% of the p-TsOH catalyst was employed; however there was only a 30% conversion of the starting material to product after 24 hrs (Table 6, entry 1). As previously highlighted, full conversion was essential for a successful reaction as the starting material and product could not be separated by column chromatography. When the amount of the catalyst was increased to 30 mol%, there was an increase in conversion to 66% (Entry 2) and full conversion was only achieved using 40 mol% of the catalyst (Entry 3). Increasing the amount of catalyst to 60 mol% did not increase the yield further (Entry 4).

When the reaction was performed on a larger scale, a basic work-up was included to remove the increased quantity of p-TsOH; however an increase in yield was not observed so this was excluded from subsequent reactions (Entry 6).
Table 6: Optimisation of the acid catalysed cyclisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale (mmol)</th>
<th>p-TsOH (mol%)</th>
<th>Time (hrs)</th>
<th>% Product 202</th>
<th>% Starting material 207</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>10</td>
<td>24</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>30</td>
<td>24</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>40</td>
<td>20</td>
<td>89</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>60</td>
<td>24</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>40</td>
<td>38</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>9.3</td>
<td>40</td>
<td>20</td>
<td>70</td>
<td>-</td>
</tr>
</tbody>
</table>

With a route to the modified Hagemann’s ester 207 in hand, investigations began on the saponification of the ester and the rearrangement and cyclisation of the resulting acid. There had already been indications the acid may be difficult to handle due to the extended conjugated system allowing decarboxylation. However, it was thought that if the acid could be kept cool until the acyl azide intermediate had been formed then decomposition could be avoided.

With a route to the modified Hagemann’s ester 207 in hand, investigations began on the saponification of the ester and the rearrangement and cyclisation of the resulting acid. There had already been indications the acid may be difficult to handle due to the extended conjugated system allowing decarboxylation. However, it was thought that if the acid could be kept cool until the acyl azide intermediate had been formed then decomposition could be avoided.

There was some literature precedent for the saponification reaction, all of which kept the reactions cool to avoid decarboxylation. Using LiOH.H₂O in MeOH/H₂O at 10 °C for 5 hrs as described by Bannerjee,¹⁴⁰,¹⁴¹ or NaOH in MeOH/H₂O at 5 °C for 24 hrs as described by Rosenberger,¹⁴² both gave mixtures of products which could not be separated. The most successful conditions found were those reported by Oritani,¹⁴³ using 1.1 eq. of KOH in EtOH/H₂O at 5 °C overnight. This reaction was performed several times during the investigation with yields of acid 208 of 80 % to quantitative. Practically, the reaction was easy to execute as it could be left in the fridge overnight. It was found that extractions needed to be

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⁶⁸
performed with diethyl ether as the organic phase because hydrolysis of ethyl acetate was observed leading to trace amounts of acetic acid contaminating the product.

Cyclisation of the acid 208 was attempted using the procedure optimised on the AB-ring analogues, but to activate the acid and form the acyl azide without concurrent decarboxylation, the reaction was cooled to 5 °C for 1 hr before heating to 90 °C. Two products were isolated from the reaction in a 1:1 ratio, but could not be separated by column chromatography; the decarboxylated material 209 and what was thought to be the acyl azide 210 as determined by a characteristic peak in the IR at 2145 cm⁻¹ correlating to an azide stretching frequency (Scheme 57).

![Scheme 57: Attempted cyclisation of acid 208](image)

Reagents and conditions: a) DPPA, Et₃N, toluene, 5 °C; b) 90 °C; c) BF₃·OEt₂

To prevent the problem of decarboxylation, it was decided that the extended conjugated system should be removed before the further cyclisation conditions were attempted. This was achieved by reduction of the ketone, followed by protection of the resulting alcohol to prevent interference with the cyclisation reaction.

The Luche reduction uses sodium borohydride and ceric chloride to selectively reduce an α,β-unsaturated ketone whilst leaving the alkene intact. Following the method of Hudlicky et al., the ketone 206 was successfully reduced to afford alcohol 211 in 80 % yield and an 80:20 mixture of diastereoisomers (Scheme 58). It was not possible to identify which was the major isomer by spectroscopic methods. However, mechanistically the hydride would be
preferentially delivered to the least hindered face of the carbonyl. This would place the hydroxyl and ester groups on the same face of the ring in the major isomer.

![Diagram of Luche reduction of unsaturated ketone 206]  
Reagents and conditions: NaBH₄, CeCl₃, MeOH

Scheme 58: Luche reduction of unsaturated ketone 206

Protection of an alcohol using a silyl group is a common protection strategy, as the protection is straightforward to perform under basic conditions and the deprotection can be affected by either fluoride or under acidic conditions. It was also anticipated that using BF₃·OEt₂ as the Lewis acid in the cyclisation would provide a source of F⁻, negating the need for a formal deprotection at the end of the synthesis. *tert*-Butyldimethylsilyl (TBDMS) chloride was chosen to protect the alcohol, as the TBDMS group would be more stable to the acidic work-up involved in the saponification step. The conditions chosen were those reported by both Shimizu,¹⁴⁷ and Petit,¹⁴⁸ using 1.1 eq. TBDMSCl and 1.1 eq. imidazole in DMF and produced the protected alcohol 212 in 63 % yield when performed on a 0.4 mmol scale and a 76 % yield when the scale was increased to 3 mmol (Scheme 59). The product remained an 80:20 mixture of diastereoisomers, but again the configuration of the major isomer could not be determined by ¹H NMR analysis.

![Diagram of silyl protection of the alcohol 211]  
Reagents and conditions: TBDMSCl, imidazole, DMF.

Scheme 59: Silyl protection of the alcohol 211
The ester 212 was exposed to the same saponification conditions previously used, however it was discovered that this ester was more stable to these conditions and so heating was required to force the reaction (Scheme 60). The acid was isolated in approximately 71 % yield, but the product contained minor impurities by $^1$H NMR analysis. Cyclisation was attempted on the material using DPPA and Et$_3$N in toluene at 90 °C followed by treatment with BF$_3$·OEt$_2$. However, a mixture of products was isolated which could not be identified by spectroscopic methods.

![Reaction Scheme](image)

Reagents and conditions: i) KOH, EtOH/H$_2$O, reflux; ii) a) DPPA, Et$_3$N, toluene, 90 °C; b) BF$_3$·OEt$_2$

**Scheme 60: Saponification and attempted cyclisation of ester 212**

### 3.2. SYNTHESIS OF THE TRIMETHOXY-ANALOGUE

#### 3.2.1. Synthesis of the Modified Hagemann’s Ester

The initial steps in the synthesis were straightforward as the route previously developed from 3,4-dimethoxyacetophenone could be used. The Claisen condensation using NaH in diethyl carbonate was successful and the reaction was performed 3 times on scales of 5-50 mmol, with yields of 67-95 % (Scheme 61).

![Reaction Scheme](image)

Reagents and Conditions: NaH, diethyl carbonate, 80 °C, 1-3 hrs.

**Scheme 61: Condensation of acetophenone with diethyl carbonate**
The Michael addition using 1.1 eq. MVK and 1.1 eq. K$_2$CO$_3$ in MeCN was also efficient, with yields of the Michael adduct 217 of 72-98% over the 3 times the reaction was performed (Scheme 62). Both steps have been performed on scales of up to 50 mmol, showing the robustness of the reactions. Column chromatography was used to purify the products; however, there is opportunity to telescope the products through to the solid Hagemann’s ester 218, which can be purified by recrystallisation, avoiding the use of chromatography on a large scale.

![Chemical structure of 216 and 217](image)

Reagents and conditions: MVK, K$_2$CO$_3$, MeCN, 0 °C-r.t.

Scheme 62: Preparation of 217 by the Michael addition of MVK to β-ketoester 216

The conditions used for the cyclisation were those previously developed on the dimethoxy-analogue using 0.4 eq. of p-TsOH in refluxing toluene (Scheme 63). The reaction was performed on 26-40 mmol scale using Dean-Stark trap to afford the ester 218 in 47-54% yield.

![Chemical structure of 217 and 218](image)

Reagents and conditions: 0.4 eq p-TsOH, toluene, reflux, 24 hrs.

Scheme 63: Acid catalysed cyclisation of 217

The remainder of the mass balance was not determined. However, as $^1$H NMR analysis of the crude reaction mixture showed clean conversion of the starting material to product, the poor yield was believed to be due to problems during
purification. In future, column chromatography might be avoided and yields increased by employing a basic work-up and recrystallisation to purify the product.

3.2.2. Saponification and Cyclisation of Modified Hagemann’s Ester

The optimised conditions for the hydrolysis of the dimethoxy- analogue 206 using 1.1 eq. KOH in EtOH/H₂O were unsuccessful, giving a mixture of products that could not be separated. A screen of bases and solvents was undertaken, leaving the reactions at 5 °C for 16 hrs, with the best results obtained with 5 eq. of LiOH.H₂O in EtOH/H₂O (Table 7, entry 1). The ¹H NMR spectra of the crude acid 219 were cleaner when the reaction was performed in EtOH/H₂O than when THF/H₂O was used. After the initial screen it was found that the reactions could be performed at room temperature, giving yields of 75-97 % in just 1 hr.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOH.H₂O</td>
<td>EtOH/H₂O</td>
<td>Clean, complete conversion by ¹H NMR and TLC</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>THF/H₂O</td>
<td>Complete conversion by TLC but impurities present by ¹H NMR</td>
</tr>
<tr>
<td>3</td>
<td>NaOH</td>
<td>EtOH/H₂O</td>
<td>Clean, complete conversion by ¹H NMR and TLC</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>THF/H₂O</td>
<td>Incomplete conversion.</td>
</tr>
</tbody>
</table>

For the first attempt at the Curtius rearrangement, the acid was stirred at room temperature with triethylamine and DPPA in toluene for 45 mins before the reaction has heated at 90 °C. As was observed during the rearrangement of the dimethoxy- analogue under similar conditions (Section 3.1.3, p. 69), the reaction yielded a mixture of products which could not be separated by column chromatography. However the decarboxylated product 220 could be identified in the ¹H NMR spectrum of the crude material. It was believed that the acid was not converted to the acyl azide before the reaction was heated, allowing decarboxylation to occur when the temperature was raised.

The isolation of acyl azides has been reported by Padwa¹⁴⁹ and Katrizky,¹⁵⁰ so to further investigate the activation of the acid isolation of the acyl azide 221 was
attempted. When reaction of acid 219 with DPPA and Et$_3$N was performed at room temperature, the acyl azide 221 was isolated in a disappointing 6 % yield, along with another product which appeared to be a carbamoyl azide 222 (Scheme 64). The IR spectrum of the compound 222 showed both amide and azide stretches at 1667 cm$^{-1}$ and 2145 cm$^{-1}$ respectively and the $^1$H NMR spectrum of the compound contained 2 aromatic protons, indicating that cyclisation had not taken place. Carbamoyl azides have been reported, along with their synthesis from isocyanates and a source of azide.$^{151,152,153}$ Interestingly, to form this product the azide must undergo a room temperature Curtius rearrangement.

Reagents and conditions: DPPA, Et$_3$N, toluene, r.t., 2 hrs

**Scheme 64: Attempted synthesis of the acyl azide**

Activation of the acid using a mixed anhydride, as previously discussed in the synthesis of the AB-ring analogues, was also investigated. The reaction was performed at room temperature using ethyl chloroformate and Et$_3$N in acetone/water followed by the addition of NaN$_3$ to generate the acyl azide, however the acyl azide was not observed. Instead, the starting acid 219 was isolated in 45 % yield and the corresponding ethyl ester 218 was isolated in 47 % yield. The initial step in the mechanism of the formation of the ester is the activation of the acid as the mixed anhydride, with the liberation of a chloride anion. This can react as a nucleophile with the ester carbonyl, to give the acyl chloride with concurrent decomposition of
the carbonate moiety releasing carbon dioxide and ethoxide. Finally, the ethoxide displaces the chloride to give the ester 218 (Scheme 65).

![Chemical structure](image)

Scheme 65: Mechanism for the formation of ethyl ester 223 from acid 219 and EtOCOCl

As the acid 219 had been sensitive to the base used during the saponification step, other bases were considered for this transformation. Pyridine was identified as an alternative organic base. With a pK<sub>a</sub> of 5.21, it is weaker than Et<sub>3</sub>N with a pK<sub>a</sub> of 10.75 but still basic enough to deprotonate the acid. Using DPPA to activate the acid, only the decarboxylated material 220 was observed (Scheme 66).

![Chemical structure](image)

Scheme 66: Using pyridine as the base in the Curtius rearrangement

Reagents and conditions: a) DPPA, pyridine, toluene, r.t. 2 hrs; b) 90 °C, 1 hr; c) BF<sub>3</sub>OEt<sub>2</sub>.
Inorganic bases were also investigated as the saponification of ester 218 was successful when LiOH.H₂O and NaOH were used, so these bases were known to be compatible with the carboxylate. However, hydroxide is nucleophilic so to avoid degradation of the DPPA or the activated acid, sodium, potassium and caesium carbonates were investigated instead. To improve the solubility of the base, the solvent was changed to acetone. In addition, the final step was also modified; after stirring the acid, carbonate and DPPA in acetone at room temperature, the solvent was removed and methanol added. This modification was an attempt to simplify the final step of the reaction, using the methanol to trap the isocyanate to give the carbamate instead of performing the cyclisation and demethylation (Scheme 67).

The carbamate 223 was isolated in 19 % yield when Na₂CO₃ was employed as the base. Carbamate 223 was also observed in the reaction using K₂CO₃ although the major product was that of decarboxylation 220. The reaction with Cs₂CO₃ also gave predominantly decarboxylated material. These results were unsurprising as in the initial saponification reactions using KOH had given a mixture of products. It was believed that the carboxylate was unstable when accompanied by larger counterions.

Sodium and potassium carbonate were also employed as bases when ethyl chloroformate was used to activate the acid. It was believed these reactions would work well as the base would be fully dissolved in the acetone/water solvent system normally used. However; the predominant product in both reactions was the corresponding ethyl ester 218 that had previously been observed, isolated in 32 % yield using sodium carbonate and 42 % using potassium carbonate. The carbamate 223 was isolated in both reactions in a 5 % yield with Na₂CO₃ and 2 % with K₂CO₃.
Activating the acid as either a mixed anhydride or phosphoric anhydride was proving to be a difficult strategy, so the acid chloride was explored as a possible route of activation. In the attempted synthesis of α-amino acids from malonic half esters, it was found that using DPPA led to the formation of esters as the major product (Scheme 68).\textsuperscript{154} It has been discussed more recently by Peterson et al. that this observation is due to the presence of acid protons alpha to the carboxylic acid leading to the formation of a ketene by the release of hydrazoic acid,\textsuperscript{155} and they extended this idea to the presence of benzylid protons α- to the carboxylic acid. To avoid this, the acid can be activated as an acid chloride using oxalyl chloride and catalytic DMF.
Yamada et. al.\textsuperscript{154}:

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{
reaction and increasing the chance of the intermolecular reaction. Targeting the acyl azide to ensure the intermolecular reaction had taken place, the acid chloride formation was carried out at −13 °C for 5 mins before the addition of sodium azide, but the 72 % of the starting material was reclaimed. When the reaction was left for 15 mins at −13 °C before the addition of azide only 65 % of the starting material was reclaimed. In these two reactions some decarboxylated cyclohexenone 220 was also observed, but the fluorenone were not seen. The acid chloride formation was also carried out at −10 °C for 1 hr before the addition of sodium azide and using methanol in the final step to target the carbamate 223. The decarboxylated material 220 was isolated in 23 % yield and the fluorenone 225 isolated in 57 % yield but the carbamate was not observed. This final reaction shows that the intramolecular cyclisation of the acyl chloride is too fast in comparison to the formation of the acyl azide, so this method of activation was not suitable for this synthesis.

It was concluded that the difficulties in activating the acid 219 towards nucleophilic attack of azide, without concurrent decarboxylation or cyclisation, were due to the extended conjugated system with unsaturated ketone. It was believed that removing this system would allow the rearrangement to work, without the complications experienced so far.

3.2.3. Removing the Conjugated System to Aid Cyclisation

Several methods of removing conjugation connecting the ester and ketone have been considered (Scheme 70). Luche reduction and silyl protection of the resulting alcohol had already been examined, but provided difficulties in saponification and cyclisation. Considering these problems, it seemed unwise to follow this route at this point. The other avenues investigated were to remove the cyclohexenyl double bond by hydrogenation leaving the ketone intact; protecting the ketone as either an acetal or dithioacetal; or completely removing the allyl ketone by reduction.
Considered methods of removing the conjugated system in ketone 218

The first method investigated was the hydrogenation of the double bond, leaving the ketone in place. Reduction of an α,β-unsaturated carbonyl with hydrogen and palladium on carbon is a well known transformation described extensively in the literature including examples by Cieplak, Mateos in the synthesis of ohchinolide analogues and Li in the synthesis of Cephalotaxine. Using 5 mol% Pd/C in EtOAc, the double bond was reduced to furnish 226 in a 49 % yield, but concurrent over-reduction also gave alcohol 230 in a 48 % yield (Scheme 71).

Reagents and conditions: H₂, 5 mol% Pd/C, EtOAc.
The desired product 226 was isolated as a single diastereoisomer, believed to be the cis-diastereomer by $^1$H NMR analysis and mechanistic insights. As shown in Figure 35, generated using an MM2 calculation in Chem3D, the ester group sits directly over one face of the cyclohexyl ring, preventing the catalyst accessing this face, resulting in the hydrogen being delivered to the opposite face, pushing the aromatic ring onto the same face as the ester.

Figure 35: Origins of stereoselectivity in the hydrogenation

The protons at the C1 and C2 position of the cyclohexene ring have a coupling constant of 10.0 Hz in the $^1$H NMR spectrum, so using the Karplus curve the protons and therefore the substituents have a syn-relationship (Figure 36).

Figure 36: Coupling constants of protons on the cyclohexyl ring

Over-reduction using Pd/C has been reported by Ohashi,$^{159}$ and Doering,$^{160}$ although they describe longer reaction times and higher pressures than were applied in this reaction. The alcohol 230 appears to be a single diastereoisomer by $^1$H NMR
analysis, though the stereochemistry cannot be confirmed by the coupling constants. However, using the same mechanistic arguments as applied to the ketone 226, a syn-relationship should exist between the alcohol, aryl ring and ester. The effect of changing the solvent to ethanol or acetic acid on the selectivity of the reaction was investigated, however over-reduction was always observed.

![Scheme 72: Epimerisation and saponification of ester 226](image)

Reagents and conditions: LiOH.H₂O or NaOH, H₂O.

Saponification of ester 226 was investigated using LiOH.H₂O and NaOH and higher yields of acid 231 were achieved with shorter reaction times using NaOH (Table 8, entries 2 and 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Reaction time (hrs)</th>
<th>Reaction temperature (°C)</th>
<th>Yield (%)</th>
<th>Diastereomeric ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOH.H₂O</td>
<td>5</td>
<td>r.t.</td>
<td>32</td>
<td>59:41</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>1.5</td>
<td>Reflux</td>
<td>99</td>
<td>35:65</td>
</tr>
<tr>
<td>3</td>
<td>NaOH</td>
<td>3</td>
<td>Reflux</td>
<td>82</td>
<td>33:67</td>
</tr>
</tbody>
</table>

The natural product has an anti-relationship at the B/C ring junction, so it was envisioned that this geometry could be installed in acid 231 by concurrent base-catalysed epimerisation at the C1 position (Scheme 72). Some epimerisation was observed with the best conversions seen in the reactions using NaOH (entries 2 and 3); however, full conversion was not achieved in the timeframes investigated. This may be because mechanistically the epimerisation must occur before the saponification as otherwise the base needs to deprotonate an anionic species which is energetically unfavourable. This means if the saponification reaction is faster than epimerisation, full conversion of the stereocentre would be slow. If this route was to
be pursued further then a non-hydrolytic base should be employed to do the epimerisation as a separate step before the saponification.

The cyclisation of acid 231 was attempted using DPPA and Et₃N in toluene and after treatment with BF₃·OEt₂, the demethylated lactam 232 was isolated in 6 % yield. Hydrolysis of the BF₂-adduct using NaOH in EtOAc was omitted and this may have lead to the low yield. This result does show that removal of the conjugated system does allow rearrangement and cyclisation, however further work would need to be carried out to optimise this approach.

Reagents and conditions: a) DPPA, Et₃N, toluene, 90 °C, b) BF₃·OEt₂

Scheme 73: Cyclisation and demethylation of acid 231

Protecting the carbonyl as either an acetal 227 or a dithioketal 228 was considered for removing the conjugated system as this approach protects the ketone without changing its oxidation state, leaving a handle to further functionalise the C-ring (Scheme 74).

Scheme 74: Acetal/dithioacetal protection of a ketone
Acetal protection is a common strategy used to mask ketones, performed under dry acidic conditions, for example p-TsOH or pyridinium para-toluenesulfonate in refluxing benzene as reported by Carreño et al., and Murakata et al., or oxalic acid in acetonitrile as reported by Kadas et al. in the synthesis of a narciclasine analogue. Deprotection is also straightforward using aqueous acid, which causes a problem with this strategy as the acetal would not be stable to the acidic conditions in the work up for the saponification. The dithioketal protecting group is more robust so would withstand the acidic conditions. The protection can be performed under Lewis acidic conditions as described by Craig et al. and Muthuisamy et al., but taken off under oxidative conditions as reported by Shi et al., and Wu et al. Although this strategy was not investigated it provides a robust method of masking the ketone without complete removal.

The route that has been most successful thus far is the complete removal of the ketone using sodium borohydride and trifluoroacetic acid. The method and conditions were first described by Gribble et al. in 1977 during his work on sodium borohydride reductions in acidic media, but has been applied selectively reduce unsaturated ketones as described by Winterfeldt et al., Hanson et al., De Riccadis et al., and Bayón et al. The mechanism is believed to proceed via a stabilized cationic species which is then quenched by the hydride.

Following the procedure reported by Bayón et al., the complete reduction of the ketone was achieved in 98% yield after 4 hrs (Scheme 75). Interestingly, after only 90 mins, two products were isolated from the reaction, cyclohexene in 72% yield and acetate in 16% yield. The acetate may be an intermediate in the reaction; however it is not known whether its substitution by a hydride occurs via an S_N1 or S_N2 process.
Scheme 75: Reduction of 218 to cyclohexene 229 and acetate 233

Saponification of ester 229 was attempted with LiOH.H₂O, but only the starting material was isolated. Instead the ester was hydrolysed using aqueous NaOH heated to reflux giving acid 234 in 79 %, yield as the precursor for the Curtius rearrangement and cyclisation (Scheme 76).

Reagents and conditions: NaOH, H₂O, reflux.

Scheme 76: Saponification of the ester 229

Following the cyclisation procedure optimised on the AB-ring analogues (Section 2.1.1, p. 39), the acid 234 was heated with DPPA and Et₃N in toluene, then the reaction mixture was treated with BF₃·OEt₂ at room temperature (Scheme 77). The reaction proceeded smoothly; evolution of gas during the reaction with DPPA and precipitation of a solid believed to be the BF₂-adduct 235 during the Lewis acid mediated step were observed. After heating the mixture in 2M NaOH and EtOAc at 50 °C, the cyclised and demethylated product 236 was isolated in a 34 % yield.
When the BF$_3$·OEt$_2$ step was performed at 50 °C, the product 236 was isolated in a slightly improved 46 % yield. The remainder of the mass balance was not identified in either of the reactions.

![Scheme 77: Synthesis of phenanthridone 236 by the cyclisation and demethylation of acid 234](image)

Reagents and conditions: a) DPPA, Et$_3$N, toluene, 90 °C; b) BF$_3$·OEt$_2$, r.t. or 50 °C; b) NaOH, 50 °C

The 8,9-dimethoxy-7-hydroxyphenanthridone 236 was synthesised in an overall 18 % yield and 6 steps. Despite further optimisation being required, the route was applied to the synthesis of the 8,9-dimethoxyphenanthridone.

3.3. SUCCESSFUL SYNTHESIS OF THE 8,9-DIMETHOXYPHENANTHRIDONE 239

The synthesis of the dimethoxy analogue was resumed at Hagemann’s ester 206. Reduction of the ketone to afford cyclohexene 237 proceeded efficiently, affording the product in 83 % yield after 4 hrs (Scheme 78).
Reagents and conditions: CF₃CO₂H, CH₂CO₂H, NaBH₄, CH₃CN, CH₂Cl₂, 4 hrs.

Scheme 78: Reduction of ketone 206 to cyclohexene 237

The ester 237 was then hydrolysed using aqueous NaOH heated at reflux and the acid 238 was isolated in 84 % yield (Scheme 79).

Reagents and conditions: NaOH, H₂O, reflux

Scheme 79: Saponification of ester 237

Following the procedure for the cyclisation of 3-(3,4-dimethoxyphenyl)propionic acid 146, acid 238 was heated at reflux with DPPA and Et₃N in toluene, before treatment with BF₃·OEt₂ at 50 °C. After heating the reaction mixture in NaOH and EtOAc at 50 °C, two products were isolated from the reaction; the lactam 239 in a 34 % yield and another cyclised product 240 in 23 % yield (Scheme 80). There was also a 28 % yield of a mixture of products 239 and 240, in a ratio of 31:69, which were not separated by column chromatography, giving a total yield of 85 % of cyclised products.
The product 240 was formed by the migration of the double bond to the B/C ring junction, to give the more thermodynamically stable tetra-substituted alkene. It is not known at what point the migration occurred, however the migration may proceed by a base catalysed mechanism (Scheme 81).

Phenanthridone 239 was synthesised in an overall yield of 15 % and 240 was synthesised in an overall yield of 10 %. The synthesis was performed in only 6 steps and the final step produced two interesting analogues. Through further optimisation of this reaction, either of the products might be accessed selectively. The synthesis of these analogues has tested the scope of this synthetic route and following further optimisation other interesting analogues may be synthesised using this short route in good yields.
3.4. BIOLOGICAL EVALUATION

The three compounds have been tested in an MTS cell proliferation assay using human HT29 colon cancer cells with 72 hrs exposure time. The compounds have been tested twice and an average taken.

![Compounds 236, 239, and 240](image)

Figure 37: Biological activity of phenanthridones 236, 239 and 240

The analogues displayed activities in the lower micromolar range (Figure 37). Addition of the C-ring to the molecule increased the activity when compared to the AB-ring analogues (Section 2.3, p. 52). Inclusion of the 7-hydroxyl also increases activity from 37 µM to 23 µM, in keeping with the SAR patterns in the natural product. Interestingly, the compound 240 where the double bond has migrated shows only a 15-fold difference to the natural product 14 where the B/C ring junction is a double bond. This indicates that in this molecule, oxygenation in the C-ring is less important for biological activity. When the double bond sits between the 10b and 1 position, there is approximately a 250-fold difference in activity between 239 and 7-deoxy narciclasine 4; and 1500-fold difference between 236 and narciclasine 3.

This increase in activity with increasing size of the molecule brings confidence that with the introduction of oxygenation, or other polar and hydrogen bonding groups onto the C-ring, nanomolar activities may be achieved.
3.5. CONCLUSIONS AND FUTURE WORK

3.5.1. Chemistry

A 6-step route to the ABC-ring tricyclic core has been developed using a Robinson annulation and a Curtius rearrangement and intramolecular Friedel-Crafts acylation as key steps in the synthesis. Using this approach 8,9-dimethoxy-7-hydroxyphenanthridone 236 was synthesised in 18% overall yield and 8,9-dimethoxyphenanthridone 239 was isolated 15% overall yield. In addition, phenanthridone 240 was isolated in 10% overall yield after the in-situ isomerisation of the double bond in 239.

This route can now be applied to the synthesis of the 8,9-methylenedioxyphenanthridone 241, to further test the scope of the route and access the third substitution pattern that was investigated in the AB-ring analogues. As 240, the product of double bond migration was active in the HT29 cells, the conditions under which this occurred should be investigated further so either of the regioisomers 241 or 242 can be synthesised selectively.

![Figure 38: 8,9-(Methylenedioxy)phenanthridone analogues 241 and 242](image)

A number of the steps within the route require further optimisation. The cyclisation of the Michael addition products using p-TsOH in refluxing toluene proved to be inefficient when performed on larger scales. Further investigations into pyrrolidine/AcOH as the catalysts for reaction may provide the cyclised product in better yields. It was originally envisaged that the Robinson annulation would be performed in one step. On reflection, it might be possible to develop the K$_2$CO$_3$/MeCN conditions for the Michael addition, heating the reaction once the addition has completed to give the cyclised product. Using t-BuOK in t-BuOH has been described for the annulation and could also be investigated. This is a bulky,
non-nucleophilic base with the larger potassium cation which would not cause the problems of chelation observed with the sodium alkoxide bases discussed in section 3.1.3 (p. 61).

The cyclisation of 234 to give the 8,9-dimethoxy-7-hydroxyphenanthridone 236 also requires further investigation to increase the yields from 42%. In a similar manner to the dihydroisoquinolinone 151, it may be possible to isolate and purify the BF$_2$-adduct then perform the hydrolysis to increase the yield.

Narciclasine contains a stereogenic centre at the 4a position, so the stereoselective synthesis of its analogues should be investigated. The configuration of the 4a position can be fixed in the Robinson annulation. Methods of achieving this were discussed in the introduction to the Robinson annulation (Section 1.4, p. 27) and can be investigated for these compounds. These include the initial synthesis of a chiral enamine followed by the Michael addition and cyclisation reactions, as was reported in the synthesis of Saudin (Scheme 82a). Alternatively, proline catalysts can be investigated, either in a two-step procedure to perform the cyclisation of the Michael addition product, or to perform the annulation in one step as has been described as Barbas III$^{98}$ and Swamainathan$^{99}$ (Scheme 82b).

Scheme 82: Methods of performing the Robinson annulation stereoselectively

Narciclasine contains a 2,3,4-trioxygenated C-ring, so the synthesis of analogues with a functionalised C-ring should also be investigated. Originally, the
target compounds contained a ketone in the C-ring which would have provided a handle to introduce other functional groups; however this was removed to aid the Curtius rearrangement. Allylic oxidation of the analogues synthesised in this project can be investigated to reinstall the ketone. Dithiane protection of the ketone was discussed in Section 3.2.3 and this could be investigated as a method of retaining the ketone allowing modification to be made to the ring after the formation of the lactam. Alternatively, the modifications could be made on the Hagemann’s ester, prior to the cyclisation of the B-ring. Other possible methods of adding functionality to the ring include the use of enolate chemistry as was discussed in section 1.2 (p. 20). Functionality could also be introduced through the use of different vinyl ketones, for example, methyl styryl ketones would lead to an aryl ring at the 4-position (Scheme 83).

![Scheme 83: Introduction of functionality in the C-ring through the use of different vinyl ketones](image)

### 3.5.2. Biology

As the cytotoxicity of the analogues has been evaluated against the human colon cancer cell line, the most active compounds should be assessed against other cancer cell lines to assess the consistency of their activity. The human prostate cancer cell line LNCaP and the human breast cancer cell line MDA-MB-231 have been used to test other compounds synthesised within the research group. These additional cell lines have been chosen as they can be easily transferred into in-vivo models, allowing in-vivo and in-vitro results to be easily compared. The selectivity of the most active compounds should also be assessed and this can be done testing them against a FEK-4 skin fibroblast cell line.
4. PRENYLATION OF ELECTRON-RICH ARENES

4.1. INTRODUCTION

4.1.1. The Prenyl Group

The prenyl group is a motif commonly found in natural products and biologically-active molecules,\textsuperscript{176} for example; novobiocin \textsuperscript{243}\textsuperscript{177} and derrubone \textsuperscript{244}\textsuperscript{178} have anti-tumour activity though inhibition of heat-shock protein 90 (Hsp90); Xanthohumol \textsuperscript{245} has anti-inflammatory activity and anti-cancer activity;\textsuperscript{179} and isobavachalcone \textsuperscript{246} induces apoptosis and inhibits tumour promotion.\textsuperscript{180} It has been shown that prenylation can increase the lipophilicity and activity of a compound;\textsuperscript{181} however, the position of the prenyl group is more important than the quantity.\textsuperscript{176}

There have been a number of reported methods of introducing the prenyl group to an arene (Scheme 84). A comprehensive review of ortho-prenylation of phenols was published in by Hoarau and Pettus.\textsuperscript{182} A common approach is to use lithium-halogen exchange or deprotonation/lithiation of an arene, followed by reaction with prenyl bromide (Scheme 84a). This approach has been applied to the
prenylation of phenols,\textsuperscript{183} benzenes,\textsuperscript{184} and indoles.\textsuperscript{185} Phenol is able to provide a useful handle for prenylation; as it can be O-prenylated, which upon a Claisen-Cope rearrangement gives the ortho- or para- C-prenylated phenol derivative (Scheme 84b).\textsuperscript{186a-c} In the synthesis of 247, a phenol derivative was O-allylated and after a Claisen rearrangement to afford the ortho-allyl material, Grubbs metathesis was used to install the gem-dimethyl group at the terminal end of the double bond (Scheme 84c).\textsuperscript{187} Direct C-prenylation of a phenol has been achieved under acidic conditions using zeolite catalysts at high temperatures;\textsuperscript{188} a silica mediated process;\textsuperscript{189} and by using oxalic acid in refluxing dioxane (Scheme 84d).\textsuperscript{190} However, these conditions have only been applied to phenols, so the challenge remains to efficiently prenylated other arene rings.

\begin{itemize}
  \item[a)]
  \[ \begin{array}{ccc}
  \text{Ph} & \text{BuLi} & \text{prenyl bromide} \\
  \text{X} = \text{H, Br} & \text{Ph} & \text{Ph} \\
  \end{array} \]

  Refs 183-185

  \item[b)]
  \[ \begin{array}{ccc}
  \text{Ph} & \text{prenyl bromide, base} & \text{Claisen-Cope rearrangement} \\
  \text{OH} & \text{Ph} & \text{Ph} \\
  \end{array} \]

  Refs 186a-c

  \item[c)]
  \[ \begin{array}{ccc}
  \text{Ph} & \text{Allyl bromide, base} \to \text{Claisen rearrangement} \to \text{Grubbs cross-metathesis} \\
  \text{OH} & \text{Ph} & \text{Ph} \\
  \end{array} \]

  Ref 187

  \item[d)]
  \[ \begin{array}{ccc}
  \text{Ph} & \text{zeolites, SiO}_2 \text{ or oxalic acid} \\
  \text{OH} & \text{Ph} & \text{Ph} \\
  \end{array} \]

  Refs 188-190

\end{itemize}

\textbf{Scheme 84:} Methods of aryl prenylation
4.1.2. The Chroman Group

Like the prenyl group, chroman is also a biologically important motif found in many natural products and medicinally interesting compounds such as Vitamin E \(^{248,191}\) cytototoxic and anti-plasmodial xanthones \(^{249,192}\) anti-mycobacterial dihydrobenzopyrans \(^{250,193}\) and the Dorsmanins A \(^{251,194}\) and B \(^{252,195}\).

![Chemical structures of Vitamin E, gartanin, dihydrobenzopyran, Dorsmanin A, and Dorsmanin B.]

Figure 40: Biologically active chromans

The main approaches to the synthesis of the chroman motif include nucleophilic addition of a Grignard reagent to the corresponding coumarin (Scheme 85a);\(^{196,197}\) or addition and cyclisation of a prenyl group with a phenol in the presence of a catalyst (Scheme 85b). There have been a number of reported methods of implementing the second approach. Claisen reported the condensation of phenol and isoprene in 1921,\(^{198}\) then interest in the transformation resumed in the late 1950’s and early 1960’s when Bader et al. reported the use of phosphoric acid\(^{199}\) and Dewhirst et al. reported the use of aluminium phenoxide\(^{200}\) to catalyse the addition and cyclisation of isoprene with phenol. In a similar manner to that reported by Bader, Ahluwalia et al. reported the use of ortho-phosphoric acid to catalyse the reaction of isoprene and a phenol in good yields.\(^{201}\) More recently Lewis acids have been explored as catalysts for the transformation. Montmorillonite clays;\(^{202}\) a
scandium triflate/ionic liquid system, a copper triflate-bipyridyl complex, and most recently BF$_3$·OEt$_2$ have all been shown to catalyse the reaction.

![Scheme 85: Synthetic approaches to the chroman ring](image)

4.1.3. Bismuth (III) Triflate

Bismuth (III) triflate is a mild, safe and easily handled Lewis acid that has proved to be useful in many chemical transformations, as reviewed by Gaspard-Iloughmane and Antoniotti. Recent applications of Bi(OTf)$_3$ as a catalyst include: acetylation of alcohols, esterifications; oxa-Pictet-Spengler reactions; Fries and Claisen rearrangements; Mannich reactions and aldol reactions. These papers also discuss the mechanism of action of Bi(OTf)$_3$, describing it as a safe and convenient source of triflic acid which is the actual catalyst in the reaction.

4.2. OPTIMISING THE REACTION CONDITIONS

During our investigations, bismuth (III) triflate was found to catalyse the addition of isoprene to methyl 3,4,5-trimethoxycinnamate (Scheme 86). Due to the biological importance of the prenol group, the mild reaction conditions and encouraging yield, it was decided that the transformation should be investigated further.
To optimise the reaction conditions, trimethoxybenzene was used as a model substrate (Scheme 87).

Scheme 87: Prenylation of trimethoxybenzene 252

To verify that Bi(OTf)$_3$ was the best catalyst for the transformation, a screen of acids was undertaken on a 0.5 mmol scale. The products were not isolated but the conversion was calculated from the $^1$H NMR spectra of the crude material (Table 9). A catalyst was essential for the reaction to proceed (Entry 1) and the protic acid TFA also had no effect on the reaction (Entry 2). Lewis acids ZrCl$_4$ and AlCl$_3$ did not catalyst the prenylation, but degradation of starting materials was observed in the $^1$H NMR spectra (Entries 3 and 4). Yb(OTf)$_3$ and Zn(OTf)$_3$ did not catalyse the reaction but degradation of the starting materials was not observed (Entries 5 and 6). Prenylation was observed when Sc(OTf)$_3$ (Entry 7) and BF$_3$·OEt$_2$ (Entry 9) were used; however, Bi(OTf)$_3$ (Entry 8) gave the best result with most of the starting material being consumed and a 70% conversion to the mono-prenylated product.
Table 9: Screen of Lewis acids for the prenylation reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>% Starting Material 255</th>
<th>% Mono-product 256</th>
<th>% Bis-product 257</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>ZrCl4</td>
<td>100(^a)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>AlCl3</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)3</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)2</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Sc(OTf)3</td>
<td>58</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Bi(OTf)3</td>
<td>11</td>
<td>70</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>BF3·OEt2</td>
<td>65</td>
<td>35</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\): Degradation of the starting material was observed by NMR

Bismuth (III) triflate has been described as a catalyst for many transformations as it has the advantages of being non-toxic and easy to handle. The mode of action of the catalyst has been discussed by both Ollevier\(^{213}\) and Dumeunier,\(^{215}\) who believe triflic acid is the active catalyst, which is released upon hydrolysis of Bi(OTf)\(_3\) (Scheme 88, route A). An alternative explanation is a bismuth species acts as a Lewis acid and coordinates to the isoprene, activating it towards nucleophilic attack by the aryl ring (Scheme 88, route B).

Scheme 88: Two possible mechanisms for the catalysis of prenylation
The determine the most probable mechanism, a series of reactions were performed on a 2 mmol scale, using 10 mol% Bi(OTf)$_3$ under anhydrous conditions under an inert atmosphere, with a range of different additives (Table 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Time (hrs)</th>
<th>Yield Starting Material 255 (%)</th>
<th>Yield Mono-Product 256 (%)</th>
<th>Yield Bis-Product 257 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dry solvent and glassware</td>
<td>1.25</td>
<td>0</td>
<td>62</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>1 drop (~ 20 μL) water</td>
<td>5</td>
<td>5</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>33 mol % DTBMP</td>
<td>6</td>
<td>87</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>“Wet” solvent and glassware</td>
<td>1.5</td>
<td>10</td>
<td>68</td>
<td>23</td>
</tr>
</tbody>
</table>

When the reaction was performed using dried glassware and anhydrous toluene, the mono-product 256 was isolated in 62 % yield after 1.25 hrs in addition to the bis-product 257 in 20 % yield (Entry 1). The reaction was performed with the addition 1 mmol water, a sufficient amount to hydrolyse the Bi(OTf)$_3$ to afford 0.6 mmol TfOH (Entry 2). After 5 hrs the mono-product 256 was isolated in 63 % yield, in addition there was a 5 % yield of the starting material showing that the reaction still proceeds with the addition of water. Following the investigations of Lherbert, the addition of 2,6-di-tert-butyl-4-dimethylpyridine (DTBMP) was explored. The bulky base would neutralise and deactivate any triflic acid produced, but leave the bismuth available to act as a Lewis acid. The addition of 33 mol% DTBMP gave an 87 % return of unreacted starting material after 6 hrs (Entry 3), suggesting that the reaction is catalysed by triflic acid liberated by the hydrolysis of Bi(OTf)$_3$. However, addition of too much water can have an adverse effect slowing the reaction down. A sufficient amount of water is introduced to the reaction by the isoprene or Bi(OTf)$_3$ to liberate enough TfOH to catalyse the reaction. The reaction has also been performed using non-anhydrous toluene without drying the glassware and the mono-product 256 was isolated in 68 % yield, with 10 % of the starting material being reclaimed (Entry 4). For consistency of results, the solvent and glassware was dried before being used in subsequent reactions.
The amount of isoprene required for complete conversion of the starting material, with minimum bis-prenylation was also assessed (Table 11). It was found that 1.1 eq. and 1.5 eq. of isoprene were not sufficient to provide full consumption of the starting material (Entries 1 and 2). The best results were obtained using 2 eq. of isoprene (Entry 3), where all the starting material 255 was consumed, but with only a 20 % yield of the bis-product 254. Increasing the amount of isoprene to 3 eq. lead to an increased yield of the bis-product (Entry 4).

**Table 11: Determining the optimal amount of isoprene needed for prenylation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents isoprene</th>
<th>Time (hrs)</th>
<th>Yield Starting Material 255 (%)</th>
<th>Yield Mono-Product 256 (%)</th>
<th>Yield Bis-Product 257 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>2</td>
<td>22</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
<td>8</td>
<td>65</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1.25</td>
<td>0</td>
<td>62</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1.25</td>
<td>0</td>
<td>41</td>
<td>36</td>
</tr>
</tbody>
</table>

**4.3. SCOPE AND LIMITATIONS**

**4.3.1. Prenylation of Electron-Rich Aryl Ethers**

The optimal reaction conditions for the prenylation of trimethoxybenzene were found to be 2 eq. of isoprene, 10 mol % Bi(OTf)₃, in anhydrous toluene at 40 °C in a dried sealed tube under argon. These conditions were applied to a series of substrates to explore the scope and limitations of the reaction (Table 12).
Table 12: Prenylation of electron rich aromatic rings

<table>
<thead>
<tr>
<th>Starting material (S.M.)</th>
<th>Product(s)</th>
<th>Time (hrs)</th>
<th>Yield Mono- (%)</th>
<th>Yield Bis- (%)</th>
<th>Yield S.M. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1.25</td>
<td>62</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>7</td>
<td>44</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Complicated mixture of products</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>6</td>
<td>15</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1.5</td>
<td>58</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>6</td>
<td>47</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>6</td>
<td>64</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>6</td>
<td>17</td>
<td>-</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>5</td>
<td>&lt;34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>52</td>
</tr>
<tr>
<td>12</td>
<td>Indole</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>47</td>
</tr>
<tr>
<td>13</td>
<td>N-Methylindole</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>49</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>6</td>
<td>~31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>~31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>~31&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>: The product was synthesised but contained 33 % starting material by <sup>1</sup>H NMR analysis which could not be removed by column chromatography. <sup>b</sup>: Obtained as an inseparable mixture by column chromatography in a 1:1 ratio by <sup>1</sup>H NMR analysis.
Several trends can be observed in Table 12. Firstly, the more electron donating groups are on the aryl ring, the more efficiently the reaction proceeds; so trimethoxy is better than dimethoxy which is better than monomethoxy. This can be seen when comparing the propionic esters, (Entries 6, 8 and 10) where the yield is significantly reduced when there are fewer methoxy- groups. Secondly, other functional groups on the aryl ring can have a dramatic effect on reactivity. The reactivity of the nucleophilic carbon in the aromatic ring can be gauged by examining the chemical shift of the attached proton in the $^1$H NMR spectrum. Increasing electron density makes a proton more shielded, reducing its chemical shift. So it follows that the more reactive aryl rings will have protons at a reduced chemical shift (Figure 41).

![Figure 41: Selected $^1$H NMR shifts in CDCl$_3$, of protons (ppm) on the electron-rich aromatic rings and the yields of mono-(and bis) products](image)

Trimethoxybenzene 255 (Table 12, entry 1), the bromo-analogue 258 (Entry 2), the propionic ester 264 (Entry 6) and the cinnamic ester 253 (Entry 7) have chemical shifts lower than 7.00 ppm and were all prenylated with modest to good yields, with the bis-prenylated product also being observed in some reactions. The alkyl group of the cinamnic ester 253 is slightly electron donating, but the aryl ring is in conjugation with the electron withdrawing ester group giving an overall reduction in electron density and reducing the reactivity of the ring as shown by the
increased chemical shift of 6.74 ppm. This has been translated in the low yield of 47 % and absence of any bis-product (Table 12, entry 7). The bromobenzene 258 was prenylated in only modest yield of 44 % and this may also be due to steric effects of the bulky bromide group (Table 12, entry 2).

Electron-poor aryl rings, where a carbonyl is in direct conjugation with the aromatic ring gave either, in the case of ester 262, poor yields of product (Table 12, entry 5), or complicated mixtures which could not be separated by column chromatography (Entries 3 and 4). This follows the pattern in the chemical shift of the aryl protons, which is >7.00 in the three compounds. Despite having the highest chemical shift, the ester gave the best yield of prenylated product 263, whereas prenylated product was not isolated from the reactions with the aldehyde 260 or ketone 261. This may be due to the difference in reactivity in the carbonyl groups, resulting in side reactions giving complicated mixtures of products. One possible route for these side reactions is the formation of a stabilised benzylic cation resulting from the protonation of the carbonyl by the strong triflic acid. This would also put a positive charge adjacent to the ring, removing the electron density needed to perform the prenylation.

To avoid this, the acetophenone 261 was protected as the acetal 277, which was then subjected to the prenylation conditions (Scheme 89). Bi(OTf)₃ in refluxing THF/H₂O has been described for the deprotection of acetals,²¹⁶ however it was anticipated that under the anhydrous acidic conditions, the prenylation would occur swiftly, as was observed with trimethoxybenzene and that deprotection of the acetal would occur slowly, so the prenylated product 278 could be accessed. Following a procedure reported by Kong et al.,²¹⁷ the acetal 277 was isolated in a poor 28 % yield. When the acetal was submitted to the optimised conditions, the only product observed was the trimethoxyacetophenone 259. Investigations in this transformation are currently being investigated as the products would be useful starting materials in the syntheses of other medicinally interesting compounds, such as chalones.²¹⁸
Indole and \( N \)-methylindole were also investigated as possible electron-rich aromatics for the reaction; however neither of the substrates underwent prenylation. This is despite the compounds containing protons that had chemical shifts of less than 7.00 ppm in the \( ^1H \) NMR spectrum. The nitrogen atom in indole is not basic, so the lack of reaction is not due to quenching of the triflic acid as was seen with DTBMP in the optimisation reactions. There was some success when the prenylation of furan 275 was investigated, however the product 276 could not be isolated from the starting material, so an accurate yield and characterization could not be obtained. As the furan ring contains a pendant ester group, it is thought the prenylation can be performed in higher yields on more electron-rich furan rings. Further investigations are ongoing to optimise the prenylation of heteroaromatic rings.

**4.3.2. Synthesis of Chromans from Phenols**

When phenols were examined as electron rich aromatic rings, the product observed in the reactions was a chroman, formed by the cyclisation of the prenylated phenol. As previously discussed, this motif is very common in natural products and
biologically active compounds, so the transformation was explored with a few examples (Table 13).

Table 13: Synthesis of chromans from phenols

<table>
<thead>
<tr>
<th>Starting Material (S.M.)</th>
<th>Product(s)</th>
<th>Time (hrs)</th>
<th>Yield products (%)</th>
<th>Yield SM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="279" /></td>
<td>5</td>
<td>38, 14</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><img src="image2" alt="280" /></td>
<td>18</td>
<td>55, 26</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="281" /></td>
<td>24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>53, 22</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="282" /></td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><img src="image5" alt="283" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>5</td>
<td>26</td>
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</tr>
<tr>
<td></td>
<td><img src="image7" alt="285" /></td>
<td>18</td>
<td>58</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td><img src="image8" alt="286" /></td>
<td>8</td>
<td>10, 24, 13</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="287" /></td>
<td>5</td>
<td>65</td>
<td>11</td>
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<tr>
<td>6</td>
<td><img src="image10" alt="288" /></td>
<td>24</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td><img src="image11" alt="289" /></td>
<td>5</td>
<td>0</td>
<td>77</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Reaction included an aqueous work-up as part of the purification

When trimethoxyphenol 279 was subjected to the reaction conditions for 5 hrs, two products were isolated; the chroman 280 in 38 % yield and the prenylated product 281 resulting from a reaction at the 4-position of the phenol in 14 % yield (Table 13, entry 1). Ketones of similar structure to 281 have been reported previously by Yang et al., so are known to exist in very electron rich systems.<sup>219</sup> Further investigation found that increasing the reaction time greatly increased the yields of both products to 55 % and 26 % respectively after 18 hrs. The addition of a basic work-up to remove the Bi(OTf)<sub>3</sub> and break up any complexes formed had no effect on the yield, compared to when the reaction mixture was purified directly by column chromatography. Monomethoxyphenol 282 was also investigated as a substrate and the reaction appeared to have worked by <sup>1</sup>H NMR analysis; however
the low polarity of the product meant that it could not be separated from its contaminants by column chromatography (Table 13, entry 2).

In contrast to the reactions with the benzaldehyde 258 and acetophenone 259, reactions with phenols containing a ketone or an ester group gave the desired chromans in good yields. When the conditions were applied to 4-hydroxyacetophenone 284 for 5 hrs, the corresponding chroman 285 was isolated in 26 % yield, with a 55 % return of unreacted starting material and degradation products were not observed. In a similar fashion to the reaction with trimethoxyphenol, the yield increased considerably to 58 % when the reaction time was increased to 18 hrs. The resorcinol motif is very common in natural products and the prenyl and chroman derivatives are also seen in nature, so acetophenone 286 was subjected to the reaction conditions. After 5 hrs, three chroman products 287, 288 and 289 were isolated in 10, 24 and 13 % yields respectively. It was thought that the yields could be improved by increasing the reaction time, but due to the poor regioselectivity of the reaction this was not carried out. The methyl 4-hydroxybenzoate 290 was identified as a possible substrate and this performed very well in the reaction with a 65 % yield of chroman 291 after 5 hrs. These results can also be related to the chemical shifts of the protons on the reacting carbon atoms in the 1H NMR spectra, which are now much lower than in the trimethoxybenzene compounds due to the electron-donating properties of the phenol, showing that the aryl ring is much more reactive (Figure 42).

![Figure 42: 1H NMR shifts in CDCl₃ of protons on the reactive carbons on the phenol ring](image)

4-Hydroxybenzoic acid 292 was also subjected to the reaction conditions as the corresponding chroman has shown to be a potential anti-sickling agent. However, the chroman 293 was prepared in only 3 % after 24 hrs. This could be due to possible coordination of the bismuth to the carboxylic acid, removing more
electron density rendering the aromatic ring less reactive. Electronically, aniline is very similar to phenol, with lone pairs of electrons available for donation into the aromatic ring, so methyl 4-aminobenzoate 294 was subjected to the reaction conditions. The product 295 was not observed and 77% of the unreacted starting material was recovered. The exact reason for its lack of activity is still unknown; however with a pK_a of approximately 5, similar to that of DTBMP which also has a pK_a of approximately 5, it could be forming a salt with the triflic acid, preventing it from acting as a catalyst.

1.4. APPLICATION TO THE SYNTHESIS OF A NATURAL PRODUCT

The isolation of 2-(3-methyl-2-butenyl)-3,4,5-trimethoxyphenol 296 from Piper clarkia was reported in 1994 by Olsen et al.221 It has been synthesised previously in one-step from trimethoxyphenol 279 and 2-methylbut-3-en-2-ol in 24% yield and its structure was confirmed by X-ray crystallography by Parmar et al.222 It has been shown to possess anti-invasive activity against human breast carcinoma cells.223

Scheme 90: Current synthesis of 2-prenyltrimethoxyphenol 296

This was an ideal substrate to synthesis using the new methodology access the compound in an improved yield. However as shown in Table 13, prenylation of trimethoxyphenol affords the chroman 280 so a protection strategy was investigated. Acetylation of a phenol in the presence of Bi(OTf)_3 has been reported by Mohammedpoor-Baltork.224 Combining this methodology with our optimised prenylation conditions would provide a one-pot protection and prenylation
procedure. Deprotection could be achieved using the standard conditions potassium carbonate in methanol.\textsuperscript{225}

Initially, the reaction sequence was attempted as a one-pot procedure (Scheme 91). The phenol 279 was stirred in toluene with acetic anhydride and Bi(OTf)$_3$ for 15 mins to give the protected phenol. Isoprene was then added to the reaction to perform the prenylation. After 4 hrs the solvent was removed and K$_2$CO$_3$ and MeOH were added to give the prenylated phenol. The product 296 was isolated from the reaction, in less than 44\% yield as there were minor impurities which could not be removed by column chromatography. The product of a Fries rearrangement 297 was also isolated in 9\% yield. The catalysis of the Fries rearrangement by Bi(OTf)$_3$ in refluxing toluene has been reported, with reaction times of 1-3 hrs.\textsuperscript{226}

\begin{center}
\begin{align*}
\text{MeO} \quad \text{OH} & \quad \text{MeO} \quad \text{OH} \\
\text{MeO} \quad \text{OMe} & \quad \text{MeO} \quad \text{OMe} \\
\quad \text{279} & \quad \text{296} <44\% \\
\end{align*}
\end{center}

Reagents and conditions: a) Bi(OTf)$_3$, Ac$_2$O, toluene, 15 mins; b) isoprene, 40 °C, 4 hrs; c) K$_2$CO$_3$, MeOH, 45 mins.

\textbf{Scheme 91: Synthesis of 296 in a one-pot procedure}

The synthesis was then performed in two steps, isolating and purifying the protected and prenylated phenol 298 before its deprotection (Scheme 92). When the prenylation was left for 4 hrs, the products were observed, but could not be purified sufficiently by column chromatography to obtain accurate yields. However, when the reaction time was reduced to 1 hr, the mono- and bis-prenylated acetates 298 and 299 were isolated in 70\% and 15\% yields respectively. Two strategies were examined for the deprotection of the phenol. Using K$_2$CO$_3$ in MeOH as described by Bates\textsuperscript{225} gave the mono-product 296 in 49\% yield and the bis-product 300 in 32\% yield. Narendar \textit{et al.}\textsuperscript{227} describe the use of NaOAc in EtOH/H$_2$O for the cleavage of aryl acetates in high yields in the presence of a prenyl group, so this methodology was applied to the deprotection of the monoprenylated acetate 298. However, the
desired phenol 296 was isolated in only 36 % after 5 hrs. In contrast to the reaction using K$_2$CO$_3$, 39 % of the starting material was also recovered.

Reagents and conditions: i) a) Bi(OTf)$_3$, Ac$_2$O, toluene, 5 mins; b) isoprene, 40 °C, 1 hr; ii) K$_2$CO$_3$, MeOH; iii) NaOAc, EtOH/H$_2$O.

Scheme 92: Stepwise protection/prenylation and deprotection of trimethoxyphenol

The mono-prenylated phenol 296 was obtained in an overall yield of 34 % from 3,4,5-trimethoxyphenol, higher than the 24 % reported in the reported one-step procedure and the spectroscopic data was consistent with that reported by Olsen et al.\textsuperscript{221}

4.4. CONCLUSIONS AND FUTURE WORK

A mild procedure has been discovered and developed using bismuth (III) triflate as a catalyst for the prenylation of electron-rich aromatic rings and the synthesis of chromans from phenols. This procedure has been applied to the synthesis of the natural product 2-(3-methyl-2-butenyl)-3,4,5-trimethoxyphenol 296 in 34 % yield over 2 steps.
Further investigations are required to establish why the prenylation of benzaldehydes and acetophenones was not successful and then a solution can be developed. Compounds containing a carbonyl group that is not in conjugation with the aryl ring should be explored as this may establish whether it is the carbonyl group or its conjugation that prevents the reaction from proceeding.

The methodology could also be extended to the prenylation of heterocycles, although investigations and further optimisation will be required for this to establish why the reactions with indole were unsuccessful.

The procedure could also be applied to the synthesis of chroman natural products, such as the dorsmanins 248 and 249.

As there is evidence that prenylation can increase the activity of a compound, the procedure could also be used to obtain prenylated narciclasine analogues and evaluate their biological activity.
5. EXPERIMENTAL

GENERAL EXPERIMENTAL

Chemicals, solvents and reagents used are commercially available and were used without further purification. Anhydrous solvents were used where indicated.

Glassware for dry reactions was dried either by heating in an oven at 120 °C for at least 1 hr, or heating with a hot air gun for 5 mins. The glassware was then allowed to cool under a stream of N₂.

TLC’s were carried out on Merck Aluminium backed TLC plates Silica Gel 60 F254 and viewed using UV light of wavelength 254 nm and then stained with potassium permanganate. Merck Silica Gel (0.040-0.063 mm) was used for column chromatography. Compounds were loaded as an oil, CH₂Cl₂ solution or dry loaded by adsorption onto silica.

Melting points were obtained using a Reichert-Jung heated-stage microscope. Infrared spectra were recorded on a Perkin-Elmer Spectrum RXI FT-IR system and all values are recorded in cm⁻¹.

¹H NMR spectra were obtained on JEOL Eclipse (270 MHz), Varian Mercury VX (400 MHz), Bruker Avance III (400 MHz) or Bruker Avance III (500 MHz) spectrometers. ¹³C NMR spectra were obtained on JEOL Eclipse (67.9 MHz), Varian Mercury VX (100 MHz) Bruker Avance III (100 MHz) or Bruker Avance III (125 MHz) spectrometers. The chemical shifts are recorded in parts per million (ppm) with reference to tetramethylsilane. The coupling constants J are quoted to the nearest 0.5 Hz are not rationalised. The multiplicities are assigned as a singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), triplet of doublets (td) and multiplet (m). Pendant NMR data is given after the ¹³C NMR chemical shifts as +ve (CH and CH₃) and –ve (C and CH₂).

Mass spectra and high resolution mass spectra were obtained on a micrOTOF™ from Bruker Daltonics (Bremen, Germany). This is a Time-of-Flight mass spectrometer coupled with an electrospray source (ESI-TOF). This instrument can be used to measure accurate mass to 5 ppm externally calibrated and 2 ppm internally calibrated. Samples are introduced either by syringe pump or flow.
injection using an autosampler in an Agilent 1100 LC system. The instrument is calibrated using a sodium formate solution, which is applicable to both positive and negative ionisation mode. These samples were analysed under standard conditions for small molecules in positive electrospray ionisation mode. The instrument acquires both accurate mass and true isotope patterns, therefore both of these dimensions of information are used to help determine or confirm the molecular formula. Ions are most often present as protonated or sodiated molecules. Data was processed using external calibration with the Bruker Daltonics software, DataAnalysis™ as part of the overall hardware control software, Compass 1.1™.

Analytical RP-HPLC was performed using a Waters 2695 Alliance module equipped with a Waters 2996 photodiode array detector (210-350 nm). The chromatographic system consisted of a Hichrom Guard column for HPLC and a Phenomenex Synergi 4 µm Max-RP19 column (150 x 4.60 mm), using a gradient of 5 to 65 % 0.1 % TFA in CH₃CN in 0.1 % TFA in MilliQ over 15 mins.

X-ray Crystallography: Single crystals were analysed at 150(2) K using graphite monochromated Mo(Kα) radiation and a Nonius Kappa CCD diffractometer. The structures were solved using SHELXS-97 and refined using SHELXL-97.

5.1. MTS CELL PROLIFERATION ASSAY PROTOCOL

This assay uses a 96 well plate format to determine cell viability and is based on the Promega Cell Titer 96 Aqueous One Solution Cell Proliferation Assay. Seed densities of 500 cells per well were used and final drug concentrations of 500 µM, 200 µM, 100 µM, 50 µM, 20 µM, 10 µM, 5 µM, 2 µM, 1 µM and 500 nM in 1% DMSO. Drugs were incubated with the HT29 cell line for 72 days prior to reading and IC₅₀ curves were generated using SigmaPlot 8 software. Each IC₅₀ value is the average of at least two independent experiments conducted on separate days.
5.2. SYNTHESIS OF AB-RING ANALOGUES

5.2.1. Synthesis of AB-ring Analogues using the Curtius Rearrangement

General Procedure 1: Preparation and cyclisation of the isocyanate.

Method A: Following the procedure reported by Kimoto et al., a solution of ethyl chloroformate (475 μL, 5 mmol) in acetone (1.5 mL) was added to a stirred solution of acid (5 mmol) and Et₃N (695 μL, 5 mmol) in acetone/H₂O (7.5 mL, 5:1) at 0 °C open to air and allowed to warm to r.t. After 1 hr, a solution of NaN₃ (487 mg, 7.5 mmol) in water (1.5 mL) was added in one portion and the reaction stirred for a further 30 mins. Upon dilution with toluene/H₂O (21.8 mL, 4:3) the organic fraction was separated, washed with water, dried with anhydrous MgSO₄ and filtered into a dry flask under N₂. The vigorously stirred solution was heated at 90 °C for 45 mins. The solvent was removed in vacuo the oil was cooled to 0 °C under N₂ and BF₃·OEt₂ (2.5 mL) added. The reaction allowed to warm to r.t. and was stirred for 18 hrs, then quenched with saturated aqueous NaHCO₃ (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic fractions were washed with brine, dried over anhydrous MgSO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc-methanol] the product was isolated.

Method B: Following the procedure reported by Kimoto et al., a solution of ethyl chloroformate (475 μL, 5 mmol) in acetone (1.5 mL) was added to a stirred solution of acid (5 mmol) and Et₃N (695 μL, 5 mmol) in acetone/H₂O (7.5 mL, 5:1) at 0 °C open to air and allowed to warm to r.t.. After 1 hr, a solution of NaN₃ (487 mg, 7.5 mmol) in water (1.5 mL) was added in one portion and the reaction stirred for a further 30 mins. Upon dilution with toluene/H₂O (21.8 mL, 4:3) the organic fraction was separated, washed with water, dried with anhydrous MgSO₄ and filtered into a dry flask under N₂. The vigorously stirred solution was heated at 90 °C for 45 mins. The solution was then cooled to 0 °C and AlCl₃ (2 g, 15 mmol) added. The reaction was allowed to warm to r.t. and was stirred for 18 hrs, then quenched with saturated aqueous NaHCO₃. The white solid was removed by filtration through celite and washed thoroughly with EtOAc. The aqueous layer was further extracted with EtOAc (20 mL). All the organic fractions were combined, washed with brine, dried
over anhydrous MgSO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc] the product was isolated.

**Method C:** Diphenylphosphoryl azide (1.12 mL, 5 mmol) was added to a stirred solution of arylpropionic acid (5 mmol) and anhydrous Et₃N (695 μL, 5 mmol) in anhydrous toluene (15 mL) under N₂ at r.t. then the reaction heated at 90 °C for 90 mins. On cooling the solvent was removed and the flask cooled to 0 °C under N₂. BF₃·OEt₂ (2.5 mL) was added then the reaction was allowed to warm to r.t. and stirred for 16 hrs. The reaction was quenched to pH 10 with 2M NaOH and diluted with EtOAc (20 mL), then heated at 50 °C for 1 hr. After cooling to r.t. the phases were separated and the aqueous fraction extracted with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc] the product was isolated.

**3,4-Dihydroisoquinolin-1(2H)-one (139)**

Following general procedure 1C, performing the cyclisation step at 80 °C, dihydrocinnamic acid 134 (750 mg, 5 mmol) gave dihydroisoquinolinone 139 (52 mg, 5 %) as an amorphous solid.

_Rf_ [PE-EtOAc 20:80] 0.20; _¹H NMR_ δ_H(400 MHz, CD₃OD) 7.94 (1H, d, J 8.0 Hz, C(8)H), 7.47 (1H, dd, J 8.0 and 8.0 Hz, C(6)H), 7.33 (1H, dd, J 8.0 and 8.0 Hz, C(7)H), 7.26 (1H, d, J 8.0 Hz, C(5)H), 3.48 (2H, t, J 6.5 Hz, C(3)H) and 2.96 (2H, t, J 6.5 Hz, C(4)H); _¹³C NMR_ δ_C(100 MHz, CD₃OD) 168.3− (C1=O), 140.9− (C8a), 133.5− (C6), 129.8− (C4a), 128.6+ (C5 or C8), 128.4+ (C5 or C8), 128.0+ (C7), 40.8− (C3) and 28.9− (C4); _MS_ (+ESI) m/z 192 (M+H⁺, 22 %), 214 (M+Na⁺, 114
78) and 405 (2M+Na⁺, 100); \textbf{HRMS} (+ESI) Found M+Na⁺, 214.0476; C_{10}H_{9}NO_{3}Na requires M+Na⁺ 214.0480.

Spectroscopic data is consistent with that reported by Winter \textit{et al.}^{228}

\textbf{3-Methyl-3-phenylbutanoic acid (141)}

\[
\begin{align*}
\text{\textsuperscript{\text{1}H NMR} \quad & \delta_{\text{H}}(270 \text{ MHz, CDCl}_3) 7.38-7.17 \text{ (5H, m, C(Ph)H), 2.65 (2H, s, C(2)H}_2\text{) and 1.47 (6H, s, CH}_3\text{))} \\
& \text{Spectroscopic data is consistent with that reported by Andersen \textit{et al.}^{229}}
\end{align*}
\]
4,4-Dimethyl-3,4-dihydro-2H-isoquinolin-1-one (142)

Following general procedure 1A, propanoic acid 141 (483 mg, 2.7 mmol) gave lactam 142 (37 mg, 8 %) as an amorphous solid.

Following general procedure 1A, propanoic acid 141 (483 mg, 2.7 mmol) gave lactam 142 (37 mg, 8 %) as an amorphous solid.

\[ \text{Rf} [\text{EtOAc}] = 0.41; \text{IR } \nu_{\text{max}}(\text{thin film}) = 3322 (\text{NH}), 2968, 2931, 2874 (\text{CH}), 1701 (\text{C=O}), 1530 (\text{Ph}) \text{ and } 1221 (\text{CO}); ^1\text{H NMR } \delta_H (400 \text{ MHz, CDCl}_3) = 8.05 (1\text{H, dd, } J = 8.0 \text{ and } 1.5 \text{ Hz, C(8)H}); 7.49 (1\text{H, ddd, } J = 8.0, 8.0 \text{ and } 1.3 \text{ Hz, C(6)H}); 7.36-7.29 (2\text{H, m, C(5)H and C(7)H}); 6.62 (1\text{H, broad s, N(2)H}); 3.30 (2\text{H, d, } J = 2.7 \text{ Hz, C(3)H}_2) \text{ and } 1.34 (6\text{H, s, C(4)(CH}_3)_2); ^13\text{C NMR } \delta_C (100 \text{ MHz, CDCl}_3) = 166.2- (\text{C1=O}), 147.4- (\text{C8a}), 132.6+ (\text{C6}); 128.2+ (\text{C8}), 127.4- (\text{C4a}), 126.6+ (\text{C5 or C7}), 123.7+ (\text{C5 or C7}), 52.3- (\text{C3}), 34.2- (\text{C4}) \text{ and } 26.6+ (\text{CH}_3); \text{MS (ESI)} m/z = 198 (M+Na}^+ , 58 \text{%}) \text{ and } 373 (2M+Na}^+ , 100 \text{%}); \text{HRMS (ESI)} \text{ Found } M+Na}^+ , 198.0884; C_{11}H_{13}\text{NONa requires } M+Na}^+ 198.0895.

Spectroscopic data is consistent with that reported by Ben-Ishai et al.\textsuperscript{230}

3-(3,4-Methylenedioxyphenyl)propionic acid (143)

10 % palladium on carbon (208 mg, 0.2 mmol) was added to a vigorously stirred mixture of 3,4-methylenedioxy-cinnamic acid (2 g, 10.4 mmol) in EtOH (50 mL). After 3 cycles of purging the flask with N\textsubscript{2} then a vacuum, the flask was put
under an atmosphere of H₂. After 2 hrs, the mixture was filtered through celite, washing thoroughly with EtOH, then the solvent removed in vacuo to afford the propionic acid 143 (1.97 g, 98 %) as a white solid without further purification.

**1H NMR** δH(400 MHz, CDCl₃) 8.60 (1H, broad s, OH), 6.74-6.64 (3H, m, C(Ar)H), 5.92 (2H, s, OCH₂O), 2.87 (2H, t, J 8.0 Hz, C(3)H₂) and 2.63 (2H, t, J 8.0 Hz, C(2)H₂); **13C NMR** δC(100 MHz, CDCl₃) 178.6, 147.7, 146.0, 134.0, 121.1, 108.8, 108.3, 100.9, 35.9 and 30.4.

Spectroscopic data is consistent with that reported by Haga et al.²³¹

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### 7,8-Dihydro-6H-[1,3]dioxolo[4,5-g]isoquinolin-5-one (144)

7,8-Dihydro-6H-[1,3]dioxolo[4,5-g]isoquinolin-5-one (144)

Propionic acid 143 (970 mg, 5 mmol) gave, following general procedure 1A lactam 144 (598 mg, 63 %); and following general procedure 1C gave lactam 144 (772 mg, 81 %) as a white solid.

Rᵣ [PE-EtOAc 20:80] 0.20; Mp 185-187 °C (from EtOAc); lit.,²³² 187-187.5 °C (from PhH); IR νₘₐₓ(KBr disc) 3456 (NH), 3188, 3046, 2900 (CH), 1657 (C=O), 1610, 1479 (Ph), 1260 (CO) and 1038; **1H NMR** δH(400 MHz, CDCl₃) 7.52 (1H, s, C(8)H), 6.93 (1H, broad s, NH), 6.67 (1H, s, C(5)H), 6.02 (2H, s, OCH₂O), 3.55 (2H, t, J 6.5 Hz, C(3)H₂) and 2.91 (2H, t, J 6.5 Hz, C(4)H₂); **13C NMR** δC(100 MHz, CDCl₃) 166.2− (C1=O), 150.7− (C7-O), 146.8− (C6-O), 134.5− (C8a), 122.8− (C4a), 107.8+ (C8), 107.2+ (C5), 101.4− (OCH₂O), 40.1− (C3) and 28.4− (C4); **MS** (+ESI) m/z 192 (M+H⁺, 22 %), 214 (M+Na⁺, 78) and 405 (2M+Na⁺, 100); **HRMS** (+ESI) Found M+Na⁺, 214.0476; C₉H₈NO₃Na requires M+Na⁺ 214.0480; **HPLC** tᵣ 9.5 (100 %).

Spectroscopic data is consistent with that reported by Hanaoka et al.²³²
6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (147)

Following general procedure 1C, performing the cyclisation step at 50 °C, propionic acid 146 (1.05 g, 5 mmol) gave lactam 147 (784 mg, 76 %) as a white solid.

$R_f$ [EtOAc] 0.11; $M_p$ 174-177 °C (from EtOAc); lit.,233 173 °C (from PhH/Et$_2$O); IR $\nu_{\text{max}}$(KBr disc) 3187, 3044, 2863 (CH), 1656 (C=O), 1603, 1510, 1481 (Ph), 1271 (CO) and 1050; $^1$H NMR $\delta$H(400 MHz, CDCl$_3$) 7.56 (1H, s, C(8)H), 6.66 (1H, s, C(5)H), 6.36 (1H, broad s, NH), 3.91 (3H, s, OCH$_3$), 3.91 (3H, s, OCH$_3$), 3.54 (2H, td, J 6.5 and 3.0 Hz, C(3)H$_2$) and 2.91 (2H, t, J 6.5 Hz, C(4)H$_2$); $^{13}$C NMR $\delta$C(100 MHz, CDCl$_3$) 166.4− (C1=O), 152.1− (C7-O), 148.0− (C6-O), 134.5− (C8a), 122.8− (C4a), 110.1+ (C8), 109.5+ (C5), 56.0+ (OCH$_3$), 56.0+ (OCH$_3$), 40.4− (C3) and 28.0− (C4); MS (+ESI) m/z 208 (M+H$^+$, 35 %), 230 (M+Na$^+$, 33) and 437 (2M+Na$^+$, 100); HRMS (+ESI) Found M+Na$^+$, 230.0767; C$_{11}$H$_{13}$NO$_3$Na requires M+Na$^+$ 230.0787; HPLC $t_R$ 8.6 (100 %).

Spectroscopic data is consistent with that reported by Zhu et al.234

8-(Difluoroboryloxy)-6,7-dimethoxy-3,4-dihydroisoquinolin-(2H)-one

(148)
Diphenylphosphoryl azide (5.6 mL, 25 mmol) was added to a stirred solution of arylpropionic acid (6.0 g, 25 mmol) and anhydrous Et$_3$N (3.5 mL, 25 mmol) in anhydrous toluene (75 mL) under N$_2$ at r.t. then the reaction heated at 90 °C for 1 hr. After cooling to r.t., the solvent was removed and the flask cooled to 0 °C under N$_2$. BF$_3$·OEt$_2$ (4 mL) was added then the reaction was allowed to warm to r.t. and stirred for 16 hrs. The reaction mixture was diluted with THF-Et$_2$O (1:1, 100 mL) and the crude solid product removed by filtration. After recrystallisation from EtOAc, the product (4.2 g, 63 %) was isolated as a white solid.

**Mp** 237-239 °C (from EtOAc); **IR** $\nu_{\text{max}}$(KBr disc) 3326, 3303 (NH), 3027, 2986, 2830, 1656, 1609, 1540, 1489, 1438, 1242, 1132, 1022 and 758; **$^1$H NMR** $\delta$(400 MHz, d$_6$-DMSO) 10.37 (1H, s, NH), 6.68 (1H, s, C(5)H), 3.87 (3H, s, OCH$_3$), 3.68 (3H, s, OCH$_3$), 3.59 (2H, t, J 7.5 Hz, C(3)H$_2$) and 2.95 (2H, t, J 7.5 Hz, C(4)H$_2$); **$^{13}$C NMR** $\delta$(100 MHz, d$_6$-DMSO) 165.7−(C1=O), 159.7−(C6-O or C7-O), 152.6−(C8), 135.2−(C8a), 134.9−(C6-O or C7-O), 103.9+ (C5-H), 100.1−(C4a), 60.1+ (OCH$_3$), 56.3+ (OCH$_3$), 39.1−(C3) and 25.1−(C4); **$^{19}$F NMR** $\delta$(376 MHz, d$_6$-DMSO) −144.24, −144.30; **$^{11}$B NMR** $\delta$(128 MHz, d$_6$-DMSO) 1.76; **MS** (+ESI) $m/z$ 294 (M+Na$^+$, 80 %) and 565 (2M+Na$^+$, 60); **HRMS** (+ESI) Found M+Na$^+$, 294.0726; C$_{11}$H$_{12}$NO$_4$BF$_2$Na requires M+Na$^+$ 294.0720.

6,7-Dimethoxy-8-hydroxy-3,4-dihydro-$2H$-isoquinolin-1-one (151)

![Chemical structure](image)

**Method A:** Following general procedure 1C, propionic acid 149 (1.20 g, 5 mmol) gave isoquinolinone 151 (818 mg, 73 %) and propionic acid 149 (5.95 g, 25 mmol) gave isoquinolinone 151 (2.91 g, 52 %) as a white solid.
Method B: Isoquinolinone 148 (1.35 g, 5 mmol) in 2M NaOH (20 mL) and EtOAc (20 mL) was heated at 50 °C for 2 hrs. After cooling to r.t. the phases were separated and the aqueous fraction extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo to give the isoquinolinone 151 (1.03 g, 92 %) as a white solid.

**RF** [EtOAc] 0.46; **Mp** 181-183 °C (from EtOAc); lit.,²³⁵ 181 °C (from MeOH); **IR** νmax (KBr disc) 3481 (NH or OH), 3328 (NH or OH), 3005, 2936, 2853 (C-H), 1649 (C=O and Ph), 1617, 1578, 1441 (Ph), 1301, 1127, 1016 (C-O) and 824; **¹H NMR** δH(400 MHz, CDCl₃) 7.26 (1H, s, OH), 6.26 (1H, s, C(5)H), 6.02 (1H, broad s, NH), 3.89 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.54 (2H, td, J 6.5 and 2.5 Hz, C(3)H₂) and 2.92 (2H, t, J 6.5 Hz, C(4)H₂); **¹³C NMR** δC(100 MHz, CDCl₃) 170.4− (C1=O), 156.9− (C6 or C7), 155.9− (C8), 135.9− (C6 or C7), 135.2− (C8a), 105.8− (C4a), 101.8+ (C5), 105.8+ (OCH₃), 60.7+ (OCH₃), 40.3− (C3) and 28.1− (C4); **MS** (+ESI) m/z 246 (M+Na⁺, 100 %) and 469 (2M+Na⁺, 44); **HRMS** (+ESI) Found M+Na⁺, 246.0724; C₁₁H₁₃NO₄Na requires M+Na⁺ 246.0742; **HPLC** tR 10.4 (100 %).

2,3,4,9-Tetrahydro-β-carbolin-1-one (153)

Following general procedure 1A, propionic acid 152 (945 mg, 5 mmol) gave carbolinone 153 (684 mg, 74 %); following general procedure 1B, 152 (567 mg, 3 mmol) gave 153 (374 mg, 67 %); and following general procedure 1C, 152 (945 mg, 5 mmol) gave 153 (806 mg, 87 %) as a white solid.
**R:** [EtOAc] 0.39; **Mp** 186-188 °C (from EtOAc); lit.,\(^{236}\) 183-185 °C; **IR** \(v_{\text{max}}\) (KBr disc) 3212 (NH), 2935, 2871 (CH), 1664 (C=O), 1545, 1512, 1489, 1459, 1416 (Ph and CH), 1327 and 1291 (CO and CN); **\(^1\)H NMR** \(\delta_H\) (400 MHz, CDCl\(_3\))

- 10.45 (1H, s, N(9)H),
- 7.58 (1H, d, \(J = 7.5\) Hz, C(5)H),
- 7.51 (1H, d, \(J = 7.5\) Hz, C(8)H),
- 7.29 (1H, ddd, \(J = 7.5, 7.5\) and 1.0 Hz, C(7)H),
- 7.13 (1H, ddd, \(J = 7.5, 7.5\) and 1.0 Hz, C(6)H),
- 6.77 (1H, broad s, N(2)H),
- 3.72 (2H, t, \(J = 7.0\) Hz, C(3)H\(_2\)) and 3.06 (2H, t, \(J = 7.0\) Hz, C(4)H\(_2\));

**\(^{13}\)C NMR** \(\delta_C\) (100 MHz, CDCl\(_3\))

- 163.7− (C1=O),
- 137.6− (C8a),
- 126.1− (C9a),
- 125.2+ (C7),
- 125.1− (C4b),
- 120.2+ (C5),
- 120.2+ (C6),
- 120.1− (C4a)

**MS** (+ESI) \(m/z\) 209 (M+Na\(^+\), 61 %) and 395 (2M+Na\(^+\), 100); **HRMS** (+ESI) Found M+Na\(^+\), 209.0681; \(\text{C}_{11}\text{H}_{10}\text{N}_{2}\text{ONa}\) requires M+Na\(^+\) 209.0691; **HPLC** \(t_R\) 11.7 (97 %).

Spectroscopic data is consistent with that reported by Luis et al.\(^{237}\) and Hamann et al.\(^{238}\)

3-(1′-Methyl-1\(H\)-indol-3′-yl)-propionic acid (159)

Following the procedure reported by Compernolle,\(^{104}\) MeI (1.56 mL, 25 mmol) was added to a rapidly stirred mixture of 3-indolepropionic acid 158 (946 mg, 5 mmol) and KOH (1.7 g, 30 mmol), in acetone (50 mL). After 16 hrs at r.t. the solvent was removed *in vacuo*. The residue was dissolved in H\(_2\)O (100 mL), KOH (1.4 g, 25 mmol) added and the solution stirred at reflux for 2.5 hrs. On cooling and acidifying to pH 2 with 6M HCl, the solid was filtered off, washed with H\(_2\)O and dried to give product 159 (889 mg, 87 %) as a white solid without further purification.

**IR** \(v_{\text{max}}\) (KBr disc) 3446 (OH), 3055, 2912, 2705, 2611 (CH), 1710 (C=O), 1473, 1424 (Ph), 1325, 1291 (CO) and 735 (CH); **\(^1\)H NMR** \(\delta_H\) (400 MHz, CDCl\(_3\))
7.94 (1H, broad s, CO₂H), 7.58 (1H, d, J 7.5 Hz, C(7’)H), 7.28 (1H, d, J 7.0 Hz, C(4’)H), 7.22 (1H, d, d, J 7.5, 7.5 and 1.1 Hz, C(6’)H), 7.10 (1H, d, d, J 7.0, 7.0 and 1.0 Hz, C(5’)H), 6.87 (1H, s, C(2’)H), 3.73 (3H, s, NCH₃), 3.10 (2H, t, J 7.5 Hz, C(3)H₂) and 2.76 (2H, t, J 7.5 Hz, C(2)H₂);¹³C NMR δC(100 MHz, CDCl₃) 178.5− (CO₂H), 127.5− (C3’), 126.3+ (C2’), 122.1− (C3a’ or C7a’), 121.6+ (C6’), 118.8+ (C5’ or C7’), 118.7+ (C5’ or C7’), 113.1− (C3a’ or C7a’), 109.2+ (C4’), 34.7− (C3), 32.6+ (NCH₃) and 20.3− (C2); MS (+ESI) m/z 204 (M+H⁺, 88 %) and 226 (M+Na⁺, 100); HRMS (+ESI) Found M+Na⁺, 226.0831; C₁₂H₁₃NO₂Na requires M+Na⁺ 226.0844.

9-Methyl-2,3,4,9-tetrahydro-β-carbolin-1-one (160)

Method A: Following the procedure reported by Compernolle,¹⁰⁴ MeI (1.8 mL, 28 mmol) was added to a vigorously stirred mixture of KOH (1.9 g, 34 mmol) and 3-indolepropionic acid 158 (1.08 mg, 5.7 mmol) in acetone (60 mL). After 72 hrs at r.t. the solvent was removed under reduced pressure. The residue was suspended in H₂O (120 mL), KOH (1.6 g, 28 mmol) was added and the solution stirred at reflux for 2 hrs. After cooling to 0 °C, the solution was acidified to pH 2 with 6M HCl and extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with brine, dried over Na₂SO₄, filtered and the solvent removed in vacuo to yield the crude intermediate acid 159 as a white solid.
Following the general procedure 1C, the crude carboxylic acid gave the lactam 160 (0.994 g, 87 %) as a white solid.

**Method B:** Following general procedure 1B, acid 159 (812 mg, 4 mmol) gave carbolinone 160 (385 mg, 45 %).

**Method C:** MeI (311 µL, 5 mmol) was added to a vigorously stirred mixture of carbolinone 153 (180 mg, 0.697 mmol) and KOH (336 mg, 6 mmol) in acetone (10 mL) as r.t.. After 5 hrs, the reaction was quenched with 2M HCl (12 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine, dried over Na$_2$SO$_4$, filtered and the solvent removed in vacuo. Column chromatography [silica, PE-EtOAc gradient from 50:50 to 40:60] afforded gave the carbolinone 160 (134 mg, 69 %) as a white solid.

**Rf** [PE-EtOAc 3:7] 0.37; **Mp** 160-162 °C (from EtOAc); lit.,$^{236}$ 157-158 °C; **IR** $\nu_{max}$(KBr disc) 3312 (NH), 2934, 2869 (CH), 1656 (C=O), 1489, 1467 (Ph), 1289 (CN) and 732 (CH); **$^1$H NMR** $\delta$H(400 MHz, CDCl$_3$) 7.59 (1H, d, $J$ 8.0 Hz, C(5)H), 7.38-7.33 (2H, m C(8)H and C(6)H), 7.15 (1H, d, $J$ 8.0 and 8.0 Hz, C(7)H), 5.70 (1H, broad s, N(2)H), 4.11 (3H, s, N(9)CH$_3$), 3.65 (2H, td, $J$ 7.0 and 2.5 Hz, C3) and 3.05 (2H, t, $J$ 7.0 Hz, C4); **$^{13}$C NMR** $\delta$C(100 MHz, CDCl$_3$) 163.3− (C=O), 139.0− (C8a), 125.8− (C9a), 124.9+ (C7), 124.1− (C4b), 120.3+ (C5), 120.0+ (C6), 119.8− (C4a), 110.2+ (C8), 41.9− (C3), 31.2+ (NCH$_3$) and 21.1− (C4); **MS** (+ESI) 201 (M+H$^+$, 62 %) and 223 (M+Na$^+$, 100); **HRMS** (+ESI) Found M+Na$^+$ 223.0847; C$_{12}$H$_{12}$N$_2$ONa requires M+Na$^+$ 223.0847; **HPLC** $t_R$ 12.1 (99 %).

2,9-Dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (161)

![Chemical Structure](image)

NaH (60 % dispersion in mineral oil) (100 mg, 2.5 mmol) was added to a vigorously stirred suspension of lactam 153 (180 mg, 0.97 mmol) in THF (3 mL) at 0 °C under Ar. After 30 mins, MeI (155 µL, 2.5 mmol) was added and the reaction
stirred at r.t. for 18 hrs. The reaction was quenched with saturated aqueous NH₄Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. Column chromatography [silica, PE-EtOAc gradient from 70:30 to 50:50] afforded the dimethylcarbolinone 161 (113 mg, 54 %) as a cream solid.

Mp 66-69 °C (Et₂O); lit., 236 65-66 °C; IR νmax(Thin film) 2934, 1647 (C=O), 1545, 1497, 1468, 1323, 1251, 1235 and 1074; ¹H NMR δH(400 MHz, CDCl₃) 7.49 (1H, d, J 8.0 Hz, C(5)H), 7.29 (1H, d, J 8.0 Hz, C(8)H), 7.24 (1H, ddd, J 8.5, 7.5 and 1.0 Hz, C(7)H), 7.06 (1H, ddd, J 8.0, 6.5 and 1.5 Hz, C(6)H), 4.04 (3H, s, N(9)CH₃), 3.58 (2H, t, J 7.0 Hz, C(3)H₂), 3.05 (3H, s, N(2)CH₃) and 2.97 (2H, t, J 7.0 Hz, C(4)H₂); ¹³C NMR δC(100 MHz, CDCl₃) 162.1− (C1=O), 139.0− (C8a), 126.4− (C9a), 124.4+ (C7), 124.0− (C4b), 120.0+ (C5), 119.9+ (C6), 118.2− (C4a), 110.1+ (C8), 49.9− (C3), 34.1+ (N(2)CH₃), 31.17+ (N(9)CH₃) and 20.6− (C4); MS (+ESI) m/z 215 (M+H⁺, 100 %) and 237 (M+Na⁺, 9); HRMS (+ESI) Found M+Na⁺ 237.0956; C₁₃H₁₄N₂ONa requires M+Na⁺ 237.0998; HPLC tR 15.7 (92 %).

3,4,5,10-Tetrahydro-2H-azepino[3,4-b]indol-1-one (163)

Following general procedure 1B, butyric acid 162 (1.02 g, 5 mmol) gave azepinone 163 (140 mg, 14 %). Following general procedure 1C, performing the cyclisation step at r.t., butyric acid 162 (1.02 g, 5 mmol) gave the lactam 163 (406 mg, 40 %); performing the cyclisation step at 50 ºC 162 (1.02 g, 5 mmol) gave azepinone 163 (686 mg, 68 %) and performing the cyclisation at 80 ºC 162 (395 mg, 1.94 mmol) gave 163 (351 mg, 90 %) as a white solid.
**Rf** [EtOAc] 0.42; **Mp**: 227-230 °C (from EtOAc); lit.,\textsuperscript{239} 220 °C (from acetone); **IR** \(v_{\text{max}}\) (KBr disc) 3268 (NH), 2940, 2865 (CH), 1628 (C=O), 1545, 1481, 1410 (Ph and CH), 1332 and 1296 (CO and CN); \(^1\text{H NMR}\) \(\delta\) (400 MHz, CDCl\(_3\)) 9.30 (1H, broad s, N(10)H), 7.60 (1H, d, \(J\) 8.0 Hz, C(6)H), 7.41 (1H, d, \(J\) 8.0 Hz, C(9)H), 7.31 (1H, ddd, \(J\) 8.0, 7.0 and 1.0 Hz, C(8)H), 7.13 (1H, ddd, \(J\) 8.0, 7.0 and 1.0 Hz, C(7)H), 6.53 (1H, broad s, N(2)H), 3.50 (1H, t, \(J\) 5.0 Hz, C(3)H\(_{A}\)), 3.49 (1H, t, \(J\) 5.0 Hz, C(3)H\(_{B}\)), 3.15 (2H, t, \(J\) 6.5 Hz, C(5)H\(_{2}\)) and 2.23-2.17 (2H, m, C(4)H\(_2\)); \(^{13}\text{C NMR}\) \(\delta\) (100 MHz, CDCl\(_3\)) 165.5− (C1=O), 135.8− (C9a), 128.0− (C5b), 126.5− (C10a), 125.2+ (C8), 120.3+ (C6), 119.8+ (C7), 119.0− (C5a), 111.8+ (C9), 43.0− (C3), 26.7− (C4) and 25.8− (C5); **MS** (+ESI) \(m/z\) 201 (M+H\(^+\), 10 %), 223 (M+Na\(^+\), 29) and 423 (2M+Na\(^+\), 100); **HRMS** (+ESI) Found M+Na\(^+\), 223.0848; C\(_{12}\)H\(_{12}\)N\(_2\)ONa requires M+Na\(^+\) 223.0847; **HPLC** \(t_R\) 13.0 (100 %).

Spectroscopic data is consistent with that reported by Thakur et al.\textsuperscript{240}

**Methyl 4-(1’-Methyl-1H-indol-3’-yl)-butanoate (164)**

\[
\begin{align*}
\text{MeI}, \\ t\text{-BuOK}, \\ DMF \\
\end{align*}
\] 73 %

\[
\begin{align*}
\text{162} & \quad \text{MeO}\text{CO} \\
\text{164} & \quad \text{MeO}\text{CO} \\
\end{align*}
\]

Following the procedure reported by Perregaard,\textsuperscript{108} \(t\)-BuOK (2.52 g, 22.5 mmol) was added portionwise over 5 min to a stirred solution of indole-3-butyric acid 162 (1.52 g, 7.5 mmol) in anhydrous DMF (15 mL) under N\(_2\). The mixture was cooled to 0 °C and MeI (3.73 mL, 60 mmol) added slowly over 10 min. The reaction was allowed to warm to r.t. and stirred for 16 h. H\(_2\)O (65 mL) was added, the layers separated and the aqueous fraction extracted with EtOAc (4 x 20 mL). The organic fractions were combined, washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered and the solvent removed in vacuo. After column chromatography [silica, PE–EtOAc gradient from 100:0 to 0:100] the \(N\)-methyl ester 164 (1.27 g, 73%) was isolated as an oil.
$R_f$ [PE-EtOAc, 70:30] 0.51; $^1$H NMR $\delta_H (400$ MHz, CDCl$_3$) 7.62 (1H, dd, $J$ 8.0 and 1.0 Hz, C(7')H), 7.31 (1H, dd, $J$ 8.0 and 1.0 Hz, C(4')H), 7.25 (1H, ddd, $J$ 8.0, 8.0 and 1.0 Hz, C(6')H), 7.13 (1H, ddd, $J$ 8.0, 8.0 and 1.0 Hz, C(5')H), 6.86 (1H, s, C(2')H), 3.76 (3H, s, NCH$_3$), 3.69 (3H, s, OCH$_3$), 2.83 (2H, t, $J$ 7.5 Hz, C(4)H$_2$), 2.42 (2H, t, $J$ 7.5 Hz, C(2)H$_2$) and 2.11-2.03 (2H, m, C(3)H$_2$); $^{13}$C NMR $\delta_C (100$ MHz, CDCl$_3$) 174.1− (CO$_2$H), 137.0− (C7a'), 127.8− (C3a'), 126.3+ (C2'), 121.4+ (C6'), 118.9+ (C7'), 118.6+ (C5'), 114.0− (C3'), 109.1+ (C4'), 51.4+ (OCH$_3$), 33.6− (C2), 32.5+ (NCH$_3$), 25.5− (C3) and 24.3− (C4); MS (+ESI) m/z 254 (M+Na$^+$, 100 %); HRMS (+ESI) Found M+Na$^+$, 254.1144; C$_{14}$H$_{17}$NO$_2$Na requires $M+Na^+$ 254.1157.

10-Methyl-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (166)

![Chemical structure](image)

KOH (1.55 g, 28 mmol) was added to a rapidly stirred suspension of the ester 164 (1.28 g, 5.6 mmol) in H$_2$O (100 mL) at r.t. and the reaction heated at reflux for 4 hrs. After cooling to 0 °C the solution was acidified to pH 2 with 6M HCl and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and the solvent removed in vacuo to afford the acid intermediate acid 165 as a white solid.

Following general procedure 1C, performing the BF$_3$·OEt$_2$ mediated cyclisation at r.t., the crude acid intermediate gave the azepinone 166 (3.9 mmol)
scale, 301 mg, 36%) and performing the cyclisation at 50 °C gave 166 (5.56 mmol scale, 1.008 g, 85%) as a white solid. 

**Rf** [PE-EtOAc 7:3] 0.15; **Mp** 131-134 °C (from EtOAc); **IR** ν<sub>max</sub> (KBr disc) 3467 (NH), 3277, 3055, 2931 (CH), 1658 (C=O), 1535, 1475, 1434 (Ar), 1318 (CN) and 735 (CH); **1H NMR** δ(H(400 MHz, CDCl<sub>3</sub>) 7.62 (1H, d, J 8.0 Hz, C(6)H), 7.37 (1H, dd, J 8.0 and 1.0 Hz, C(9)H), 7.34 (1H, ddd, J 8.5, 8.0 and 1.0 Hz, C(8)H), 7.15 (1H, ddd, J 8.0, 6.0 and 2.0 Hz, C(7)H), 6.53 (1H, broad s, N(2)H), 4.00 (3H, s, N(10)CH<sub>3</sub>), 3.35 (1H, t, J 6.0 Hz, C(3)H<sub>A</sub>), 3.34 (1H, t, J 6.0Hz, C(3)H<sub>B</sub>), 3.12 (2H, t, J 7.0 Hz, C(5)H<sub>2</sub>) and 2.17-2.11 (2H, m, C(4)H<sub>2</sub>); **13C NMR** δ(C(100 MHz, CDCl<sub>3</sub>) 167.2− (C1=O), 138.7− (C9a), 127.8− (C10a), 126.2− (C5b), 124.6+ (C8), 119.8+ (C6), 119.6+ (C7), 118.9− (C5a), 110.0+ (C9), 41.4− (C3), 31.8+ (NCH<sub>3</sub>), 29.0− (C4) and 22.3− (C5); **MS** (+ESI) m/z 237 (M+Na<sup>+</sup>, 69 %) and 451 (2M+Na<sup>+</sup>, 100); **HRMS** (+ESI) Found M+Na<sup>+</sup>, 237.1001; C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>ONa requires M+Na<sup>+</sup> 237.1004; **HPLC** t<sub>R</sub> 14.3 (100 %).

2,10-Dimethyl-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (167)

NaH (60 % dispersion in mineral oil) (120 mg, 3 mmol) was added to a vigorously stirred suspension of lactam 163 (187 mg, 0.935 mmol) in THF (5 mL) at 0 °C under Ar. After 30 mins, MeI (185 μL, 3 mmol) was added and the reaction stirred at r.t. for 16 hrs, then quenched with saturated aqueous NH₄Cl (15mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, light PE-EtOAc gradient from 100:0 to 50:50] azepinone 167 (183 mg, 86 %) was isolated as a white solid.
**Mp** 106-110 °C (Et₂O); lit.,²⁴¹ 104-106 °C (PE 60-80 °C); **¹H NMR** δₕ(400 MHz, CDCl₃) 7.60 (1H, ddd J 8.0, 1.0 and 1.0 Hz, C(6)H), 7.35 (1H, ddd, J 8.0, 1.0 and 1.0 Hz, C(9)H), 7.31 (1H, ddd, J 8.0, 6.5 and 1.0 Hz, C(8)H), 7.13 (1H, ddd, J 8.0, 6.5 and 1.0 Hz, C(7)H), 3.96 (3H, s, N(2)CH₃), 3.45 (2H, dd, J 6.0 and 6.0 Hz, C(3)H₂), 3.20 (3H, s, N(10)CH₃), 3.02 (2H, dd, J 6.0 and 6.0 Hz, C(5)H₂) and 2.20-2.13 (2H, m, C(4)H₂); **¹³C NMR** δₖ(100 MHz, CDCl₃) 165.3− (C1=O), 138.4− (C9a), 129.5− (C10a), 126.0− (C5b), 124.1+ (C8), 119.5+ (C6 or C7), 119.5+ (C6 or C7), 117.2− (C5a), 109.9+ (C9), 49.6− (C3), 34.9+ (N(2)CH₃), 31.5+ (N(10)CH₃), 28.0− (C4) and 20.7− (C5); **MS** (+ESI) m/z 229 (M+H⁺, 100 %) and 251 (M+Na⁺, 25); **HRMS** (+ESI) Found M+Na⁺, 251.1171; C₁₄H₁₆N₂ONa requires M+Na⁺ 251.1160; **HPLC** tᵣ 13.5 (100 %).

### 5.2.2. Synthesis of AB-ring Analogues by Dehydrogenation of Lactams

**General Procedure 2: Dehydrogenation of lactam rings**

**Method A:** Dichlorodicyanoquinoline (452 mg, 4 mmol) was added to a stirred solution of lactam (0.5 mmol) in dioxane (10 mL) at r.t. under N₂, then the reaction heated at 110 °C for between 1 and 24 hrs. After cooling, the solvent was removed and the residue stirred in 2M NaOH (10 mL) for 30 mins then extracted with EtOAc (4 x 10 mL). The combined organic fractions were washed with H₂O (2 x 10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, MeOH-CH₂Cl₂ gradient from 0:100 to 5:95] the product was isolated.

**Method B:** 10 % Palladium on activated carbon (7 mol%) was added to a vigorously stirred, degassed solution of lactam in anhydrous xylene (8 mL/mmol) under N₂, then the reaction was heated at reflux for 24 hrs. The catalyst was removed by filtration through celite and washed with hot MeOH, then the solvent was removed in vacuo. The product was recrystallised from EtOAc, without need for column chromatography.

**Method C:** 10 % Palladium on activated carbon (15 mol%) was added to a vigorously stirred, degassed solution of lactam in anhydrous xylene (8 mL/mmol) under N₂, then the reaction was heated at reflux for 24 hrs. After cooling to r.t., the
The mixture was diluted with MeOH, SiO\textsubscript{2} added and then heated at reflux for 30 mins. The solvent was removed \textit{in vacuo} and column chromatography [silica, MeOH-CH\textsubscript{2}Cl\textsubscript{2} gradient from 0:100 to 5:95] afforded the product.

\textbf{Method D}: A degassed suspension lactam and 10 % palladium on activated carbon (10 mol %) in xylene (5 mL/ mmol) was heated in the microwave at 200 °C for 30-60 mins. The mixture was diluted with MeOH, SiO\textsubscript{2} added and then heated at reflux for 30 mins. The solvent was removed \textit{in vacuo} and column chromatography [silica, MeOH-CH\textsubscript{2}Cl\textsubscript{2} gradient from 0:100 to 5:95] afforded the product.

\begin{center}
\begin{tabular}{c}

\textbf{6H-1,3-Dioxolo[4,5-g]isoquinolin-5-one (172)}

\begin{tikzcd}
\text{144} \\
\text{DDQ or Pd/C, xylene} \\
\text{37-67 %} \\
\text{172}
\end{tikzcd}

Following general procedure 2A dihydroisoquinolinone \textbf{144} (96 mg, 0.5 mmol) gave isoquinolinone \textbf{172} (35 mg, 37 %); following general procedure 2B \textbf{144} (199 mg, 1.04 mmol) gave \textbf{172} (106 mg, 54 %); following procedure 2B using 33 mol% Pd/C \textbf{144} (1.53 g, 8 mmol) gave \textbf{172} (637 mg, 42 %); and following procedure 2C \textbf{144} (192g, 1 mmol) gave \textbf{172} (127 mg, 67 %) as a white solid.

\textbf{Mp} sublimes above 185 °C, then recrystallises and melts 281-284 °C with accompanying decomposition (from EtOAc); IR ν\textsubscript{max}(KBr disc) 2907, 2847, 1654 (C=O), 1582, 1498, 1479, 1460, 1254 and 1036; \textbf{\textit{1H NMR}} δ\textsubscript{H}(400 MHz, d\textsubscript{6}-DMSO) 11.14 (1H, broad s, NH), 7.49 (1H, s, C(8)H), 7.14 (1H, s, C(5)H), 7.05 (1 H, dd, J 7.0 and 5.5 Hz, C(3)H), 6.44 (1H, d, J 7.0 Hz, C(4)H) and 6.15 (2H, s, OCH\textsubscript{2}O); \textbf{\textit{13C NMR}} δ\textsubscript{C}(100 MHz, d\textsubscript{6}-DMSO) 161.1− (C1=O), 151.4− (C7-O), 147.1− (C6-O), 135.1− (C4a or C8a), 127.5+ (C3), 121.3− (C4a or C8a), 104.7+ (C4), 104.0+ (C8), 103.9+ (C5) and 101.8− (CH\textsubscript{2}); \textbf{MS} (+ESI) m/z 212 (M+Na\textsuperscript{+}, 85 %) and 401 (2M+Na\textsuperscript{+}, 100); \textbf{HRMS} (+ESI) (Found M+Na\textsuperscript{+}, 212.0316; C\textsubscript{10}H\textsubscript{7}NO\textsubscript{3}Na requires M+Na\textsuperscript{+} 212.0324; \textbf{HPLC} t\textsubscript{R} 9.5 (100 %).

Spectroscopic data is consistent with that reported by Xie \textit{et al.}\textsuperscript{242}
6,7-Dimethoxyisoquinolin-1(2H)-one (173)

Following general procedure 2A, dihydroisoquinolinone 147 (104 mg, 0.5 mmol) gave isoquinolinone 173 (32 mg, 31 %); following general procedure 2B 147 (207 mg, 1 mmol) gave 173 (126 mg, 61 %); and following general procedure 2C 147 (207 mg, 1 mmol) gave 173 (178 mg, 86 %) as a white solid.

Mp sublimes above 205 °C then recrystallises and melts at 244-246 °C (EtOAc), lit.,243 244-245 °C (from CHCl₃-PhH); IR ν max(KBr disc) 2923, 2853, 1639 (C=O), 1607, 1505, 1470 and 1273; ¹H NMR δH(400 MHz, CD₃OD) 7.70 (1H, s, C(8)H), 7.13 (1H, s, C(5)H), 7.09 (1 H, d, J 7.0 Hz, C(3)H), 6.34 (1H, d, J 7.0 Hz, C(4)H), 3.96 (3H, s, C(7)OCH₃) and 3.94 (3H, s, C(6)OCH₃); ¹³C NMR δC(100 MHz, CD₃OD) 164.3− (C=O), 155.6− (C7-O), 150.9− (C6-O), 135.8− (C8a), 127.3+ (C3), 120.7− (C4a), 107.8+ (C4, C5 or C8), 107.7+ (C4, C5 or C8), 107.7+ (C4, C5 or C8), 56.5+ (OCH₃) and 56.4+ (OCH₃); MS (+ESI) m/z 206 (M+H⁺, 35 %), 228 (M+Na⁺, 17) and 433 (2M+Na⁺, 100); HRMS (+ESI) Found M+H⁺, 206.796; C₁₁H₁₂NO₃ requires M+H⁺ 206.0817; HPLC tR 8.8 (100 %).

Spectroscopic data is consistent with that reported by Sakamoto et al.244

8-Hydroxy-6,7-dimethoxy-1-oxoquinoline (174)

8-Hydroxy-6,7-dimethoxy-1-oxoquinoline (174)
Following general procedure 2B, dihydroisoquinolinone 151 (123 mg, 0.55 mmol) gave isoquinolinone 174 (62 mg, 51 %); following general procedure 2B using 33 mol% Pd/C 151 (1.31 g, 5.95 mmol) gave 174 (644 mg, 49 %); following general procedure 2C 151 (223 mg, 1 mmol) gave 174 (85 mg, 38 %); and following general procedure 2D 151 (112 mg, 0.5 mmol) gave 174 (88 mg, 80 %) as a white solid.

**Mp** sublimes above 210 °C then recrystallises, melts at 244-247 °C (from EtOAc); **IR** \( \nu_{\text{max}} \) (KBr disc) 3329 (OH), 2936, 2853 (CH), 1648, 1618, 1578, 1440, 1382, 1303 (C-O), 1235, 1127, 1017 and 824; **\(^1\)H NMR** \( \delta_{\text{H}} \) (400 MHz, d\(_6\)-DMSO) 13.26 (1H, s, OH), 11.53 (1H, s, NH), 7.11 (1H, d, \( J = 7.0 \) Hz, C(3)H), 6.73 (1H, s, C(5)H), 6.56 (1H, d, \( J = 7.5 \) Hz, C(4)H), 3.87 (3H, s, OCH\(_3\)) and 3.72 (3H, s, OCH\(_3\)); **\(^{13}\)C NMR** \( \delta_{\text{C}} \) (100 MHz, d\(_6\)-DMSO) 165.7– (C1=O), 157.8– (C7), 153.7– (C8), 135.1– (C8a), 132.8– (C6), 127.8+ (C3), 106.9– (C4a), 106.7+ (C4), 97.9+ (C5), 59.8+ (OCH\(_3\)) and 55.8+ (OCH\(_3\)) ; **MS** (+ESI) \( m/z \) 222 (M+H\(^+\), 100 %) and 244 (M+Na\(^+\), 56); **HRMS** (+ESI) Found M+Na\(^+\), 244.0619; \( \text{C}_{11}\text{H}_{11}\text{NO}_4\text{Na} \) requires M+Na\(^+\) 244.0580; **HPLC** \( t_R \) 10.6 (96 %).

**2,9-Dihydro-1H-pyrido[3,4-b]indol-1-one (175)**

\[
\begin{align*}
\text{153} & \xrightarrow{\text{DDQ or Pd/C, xylene}} \text{175} \\
& \text{25-90 %} \\
\end{align*}
\]

Following general procedure 2A carbolinone 153 (93 mg, 0.5 mmol) gave carbolinone 175 (23 mg, 25 %); following general procedure 2A using 3 mmol DDQ, carbolinone 153 (93 mg, 0.5 mmol) gave carbolinone 175 (53 mg, 58 %); following general procedure 2B 153 (186 mg, 1 mmol) gave 175 (72 mg, 39 %); and following procedure 2D 153 (558 mg, 3 mmol) gave 175 (497 mg, 90 %) as a white solid.

**R\(_f\)** [CH\(_2\)Cl\(_2\)-MeOH 95:5] 0.28; **Mp** sublimes above 236 °C (from EtOAc); lit.,\(^{245}\) 259 °C (from PhH); **IR** \( \nu_{\text{max}} \) (Thin film) 2918, 1651 (C=O), 1614, 1424, 1327

\[131\]
and 725; \(^1\)H NMR \(\delta_H(400\ \text{MHz}, \text{d}_6\text{-DMSO})\) 11.90 (1H, s, N(9)H), 11.35 (1H, s, N(2)H), 8.00 (1H, d, \(J\ 8.0\ \text{Hz}, \text{C}(5)\text{H}\)), 7.49 (1H, d, \(J\ 8.0\ \text{Hz}, \text{C}(8)\text{H}\)), 7.38 (1H, ddd, \(J\ 8.0, 7.0\ \text{and} 1.0\ \text{Hz}, \text{C}(7)\text{H}\)), 7.15 (1H, ddd \(J\ 8.0, 7.0\ \text{and} 1.0\ \text{Hz}, \text{C}(6)\text{H}\)), 7.07-7.04 (1H, m, \(\text{C}(3)\text{H}\)) and 6.96 (1H, d, \(J\ 7.0\ \text{Hz}, \text{C}(4)\text{H}\)); \(^{13}\)C NMR \(\delta_C(100\ \text{MHz}, \text{d}_6\text{-DMSO})\) 155.7− (C=O), 139.0− (C8a), 128.0− (C4a), 126.2+ (C7), 124.5+ (C3), 124.2− (C9a), 122.0− (C4b), 121.3+ (C5), 119.4+ (C6), 112.4+ (C8) and 99.7+ (C4); MS (+ESI) \(m/z\) 185 (M+H\(^+\), 100 \%), 207 (M+Na\(^+\), 20) and 391 (2M+Na\(^+\), 76); HRMS (+ESI) Found M+H\(^+\), 185.0710; C\(_{11}\)H\(_9\)N\(_2\)O requires M+H\(^+\) 185.0715; HPLC \(t_R\) 10.0 (100 \%).

Spectroscopic data is consistent with that reported by Tahri et al.\(^{246}\)

9-Methyl-2,9-dihydro-1H-pyrido[3,4-b]indol-1-one (176)

Following general procedure 2A carbolinone 160 (100 mg, 0.5 mmol) gave carbolinone 176 (22 mg, 22 \%); and following general procedure 2B 160 (200 mg, 1 mmol) after 6 days gave 176 (119 mg, 60 \%) as a white solid.

Mp 161-164 °C (from EtOAc); lit.,\(^{247}\) 242-242.5 °C (from EtOH); IR \(\nu_{\text{max}}\) (KBr disc) 3116 (NH), 2881, 2836 (CH), 1656 (C=O) 1464, 1351, 1279, 1215 and 949; \(^1\)H NMR \(\delta_H(400\ \text{MHz}, \text{d}_6\text{-DMSO})\) 11.4 (1H, s, N(2)H), 8.06 (1H, d, \(J\ 8.0\ \text{Hz}, \text{C}(5)\text{H}\)), 7.62 (1H, d, \(J\ 8.5\ \text{Hz}, \text{C}(8)\text{H}\)), 7.50 (1H, ddd, \(J\ 8.0, 7.0\ \text{and} 1.0\ \text{Hz}, \text{C}(6)\text{H}\)), 7.07 (1H, ddd, \(J\ 7.0, 7.0\ \text{Hz}, \text{C}(3)\text{H}\)), 6.99 (1H, d, \(J\ 6.0\ \text{Hz}, \text{C}(4)\text{H}\)) and 7.23 (3H, s, N(9)CH\(_3\)); \(^{13}\)C NMR \(\delta_C(100\ \text{MHz}, \text{d}_6\text{-DMSO})\) 156.4− (C1=O), 140.2− (C8a), 127.0− (C9a), 126.5+ (C7), 124.9+ (C3), 124.6− (C4a), 121.4+ (C5), 121.1− (C4b), 119.8+ (C6), 110.4+ (C8), 99.6+ (C4) and 31.0+ (N(9)CH\(_3\)); MS (+ESI) \(m/z\) 199 (M+H\(^+\), 100 \%), 221 (M+Na\(^+\), 40) and 419 (2M+Na\(^+\), 75); HRMS (+ESI) Found M+Na\(^+\), 221.0675; C\(_{12}\)H\(_{10}\)N\(_2\)ONa requires M+Na\(^+\) 221.0691; HPLC \(t_R\) 14.8 (100 \%).
2,9-Dimethyl-2,9-dihydro-1H-pyrido[3,4-b]indol-1-one (177)

NaH (60 % dispersion in mineral oil) (100 mg, 2.5 mmol) was added to a vigorously stirred suspension of lactam 175 (144 mg, 0.78 mmol) in THF (3 mL) at 0 °C under Ar. After 30 mins, MeI (155 μL, 2.5 mmol) was added and the reaction stirred at r.t. for 18 hrs. The reaction was quenched with saturated aqueous NH₄Cl (15mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 50:50] the carbolinone 177 (90 mg, 54 %) was isolated as a yellow solid.

Mp 164-166 °C (from Et₂O); lit.,²⁴⁷ 158.5-159 °C (from EtOH); IR ν max(Thin film) 309, 2926, 1648 (C=O), 1589, 1531, 1473, 1331 and 1268; ¹H NMR δH(400 MHz, CDCl₃) 7.84 (1H, d, J 8.0 Hz, C(8)H), 7.42 (1H, ddd, J 8.0, 7.0 and 1.0 Hz, C(7)H), 7.36 (1H, d, J 8.0 Hz, C(5)H), 7.16 (1H, ddd, J 8.0, 8.0 and 2.0 Hz, C(6)H), 6.97 (1H, d, J 7.0 Hz, C(3)H), 6.79 (1H, d, J 7.0 Hz, C(4)H), 4.24 (3H, s, N(9)CH₃) and 3.60 (3H, s, N(2)CH₃); ¹³C NMR δC(100 MHz, CDCl₃) 156.8– (C1=O), 140.9– (C8a), 128.7+ (C3), 127.3– (C9a), 126.6+ (C7), 124.6– (C4a), 121.3– (C4b), 121.0+ (C8), 119.9+ (C6), 110.0+ (C5), 100.4+ (C4), 36.7+ (N(2)CH₃) and 31.5+ (N(9)CH₃); MS (+ESI) m/z 213 (M+H⁺, 100 %), 235 (M+Na⁺, 9); HRMS (+ESI) Found M+Na⁺, 235.0836; C₁₃H₁₆N₂ONa requires M+Na⁺ 235.0842; HPLC tR 14.8 (96 %).
5.2.3. Pro-drug Synthesis

8-Hydroxy-6,7-dimethoxy-1-oxo-1H-isooquinoline-2-carboxylic acid ethyl ester (178)

Ethyl chloroformate (53 µL, 0.55 mmol) was added to a stirred suspension of isoquinolinone 174 (110 mg, 0.5 mmol) and Et₃N (76 µL, 0.55 mmol) in anhydrous THF (1.5 mL) at 0 °C under N₂. The reaction was allowed to warm to r.t. and stirred for 2 hrs, then quenched with H₂O (6 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc 70:30] the carbamate product 178 (75 mg, 51 %) was isolated as a white solid.

Rf [PE-EtOAc 70:30] 0.70; IR ν_max (Thin film) 2980, 1941, 1770 (C=O), 1667 (C=O), 1594, 1559, 1505, 1411, 1300, 1246, 1199 and 1127; ¹H NMR δ_H (400 MHz, CDCl₃) 12.41 (1H, s, OH), 7.46 (1H, d, J 8.0 Hz, C(3)H), 6.43 (1H, s, C(5)H), 6.38 (1H, d, J 8.0 Hz, C(4)H), 4.52 (2H, q, J 7.0 Hz, OCH₂CH₃), 3.95 (3H, s, CH₃), 3.91 (3H, s, OCH₃) and 1.46 (3H, t, J 7.0 Hz, OCH₂CH₃); ¹³C NMR δ_C (100 MHz, CDCl₃) 164.9− (C1=O), 158.9− (C6 or C7), 155.9− (C8-OH), 151.7− (CO₂Et), 135.4− (C6 or C7), 133.5− (C4a or C8a), 126.1+ (C3), 108.6+ (C4), 107.2− (C4a or C8a), 98.6+ (C5), 65.2− (OCH₂CH₃), 60.7+ (OCH₃), 56.1+ (OCH₃) and 14.1+ (OCH₂CH₃). MS (+ESI) m/z 294 (M+H⁺, 31 %), 316 (M+Na⁺, 17) and 609 (2M+H⁺, 100); HRMS (+ESI) Found M+H⁺, 294.0975; C₁₄H₁₆NO₆ requires M+H⁺ 294.0972.
8-Ethoxycarbonyloxy-6,7-dimethoxy-1-oxo-1H-isoquinoline-2-carboxylic acid ethyl ester (180)

NaH (60 % dispersion in mineral oil) (80 mg, 1.2 mmol) was added to a vigorously stirred suspension of isoquinolinone 174 (110 mg, 0.5 mmol) in anhydrous THF (3 mL) at 0 °C under N₂. After 45 mins, ethyl chloroformate (115 µL, 1.2 mmol) was added, the reaction was allowed to warm to r.t. and stirred for 3 hrs, then quenched with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc 70:30] the carbonate product 180 (48 mg, 26 %) was isolated as a white solid and the carbamate 178 (54 mg, 37 %) as white a solid.

**Rf** [PE-EtOAc 60:40] 0.80; IR ν<sub>max</sub>(KBr disc) 2990, 3947, 1753 (C=O), 1731 (C=O), 1731 (C=O), 1685 (C=O), 1605, 1503, 1469, 1409, 1370, 1311, 1243, 1130, 1091, 1030, 1006 and 975; ¹H NMR δ<sub>H</sub>(400 MHz, CDCl₃) 7.44 (1H, d, J 8.0 Hz, C(3)H), 6.73 (1H, s, C(5)H), 6.27 (1H, d, J 8.0 Hz, C(4)H), 4.44 (2H, q, J 7.0 Hz, OCH₂CH₃), 4.36 (2H, q, J 7.0 Hz, OCH₂CH₃), 3.94 (3H, s, OCH₃), 3.87 (3H, s, OCH₃) and 1.42-1.38 (6H, m, OCH₂CH₃); ¹³C NMR δ<sub>C</sub>(100 MHz, CDCl₃) 158.1− (C₁=O), 157.8− (C₆ or C₇), 152.8− (NCO₂Et or OCO₂Et), 152.7− (NCO₂Et or OCO₂Et), 145.1− (C₈), 141.7− (C₆ or C₇), 134.6− (C₄a or C₈a), 127.5+ (C₃), 113.7− (C₄a or C₈a), 106.4+ (C₄), 105.2+ (C₅), 65.1− (OCH₂CH₃), 64.7− (OCH₂CH₃), 61.5+ (OCH₃), 56.1+ (OCH₃), 14.2+ (OCH₂CH₃) and 14.0+ (OCH₂CH₃); MS (+ESI) m/z 366 (M+H⁺, 35 %), 388 (M+Na⁺, 13) and 753 (2M+Na⁺, 100); HRMS (+ESI) Found M+H⁺, 366.1187; C₁₇H₂₀N₇O₈ requires M+H⁺ 366.1183.
Benzyl 8-hydroxy-6,7-dimethoxy-1-oxoisouquinoline-2(1H)-carboxylate (179) and benzyl 8-(benzyloxyacarbonyloxy)-6,7-dimethoxy-1-oxoisouquinoline-2(1H)-carboxylate (181)

NaH (60 % dispersion in mineral oil) (80 mg, 2 mmol) was added to a vigorously stirred suspension of isoquinolinone 174 (110 mg, 0.5 mmol) in anhydrous THF (3 mL) at 0 °C under N₂. After 45 mins, benzyl chloroformate (171 µL, 1.2 mmol) was added. The reaction was allowed to warm to r.t. and stirred for 3 hrs, then quenched with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 60:40] the phenol product 179 (22 mg, 12 %) was isolated as a white solid and carbonate product 181 (100 mg, 41 %) as an oil.

**Phenol (179)**

Rᵣ [PE-EtOAc 50:50] 0.4; ¹H NMR δₚ(400 MHz, CDCl₃) 12.41 (1H, s, OH) 7.49 (2H, d, J 7.0 Hz, Ph), 7.45 (1H, d, J 8.0 Hz, C(3)H), 7.43-7.37 (3H, m, Ph), 6.41 (1H, s, C(5)H), 6.36 (1H, d, J 8.0 Hz, C(4)H), 5.46 (2H, s, OCH₂Ph), 3.94 (3H, s, OCH₃) and 3.91 (3H, s, OCH₃); ¹³C NMR δₚ(100 MHz, CDCl₃) 164.9− (C(1)=O), 158.9− (C6 or C7), 155.9− (C8), 151.6− (CO₂Bn), 135.4− (C6 or C7), 134.1− (C4a or C8a), 133.4− (Ph), 128.9+ (Ph), 128.8+ (Ph), 128.5+ (Ph), 126.0+ (C3), 108.7+ (C4), 107.1− (C4a or C8a), 98.7+ (C5), 70.4− (OCH₂Ph), 61.7+ (OCH₃) and 56.1+ (OCH₃); MS (+ESI) m/z 356 (M+H⁺, 100 %) and 378 (M+Na⁺, 61); HRMS (+ESI)
Found M+Na⁺, 378.0941; C₁₀H₁₇NO₆Na requires M+Na⁺ 378.0954; HPLC tᵣ 10.5 (85 %).

**Carbonate (181)**

Decomposes in air at r.t. to 179

Rᵣ [PE-EtOAc 50:50] 0.26; H NMR δₓ̄ (400 MHz, CDCl₃) 7.50-7.47 (4H, m, Ph), 7.43 (1H, d, J 8.0 Hz, C(3)H), 7.38-7.30 (9H, m, Ph), 6.70 (1H, s, C(5)H), 6.24 (1H, d, J 8.0 Hz, C(4)H), 5.42 (2H, s, CH₂Ph), 5.35 (2H, s, CH₂Ph), 3.91 (3H, s, OCH₃) and 3.82 (3H, s, OCH₃); C NMR δₓ (100 MHz, CDCl₃) 158.1− (C₁=O), 157.8− (C6 or C7), 152.8− (NCO₂Bn or OCO₂Bn), 152.5− (NCO₂Bn or OCO₂Bn), 145.0− (C₈), 141.6− (C6 or C7), 135.0− (Ph), 134.5 (Ph), 128.5+ (Ph), 128.5+ (Ph), 128.4+ (Ph), 128.3+ (Ph), 128.2+ (Ph), 128.0+ (Ph), 127.2+ (C₃), 113.5− (C₄a or C₈a), 108.5− (C₄a or C₈a), 106.5+ (C₄), 105.3+ (C₅), 70.4− (CH₂Ph), 69.8− (CH₂Ph), 61.4+ (OCH₃) and 56.1+ (OCH₃); MS (+ESI) m/𝑧 356 (M-BnOCO₂⁺H⁺, 100 %), 490 (M+H⁺, 27), 512 (M+Na⁺, 36); HRMS (+ESI) Found M+H⁺, 490.1498; C₂₇H₂₄NO₈ requires M+H⁺ 490.1502.
5.3. SYNTHESIS OF ABC-RING ANALOGUES

5.3.1. Synthesis of the Dimethoxy Analogue

**Ethyl 3-(3’,4’-dimethoxyphenyl)-3-oxopropanoate (194)**

![Chemical Structure](image)

Following the procedure reported by Arnould et al., NaH (60 % dispersion in mineral oil) (3 g, 75 mmol) was added portionwise over 3 mins to a stirred solution of 3,4-dimethoxyacetophenone 193 (9 g, 50 mmol) in diethyl carbonate (100 mL) at 0 °C under N₂, then the reaction was heated at 80 °C for 1 ½ hrs. After cooling to r.t., the reaction was quenched with saturated aqueous NH₄Cl (30 mL) and H₂O (300 mL), then extracted with EtOAc (3 x 125 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc 65:35] β-ketoester 194 (12.13 g, 96 %) was isolated as a pale yellow oil.

**Rf [PE-EtOAc: 30:70] 0.93; **[^1] **H NMR** δₓ(400 MHz, CDCl₃) 7.51 (1H, dd, J 8.0 and 2.0 Hz, C(6’)H), 7.49 (1H, d, J 2.0 Hz, C(2’)H), 6.85 (1H, d, J 8.0 Hz, C(5’)H), 4.17 (2H, q, J 7.0 Hz, OCH₂CH₃), 3.91 (5H, s, OCH₃ and C(2)H₂), 3.89 (3H, s, OCH₃) and 1.22 (3H, t, J 7.0 Hz, OCH₂CH₃); **[^13]C NMR** δₓ(100 MHz, CDCl₃) 190.9– (C3=O), 167.6– (CO₂Et), 153.7– (C3’-O or C4’-O), 149.0– (C3’-O or C4’-O), 129.2– (C1’), 123.4+ (C(Ar)-H), 110.2+ (C(Ar)-H), 110.0+ (C(Ar)-H), 61.3– (OCH₂CH₃), 56.0+ (OCH₃), 55.9+ (OCH₃), 45.6– (C2) and 14.0+ (OCH₂CH₃).

Spectroscopic data is consistent with that reported by Jung *et al.*[^248]
Ethyl 2-(3,4-dimethoxyphenyl)-2-hydroxy-4-oxo-1-(3-oxobutyl)cyclohexanecarboxylate or ethyl 2-(3,4-Dimethoxyphenyl)-2-hydroxy-4-oxo-3-(3-oxobutyl)cyclohexanecarboxylate or ethyl 2-(3,4-Dimethoxyphenyl)-2-hydroxy-4-oxo-5-(3-oxobutyl)cyclohexanecarboxylate (204)

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{K}_2\text{CO}_3, \text{MeCN}, \quad 50 \degree \text{C} & \quad \rightarrow \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

K\textsubscript{2}CO\textsubscript{3} (345 mg, 2.5 mmol) was added to a vigorously stirred solution of \(\beta\)-ketoester 194 (252 mg, 1 mmol) in anhydrous MeCN (5 mL) at r.t. under N\textsubscript{2}. After 5 mins, MVK (202 \(\mu\)L, 2.5 mmol) was added and the reaction stirred for 24 hrs at 50 \degree\text{C}. The reaction was quenched with saturated aqueous NH\textsubscript{4}Cl (15 mL) then extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 80:20 to 40:60] the product 204 (221 mg, 56 \%) was isolated as a yellow oil.

**R\textsubscript{f}** [PE-EtOAc 50:50] 0.49; **IR** \(\nu_{\text{max}}\) (thin film) 3506 (OH), 2968 (CH), 2841 (CH), 1731 (C=O), 1672 (C=O), 1595 (C=C), 1515 (C=C), 1463, 1416, 1264 (C-O), 1228 (C-O), 1148, 1023 and 764; **\textsuperscript{1}H NMR** \(\delta\) (400 MHz, CDCl\textsubscript{3}) 7.57-7.44 (2H, m, Ar C-H), 6.82 (1H, d, \(J=8.0\) Hz, Ar C-H), 4.18-4.08 (2H, m, OCH\textsubscript{2}CH\textsubscript{3}), 3.92 (3H, s, OCH\textsubscript{3}), 3.91 (3H, s, OCH\textsubscript{3}), 3.01 (1H, dd \(J=13.0\) and 3.5 Hz), 2.60 (1H, td, \(J=14.0\) and 4.0 Hz) 2.45 (1H, \(J=13.0\) and 3.0 Hz) 2.32-2.16 (5H, m), 2.03 (2H, t, \(J=6.5\) Hz), 1.58 (1H, dt, \(J=14.0\) and 3.5 Hz) 1.24 (1H, t, \(J=7\) Hz) and 1.20-1.10 (5H, m); **\textsuperscript{13}C NMR** \(\delta\) (100 MHz, CDCl\textsubscript{3}) 215.4 (ketone C=O), 196.1 (ketone C=O), 173.3 (CO\textsubscript{2}Et), 155.1, 149.0, 127.8, 123.0, 111.2, 109.9, 68.8, 61.8, 56.6, 56.0, 55.9, 52.6, 34.7, 31.3, 30.9, 28.7, 27.2 and 13.9; **MS** (+ESI) \(m/z\) 375 (M-H\textsubscript{2}O+H\textsuperscript{+}, 100 \%); **HRMS** (+ESI) Found M-H\textsubscript{2}O+H\textsuperscript{+}, 375.1801; C\textsubscript{21}H\textsubscript{26}O\textsubscript{6} requires \(M-H\textsubscript{2}O+H\textsuperscript{+}\) 375.1802.
Ethyl 3',4'-dimethoxy-5-oxo-4-(3-oxobutyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate, or ethyl 3',4'-dimethoxy-5-oxo-6-(3-oxobutyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate, or ethyl 3',4'-dimethoxy-5-oxo-6-(3-oxobutyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (205)

Method A: 4M HCl in dioxane (0.25 mL) was added dropwise to a stirred solution of alcohol 204 (119 mg, 0.30 mmol) in THF at r.t. and stirred for 3 ½ hrs, then the reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 90:10 to 70:30] the product 205 (74 mg, 66 %) was isolated as a yellow oil.

Method B: p-TsOH (18 mg, 0.06 mmol) was added to a stirred solution of 204 (130 mg, 0.34 mmol) in anhydrous toluene (3.5 mL) at r.t. under N₂ and the reaction was heated at reflux for 1 hr. The reaction was quenched with saturated aqueous NaHCO₃ (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na₂SO₄,
filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 75:25] the product 205 (89 mg, 72 %) was isolated as a yellow oil.

**Rf** [PE-EtOAc 50:50] 0.58; **IR** $\nu_{\text{max}}$(KBr disc) 2951, 2856 (CH), 1730 (C=O), 1675 (C=O), 1589, 1515, 1416, 1348, 1266 (C=O), 1221, 1151, 1022 and 765; **$^1$H NMR** $\delta$ (400 MHz, CDCl$_3$) 7.49 (1H, d, $J$ 8.0 Hz, C(Ar)H), 7.48 (1H, s, C(Ar)H), 6.82 (1H, d, $J$ 8.0 Hz, C(Ar)H), 4.12 (2H, q, $J$ 7.0 Hz, OCH$_2$CH$_3$), 3.91 (3H, s, OCH$_3$), 3.88 (3H, s, OCH$_3$), 2.89 (1H, d, $J$ 17.0 Hz), 2.72 (1H, d, $J$ 17.0 Hz), 2.28 – 2.00 (7H, m), 1.84 (3H, s, CH$_3$C=O) and 1.09 (3H, t, $J$ 7.0 Hz, OCH$_2$CH$_3$); **$^{13}$C NMR** $\delta$ (100 MHz, CDCl$_3$) 202.8 (ketone C=O), 194.2 (ketone C=O), 173.3 (CO$_2$Et), 153.1, 149.0, 139.6, 130.6, 127.8, 122.7, 111.3, 109.9, 61.6, 56.1, 56.0, 55.9, 32.9, 30.1, 29.9, 28.4, 21.2 and 13.9; **MS** (+ESI) m/z 375 (M+H$^+$, 100 %); **HRMS** (+ESI) Found M+H$^+$, 375.1795; C$_{21}$H$_{26}$O$_6$ requires M+H$^+$ 375.1802.

**Ethyl 2-(3',4'-dimethoxybenzoyl)-5-oxohexanoate (202)**

![Chemical Structure](image)

K$_2$CO$_3$ (834 mg, 5.5 mmol) was added to a vigorously stirred solution of β-ketoester 194 (1.26 g, 5 mmol) in anhydrous MeCN (20 mL) at 0 °C under N$_2$. After 10 mins, MVK (446 μL, 5.5 mmol) was added and the reaction allowed to warm to r.t. and stirred for a further 2½ hrs. The reaction was quenched with saturated aqueous NH$_4$Cl (20 mL) then extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried over anhydrous Na$_2$SO$_4$, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 90:10 to 60:40] the Michael addition product 202 (1.566 g, 97 %) was isolated as a pale yellow oil.
**R**f [PE-EtOAc 50:50] 0.53; IR ν_{max}(Thin film) 2976, 2938, 2841, 1731 (C=O), 1721 (C=O), 1673 (C=O), 1594, 1514, 1463, 1418, 1368, 1345, 1266, 1155, and 1021; $^1$H NMR δ_{H}(400 MHz, CDCl$_3$) 7.69 (1H, dd, J 8.5 and 1.5 Hz, C(6’H)), 7.59 (1H, d, J 1.5 Hz, C(2’H)), 6.90 (1H, d, J 8.5 Hz, C(5’H)), 4.41 (1H, dd, J 8.0 and 6.5 Hz, C(2)H), 4.14 (2H, q, J 7.0 Hz, OCH$_2$CH$_3$), 3.94 (6H, s, OCH$_3$), 2.62-2.54 (2H, m, C(4)H$_2$), 2.25-2.17 (2H, m, C(3)H$_2$), 2.12 (3H, s, C(6)H$_3$) and 1.18 (3H, t, J 7.0Hz, OCH$_2$CH$_3$); $^{13}$C NMR δ_{C}(100 MHz, CDCl$_3$) 208.0− (CH$_3$C5=O), 193.8− (ArC=O), 170.0− (CO$_2$Et), 153.8− (C(Ar)-O), 149.1− (C(Ar)-O), 129.0− (C1’-C), 123.6+ (C(Ar)-H), 110.7+ (C(Ar)-H), 110.1+ (C(Ar)-H), 61.3− (OCH$_2$CH$_3$), 56.1+ (OCH$_3$), 56.0+ (OCH$_3$), 52.3+ (C2), 40.5− (C4), 30.0+ (C6), 23.0− (C3) and 14.6+ (OCH$_2$CH$_3$); MS (+ESI) m/z 323 (M+H$^+$, 29 %) and 345 (M+Na$^+$, 100 %); HRMS (+ESI) Found M+H$^+$, 323.1491; C$_{17}$H$_{23}$O$_6$ requires M+H$^+$ 323.1495.

**Ethyl 2-(3,4-dimethoxyphenyl)-4-oxocyclohex-2-ene carboxylate (206)**

\[ \text{MeO} \quad \text{MeO} \quad \text{Et} \quad \text{MeO} \quad \text{MeO} \quad \text{Et} \]

\[ \text{202} \quad \xrightarrow{p\text{-TsOH, toluene}} \quad \text{70 %} \quad \text{206} \]

**Method A:** Following the procedure reported by Nour et al.,$^{87}$ pyrrolidine (33 μL, 0.4 mmol) and AcOH (27 μL, 0.475 mmol) were added to a stirred solution of Michael adduct 202 (160 mg, 0.5 mmol) in refluxing toluene (1 mL) under N$_2$. After 2 ½ hrs, the reaction was cooled to r.t. and H$_2$O (20 mL) was added, then extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na$_2$SO$_4$, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 85:15 to 75:25] cyclohexenone 206 (79 mg, 52 %) was isolated as an oil.

**Method B:** $p$-TsOH (288 mg, 1.2 mmol) was added to a stirred mixture of Michael adduct 202 (975 g, 3.0 mmol) and activated 3Å molecular sieves in anhydrous toluene (30 mL) at r.t. under N$_2$ and the reaction was heated at reflux for
38 hrs. After column chromatography [silica, PE-EtOAc gradient from 80:20 to 70:30] the cyclised enone product 206 (644 mg, 70 %) was isolated as a yellow oil.

R_f [PE-EtOAc 50:50] 0.30; IR v_max (thin film) 2938, 2839 (C-H), 1728 (C=O), 1661 (C=O), 1597, 1576, 1518 (C=C), 1463, 1419, 1328, 1252 (C-O), 1151 and 1022; H NMR δ_H (400 MHz, CDCl_3) 7.10 (1H, dd, J 8.0 and 2.0 Hz, C(6’)H), 7.05 (1H, d, J 2.0 Hz, C(2’)H), 6.87 (1H, d, J 8.0 Hz, C(5’)H), 6.46 (1H, s, C(3)H), 4.11 (2H, q, J 7.0 Hz, OCH_2CH_3), 3.97-9.93 (1H, m, C(1)HCO_2Et), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 2.66-2.59 (1H, m, C(5)H_AH_B), 2.50-2.44 (2H, m, C(5)H_AH_B and C(6)H_AH_B), 2.43-2.35 (1H, m, C(6)H_AH_B), 1.15 (3H, t, J 7.0 Hz, OCH_2CH_3); C NMR δ_C (100 MHz, CDCl_3) 198.6− (C(4)=O), 171.7− (CO_2Et), 154.9− (C1’), 151.0− (C3’-O or C4’-O), 149.1− (C3’-O or C4’-O), 130.1− (C2), 125.5+ (C3), 119.6+ (C6’), 110.9+ (C2’), 109.1+ (C5’), 61.4− (OCH_2CH_3), 55.9+ (OCH_3), 55.9+ (OCH_3), 43.3+ (C1), 33.9− (C5), 26.5− (C6) and 14.0+ (OCH_2CH_3); MS (+ESI) m/z 305 (M+H+, 100 %) and 327 (M+Na+, 9); HRMS (+ESI) Found M+Na+, 327.1197; C_{17}H_{20}O_5Na requires M+Na+ 327.1208.

Ethyl 3’,4’-dimethoxy-5-(pyrrolidin-1-yl)biphenyl-2-carboxylate (207)

Following the procedure reported by Boeckman,^80^ pyrrolidine (125 μL, 1.5 mmol) and AcOH (112 μL, 2 mmol) were added to a stirred solution of 202 (160 mg, 0.5 mmol) in refluxing toluene (6 mL) under N_2. After 24 hrs, the reaction was cooled to r.t. and saturated aqueous Na_2CO_3 (15 mL) was added, then extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo. After
column chromatography [silica, PE-EtOAc gradient from 100:0 to 60:40] aniline 207 (43 mg, 25 %) was isolated as an oil and cyclohexenone 206 (25 mg, 16 %) as an oil.

\( \text{Rf} \) [PE-EtOAc 50:50] 0.5; \( \text{IR} \ \nu_{\text{max}} \) (thin film) 2972, 2836 (C-H), 1694 (C=O), 1600, 1505, 1463, 1383, 1281, 1244 (C-O), 1140, 1095 and 1028; \( \text{\textsuperscript{1}H NMR} \ \delta_H \) (400 MHz, CDCl\(_3\)) 7.87 (1H, d, \( \text{J} \) 9.0 Hz, C(3)H), 6.88-6.84 (3H, m, C(2')H, C(5')H and C(6')H), 6.50 (1H, dd, J 9.0 and 2.5 Hz, C(6)H), 4.06 (2H, q, J 7 Hz, OCH\(_2\)CH\(_3\)), 3.91 (3H, s, OCH\(_3\)), 3.86 (3H, s, OCH\(_3\)), 3.36-3.33 (4H, m, NCH\(_2\)CH\(_2\)), 2.03-2.01 (4H, m, NCH\(_2\)CH\(_2\)) and 1.04 (3H, t, J 7 Hz, OCH\(_2\)CH\(_3\)); \( \text{\textsuperscript{13}C NMR} \ \delta_C \) (100 MHz, CDCl\(_3\)) 168.1− (C=O), 149.6− (C2), 149.6− (C2'), 148.0− (C3' or C4'), 145.0− (C1'), 136.1− (C1), 132.6− (C3), 120.5+ (C2', C5' or C6'), 116.5− (C5), 113.7+ (C6), 112.2+ (C2', C5' or C6'), 110.5+ (C2', C5' or C6'), 109.7+ (C4), 59.9− (OCH\(_2\)CH\(_3\)), 55.9+ (OCH\(_3\)), 47.5− (NCH\(_2\)CH\(_3\)), 25.4− (NCH\(_2\)CH\(_3\)) and 14.0+ (OCH\(_2\)CH\(_3\)); \( \text{MS} \ (\pm \text{ESI}) \ m/z \) 356 (M+H\(^+\), 100 %) and 378 (M+Na\(^+\), 40); \( \text{HRMS} \ (\pm \text{ESI}) \) Found M+H\(^+\), 356.1847; \( \text{C}_{21}\text{H}_{26}\text{NO}_4 \) requires M+H\(^+\) 356.1862.

**Ethyl 5-hydroxy-3',4'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (211)**

![](image)

CeCl\(_3\) (184 mg, 0.75 mmol) was added to a stirred solution of enone 206 (160 mg, 0.5 mmol) in MeOH (3 mL) at r.t. then the reaction was cooled in an ice bath and NaBH\(_4\) (21 mg, 0.55 mmol) added. After 45 mins, the reaction was quenched with saturated aqueous NH\(_4\)Cl (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 50:50] the alcohol product
211 (122 mg, 80 %) was isolated as an oil and a 75:25 mixture of diastereoisomers by $^1$H NMR.

$^1$H NMR $\delta$H (400 MHz, CDCl$_3$) 6.95-6.93 (2H, m, C(2')H and C(6')H), 6.79 (1H, d, $J$ 8.0 Hz, C(5')H), 6.17-6.15 (1H, m, C(6)H), 4.44 (0.25H, broad s, C(5)HOH), 4.36 (0.75H, broad s, C(5)HOH), 4.05-3.98 (2H, m, OCH$_2$CH$_3$), 3.88 (3H, s, OCH$_3$), 3.83 (3H, s, OCH$_3$), 3.69 (0.25H, t, 5.5 Hz C(2)HCO$_2$Et), 3.61 (0.75H, t, 5.5 Hz C(2)HCO$_2$Et), 2.16-1.68 (5H, m, C(3)H$_2$, C(4)H$_2$ and OH) and 1.10-1.05 (3H, m, OCH$_2$CH$_3$); $^{13}$C NMR $\delta$C (100 MHz, CDCl$_3$) 174.0− (Isomer A C=O), 173.7− (Isomer B C=O), 148.7− (Isomer A), 148.7− (Isomer B), 137.6− (Isomer B), 137.2− (Isomer A), 133.2− (Isomer B), 133.0− (Isomer A), 128.9+ (Isomer A C6, C2', C5' or C6'), 128.5+ (Isomer B C6, C2', C5' or C6'), 118.2+ (Isomer B C6, C2', C5' or C6'), 118.1+ (Isomer A C6, C2', C5' or C6'), 110.8+ (Isomer B C6, C2', C5' or C6'), 109.2+ (C6, C2', C5' or C6'), 109.2+ (C6, C2', C5' or C6'), 66.1+ (Isomer A C5HOH), 65.6+ (Isomer B C5HOH), 60.7− (OCH$_2$CH$_3$), 60.6− (OCH$_2$CH$_3$), 55.8+ (OCH$_3$), 55.8+ (OCH$_3$), 43.8+ (Isomer B C2HCO$_2$Et), 43.5+ (Isomer A C2HCO$_2$Et), 29.2− (Isomer B C3 or C4), 28.9− (Isomer A C3 or C4), 24.2− (Isomer A C3 or C4), 23.4− (Isomer B C3 or C4) and 14.0+ (OCH$_2$CH$_3$); MS (+ESI) m/z 329 (M+Na$^+$, 100 %); HRMS (+ESI) Found M+Na$^+$, 329.1352; C$_{17}$H$_{22}$O$_5$Na requires M+Na$^+$ 329.1365.

**Ethyl 5-(((tert-butyldimethylsilyl)oxy)-3',4'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate 212**

![Chemical structure of 212](image-url)
t-Butyldimethylsilyl chloride (497 mg, 3.3 mmol) was added to a stirred solution of cyclohexenol 211 (900 mg, 3 mmol) and imidazole (225 mg, 3.3 mmol) in anhydrous DMF (6 mL) at 0 °C under N₂ and the reaction stirred for 5 mins then was allowed to warm to r.t.. After 4 hrs, the reaction was quenched with saturated aqueous NH₄Cl (25 mL) then extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 80:20 to 20:80] the silyl ether 212 (960 mg, 76 %) was isolated as an oil and a 4:1 mixture of diastereoisomers by ¹H NMR.

Rᶠ[PE-EtOAc 30:70] 0.77; IR νmax(thin film) 2932, 2856 (CH), 1732 (C=O), 1603, 1583, 1517 (C=O), 1463, 1365, 1250 (C-O), 1168, 1084 (Si-C), 1028, 836, 774; ¹H NMR δH(400 MHz, CDCl₃) 6.90 (1H, broad s, C(2')H), 6.87 (1H, d, J 7.0 Hz, C(5')H), 6.79 (1H, dd, J 7.0 and 2.5 Hz, C(6')H), 6.00 (0.8H, broad s, C(6)H), 5.98 (0.2H, broad s, C(6)H), 4.46-4.42 (0.2H, m, C(5)HOSi), 4.39-4.34 (0.8H, m, C(5)HOSi), 4.02-3.70 (2H, m, OC₂H₂CH₃), 3.88 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.68 (0.2H, t, J 5.0 Hz, C(2)HCO₂Et), 3.56 (0.2H, t, J 5.0 Hz, C(2)HCO₂Et), 2.21-2.12 (1H, m, C(3)H₃H₄ or C(4)H₃H₄), 2.04-1.89 (1H, m, C(3)H₃H₄ or C(4)H₃H₄), 1.83-1.78 (2H, m, C(3)H₂ or C(4)H₂), 1.07-1.03 (3H, m, OCH₂CH₃), 0.93 (7.2H, s, C(CH₃)₃), 0.93 (1.8H, s, C(CH₃)₃), 0.13 (2.4H, s, SiCH₃), 0.11 (2.4H, s, SiCH₃), 0.10 (0.6H, s, SiCH₃) and 0.09 (0.6H, s, SiCH₃); ¹³C NMR δC(100 MHz, CDCl₃) 174.2− (Isomer B C=O), 173.9− (Isomer A C=O), 148.6− (Isomer A), 148.6− (Isomer B), 136.3− (Isomer B), 135.6−(Isomer A), 133.8− (Isomer B), 133.6− (Isomer A), 130.8+ (Isomer A), 130.3+ (Isomer B), 118.3+ (Isomer B), 118.2+ (Isomer A), 110.8+, 109.4+ (Isomer A), 109.4+ (Isomer B), 67.2+ (Isomer A CHOH), 66.6+ (Isomer B CHOH), 60.5− (OCH₂CH₃), 55.8+ (OCH₃), 55.8+ (OCH₃), 44.3+ (Isomer B C2), 43.2+ (Isomer A C2), 30.2− (Isomer B), 29.1− (Isomer A), 25.9+ (Isomer A CCH₃), 25.9+ (Isomer B CCH₃), 24.0− (Isomer A), 24.0− (Isomer B), 18.3− (Isomer A CCH₃), 18.2− (Isomer B CCH₃), 14.0+ (OCH₂CH₃), -4.32+ (Isomer A SiCH₃), -4.36+ (Isomer B SiCH₃) and -4.57+ (SiCH₃); MS (+ESI) m/z 289 (M⁻BuMe₂SiOH+H⁺, 100 %) and 443 (M+Na⁺, 46); HRMS (+ESI) Found M+Na⁺, 443.2205; C₂₃H₃₆O₅NaSi requires M+Na⁺ 443.2230.
5.3.2. Synthesis of the Trimethoxy-Analogue

**Ethyl 3-(3’,4’,5’-trimethoxyphenyl)-3-oxopropanoate (216)**

NaH (60 % dispersion in mineral oil) (3.0 g, 75 mmol) was added portionwise over 3 mins to a stirred solution of 3,4,5-trimethoxyacetophenone 215 (10.5 g, 50 mmol) in diethyl carbonate (100 mL) at 0 °C under N₂, then the reaction was heated at 80 °C for 1 ½ hrs. On cooling, the reaction was quenched with saturated aqueous NH₄Cl (30 mL) and water (200 mL), then extracted with EtOAc (3 x 120 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60] β-ketoester 216 (13.8 g, 95 %) was isolated as a pale yellow solid.

\[ R_f \text{ [PE-EtOAc 50:50]} \ 0.43; \ Mp \ 84-88 ^\circ \text{C (from EtOAc); lit.,}^{249} 87-88 ^\circ \text{C (from EtOH);} \]

\[ ^1H \text{ NMR } \delta_H (400 MHz, CDCl}_3 \]: 7.20 (2H, s, C(2’)H and C(6’)H), 4.20 (2H, q, J 7.0 Hz, OCH₂CH₃), 3.95 (2H, s, C(2)H₂), 3.91 (3H, s, OCH₃), 3.90 (6H, s, OCH) and 1.25 (3H, t, J 7.0 Hz, OCH₂CH₃); \[ ^13C \text{ NMR } \delta_C (100 MHz, CDCl}_3 \]: 191.2− (C₃=O), 167.5− (CO₂Et), 153.1− (C(Ar)-O), 143.1− (C(Ar)-O), 133.1− (C¹'-C), 106.1+ (C²'-H), 61.5− (OCH₂CH₃), 61.0+ (OCH₃), 56.3+ (OCH₃), 46.1− (C₂) and 14.1+ (OCH₂CH₃);

Spectroscopic data is consistent with that reported by Lawrence *et al.*²⁵⁰
**Ethyl 2-(3',4',5'-trimethoxybenzoyl)-5-oxohexanoate (217)**

K$_2$CO$_3$ (4.1 g, 29.7 mmol) was added to a vigorously stirred solution of β-ketoester 216 (7.60 g, 27 mmol) in anhydrous MeCN (120 mL) at 0°C under N$_2$. After 10 mins, MVK (2.41 mL, 29.7 mmol) was added and the reaction allowed to warm to r.t.. After 1 ½ hrs, the reaction was quenched with saturated aqueous NH$_4$Cl (20 mL), then extracted with EtOAc (3 x 100 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na$_2$SO$_4$, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 90:10 to 50:50] the product 217 (9.30 g, 98 %) was isolated as a pale yellow oil.

**R$_f$ [PE-EtOAc 50:50] 0.53; IR $\nu_{\text{max}}$ (Thin film) 2979, 2840, 1731 (C=O), 1722 (C=O), 1681 (C=O), 1584, 1505, 1455, 1416, 1337, 1234, 1126 and 1002; $^1$H NMR $\delta_H$ (400 MHz, CDCl$_3$) 7.37 (2H, s, C(2')H and C(6')H), 4.43 (1H, dd, J 9.0 and 6.0 Hz, C(2)H), 4.19-4.13 (2H, m, OCH$_2$CH$_3$), 3.94 (6H, s, OCH$_3$), 3.92 (3H, s, OCH$_3$), 2.64-2.55 (2H, m, C(4)H$_2$), 2.28-2.15 (2H, m, C(3)H$_2$), 2.13 (3H, s, C(6)H$_3$) and 1.20 (3H, t, J 7.5 Hz, OCH$_2$CH$_3$); $^{13}$C NMR $\delta_C$ (100 MHz, CDCl$_3$) 208.0− (C5=O), 194.2− (ArC=O), 170.0− (CO$_2$Et), 153.1− (C(Ar)-O), 143.0− (C(Ar)-O), 130.8− (C1'), 106.2+ (C2' and C6'), 61.4− (OCH$_2$CH$_3$), 60.9+ (OCH$_3$), 56.3+ (OCH$_3$), 52.6+ (C2), 40.5− (C4), 30.0+ (C6), 23.0− (C3) and 14.0+ (OCH$_2$CH$_3$); MS (+ESI) m/z 353 (M+H$^+$ 100 %) and 375 (M+Na$^+$, 69); HRMS (+ESI) Found M+H$^+$, 353.1601; C$_{18}$H$_{25}$O$_7$ requires $M+H^+$ 353.1600.
Ethyl 2-(3',4',5'trimethoxyphenyl)-4-oxocyclohex-2-enecarboxylate (218)

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\text{OEt} & \quad \text{OEt} \\
\end{align*}
\]

\[ p\text{-TsOH, toluene} \quad \text{53 \%} \]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\text{OEt} & \quad \text{OEt} \\
\end{align*}
\]

\( p\text{-TsOH} (2.85 \text{ g}, 15.2 \text{ mmol}) \) in toluene (225 mL) was heated at reflux with azeotropic removal of water using Dean-Stark trap under Ar for 1 hr, then \( \beta \)-ketoester 217 (12.31 g, 34.9 mmol) was added and heated continued for a further 24 hrs. After cooling to r.t., the solvent was removed \textit{in vacuo} and column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30] afforded the enone product 218 (6.18 g, 53 \%) as a pale yellow solid.

**R\text{f}** [PE-EtOAc 50:50] 0.52; **Mp** 107-110 °C (from Et\(_2\)O); **IR** \( \nu_{\text{max}} \) (thin film) 2938, 2839 (C-H), 1728 (C=O), 1661 (C=O), 1597, 1576, 1518 (C=C), 1463, 1419, 1328, 1252 (C-O), 1151, 1022; **\(^1\)H NMR** \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 6.72 (2H, s, C(2')H), 6.45 (1H, s, C(3')H), 4.13 (2H, q, \( J \) 7.0 Hz, OCH\(_2\)CH\(_3\)), 3.93 (1H, t, \( J \) 4.5 Hz, C(1)H), 3.87 (9H, s, OCH\(_3\)), 2.69-2.61 (1H, m, C(5)H\(_A\)H\(_B\)), 2.51-2.36 (3H, m, C(5)H\(_A\)H\(_B\) and C(6)H\(_2\)) and 1.14 (3H, t, \( J \) 7.0 Hz, OCH\(_2\)CH\(_3\)); **\(^{13}\)C NMR** \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 198.5− (C4=O), 171.7− (CO\(_2\)Et), 155.3− (C1’), 153.3− (C3’), 139.9− (C4’), 133.2− (C1), 126.7+ (C6), 103.8+ (C2’), 61.5− (OCH\(_2\)CH\(_3\)), 60.9+ (C(4’)OCH\(_3\)), 56.2+ (C(3’)OCH\(_3\)), 43.7+ (C1), 34.0− (C5), 26.6− (C6) and 14.1+ (OCH\(_2\)CH\(_3\)); **MS** (+ESI) \( m/z \) 335 (M+H\(^+\), 100 \%); **HRMS** (+ESI) Found M+H\(^+\), 335.1495; \( C_{18}H_{22}O_6 \) requires \( M+H^+ \) 335.1495; **HPLC** \( t_R \) 14.7 (98 \%).
2-(3,4',5'-Trimethoxyphenyl)-4-oxocyclohex-2-ene carboxylic acid (219)

LiOH.H₂O (1.05 g, 25 mmol) was added to a stirred suspension of ester 218 (1.67 g, 5 mmol) in 1:1 EtOH/H₂O (25 mL) at 0 °C then the reaction was allowed to warm to r.t. After 45 mins, the reaction was diluted with H₂O (20 mL) and washed with Et₂O (3 x 20 mL). The aqueous fraction was cooled to 0 °C and acidified to pH 2 with 6M HCl, then extracted with Et₂O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo to afford the acid 219 (1.19 g, 78 %) as a brown oil without further purification.

Rᵣ [CH₂Cl₂-MeOH 90:10] 0.41; IR νₑₓ (thin film) 2938, 2839 (C-H), 1728 (C=O), 1661 (C=O), 1597, 1576, 1518 (C=C), 1463, 1419, 1328, 1252 (C=O), 1151, 1022; ¹H NMR δₓ (400 MHz, CDCl₃) 6.75 (2H, s, C(2')H), 6.50 (1H, s, C(3)H), 3.99 (1H, dd, J 4.5, 4.0 Hz, C(1)H), 3.87 (3H, s, C(4')OCH₃), 3.86 (6H, s, C(3')OCH₃), 2.71-2.63 (1H, m, C(5)HₐHₖ) and 2.54-2.40 (3H, m, C(5)HₐHₖ and C(6)H₂); ¹³C NMR δₓ (100 MHz, CDCl₃) 198.8− (C₄=O), 176.4− (CO₂H), 154.7− (C₁'), 153.4− (C₃'), 140.2− (C₄'), 132.6− (C₂), 126.7+ (C₃), 103.9+ (C₂'), 60.9+ (C₄')+OCH₃), 56.2+ (C(3')OCH₃), 42.8+ (C₁), 33.6− (C₅) and 26.3− (C₆).
Methyl (3',4',5'-trimethoxy-5-oxo-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)carbamate (223)

Diphenylphosphoryl azide (172 µL, 0.78 mmol) was added to a vigorously stirred solution of acid 219 (130 mg, 0.39 mmol), Na₂CO₃ (64 mg, 0.60 mmol) and NaN₃ (130 mg, 2 mmol) in anhydrous acetone (3 mL) at r.t. under Ar. After 1 hr, the reaction was heated at reflux for 1 hr. The solvent was removed in vacuo, MeOH (4 mL) added and the reaction stirred at r.t. for 16 hrs. The reaction was quenched with saturated aqueous NaHCO₃ (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 0:100] the methyl carbamate 223 (25 mg, 19 %) was obtained as an amorphous solid.

Rᶠ [PE-EtOAc 50:50] 0.15; IR νₘₐₓ(thin film) 3318 (NH), 2945, 2840, 1696 (C=O), 1664 (C=O), 1578, 1508, 1452, 1416, 1345, 1244 and 1127; ¹H NMR δ_H(400 MHz, CDCl₃) 6.79 (2H, s, C(2')H), 6.38 (1H, s, C(6)H), 5.14 (1H, broad s, C(2)H), 4.91 (1H, broad d, J 9.0 Hz, NH), 3.88 (3H, s, C(4')OCH₃), 3.86 (6H, s, C(3')OCH₃), 3.66 (3H, s, carbamate OCH₃), 2.60-2.48 (2H, m, C(4)H₂) and 2.36-2.19 (2H, m, C(3)H₂); ¹³C NMR δ_C(100 MHz, CDCl₃) 198.4− (C5=O), 157.1− (C1), 156.4− (CO₂Me), 153.4− (C3'), 140.2− (C4'), 131.0− (C1'), 126.4+ (C6), 104.2+ (C2'), 60.9+ (C(4')OCH₃), 56.2+ (C(3')OCH₃), 52.5+ (CO₂CH₃), 46.6+ (C2), 33.3− (C4) and 29.4− (C3); MS (+ESI) m/z 336 (M+H⁺, 100 %) and 358 (M+Na⁺, 9); HRMS (+ESI) Found M+H⁺ 336.1441; C₁₇H₂₁NO₆ requires M+H⁺ 336.1447.
Oxalyl chloride (175 µL, 2 mmol) and DMF (39 µL, 0.5 mmol) were added to the acid 219 (309 mg, 1 mmol) in CH₂Cl₂ (5 mL) under Ar at 0 °C and the reaction was allowed to warm to r.t. After 1 hr, the solvent was removed and the residue dissolved in acetone (5 mL), then the solution was added dropwise over 10 mins to a stirred solution of NaN₃ (130 mg, 2 mmol) in H₂O (5 mL) at 0 °C and the biphasic mixture stirred vigorously for a further 20 mins. The reaction was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. The orange/brown solid was treated with BF₃·OEt₂ (1 mL) under Ar and the reaction stirred at r.t. for 18 hrs. The mixture was quenched with 2M NaOH (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60] the fluoren-9-one product 224 (27 mg, 9 %) was isolated as an oil and the fluoren-3,9-dione product 225 (81 mg, 28 %) as a solid.

**Fluoren-9-one (224)**

Rᵣ[PE-EtOAc 50:50] 0.75; IR νₘₐₓ(thin film) 2940, 1704 (C=O), 1605, 1476, 1410, 1308, 1289, 1245, 1199, 1128 and 975; ¹H NMR δ(H(400 MHz, CDCl₃)) 7.49
(1H, d, J 8.0 Hz, C(8)H), 7.38 (1H, d, J 1.5 Hz, C(5)H), 7.21 (1H, dd, J 8.0 and 1.5 Hz, C(7)H), 6.80 (1H, s, C(4)H), 4.11 (3H, s, OCH$_3$), 3.98 (3H, s, OCH$_3$) and 3.86 (3H, s, OCH$_3$); $^{13}$C NMR $\delta$C(100 MHz, CDCl$_3$) 189.0− (C9=O), 159.3− (C3-O), 153.7− (C1-O), 144.6− (C4b), 142.7− (C2-O), 140.6− (C9a), 140.1− (C8a), 133.5− (C6-Cl), 128.6+ (C7), 124.7+ (C8), 120.0+ (C5), 118.4− (C4a), 62.2+ (OCH$_3$), 61.4+ (OCH$_3$) and 56.5+ (OCH$_3$); MS (+ESI) m/z 305 (M+H$^+$, 100 %); HRMS (+ESI) Found M+H$^+$, 305.0587; C$_{16}$H$_{14}$O$_4$Cl requires M+H$^+$ 305.0575.

Fluoren-3,9-dione (225)

R$_f$[PE-EtOAc 50:50] 0.25; Mp 152-156 °C (from EtOAc); IR $\nu_{max}$(thin film) 2942, 1715 (C=O), 1660 (C=O), 1586, 1480, 1335, 1255, 1137 and 1007; $^1$H NMR $\delta$H(400 MHz, CDCl$_3$) 7.26 (1H, s, C(5)H), 6.32 (1H, d, J 2.0 Hz, C(4)H), 4.06 (3H, s, OCH$_3$), 3.98 (3H, s, OCH$_3$), 3.90 (3H, s, OCH$_3$), 3.33 (1H, ddd, J 12.5, 5.0 and 2.0 Hz, C(9a)H), 2.66 (1H, ddd, J 17.5, 4.5 and 1.5 Hz, C(2)H$_A$H$_B$), 2.57 (1H, dddd, J 13.0, 5.0, 5.0 and 2.0 Hz, C(1)H$_A$H$_B$), 2.47 (1H, ddd, J 15.5, 13.0 and 4.0 Hz, C(2)H$_A$H$_B$) and 1.79 (1H, ddd, J 26.5, 13.5 and 4.5 Hz, C(1)H$_A$H$_B$); $^{13}$C NMR $\delta$C(100 MHz, CDCl$_3$) 198.9− (C3=O), 196.4− (C9=O), 160.1− (C(Ar)-O), 156.9− (C8a), 151.6− (C(Ar)-O), 145.2− (C(Ar)-O), 142.0− (C4a), 123.9− (C4b), 118.1+ (C4), 100.0+ (C5), 62.2+ (OCH$_3$), 61.5+ (OCH$_3$), 56.6+ (OCH$_3$), 48.9+ (C9a), 37.5− (C2) and 23.2− (C1); MS (+ESI) m/z 289 (M+H$^+$, 100 %) and 311 (M+Na$^+$, 8); HRMS (+ESI) Found M+H$^+$, 289.1076; C$_{16}$H$_{17}$O$_5$ requires M+H$^+$ 289.1076.
Oxalyl chloride (175 µL, 2 mmol) and DMF (39 µL, 0.5 mmol) were added to a stirred solution of acid 219 (309 mg, 1 mmol) in CH₂Cl₂ (5 mL) under Ar at −10 °C. After 1 hr, the solution was added dropwise over 10 mins to a stirred of biphasic mixture NaN₃ (130 mg, 2 mmol) in acetone/H₂O (1:1, 8 mL) at 0 °C. After 20 mins, the reaction was diluted with H₂O (10 mL) and extracted with CH₂Cl₂ (2 x 15 mL). The combined organic fractions were washed with brine (10 mL), filtered and the solvent removed in vacuo. The orange/brown solid was treated with MeOH (5 mL) under Ar and the reaction stirred at r.t. for 24 hrs. The mixture was quenched with saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 0:100] the fluoren-3,9-dione product 225 (164 mg, 57 %) was isolated as a solid and cyclohexenone 220 (60 mg, 23 %) as an amorphous solid.

¹H NMR δH(400 MHz, CDCl₃) 6.75 (2H, s, C(2')H and C(6')H), 6.39 (1H, t, J 1.5 Hz, C(2)H), 3.88 (9H, s, OCH₃), 2.75 (2H, ddd, J 6.0, 6.0 and 1.5 Hz, C(4)H₂), 2.49 (2H, dd, J 7.0 and 6.0 Hz, C(6)H₂) and 2.19-2.14 (2H, m, C(5)H₂); ¹³C NMR δC(100 MHz, CDCl₃) 199.8− (C3), 159.6− (C1), 153.3− (C3’ and C5’), 140.0− (C4’), 134.4− (C1’), 125.1+ (C2), 103.8+ (C2’ and C6’), 61.0+ (C(3’)OCH₃ and C(5’)OCH₃), 56.3+ (C(4)OCH₃), 37.2− (C6), 28.3− (C4) and 22.8− (C5).
Ethyl 4-oxo-2-(3',4',5'-trimethoxyphenyl)cyclohexanecarboxylate (226) and ethyl 4-hydroxy-2-(3',4',5'-trimethoxyphenyl)cyclohexanecarboxylate (230)

10 % Palladium on activated carbon (50 mg, 0.05 mmol) was added to a vigorously stirred solution of ester 218 (334 mg, 1 mmol) in EtOAc (5 mL). The suspension was degassed then placed under an atmosphere of H$_2$ at r.t. for 4 hrs. The solvent was removed in vacuo and after column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60] the ketone 226 (164 mg, 49 %) was isolated as an oil and the alcohol 230 (161 mg, 48 %) as a white solid.

**Ketone (226)**

R$_f$ [PE-EtOAc 50:50] 0.51; IR $\nu_{\text{max}}$(thin film) 2939, 2839 (C-H), 1714 (ester C=O), 1590, 1510, 1462, 1423, 1331, 1251, 1176 and 1127; $^1$H NMR $\delta$H(400 MHz, CDCl$_3$) 6.33 (2H, s, C(2')H), 4.00-3.95 (2H, m, OCH$_2$CH$_3$), 3.77 (9H, s, OCH$_3$), 3.40 (1H, dt, J 10.5 and 5.0, C(2)H), 3.21 (1H, ddd, J 14.5, 10.5 and 1.0 Hz, C(3)H$_A$H$_B$), 3.04 (1H, dt, J 10.0 and 5.0 Hz, C(1)H), 2.74 (1H, dddd, J 15.0, 10.5, 6.0 and 1.0 Hz, C(5)H$_A$H$_B$), 2.55 (1H, ddd, J 14.5, 5.0 and 1.0 Hz, C(3)H$_A$H$_B$), 2.34 (1H, dtd, J 15.0, 5.5 and 1.5 Hz, C(5)H$_A$H$_B$), 2.20 (1H, dtd, J 14.0, 11.5 and 6.0 Hz, C(6)H$_A$H$_B$), 2.08-2.02 (1H, m, C(6)H$_A$H$_B$) and 1.07 (3H, t, J 7.0 Hz, OCH$_2$CH$_3$); $^{13}$C NMR $\delta$C(100 MHz, CDCl$_3$) 210.4− (C=O), 173.1− (CO$_2$Et), 153.1− (C(Ar)-O), 137.2− (C(Ar)-O), 136.5− (C1'-C), 104.8+ (C2'-H), 60.8+ (OCH$_3$), 60.3− (OCH$_2$CH$_3$), 56.2+ (OCH$_3$), 45.2+ (C1 or C2), 44.8+ (C1 or C2), 43.7− (C3), 38.1−
(C5), 26.3– (C6) and 14.0+ (OCH₂CH₃); MS (+ESI) m/z 337 (M+H⁺, 100 %) and 359 (M+Na⁺, 17); HRMS (+ESI) Found M+H⁺, 337.1642; C₁₈H₂₄O₆ requires M+H⁺ 337.1651.

**Alcohol (230)**

Rf[PE-EtOAc 50:50] 0.23; Mp 112-115 °C (from EtOAc); IR ν max (thin film) 3422 (OH), 2937 (C-H), 1722 (ester C=O), 1590, 1509, 1456, 1422, 1329, 1234, 1184 and 1125; ¹H NMR δH(400 MHz, CDCl₃) 6.43 (2H, s, C(2’)H), 3.88 (2H, q, J 7.0 Hz, OCH₂CH₃), 3.80 (6H, s, C(3’)OCH₃), 3.79 (3H, s, C(4’)OCH₃), 3.74-3.69 (1H, m, C(4)OH), 2.83-2.81 (2H, m, C(1)H and C(2)H), 2.39-2.33 (1H, m, C(3)HₐHₐ), 2.08-2.02 (2H, m, C(3)HₐHₐ and C(5)HₐHₐ), 1.90-1.71 (4H, m, C(5)HₐHₐ, C(6)H₂ and OH) and 0.99 (3H, t, J 7.0 Hz, OCH₂CH₃); ¹³C NMR δC(100 MHz, CDCl₃) 173.6– (C₄=O), 152.9– (C(Ar)-O), 138.6– (C₁’), 136.7– (C(Ar)-O), 104.7+ (C₂’), 70.8+ (C₄), 60.8+ (OCH₃), 59.7– (OCH₂CH₃), 56.1+ (OCH₃), 44.8+ (C₁ or C₂), 43.6– (C₁ or C₂), 35.6– (C₃), 30.7– (C₆), 27.3– (C₅) and 14.0+ (OCH₂CH₃); MS (+ESI) m/z 339 (M+H⁺, 100 %) and 361 (M+Na⁺, 18); HRMS (+ESI) Found M+H⁺, 339.1808; C₁₈H₂₆O₆ requires M+H⁺ 339.1808.

**4-Oxo-2-(3,4,5-trimethoxyphenyl)cyclohexanecarboxylic acid (231)**

LiOH.H₂O (105 mg, 2.4 mmol) was added to a stirred solution of ester 226 (160 mg, 0.48 mmol) in EtOH/H₂O (1:1, 2.5 mL) and the reaction stirred for 5 hrs at r.t. The reaction was diluted with H₂O (10 mL) and washed with Et₂O (3 x 15 mL). The aqueous fraction was acidified with 6M HCl then extracted with CH₂Cl₂ (3 x 15 mL). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered
and the solvent removed in vacuo to afford the acid 231 (50 mg, 32 %) as white solid in a 59:41 mixture of diastereoisomers without further purification.

**Rf** [PE-EtOAc 50:50] 0.1; **1H NMR** δ_H(400 MHz, CDCl₃) 6.39 (1.2H, s, C(2')H), 6.36 (0.8H, s, C(2')H), 6.13 (1H, broad s, OH), 3.78 (3.6H, s, C(3')OCH₃), 3.77 (1.8H, s, C(4')OCH₃), 3.77 (1.4H, s, C(4')OCH₃), 3.73 (2.2H, s, C(3')OCH₃), 3.49 (0.4H, m, C(2)H), 3.24 (0.6H, ddd J 10.5, 10.5 and 5.0 Hz, C(2)H), 3.18-3.14 (0.4H, m, C(3)H₄H₆ or C(5)H₄H₆), 3.11-3.08 (0.4H, m, C(1)H), 2.97 (0.6H, ddd, J 10.5, 10.5 and 4.0 Hz, C(1)H) and 2.70-1.93 (5H, m, C(3)H₄H₆ or C(5)H₄H₆, C(3)H₂ or C(5)H₂ and C(6)H₂); **13C NMR** δ_C(100 MHz, CDCl₃) 210.8− (ketone C4=O isomer B), 208.9− (ketone C4=O isomer A), 178.2− (acid C=O isomer A), 177.7− (acid C=O isomer B), 153.3− (C3' isomer A), 153.1− (C3' isomer B), 137.4− (C1' or C4'), 137.1− (C1' or C4'), 137.1− (C1' or C4'), 136.2− (C1' or C4'), 105.0+ (C2' isomer B), 104.2+ (C2' isomer A), 60.8+ (OCH₃), 56.1+ (OCH₃ isomer A), 56.0+ (OCH₃ isomer B), 47.9+ (C1 isomer A), 47.6− (C3 or C5 isomer A), 46.1+ (C2 isomer A), 45.0+ (C1 isomer B), 44.4+ (C2 isomer B), 43.9− (C3 or C5 isomer B), 39.5− (C3 or C5 isomer A), 38.2− (C3 or C5 isomer B), 28.3− (C6 isomer A) and 25.7− (C6 isomer B);

7-Hydroxy-8,9-dimethoxy-1,3,4,4a,5,10b-hexahydrophenanthridine-2,6-dione (232)

Diphenylphosphoryl azide (204 µL, 0.95 mmol) was added to a stirred solution of ary1propionic acid 231 (0.95 mmol) and anhydrous Et₃N (264 µL, 1.9 mmol) in anhydrous toluene (3 mL) under N₂ at r.t. then the reaction heated at 90 °C for 30 mins. After cooling to r.t., the solvent was removed in vacuo and the flask
cooled to 0 °C under N₂. BF₃·OEt₂ (2.5 mL) was added then the reaction was allowed to warm to r.t. and stirred for 16 hrs. The reaction was quenched to pH 10 with 2M NaOH and extracted with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc-MeOH gradient from 100:0:0 to 0:90:10] the product 232 (17 mg, 6 %) was isolated as an amorphous solid.

**IR** νₘₐₓ(thin film) 3282, 2937, 1715 (C=O), 1651, 1614, 1575, 1455, 1297, 1239 and 1129; **¹H NMR** δ (400 MHz, CDCl₃) 12.39 (0.25H, broad s, C(7)OH), 12.24 (0.75H, broad s, C(7)OH), 6.71 (1H, broad s, N(5)H), 6.23 (0.75H, s, C(10)H), 6.18 (0.25H, s, C(10)H), 4.06-4.04 (1H, m, C(4a)H), 3.89 (3H, s, OCH₃). 3.88 (3H, s, OCH₃), 3.19-3.14 (1H, m, C(10b)H), 2.72-2.57 (2H, m, C(1)HₐHₐ and C(3)HₐH₉B), 2.52-2.37 (2H, m, C(1)HₐH₉B and C(3)HₐH₉B), 2.34-2.24 (1H, m, C(4)HₐHₐ and C(3)HₐHₐB) and 2.15-2.06 (1H, m, C(4)HₐHₐB); **¹³C NMR** δ (100 MHz, CDCl₃) 207.7-, 206.8-, 171.3-, 157.6-, 157.4-, 156.4-, 137.5-, 136.3, 135.8-, 129.4+, 120.2+, 103.8-, 101.3+, 98.6+, 60.7+, 56.1+, 53.8+, 49.3+, 44.2+, 41.7-, 41.6+, 40.6+, 38.6+, 35.5-, 30.1- and 28.8-; **MS** (+ESI) m/z 292 (M+H⁺, 33 %) 324 (M+Na⁺, 100); **HRMS** (+ESI) Found M+H⁺, 292.1189; C₁₅H₁₇NO₅ requires M+H⁺ 292.1179).
was allowed to warm to r.t. and stirred for 4 hrs. The reaction was neutralised with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography (silica, PE-EtOAc gradient from 100:0 to 60:40 the ester product 229 (315 mg, 98 %) was isolated as a solid.

**Rf [PE-EtOAc 60:40] 0.59; Mp 75-80 °C (from CHCl₃); IR νmax (thin film) 2937, 1731 (C=O), 1581, 1509, 1458, 1414, 1339, 1243, 1152, 1127 and 1009; \(^1\)H NMR δ H (400 MHz, CDCl₃) 6.53 (2H, s, C(2')H), 6.14 (1H, td, J 4.0 and 1.0 Hz, C(6)H), 4.06-3.97 (2H, m, OCH₂CH₃), 3.83 (6H, s, C(3')OCH₃), 3.80 (3H, s, C(4')OCH₃), 3.65-3.62 (1H, m, C(2)H), 2.88-2.20 (2H, m, C(5)H₂), 2.03-1.98 (2H, m, C(3)H₂), 1.82-1.75 (1H, m, C(4)H₂H₃), 1.69-1.60 (1H, m, C(4)H₄H₅) and 1.07 (3H, t, J 7.0 Hz, OCH₂CH₃); \(^1\)C NMR δ C (100 MHz, CDCl₃) 174.6− (C=O), 153.0− (C3'), 137.6− (C1' or C4'), 137.3− (C1' or C4'), 134.9− (C1), 128.0+ (C6), 103.1+ (C2'), 60.8+ (C(4')OCH₃), 60.4− (OCH₂CH₃), 56.1+ (C(3')OCH₃), 43.9+ (C2), 27.1− (C3), 25.5− (C5), 19.4− (C4) and 14.1+ (OCH₂CH₃); MS (+ESI) m/z 321 (M+H⁺, 100 %); HRMS (+ESI) Found M+H⁺, 321.1684; C₁₈H₂₅O₅ requires M+H⁺ 321.1702.

**Ethyl 5-acetoxy-3',4',5'-trimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (233)**

![Molecular structure of 218](image1.png)

![Molecular structure of 229](image2.png)

![Molecular structure of 233](image3.png)
NaBH₄ (66 mg, 1.56 mmol) was added portionwise over 3 mins to a stirred solution of TFA (0.4 mL), AcOH (0.4 mL) and MeCN (0.4 mL) at 0 °C under Ar. Ketone 218 (113 mg, 0.3 mmol) in CH₂Cl₂ (2 mL) was added and then the reaction was allowed to warm to r.t. and stirred for 90 mins. The reaction was neutralised with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 60:40] the ester product 229 (69 mg, 72%) was isolated as a white solid and acetate 233 (18 mg, 16%) as an oil in a 0.55:0.45 mixture of diastereoisomers.

Rᵣ[PE-EtOAc 60:40] 0.38; IR νₘₐₓ(thin film) 2940, 1731 (C=O), 1582, 1508, 1455, 1415, 1367, 1344, 1240, 1158 and 1127; ¹H NMR δₕ(400 MHz, CDCl₃) 6.56 (1.1H, s, C(2')H), 6.55 (0.9H, s, C(2')H), 6.12 (0.55H, dd, J 4.0 and 1.5 Hz, C(6)H), 6.09 (0.45H, dd, J 4.0 and 1.5 Hz, C(6)H), 5.48-5.45 (0.55H, m, C(5)H), 5.44-5.40 (0.45H, m, C(5)H), 4.06-3.99 (2H, m, OCH₂CH₃), 3.84 (6H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.73-3.69 (0.55H, m, C(2)H), 3.63-3.60 (0.45H, m, C(2)H), 2.20-1.74 (7H, m, CH₃C=O, C(3)H₂ and C(4)H₂) 1.07 (1.35H, t, J 7.0 Hz, OCH₂CH₃) and 1.07 (1.65H, t, J 7.0 Hz, OCH₂CH₃); ¹³C NMR δ₁₃C(100 MHz, CDCl₃) 173.6− (CO₂Et isomer B), 173.3− (CO₂Et isomer A), 170.9− (CH₃C=O isomer B), 170.6− (CH₃C=O isomer A), 153.1− (C3'), 139.9− (C1 isomer A), 139.7− (C1 isomer B), 138.1− (C4'), 135.9− (C1’ Isomer A), 135.8− (C1’ isomer B), 125.5+ (C6 isomer B), 125.3+ (C6 isomer A), 103.5+ (C2’ isomer A), 103.4+ (C2’ isomer B), 68.1+ (C5 isomer B), 68.0+ (C5 isomer A), 60.9+ (C(4')OCH₃), 60.8− (OCH₂CH₃), 56.2+ (C(3’)OCH₃), 43.9+ (C2 isomer B), 43.6+ (C2 isomer A), 25.5− (C3 or C4 isomer A), 25.4− (C3 or C4 isomer B), 24.1− (C3 or C4 isomer A), 23.4− (C3 or C4isomer A), 21.4+ (CH₃C=O isomer B), 21.3+ (CH₃C=O isomer A) and 14.0+ (OCH₂CH₃); MS (+ESI) m/z 319 (M-CH₃CO₂H+H⁺, 100%) and 401 (M+Na⁺, 20); HRMS (+ESI) Found M+Na⁺, 401.1586; C₂₀H₂₆O₇Na requires M+Na⁺ 401.1576.
3',4',5'-Trimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylic acid (234)

A stirred solution of ester 229 (315 mg, 0.98 mmol) in 1M NaOH/EtOH (1:1 10 mL) was heated at reflux for 6 hrs. The solution was cooled to 0 °C, acidified to pH 2 with 6M HCl and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo to afford the acid 234 (226 mg, 79 %) as a white solid without further purification

Mp 143-147 °C (from CHCl₃); IR νmax(thin film) 3161 (OH), 2937, 1073 (C=O), 1582, 1509, 1451, 1414, 1346, 1124 and 1004; ¹H NMR δH(400 MHz, CDCl₃) 6.55 (2H, s, C(2')H), 6.20 (1H, dt, J 4.0 and 1.0 Hz, C(6)H), 3.84 (6H, s, C(3')OCH₃), 3.83 (3H, s, C(4')OCH₃), 3.68 (1H, t, J 4.5 Hz, C(2)H), 2.33-2.18 (2H, m, C(5)H₂), 2.15-2.09 (1H, m, C(3)HAH₅B), 2.06-1.97 (1H, m, C(3)HAH₅B) and 1.83-1.65 (2H, m, C(4)H₂); ¹³C NMR δC(100 MHz, CDCl₃) 178.8− (CO₂H), 153.1− (C3'), 137.5− (C1'), 137.1− (C4'), 134.1− (C1), 128.6+ (C6), 103.0+ (C2'), 60.8+ (OCH₃), 56.1+ (OCH₃), 42.9+ (C2), 27.0− (C5), 25.5− (C3) and 19.1− (C4); MS (+ESI) m/z 293 (M+H+, 100 %) and 315 (M+Na+, 20); HRMS (+ESI) Found M+Na⁺, 315.1196; C₁₆H₂₀O₅Na requires M+Na⁺ 315.1208.
7-Hydroxy-8,9-dimethoxy-3,4,4a,5-tetrahydrophenanthridin-6(2H)-one (236)

Diphenylphosphoryl azide (81 μL, 0.37 mmol) and Et$_3$N (51 μL, 0.37 mmol) were added to a stirred suspension of acid 234 (100 mg, 0.34 mmol) in anhydrous toluene (1 mL) at r.t. under Ar. The reaction was heated at 90 °C for 45 mins, then the solvent was removed in vacuo and the residue treated with BF$_3$·OEt$_2$ (0.3 mL) and heated at 50 °C under Ar. After 16 hrs, the reaction mixture was quenched with 2M NaOH (5 mL), diluted with EtOAc (2 mL) and heated at 50 °C for 4 hrs. After cooling, the layers were separated and the aqueous fraction further extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na$_2$SO$_4$, filtered and the solvent removed in vacuo. After column chromatography [silica, EtOAc-PE gradient from 0:100 to 50:50] the lactam 236 (43 mg, 46 %) was isolated as a white solid.

$R_f$ [EtOAc-PE 4:6] 0.26; $M_p$ 202-205 °C (from EtOAc); $\text{IR} \nu_{\text{max}}$(thin film) 3417, 2935, 1651 (C=O), 1568, 1455, 1376, 1336, 1287, 1255 and 1122; $^1$H NMR $\delta_H$(400 MHz, CDCl$_3$) 12.67 (1H, s, C(7)OH), 6.73 (1H, s, N(5)H), 6.51 (1H, s, C(10)H), 6.20 (1H, ddd, $J$ 5.0, 2.5 and 2.5 Hz, C(1)H), 4.30-4.27 (1H, m, C(4a)H), 3.90 (3H, s, C(9)OCH$_3$), 3.88 (3H, s, C(8)OCH$_3$), 2.40-2.21 (2H, m, C(2)H$_2$), 2.16-2.11 (1H, m, C(4)H$_3$H$_B$), 1.90-1.87 (1H, m, C(3)H$_3$H$_B$ and 1.68-1.59 (2H, m, C(3)H$_3$H$_B$ and C(4)H$_3$H$_B$); $^{13}$C NMR $\delta_C$(100 MHz, CDCl$_3$) 169.7− (C6=O), 157.2− (C9), 155.5− (C7-OH), 136.3− (C8), 133.7− (C10b), 130.4− (C10a), 125.9+ (C1), 104.3− (C6a), 97.4+ (C10), 60.7+ (C(8)OCH$_3$), 56.0+ (C(9)OCH$_3$), 50.7+ (C4a), 29.6− (C4), 25.9− (C2) and 20.0− (C3); MS (+ESI) $m/\ell$ 276 (M+H$^+$, 100 %) and 298 (M+Na$^+$, 13); HRMS (+ESI) Found M+Na$^+$, 298.1054; C$_{15}$H$_{27}$NO$_4$Na requires M+Na$^+$ 298.1055; HPLC $t_R$ 13.0 (97 %).
5.3.3. Successful Synthesis of the Dimethoxy Analogue

Ethyl 3’,4’-dimethoxy-2,3,4,5-tetrahydro-[1,1’-biphenyl]-2-carboxylate (237)

NaBH₄ (197 mg, 5.2 mmol) was added portionwise over 3 mins to a stirred solution of TFA (1.2mL), AcOH (1.2 mL) and MeCN (1.2 mL) at 0 °C under Ar. Ketone 206 (304 mg, 1 mmol) in CH₂Cl₂ (6 mL) was added and then the reaction was allowed to warm to r.t. and stirred for 4 hrs. The reaction was neutralised with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 80:20] the ester product 237 (241 mg, 83 %) was isolated as a colourless oil.

**Rf** [PE-EtOAc 60:40] 0.57; **IR ν** (thin film) 2935, 1731 (C=O), 1603, 1582, 1517, 1463, 1252, 1169, 1149, 1028 and 803; **¹H NMR δ** (400 MHz, CDCl₃) 6.87 (1H, d, J 2.0 Hz, C(2’)H), 6.84 (1H, dd, J 8.5 and 2.0 Hz, C(6’)H), 6.77 (1H, d, J 8.5 Hz, C(5’)H), 6.12 (1H, td, J 4.0 and 1.0 Hz, C(6)H), 4.05-3.96 (2H, m, OCH₂CH₃), 3.86 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 3.66-3.63 (1H, m, C(2)H), 2.32-2.15 (2H, m, C(5)H₂), 2.07-1.94 (2H, m, C(3)H₂), 1.83-1.73 (1H, m, C(4)H₂), 1.69-1.60 (1H, m, C(4)H₃H₅) and 1.07 (3H, t, J 7.0 Hz, OCH₂CH₃); **¹³C NMR δ** (100 MHz, CDCl₃) 174.7− (C=O), 148.7− (C4’), 148.2− (C3’), 134.8− (C1), 134.5− (C1’), 127.0+ (C6), 117.8+ (C5’), 111.0+ (C6’), 109.3+ (C2’), 60.4− (OCH₂CH₃), 55.9+ (OCH₃), 55.8+ (OCH₃), 43.9+ (C2), 27.1− (C3), 25.5− (C5), 19.4− (C4) and 14.1+ (OCH₂CH₃); **MS (+ESI) m/z** 291 (M+H⁺, 93 %); **HRMS (+ESI) Found M+H⁺, 291.1593; C₁₇H₂₃O₄ requires M+H⁺ 291.1596.
Ester 237 (212 mg, 0.73 mmol) was stirred in refluxing 1M NaOH/EtOH (1:1, 8 mL) for 5 hrs. The solution was then cooled to 0 °C, acidified to pH 2 with 6M HCl and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo to afford the acid 238 (160 mg, 84 %) as a white solid without further purification.

**Mp** 102-106 °C (from CHCl₃); **IR ν**max(thin film) 2935, 1703 (C=O), 1516, 1463, 1251, 1168, 1145 and 1025; **¹H NMR δ**(400 MHz, CDCl₃) 6.89 (1H, d, J 2.0 Hz, C(5’)H), 6.86 (1H, dd, J 8.5 and 2.0 Hz, C(6’)H), 6.79 (1H, d, J 8.5 Hz, C(2’)H), 6.17 (1H, td, J 4.5 and 1.0 Hz, C(6)H), 3.86 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.69-3.67 (1H, m, C(2)H), 2.33-2.22 (2H, m, C(5)H₂), 2.15-2.01 (1H, m, C(3)H₄H₅), 2.04-1.95 (1H, m, C(3)H₆H₇) and 1.83-1.62 (2H, m, C(4)H₂); **¹³C NMR δ**(100 MHz, CDCl₃) 179.3− (C=O), 148.9− (C4’), 148.3− (C3’), 134.3− (C1), 133.6− (C1’), 127.6+ (C6), 117.6+ (C6’), 111.1+ (C5’), 109.2+ (C2’), 55.9+ (OCH₃), 55.8+ (OCH₃), 42.8+ (C2), 27.0− (C3), 25.5− (C5) and 19.4− (C4); **MS (+ESI) m/z** 263 (M+H⁺, 44 %), 285 (M+Na⁺, 100); **HRMS (+ESI) Found** M+H⁺, 263.1284; C₁₅H₁₉O₄ requires M+H⁺ 263.1283.
8,9-Dimethoxy-3,4,4a,5-tetrahydrophenanthridin-6(2H)-one (239) and
8,9-Dimethoxy-1,2,3,4-tetrahydrophenanthridin-6(5H)-one (240)

Diphenylphosphoryl azide (131 μL, 0.61 mmol) was added to a stirred mixture of acid 238 (160mg, 0.61 mmol) and Et₃N (84 μL, 0.61 mmol) in anhydrous toluene (5 mL) at r.t. under Ar. The reaction was heated at 90 °C for 1 hr, then the solvent was removed *in vacuo* and the residue was treated with BF₃·OEt₂ (1.5 mL) at r.t. under Ar. The mixture was heated at 50 °C for 16 hrs then was quenched with 2M NaOH (15 mL), diluted with EtOAc (10 mL) and heated at 50 °C for 3 hrs. After cooling to r.t., the layers were separated and the aqueous fraction further extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc-MeOH gradient from 100:0:0 to 0:100:0 to 0:90:10] the lactam 239 (53 mg, 34 %) was isolated as a white solid and lactam 240 (37 mg, 23 %) as a white solid.

**Lactam (239)**

Rf [EtOAc] 0.38; Mp 250-253 °C (from EtOAc); IR νmax(thin film) 3175 (NH), 2905, 2843, 1659 (C=O), 1591, 1555, 1508, 1469, 1456, 1425, 1381, 1277 and 1210; ¹H NMR  δH(400 MHz, d₆-DMSO) 7.85 (1H, s, N(5)H), 7.37 (1H, s, C(7)H), 7.08 (1H, s, C(10)H), 6.30-6.28 (1H, m, C(1)H), 4.24-4.23 (1H, m, C(4a)H), 3.86 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 2.33-2.26 (1H, m, C(2)H₃), 2.22-2.18 (1H, m, C(2)H₃), 2.13-2.11 (1H, m, C(2)H₃), 1.82-1.76 (1H, m, C(3)H₃), and 1.60-1.46 (2H, m, C(3)H₃ and C(4)H₃); ¹³C NMR  δC(100 MHz, d₆-
DMSO) 163.7− (C6=O), 152.0− (C9), 148.5− (C8), 130.7− (C10 a or C10 b), 130.6− (C10a or C10b), 123.8+ (C1), 119.9− (C6a), 109.1+ (C7), 105.5+ (C10), 55.7+ (C(9)OCH3), 55.4+ (C(8)OCH3), 50.3+ (C4a), 29.2− (C4), 25.2− (C2) and 19.8− (C3); MS (+ESI) m/z 260 (M+H+, 100 %) and 282 (M+Na+, 33); HRMS (+ESI) Found M+H+, 260.1305; C13H18NO3 requires M+H+ 260.1281; HPLC tR 11.4 (98 %).

**Lactam (240)**

Rf [EtOAc] 0.25; Mp sublimes above 255 °C then recrystallises and melts 297-300 °C but with accompanying decomposition (from EtOAc); IR vmax(thin film) 3735 (NH), 2918, 1637 (C=O), 1609, 1508, 1266, 1206 and 1021; 1H NMR δH (500 MHz, d6-DMSO) 10.89 (1H, s, N(5)H), 7.58 (1H, s, C(10)H), 6.98 (1H, s, C(7)H), 3.91 (3H, s, C(9)OCH3), 3.85 (3H, s, C(8)OCH3), 2.61 (2H, t, J 5.5H, C(1)H2), 2.52-2.49 (2H, m, C(4)H2) and 1.79-1.74 (4H, m, C(2)H2 and C(3)H2); 13C NMR δc (125 MHz, d6-DMSO) 160.8− (C6=O), 152.9− (C9), 147.6− (C8), 134.5− (C4a); 133.3− (C10a), 118.3− (C6a), 107.1+ (C10 and C10b), 102.9+ (C7), 55.6+ (C(9)OCH3), 55.4+ (C(8)OCH3), 26.4− (C1), 22.8+ (C4), 22.1− (C2 or C3) and 21.6− (C2 or C3); MS (+ESI) m/z 260 (M+H+, 100 %), 282 (M+Na+, 9) and 519 (2M+Na+, 56); HRMS (+ESI) Found M+H+, 260.1324; C15H18NO3 requires M+H+ 260.1281; HPLC tR 11.4 (100 %).
5.4. PRENYLATIONS

General procedure 3: Esterification of carboxylic acids

Following the procedure reported by Bourdron et al.,\textsuperscript{251} \( \text{H}_2\text{SO}_4 \) (1 drop/mmol) was added to a rapidly stirred solution of carboxylic acid in MeOH (10 mL/mmol) at r.t. The reaction was heated at reflux until the acid had been consumed by TLC. The solvent was then removed \textit{in vacuo}, the residue taken up in saturated aqueous NaHCO\textsubscript{3} and extracted with 3 x EtOAc. The combined organic fractions were washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and the solvent removed \textit{in vacuo} to afford the ester without need for further purification.

Methyl 3-(3',4',5'-trimethoxyphenyl)propanoate (262)

Following general procedure 3, acid 149 (1.20 g, 5 mmol) gave ester 262 (1.20 g, 94 %) as an oil.

\textbf{IR} \( \nu_{\text{max}} \) (thin film) 2947, 2839, 1737 (C=O), 1590, 1508, 1456, 1422, 1240, 1127 and 1009; \textbf{\textit{\textit{1}}}H NMR \( \delta_{\text{H}} \) (400 MHz, CDCl\textsubscript{3}) 6.41 (2H, s, C(Ar)-H), 3.83 (6H, s, OCH\textsubscript{3}), 3.81 (3H, s, OCH\textsubscript{3}), 3.67 (3H, s, OCH\textsubscript{3}), 2.89 (2H, t, \( J \) 8.0 Hz, C(3)H\textsubscript{2}) and 2.62 (2H, t, \( J \) 8.0 Hz, C(2)H\textsubscript{2}); \textbf{\textit{\textit{13}}}C NMR \( \delta_{\text{C}} \) (100 MHz, CDCl\textsubscript{3}) 173.2− (C1=O), 153.2− (C(Ar)-O), 136.3− (C(Ar)-O), 105.3+ (C2' and C6'), 60.8+ (ArOCH\textsubscript{3}), 56.0+ (ArOCH\textsubscript{3}), 51.6+ (CO\textsubscript{2}CH\textsubscript{3}), 35.8− (C3) and 31.3− (C2).

Spectroscopic data is consistent with reported by Kumar et al.\textsuperscript{252}
(E)-Methyl 3-(3',4',5'-trimethoxyphenyl)acrylate (253)

Following general procedure 3, the acid (1.19 g, 5 mmol) gave ester 253 (1.18 g, 94 %) as a white solid.

**Rf** [PE-EtOAc 80:20] 0.38; **1H NMR** δH (400 MHz, CDCl3) 7.60 (1H, d, J 16.0 Hz, C(3)H), 6.75 (2H, s, C(2')H and C(6')H), 6.34 (1H, d, J 16.0 Hz, C(2)H), 3.88 (6H, s, OCH3), 3.87 (3H, s, OCH3) and 3.80 (3H, s, OCH3); **13C NMR** δC (100 MHz, CDCl3) 167.4− (C1=O), 153.4− (Ar), 144.8+ (C3), 140.1− (Ar), 129.9− (Ar), 117.0+ (C2), 105.2+ (C2' and C6'), 60.9+ (OCH3), 56.1+ (OCH3) and 51.7+ (OCH3).

Spectroscopic data is consistent with that reported by Bourdron et al.251

(E)-Methyl 3-(3',4'-dimethoxyphenyl)acrylate (269)

Following general procedure 3, the acid (1.56 g, 7.5 mmol) gave ester 269 (1.50 g, 90 %) as a white solid.

**IR** νmax(thin film) 2950, 2838, 1712 (C=O), 1636, 1599, 1514, 1464, 1438, 1259, 1196, 1140 and 1024; **1H NMR** δH (400 MHz, CDCl3) 7.66 (1H, d, J 16.0 Hz, C(3)H), 7.13 (1H, dd, J 8.5 and 2.0 Hz, C(6')H), 7.08 (1H, d, J 2.0 Hz, C(2')H), 6.89 (1H, d, J 8.5 Hz, C(5')H), 6.34 (1H, d, J 16.0 Hz, C(2)H), 3.94 (6H, s, ArOCH3) and 3.82 (3H, s, CO2CH3); **13C NMR** δC (100 MHz, CDCl3) 167.6− (C=O), 151.2− (C(Ar)-O), 149.3− (C(Ar)-O), 144.8+ (C3), 127.4− (C1'), 122.6+ (C(Ar)-H), 115.6−
(C2), 111.1+ (C(Ar)-H), 109.8+ (C(Ar)-H), 56.0+ (ArOCH₃), 55.9+ (ArOCH₃) and 51.6+ (CO₂CH₃).

Spectroscopic data is consistent with that reported by El-Batta et al.²⁵³

**Methyl 3,4,5-trimethoxybenzoate (262)**

Following general procedure 3, the acid (1.06 g, 5 mmol) gave the ester 262 (1.05 g, 93 %) as a white solid.

$^1$H NMR $\delta_H$(400 MHz, CDCl₃) 7.30 (2H, s, C(Ar)-H) and 3.90 (12H, s, OCH₃); $^{13}$C NMR $\delta_C$(100 MHz, CDCl₃) 166.7− (C=O), 153.0− (C(Ar)-O), 142.3− (C(Ar)-O), 125.2− (C(Ar)-C), 107.0+ (C(Ar)-H), 60.9+ (OCH₃), 56.3+ (OCH₃) and 52.3+ (OCH₃);

Spectroscopic data is consistent with that reported by Elsinghorst et al.²⁵⁴

**Methyl 4-hydroxybenzoate (290)**

Following general procedure 3, acid 292 (966 mg, 7 mmol) gave ester 290 (1.04 g, 98 %) as a white solid.

IR $\nu_{\text{max}}$(thin film) 3253 (OH), 2946, 1687 (C=O), 1608, 1585, 1517, 1438, 1280, 1233, 1171 and 1101; $^1$H NMR $\delta_H$(400 MHz, CDCl₃) 7.96 (2H, d, $J$ 9.0 Hz, C(Ar)-H), 6.87 (2H, d, $J$ 9.0 Hz, C(Ar)-H), 6.03 (1H, s, OH) and 3.89 (3H, s, OCH₃);
**Methyl 3-(3',4'-dimethoxyphenyl)propanoate (267)**

![Methyl 3-(3',4'-dimethoxyphenyl)propanoate (267)](image)

10 % Palladium on carbon (50 mg, 0.05 mmol) was added to a vigorously stirred mixture of methyl 3,4-methylenedioxyccinnamate 253 (819 mg, 3.69 mmol) in EtOH (20 mL). After 3 cycles of purging the flask with N₂ then a vacuum, the flask was put under an atmosphere of H₂. After 2 hrs, the mixture was filtered through celite, washing thoroughly with EtOH, then the solvent removed in vacuo to afford the methyl propionate 267 (821 mg, 99 %) as a colourless oil without need for further purification.

**1H NMR** \( \delta_{\text{H}}(400 \text{ MHz, CDCl}_3) \) 6.84 (1H, d, \( J = 8.5 \text{ Hz, C(5')-H} \)), 6.77 (1H, dd, \( J = 8.5 \text{ and 2.0 Hz, C(6')-H} \)), 6.76 (1H, d, \( J = 2.0 \text{ Hz, C(2')-H} \)), 3.90 (3H, s, ArOCH\(_3\)), 3.88 (3H, s, ArOCH\(_3\)), 3.70 (3H, s, CO\(_2\)CH\(_3\)), 2.93 (2H, t, \( J = 7.5 \text{ Hz, C(3)H}_2 \)), 2.64 (2H, t, \( J = 7.5 \text{ Hz, C(2)H}_2 \)); **13C NMR** \( \delta_{\text{C}}(100 \text{ MHz, CDCl}_3) \) 173.4− (C=O), 149.0− (C(Ar)-O), 147.6− (C(Ar)-O), 133.2− (C1'), 120.1+ (C(Ar)-H), 111.8+ (C(Ar)-H), 111.4+ (C(Ar)-H), 56.0+ (ArOCH\(_3\)), 55.9+ (ArOCH\(_3\)), 51.6+ (CO\(_2\)CH\(_3\)), 36.0− (C3) and 30.6− (C2);

Spectroscopic data is consistent with that reported by Moreira et al.\(^\text{256}\)
2-Methyl-2-(3',4',5'-trimethoxyphenyl)-1,3-dioxolane (277)

Following a procedure reported by Kong et al., ethylene glycol (2 mL, 36 mmol) and p-TsOH·H₂O (190 mg, 1 mmol) in toluene (150 mL) were heated at reflux with azeotropic removal of water using Dean-Stark trap conditions for 1 hr. Acetophenone 261 (1.19 g, 6 mmol) was added in one portion and the reaction heated at reflux for a further 20 hrs. After cooling to r.t., the reaction was washed with saturated aqueous NaHCO₃ (2 x 50 mL) and brine (2 x 50 mL), then dried over anhydrous Na₂SO₄, filtered and the solvent removed in vacuo. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 75:25] the ketal product 277 (428 mg, 28 %) was isolated as a yellow oil in addition to acetophenone 261 (201 mg, 17 %).

¹H NMR δH(400 MHz, CDCl₃) 6.70 (2H, s, C(2')H and C(6')H), 4.04-4.00 (2H, m, C(4)H₄H₄ and C(5)H₄H₄), 3.86 (6H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.82-3.78 (2H, m, C(4)H₄H₄ and C(5)H₄H₄) and 1.64 (3H, s, C(2)CH₃); ¹³C NMR δC(100 MHz, CDCl₃) 153.1− (C(Ar)-O), 139.2− (C1'), 137.6− (C(Ar)-O), 108.8− (C2), 102.4+ (C2' and C6'), 64.5− (C4 and C5), 60.8+ (C(Ar)OCH₃), 56.2+ (C(Ar)OCH₃) and 27.7+ (C(2)CH₃).

General procedure 4: Formation of prenylated and chroman compounds

Bi(OTf)₃ (136 mg, 0.2 mmol) was added to a vigorously stirred mixture of substituted aryl (2 mmol) and isoprene (400 µL, 4 mmol) in anhydrous toluene (10 ml) in a thick-walled pressure tube at r.t. under Ar. The flask was sealed and the reaction heated at 40 °C for between 75 mins and 24 hrs then the reaction allowed to cool to r.t.. After column chromatography [silica, PE-Et₂O-EtOAc] the product was isolated.
1,2,3-Trimethoxy-4-(3-methylbut-2-en-1-yl)benzene (256) and 2,3,4-trimethoxy-1,5-bis(3-methylbut-2-en-1-yl)benzene (257)

Following general procedure 4, 1,2,3-trimethoxybenzene 255 (336 mg, 2 mmol) gave, after 75 mins at 40 °C and column chromatography [silica, PE-Et₂O gradient from 100 to 90:10], the mono-product 256 (292 mg, 62 %) as a colourless oil and the bis-product 257 (122 mg, 20 %) as a colourless oil.

Mono-product (256)

IR νₘₐₓ(thin film) 2936, 1599, 1495, 1464, 1416, 1294, 1256, 1096 (C=O) and 1017; ¹H NMR δ_H(400 MHz, CDCl₃) 6.86 (1H, d, J 8.5 Hz, C(6)H), 6.64 (1H, d, J 8.5 Hz, C(5)H), 5.28 (1H, triplet of septets, J 7.5 and 1.5 Hz, ArCH₂CHC), 3.91 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.31 (2H, d, J 7.5 Hz, ArCH₂CHC), 1.77 (3H, s, C(CH₃)₂) and 1.77 (3H, s, C(CH₃)₂); ¹³C NMR δ_C(100 MHz, CDCl₃) 152.0− (C1 or C3), 151.8− (C1 or C3), 142.4− (C2), 132.0− (ArCH₂CHC), 127.9− (C4), 123.5+ (C5 or C6), 123.3+ (ArCH₂CHC), 107.4+ (C5 or C6), 60.7+ (OCH₃), 56.0+ (OCH₃), 28.2− (ArCH₂CHC), 25.7+ (C(CH₃)₂) and 17.7 (C(CH₃)₂).

Spectroscopic data is consistent with that of Tarselli et al.²⁵⁷

Bis-product (257)

IR νₘₐₓ(thin film) 2965, 2931, 1479, 1460, 1411, 1325, 1235, 1092, 1065 and 1015; ¹H NMR δ_H(400 MHz, CDCl₃) 6.67 (1H, s, C(6)H), 5.25 (2H, triplet of septets, J 7.0 and 1.5 Hz, ArCH₂CHC), 3.91 (3H, s, OCH₃), 3.83 (6H, s, OCH₃), 3.27 (4H, d, J 7.0 Hz, ArCH₂CHC) and 1.74 (12H, s, C(CH₃)₂); ¹³C NMR δ_C(100 MHz, CDCl₃) 149.8− (C2 and C4), 146.3− (C3), 132.0− (ArCH₂CHC), 130.3− (C1 and
C5), 124.2+ (C6), 123.3+ (ArCH₂CHC), 60.8+ (OCH₃), 60.6+ (OCH₃), 28.4− (ArCH₂CHC), 25.7+ (CCH₃) and 17.8+ (CCH₃); MS (+ESI) m/z 305 (M+H⁺, 9 %); HRMS (+ESI) Found M+H⁺, 305.2103; C₁₉H₂₉O₃ requires M⁺H⁺ 305.2111.

1-Bromo-3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)benzene (259)

Following general procedure 4, aryl bromide 258 (494 mg, 2 mmol) gave, after 7 hrs at 40 °C and column chromatography [silica, PE-Et₂O gradient from 100:0 to 95:5], the product 259 (275 mg, 44 %) as a colourless oil and starting material (246 mg, 50 %).

Rf [PE-Et₂O 70:30] 0.63; IR νmax(thin film) 2935, 1590, 1482, 1452, 1430, 1396, 1313, 1270, 1237, 1195, 1156, 1113 (C-O), 1045 and 1019; ¹H NMR δH(400 MHz, CDCl₃) 6.87 (1H, s, C(Ar)H), 5.12 (1H, triplet of septets, J 7.0 and 1.5 Hz, ArCH₂CHC), 3.84, (6H, s, C(3)OCH₃ and C(4)OCH₃), 3.82 (3H, s, C(5)OCH₃), 3.42, (2H, d, J 7.0 Hz, ArCH₂CHC), 1.79 (3H, s, CH₃) and 1.68 (3H, s, CH₃); ¹³C NMR δC(100 MHz, CDCl₃) 152.6− (C₃-O), 152.1− (C₄-O or C₅), 142.0− (C₄-O or C₅-O), 131.8− (ArCH₂CHC), 128.1− (C₂), 122.1+ (ArCH₂CHC), 117.9− (C₁-Br), 112.0+ (C₆), 61.1+ (C(3)OCH₃ or C(4)OCH₃), 60.7+ (C(3)OCH₃ or C(4)OCH₃), 56.2+ (C(5)OCH₃), 29.3− (ArCH₂CHC), 25.7+ (CCH₃) and 18.1+ (CCH₃); MS (+ESI) m/z 315 (M+H⁺, 97 %), 317 (M+H⁺, 100) and 337 (M+Na⁺, 23); HRMS (+ESI) Found M+Na⁺, 337.0400; C₁₄H₁₉O₃BrNa requires M+Na⁺ 337.0415.
Methyl 3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)benzoate (263)

Following general procedure 4, ester 262 (452 mg, 2 mmol) gave, after 5 hrs at 40 °C and column chromatography [silica, PE-Et₂O gradient from 100:0 to 95:5], the product 263 (87 mg, 15 %) as a colourless oil in addition to ester 262 (384 mg, 85 %).

**IR** \( \nu_{\text{max}} \) (thin film) 2939, 1723 (C=O), 1594, 1491, 1455, 1431, 1401, 1337, 1222, 1154, 1115 and 1055; **¹H NMR** \( \delta_H \) (400 MHz, CDCl₃) 7.17 (1H, s, C(6)H), 5.12 (1H, triplet of septets, \( J \) 6.5 and 1.5 Hz, ArCH₂CHC), 3.91 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.62 (2H, d, \( J \) 6.5 Hz, ArCH₂CHC), 1.75 (3H, d, \( J \) 0.5 Hz, CCH₃) and 1.66 (3H, d, \( J \) 1.0 Hz, CCH₃); **¹³C NMR** \( \delta_C \) (100 MHz, CDCl₃) 168.0− (C=O), 152.3− (C(Ar)-O), 151.0− (C(Ar)-O), 145.7− (C(Ar)-O), 131.1− (ArCH₂CHC), 130.7− (C1), 125.2− (C2), 123.8+ (ArCH₂CHC), 109.7+ (C6), 61.0+ (OCH₃), 60.7+ (OCH₃), 56.1+ (OCH₃), 52.0+ (OCH₃), 25.9− (ArCH₂CHC), 25.7+ (CCH₃) and 17.9+ (CCH₃); **MS** (+ESI) \( m/z \) 295 (M+H⁺, 29 %) and 317 (M+Na⁺, 12); **HRMS** (+ESI) Found M+H⁺, 295.1551; \( \text{C}_{16}\text{H}_{23}\text{O}_5 \) requires \( M+H^+ \) 295.1545.
Methyl 3-(3',4',5'-trimethoxy-2'- (3-methylbut-2-en-1-yl)phenyl)propanoate (265) and methyl 3-(3',4',5'-trimethoxy-2',6'-bis(3-methylbut-2-en-1-yl)phenyl)propanoate (266)

Following general procedure 4, propionic ester 264 (508 mg, 2 mmol) gave, after 90 mins at 40 °C and column chromatography [silica, PE-Et₂O gradient from 100:0 to 80:20], the mono-product 265 (376 mg, 58 %) as a colourless oil and the bis-product 266 (233 mg, 30 %) as a colourless oil.

Mono-product (265)

$R_f$ [PE-Et₂O 80:20] 0.27; $\text{IR} \nu_{\text{max}}$ (thin film) 2935, 1739 (C=O), 1599, 1578, 1494, 1453, 1406, 1338, 1283, 1239, 1196, 1121, 1073 and 1042; $^1\text{H NMR} \delta_H$(400 MHz, CDCl₃) 6.53 (1H, s, C(6')H), 5.08-5.04 (1H, m, ArCH₂CH₂C), 3.87 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 3.71 (3H, s, CO₂CH₃), 3.33 (2H, d, J 6.5 Hz, ArCH₂CH₂C), 2.93-2.89 (2H, m, C(3)H₂) 2.60-2.56 (2H, m, C(2)H₂), 1.79 (3H, s, CCH₃) and 1.71 (3H, s, CCH₃); $^{13}\text{C NMR} \delta_C$(100 MHz, CDCl₃) 173.4− (C1=O), 152.1− (C(Ar)-O), 151.5− (C(Ar)-O), 140.9− (C(Ar)-O), 134.2− (C1' or C2'), 131.1− (ArCH₂CH₂C), 126.2− (C1' or C2'), 123.8+ (ArCH₂CH₂C), 108.4+ (C6'), 60.9+ (ArOCH₃), 60.7+ (ArOCH₃), 56.0+ (ArOCH₃), 51.6+ (CO₂CH₃), 35.5− (C2), 28.3− (C3), 25.6+ (CCH₃), 25.2− (ArCH₂CH₂C) and 17.8+ (CCH₃); MS (+ESI)
m/z 345 (M+Na+, 24%); HRMS (+ESI) Found M+Na+, 345.1661; C_{18}H_{20}O_{5}Na requires M+Na+ 345.1672.

**Bis-product (266)**

Rf [PE-Et₂O 80:20] 0.51; IR ν_{max}(thin film) 2948, 2933, 1740 (C=O), 1463, 1416, 1334, 1195, 1170, 1096, 1048 and 982; \(^1^H\) NMR δ_{H}(400 MHz, CDCl₃) 5.10-5.06 (2H, m, ArCH₂CH), 3.91 (3H, s, OCH₃), 3.85 (6H, s, OCH₃), 3.72 (3H, s, CO₂CH₃), 3.36 (4H, d, J 6.5 Hz, ArCH₂CHC), 2.93-2.89 (2H, m, C(3)H₂), 2.50-2.46 (2H, m, C(2)H₂), 1.79 (6H, s, CCH₃) and 1.71 (6H, s, CCH₃); \(^1^C\) NMR δ_{C}(100 MHz, CDCl₃) 173.4− (C₁=O), 150.3− (C(Ar)-O), 144.8− (C(Ar)-O), 133.0− (C’₁), 131.1− (ArCH₂CHC), 129.5− (C₂’ and C₅’), 124.0+ (ArCH₂CHC), 60.8+ (OCH₃), 60.4+ (OCH₃), 51.5+ (CO₂CH₃), 34.9− (C₃), 25.7− (ArCH₂CHC), 25.6+ (CCH₃), 24.8− (C₂) and 17.8+ (CCH₃); MS (+ESI) m/z 391 (M+H+, 20%); HRMS (+ESI) Found M+H+, 391.2652; C_{23}H_{35}O₃ requires M+H⁺ 391.2479.

**3-(3’’,4’’,5’’-trimethoxy-2’-(3-methylbut-2-en-1-yl)phenyl)acrylate (254)**

Following general procedure 4, ester 253 (504 mg, 2 mmol) gave, after 4 hrs at 40 °C and column chromatography [silica, PE-Et₂O gradient from 100:0 to 90:10], the mono-product 254 (302 mg, 47%) as a colourless oil in addition to ester 253 (90 mg, 18%).

IR ν_{max}(thin film) 2937, 1719 (C=O), 1631, 1592, 1566, 1487, 1409, 1347, 1289, 1254, 1168, 1124; \(^1^H\) NMR δ_{H}(400 MHz, CDCl₃) 7.92 (1H, d, J 15.5 Hz, C(3)H), 6.87 (1H, s, C(6’’)-H), 6.26 (1H, d, J 15.5 Hz, C(2)H), 5.02 (1H, t, J 6.5 Hz, ArCH₂CHC), 3.89 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.79 (3H,
Methyl 3-(4',5'-dimethoxy-2'- (3-methylbut-2-en-1-yl)phenyl)propanoate (268)

Following general procedure 4, ester 267 (448 mg, 2 mmol) gave, after 6 hrs at 40 °C and column chromatography [silica, PE-Et$_2$O gradient from 100:0 to 90:10], the mono-product 268 (376 mg, 64 %) as a colourless oil.

**R$_f$** [PE-Et$_2$O 50:50] 0.32; **IR** $\nu_{\text{max}}$ (thin film) 2934, 2851, 1737 (C=O), 1516, 1458, 1361, 1271, 1209 and 1093; **$^1$H NMR** $\delta_H$ (400 MHz, CDCl$_3$) 6.69 (1H, s, C(3')H or C(6')H), 6.69 (1H, s, C(3')H or C(6')H), 5.21 (1H, triplet of septets, J 7.0 and 1.4 Hz, ArCH$_2$CHC), 3.85 (3H, s, OCH$_3$), 3.85 (3H, s, OCH$_3$), 3.69 (3H, s, CO$_2$CH$_3$), 3.29 (2H, d, J 7.0 Hz, ArCH$_2$CHC), 2.92-2.88 (2H, m, C(3)H$_2$), 2.59-2.55 (2H, m, C(2)H$_2$), 1.75 (3H, s, CCH$_3$) and 1.74 (3H, s, CCH$_3$); **$^{13}$C NMR** $\delta_C$ (100 MHz, CDCl$_3$) 173.4− (C=O), 147.5− (C(Ar)-O), 147.2− (C(Ar)-O), 132.1− (ArCH$_2$CHC), 131.7− (C2'), 130.4− (C1'), 123.4+ (ArCH$_2$CHC), 113.0+ (C3' or C6'), 112.7+ (C3' or C6'), 56.0+ (OCH$_3$), 55.9+ (OCH$_3$), 51.5+ (CO$_2$CH$_3$), 35.5− (C2), 31.3− (ArCH$_2$CHC), 27.8− (C3), 25.7+ (CCH$_3$) and 17.9+ (CCH$_3$); **MS** (+ESI) m/z 293 (M+H$^+$, 15 %) and 315 (M+Na$^+$, 27); **HRMS** (+ESI) Found M+H$^+$, 293.1723; C$_{17}$H$_{25}$O$_4$ requires M+H$^+$ 293.1752.
(E)-Methyl 3-(4,5-dimethoxy-2-(3-methylbut-2-en-1-yl)phenyl)acrylate (KJ7/23/P) (270)

Following general procedure 4, ester 269 (446 mg, 2 mmol) gave, after 6 hrs at 40 °C and column chromatography [silica, PE-Et₂O gradient from 100:0 to 90:10], the mono-product 270 (100 mg, 17 %) as a colourless oil.

**IR** ν max (thin film) 2934, 1715 (C=O), 1602, 1514, 1458, 1268, 1167 and 1102; **¹H NMR** δ_H (400 MHz, CDCl₃) 7.95 (1H, d, J 16.0 Hz, C(3)H), 7.05 (1H, s, C(3')H or C(6')H), 6.68 (1H, s, C(3')H or C(6')H), 6.24 (1H, d, J 16.0 Hz, C(2)H), 5.16 (1H, triplet of septets, J 7.0 and 1.5 Hz, ArCH₂CHC), 3.87 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.78 (3H, s, CO₂CH₃), 3.40 (2H, d, J 7.0 Hz, ArCH₂CHC), 1.76 (3H, s, CCH₃) and 1.71 (3H, s, CCH₃); **¹³C NMR** δ_C (100 MHz, CDCl₃) 167.7− (C1=O), 151.0− (C(Ar)-O), 147.6− (C(Ar)-O), 142.1+ (C3), 135.5− (C2'), 132.6− (ArCH₂CHC), 125.0− (C1'), 122.9+ (ArCH₂CHC), 116.3+ (C2), 112.6+ (C3' or C6'), 109.0+ (C3' or C6'), 56.0+ (OCH₃), 55.9+ (OCH₃), 51.5+ (CO₂CH₃), 31.8− (ArCH₂CHC), 25.7+ (CCH₃) and 17.9+ (CCH₃); **MS** (+ESI) m/z 313 (M+Na⁺, 9 %); **HRMS** (+ESI) Found M+Na⁺, 313.142; C₁₇H₂₂O₄Na requires M+Na⁺ 313.1410.

5,6,7-Trimethoxy-2,2-dimethylchroman (280) and 3,4,5-trimethoxy-4-(3-methylbut-2-en-1-yl)cyclohexa-2,5-dienone (281)
Following general procedure 4, acid 279 (368 mg, 2 mmol) gave, after 18 hrs at 40 °C and column chromatography [silica, PE-Et₂O gradient from 100:0 to 85.15 then PE-EtOAc gradient from 50:50 to 30:70], the chroman product 280 (279 mg, 55 %) as an oil and ketone product 281 (132 mg, 26 %) as a white solid.

**Chroman (280)**

Rf [PE-Et₂O 80:20] 0.52; IR νₘₐₓ(thin film) 2973, 2937, 1611, 1489, 1460, 1413, 1324, 1158, 1311, 1098, 1045 and 1013; ¹H NMR δH(400 MHz, CDCl₃) 6.15 (1H, s, C(8)H), 3.87 (3H, s, C(6)OCH₃), 3.79 (3H, s, C(5)OCH₃), 3.78 (3H, s, C(7)OCH₃), 2.63 (2H, t, J 7.0 Hz, C(4)H₂), 1.73 (2H, t, J 7.0 Hz, C(3)H₂), 1.30 (3H, s, C(2)CH₃) and 1.28 (3H, s, C(2)CH₃); ¹³C NMR δC(100 MHz, CDCl₃) 152.4− (C7), 151.4− (C5), 150.0− (C8a), 135.4− (C6), 106.7− (C4a), 96.6+ (C8), 74.0− (C2), 61.0+ (C(5)OCH₃), 60.5+ (C(6)OCH₃), 55.8+ (C(7)OCH₃), 32.4− (C3), 26.7+ (CCH₃), 26.7+ (C(2)(CH₃)₂) and 17.0− (C4).

Spectroscopic data was consistent with that reported by Nishikata et.al.²⁵⁸

**Ketone (281)**

Rf [PE-EtOAc 40:60] 0.50; Mp 106-109 °C (from CH₂Cl₂); IR νₘₐₓ(thin film) 2934, 2852, 1659 (C=O), 1625, 1597, 1459, 1374, 1240, 1215, 1163, 1078 and 888; ¹H NMR δH(400 MHz, CDCl₃) 5.56 (2H, s, C(2)H and C(5)H), 4.66 (1H, triplet of septets, J 7.5 and 1.5 Hz, CH₂CHCMe₂), 3.73 (6H, s, C(3)OCH₃), 3.08 (3H, s, C(4)OCH₃), 2.67 (2H, d, J 7.5 Hz, CH₂CHCMe₂), 1.56 (3H, s, CCH₃) and 1.52 (3H, s, CCH₃); ¹³C NMR δC(100 MHz, CDCl₃) 187.3− (C1=O), 169.4− (C3), 136.3− (C4), 115.7+ (CH₂CHCMe₂), 104.3+ (C2), 79.4− (CH₂CHCMe₂), 56.0+ (C(3)OCH₃), 52.5 (C(4)OCH₃), 35.6− (CH₂CHCMe₂), 25.7+ (CCH₃) and 17.6+ (CCH₃); MS (+ESI) m/z 253 (M+H⁺); HRMS (+ESI) Found M+H⁺, 253.1427; C₁₄H₂₁O₄ requires M+H⁺ 253.1434.
1-(2,2-Dimethylchroman-6-yl)ethanone (285)

Following general procedure 4, acid 284 (272 mg, 2 mmol) gave, after 18 hrs at 40 °C and column chromatography [silica, PE-Et₂O-EtOAc gradient from 100:0:0 to 85:15:0 then 50:0:50], the product 285 (235 mg, 58 %) as a white solid in addition to phenol 284 (62 mg, 23 %).

Rf [PE-Et₂O 70:30] 0.63; Mp 89-93 °C (from CH₂Cl₂); IR νmax(thin film) 2976, 1670 (C=O), 1537, 1419, 1358, 1289, 1265, 1156, 1117; ¹H NMR δH(400 MHz, CDCl₃) 7.75 (1H, d, J 2.5 Hz, C(5)H), 7.73 (1H, dd, J 8.5 and 2.5 Hz, C(7)H), 6.81 (1H, d, J 8.5 Hz, C(8)H), 2.83 (2H, t, J 6.5 Hz, C(4)H₂), 2.54 (3H, s, CH₃C=O), 1.84 (2H, t, J 6.5 Hz, C(3)H₂) and 1.37 (6H, s, C(CH₃)₂); ¹³C NMR δC(100 MHz, CDCl₃) 196.9− (C=O), 158.6− (C₈a), 130.5+ (C₅), 129.4− (C₆), 128.3+ (C₇), 120.7− (C₄a), 117.2+ (C₈), 75.5− (C₂), 32.5− (C₃), 26.9+ (C(CH₃)₂), 26.2+ (CH₃C=O) and 22.4− (C₄).

Spectroscopic data is consistent with that reported by Teng et al.¹⁹⁷
1-(5-Hydroxy-2,2-dimethylchroman-8-yl)ethanone (287), 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone (288), and 1-(2,2,8,8-tetramethyl-2,3,4,8,9,10-hexahydropyrano[2,3-f]chromen-6-yl)ethanone (289)

Following general procedure 4, acid 286 (304 mg, 2 mmol) gave, after 8 hrs at 40 °C and column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30], the chroman products 287 (46 mg, 10 %) as a white solid, 288 (105 mg, 24 %) as a white solid and 289 (77 mg, 13 %) as an oil.

**Chroman (287)**

**Mp** 165-170 °C (from EtOAc); **IR** \( \nu_{\text{max}} \) (thin film) 3172 (OH), 2974, 2931, 1638, 1583 (C=O), 1433, 1362, 1277, 1217, 1157, 1119 and 1051; **\(^1\)H NMR** \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.68 (1H, d, \( J \) 8.5 Hz, C(7)H), 7.20 (1H, broad s, OH), 6.47 (1H, d, \( J \) 8.5 Hz, C(6)H), 2.74 (2H, t, \( J \) 7.0 Hz, C(4)H\(_2\)), 2.64 (3H, s, CH\(_3\)C=O), 1.87 (2H, t, \( J \) 7.0 Hz, C(3)H\(_2\)) and 1.43 (6H, s, C(2)(CH\(_3\))\(_2\)); **\(^{13}\)C NMR** \( \delta_C \) (100 MHz, CDCl\(_3\)) 199.7− (C=O), 159.2− (C5), 156.4− (C8a), 129.9+ (C7), 120.3− (C8), 108.5− (C4a), 107.0+ (C6), 75.3− (C2), 32.2+ (CH\(_3\)C=O), 31.6− (C3), 26.9+ (C(CH\(_3\))\(_2\)) and 17.0− (C4).
Chroman (288)

**Mp** 115-118 °C (from EtOAc); lit.,259 116-117 °C; **IR** \(\nu_{\text{max}}\) (thin film) 2937, 2957, 1647, 1612, 1495, 1369, 1288, 1280, 1161, 1118, 1058 1020 and 885; **\(^1\)H NMR** \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 12.30 (1H, s, OH), 7.41 (1H, s, C(5)H), 6.28 (1H, s, C(8)H), 2.71 (2H, t, J 7.0 Hz, C(4)H\(_2\)), 2.70 (3H, s, CH\(_3\)C=O), 1.80 (2H, t, J 7.0Hz, C(3)H\(_2\)) and 1.33 (6H, s, C(2)(CH\(_3\))\(_2\)); **\(^{13}\)C NMR** \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 202.3− (C=O), 162.8− (C7), 161.4− (C8a), 132.2+ (C5), 113.9− (C6), 112.7− (C4a), 104.6+ (C8), 75.9− (C2), 32.7− (C3), 26.4+ (C(2)CH\(_3\)), 26.1+ (CH\(_3\)C=O) and 21.7− (C4).

Spectroscopic data was consistent with that reported by Alhuwalia et al.259

Chroman (289)

**IR** \(\nu_{\text{max}}\) (thin film) 2974, 2933, 1662, 1603, 1579, 1457, 1357, 1298, 1258, 1178, 1154, 1120 and 1096; **\(^1\)H NMR** \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 7.48 (1H, s, C(5)H), 2.70 (2H, t, J 7.0 Hz, C(4)H\(_2\)), 2.60 (2H, t, J 7.0 Hz, C(10)H\(_2\)), 2.56 (3H, s, CH\(_3\)C=O), 1.76 (2H, t, J 7.0 Hz, C(9)H\(_2\)), 1.76 (2H, t, J 7.0 Hz, C(3)H\(_2\)), 1.35 (6H, s, CH(8)(CH\(_3\))\(_2\)) and 1.32 (6H, s, C(2)(CH\(_3\))\(_2\)); **\(^{13}\)C NMR** \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 198.6− (C=O), 156.2− (C10b), 153.8− (C6a), 129.2+ (C5), 120.0− (C6), 111.9− (C4a), 109.4− (C10a), 75.3− (C2), 74.7− (C8), 32.8− (C3), 32.3+ (CH\(_3\)C=O), 31.8− (C9), 27.1+ (C(8)CH\(_3\)), 26.8+ (C(2)CH\(_3\)), 21.7− (C4) and 17.2+ (C10).

Spectroscopic data was consistent with that reported by Alhuwalia et al.259

Methyl 2,2-dimethylchroman-6-carboxylate (291)

![Diagram of reaction](image)

Following general procedure 4, phenol 290 (304 mg, 2 mmol) gave, after 5 hrs at 40 °C and column chromatography [silica, PE-Et\(_2\)O gradient from 100:0 to 85:15] afforded the chroman 291 (285 mg, 65 %) as a white solid in addition to phenol 290 (32 mg, 11 %).
2,2-Dimethylchroman-6-carboxylic acid (293)

Following general procedure 4, acid 292 (276 mg, 2 mmol) gave, after 24 hrs at 40 °C and column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60], the product 293 (14 mg, 3 %) as a white solid in addition to phenol 292 (254 mg, 92 %).

Spectroscopic data is consistent with that reported by Batista Jr. et al. 

Spectroscopic data is consistent with that reported by Fatope et al. 

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R<sub>f</sub> [PE-Et<sub>2</sub>O 70:30] 0.61; Mp 70-74 °C (from CH<sub>2</sub>Cl<sub>2</sub>); IR ν<sub>max</sub>(thin film) 2975, 2948 (C-H), 1716 (C=O), 1613, 1581, 1493, 1437, 1290, 1263 (C-O), 1155 and 1118; ^1^H NMR δ<sub>H</sub>(400 MHz, CDCl<sub>3</sub>) 7.78 (1H, d, J 2.0 Hz, C(5)H), 7.76 (1H, dd, J 8.5 and 2.0 Hz, C(7)H), 6.77 (1H, d, J 8.5 Hz, C(8)H), 3.86 (3H, s, OCH<sub>3</sub>), 2.80 (2H, t, J 7.0 Hz, C(4)H<sub>2</sub>), 1.82 (2H, t, J 7.0 Hz, C(3)H<sub>2</sub>) and 1.34 (6H, s, C(2)(CH<sub>3</sub>)<sub>2</sub>); ^13^C NMR δ<sub>C</sub>(100 MHz, CDCl<sub>3</sub>) 167.1− (C=O), 153.3− (C8a), 131.6+ (C5), 129.1+ (C7), 121.5− (C6), 120.6− (C4a), 117.2+ (C8), 75.3− (C2), 51.7+ (OCH<sub>3</sub>), 26.9+ (C(CH<sub>3</sub>)<sub>2</sub>) and 22.3− (C4);

IR ν<sub>max</sub>(thin film) 2975, 1681 (C=O), 1608, 1578, 1443, 1411, 1324, 1296, 1265, 1156 and 1120; ^1^H NMR δ<sub>H</sub>(400 MHz, CDCl<sub>3</sub>) 7.86 (1H, d, J 2.0 Hz, C(5)H), 7.84 (1H, dd, J 8.5 and 2.0 Hz, C(7)H), 6.82 (1H, d, J 8.5 Hz, C(8)H), 2.84 (2H, t, J 7.0 Hz, C(4)H<sub>2</sub>), 1.84 (2H, t, J 7.0 Hz, C(3)H<sub>2</sub>) and 1.36 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>); ^13^C NMR δ<sub>C</sub>(100 MHz, CDCl<sub>3</sub>) 172.1− (C=O), 159.1− (C8a), 132.4+ (C5), 129.9+ (C7), 120.8− (C4a or C7), 120.7− (C4a or C7), 117.4+ (C8), 75.6− (C2), 32.5− (C3), 26.9+ (C(CH<sub>3</sub>)<sub>2</sub>) and 22.3− (C4); MS (+ESI) m/z 207 (M+H<sup>+</sup>, 100 %) and 229 (M+Na<sup>+</sup>, 45); HRMS (+ESI) Found M+H<sup>+</sup>, 207.1033; C<sub>12</sub>H<sub>15</sub>O<sub>3</sub> requires M+H<sup>+</sup> 207.1021.

Spectroscopic data is consistent with that reported by Fatope et al. 

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3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenol (296) and 1-(6-hydroxy-2,3,4-trimethoxyphenyl)ethanone (297)

Following a procedure reported by Mohammadpoor-Baltork et al.,224 Bi(OTf)3 (136 mg, 0.2 mmol) then Ac2O (283 µL, 3 mmol) were added to a stirred suspension of phenol 279 (368 mg, 2 mmol) in anhydrous toluene (10 mL) at r.t. under Ar. After 5 mins, isoprene (400 µL, 4 mmol) was added to the solution, then the flask was sealed and heated at 40 °C for 4 hrs. The solvent was removed and, following a procedure reported by Bates et al.,225 the residue was taken up in MeOH (10 mL) and K2CO3 (552 mg, 4 mmol) was added. The reaction was stirred for a 50 mins at r.t. then quenched with saturated aqueous NH4Cl (30 mL) and extracted with CH2Cl2 (3 x 30 mL). The combined organic fractions were washed with brine (30 mL), dried over anhydrous Na2SO4, filtered and the solvent removed in vacuo. Column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30] afforded the mono-prenylated product 296 (223 mg, <44 %) as a clear oil and the acetophenone product 297 (39 mg, 9 %) as a clear oil.

Acetophenone product 297

1H NMR δH(400 MHz, CDCl3) 13.39 (1H, s, C(6)OH), 6.22 (1H, s, C(5)H), 3.97 (3H, s, C(2)OCH3), 3.87 (3H, s, C(3)OCH3), 3.76 (3H, s, C(4)OCH3) and 2.63 (3H, s, CCH3); 13C NMR δC(100 MHz, CDCl3) 203.3− (C=O), 161.9− (C6-OH), 160.1− (C3), 155.2− (C2), 134.8− (C4), 108.5− (C1), 96.1+ (C5), 61.0+ (C(2)OCH3 or C(4)OCH3), 60.9+ (C(2)OCH3 or C(4)OCH3), 56.0+ (C(3)OCH3) and 31.8+ (CH3C=O).

Spectroscopic data is consistent with that reported by Combes et al.261
3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenyl acetate (298) and 3,4,5-trimethoxy-2,6-bis(3-methylbut-2-en-1-yl)phenyl acetate (299)

Following the procedure reported by Mohammadpoor-Baltork et al.,224 Bi(OTf)$_3$ (136 mg, 0.2 mmol) then Ac$_2$O (283 µL, 3 mmol) were added to a stirred suspension of phenol (368 mg, 2 mmol) in anhydrous toluene (10 mL) at r.t. under Ar. After 5 mins, isoprene (400 µL, 4 mmol) was added to the solution then the flask was sealed and heated at 40 °C for 1 hr. After column chromatography [silica, PE-Et$_2$O gradient from 100:0 to 90:10] the mono-prenylated acetate 298 (414 mg, 70 %) was isolated as a clear oil and the bis-prenylated acetate 299 (108 mg, 15 %) as a clear oil.

**Mono-product (298)**

$R_f$ [PE-Et$_2$O 80:20] 0.37; **IR** $\nu_{\text{max}}$(thin film) 2937, 1767 (C=O), 1608, 1490, 1456, 1408, 1368, 1339, 1206, 1122, 1075 and 1042; **$^1$H NMR** $\delta_H$(400 MHz, CDCl$_3$) 6.38 (1H, s, C(6)H), 5.06 (1H, triplet of septets, $J$ 7.0 and 1.5 Hz, CH$_2$CHC), 3.85 (3H, s, C(3)OCH$_3$ or C(4)OCH$_3$), 3.84 (3H, s, C(3)OCH$_3$ or C(4)OCH$_3$), 3.80 (3H, s, C(5)OCH$_3$), 3.17 (2H, d, $J$ 7.0 Hz, CH$_2$CHC), 2.27 (3H, s, C=OCH$_3$), 1.73 (3H, s, CCH$_3$) and 1.66 (3H, d, $J$ 1.0 Hz, CCH$_3$); **$^{13}$C NMR** $\delta_C$(100 MHz, CDCl$_3$) 169.5– (C=O), 152.3– (C3), 151.7– (C4), 144.5– (C1), 140.5– (C5), 131.3 (C(CH$_3$)$_2$), 122.7+ (CH$_2$CHC), 120.1– (C2), 102.4+ (C6), 61.0+ (C(3)OCH$_3$ or C(4)OCH$_3$), 60.8+ (C(3)OCH$_3$ or C(4)OCH$_3$), 56.0+ (C(5)OCH$_3$), 25.6+ (CCH$_3$), 23.5– (CH$_2$CHC), 20.8+ (C=OCH$_3$) and 17.7 (CCH$_3$); **MS** (+ESI) $m/z$ 295 (M+H$^+$, 24 %), 317 (M+Na$^+$, 20); **HRMS** (+ESI) Found M+H$^+$, 239.1533; C$_{16}$H$_{23}$O$_5$ requires $M+H^+$ 295.1545.
Bis-product (299)

*Rf* [PE-Et₂O 80:20] 0.61; *IR ν* \(_{max}\) (thin film) 2935, 1765 (C=O), 1600, 1463, 1416, 1367, 1346, 1204, 1097, 1048 and 982; \(^1\)H NMR \(δ(400\text{ MHz, CDCl}_3)\) 5.08 (2H, triplet of septets, \(J\) 7.0 and 1.5 Hz, CH₂CHC), 3.87 (3H, s, C(4)OCH₃), 3.82 (6H, s, C(3)OCH₃ and C(5)OCH₃), 3.16 (4H, broad s, CH₂CHC), 2.52 (3H, s, C=OCH₃), 1.73 (6H, d, \(J\) 1.0 Hz, CCH₃) and 1.73 (6H, d, \(J\) 1.0 Hz, CCH₃); \(^{13}\)C NMR \(δ(100\text{ MHz, CDCl}_3)\) 169.3− (C=O), 150.3− (C3 and C5), 144.8− (C4), 143.2− (C1), 131.3− (C(CH₃)₂), 123.7− (C2 and C5), 122.7+ (CH₂CHC), 61.0+ (C(3)OCH₃ and C(5)OCH₃), 60.6+ (C(4)OCH₃), 25.6+ (CCH₃), 24.1− (CH₂CHC), 20.6+ (CH₃C=O) and 17.8+ (CCH₃); MS (+ESI) \(m/z\) 363 (M+H⁺, 5 %), 385 (M+Na⁺, 14); HRMS (+ESI) Found M+Na⁺, 385.1975. \(C_{21}H_{30}O_5Na\) requires \(M+Na⁺\) 385.1991.

**General Procedure 5: Hydrolysis of phenolic acetates**

**Method A:** Following a procedure reported by Bates *et al.*,\(^{225}\) K₂CO₃ (2 eq) was added to a solution of the acetate (1 eq) in MeOH (5 mL/mmol) at r.t. and the reaction was stirred for 2 hrs. The suspension was quenched with saturated aqueous NH₄Cl (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed *in vacuo*. Column chromatography [silica, PE-EtOAc gradient from 100:1 to 75:25] afforded the phenol product.

**Method B:** Following a procedure reported by Narender *et al.*,\(^{227}\) NaOAc (10 eq) was added to a solution of the acetate (1 eq) in EtOH/H₂O (10:1, 5.5 mL/mmol) and the reaction heated at reflux for 5 hrs. After cooling, the reaction was diluted with H₂O (15 mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the solvent removed *in vacuo*. Column chromatography [silica, PE-EtOAc gradient from 100:0 to 75:25] afforded the phenol product.
3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenol (296)

Following general procedure 5A, acetate 298 (411 mg, 1.4 mmol) gave the phenol 296 (173 mg, 49 %) as a yellow amorphous solid. Following general procedure 5B, acetate 298 (132 mg, 0.45 mmol) gave the phenol 296 (41 mg, 36 %), in addition to acetate 298 (53 mg, 40 %).

Rf [PE-EtOAc 75:25] 0.25; IR νmax (thin film) 3392 (OH), 2963, 1935, 1607, 1505, 1463, 1415, 1357, 1237, 1197, 1164, 1126, 1082, 1040 and 993; 1H NMR δH (400 MHz, CDCl3) 6.20 (1H, s, C(6)H), 5.70 (1H, s, C(1)OH), 5.19 (1H, triplet of septets, J 7.0 and 1.5 Hz, CH2CHC), 3.83 (3H, s, OCH3), 3.79 (3H, s, OCH3), 3.72 (3H, s, OCH3), 3.31 (2H, d, J 7.0 Hz, CH2CHC), 1.78 (3H, d, J 1.0 Hz, CCH3) and 1.70 (3H, d, J 1.0 Hz, CCH3); 13C NMR δc (100 MHz, CDCl3) 151.9− (C3, C4, or C5), 150.9− (C1), 136.1− (C3, C4, or C5), 133.6− (C(CH3)2), 122.6+ (CH2CHC), 113.0− (C2), 96.6+ (C6), 61.2+ (OCH3), 61.0+ (OCH3), 55.9+ (OCH3), 25.7+ (CCH3), 22.8− (CH2CHC) and 17.8+ (CCH3); MS (+ESI) m/z 253 (M+H+ 100 %) and 275 (M+Na+, 92); HRMS (+ESI) Found M+Na+, 275.1272 C14H20O4Na requires M+Na+ 275.1259.

Spectroscopic data was consistent with that reported by Parmar et al.222

3,4,5-Trimethoxy-2,6-bis(3-methylbut-2-en-1-yl)phenol (300)

K2CO3, MeOH

187
Following general procedure 5A, acetate 299 (100 mg, 0.27 mmol) gave the phenol 300 (28 mg, 32 %) as an oil.

**IR** ν<sub>max</sub>(thin film) 3461 (OH), 2964, 2933, 1605, 1462, 1357, 1256, 1171, 1097, 1051 and 987; **<sup>1</sup>H NMR** δ<sub>H</sub>(400 MHz, CDCl<sub>3</sub>) 5.59 (1H, s, C(1)OH), 5.21 (2H, triplet of septets, J 7.0 and 1.5 Hz, CH<sub>2</sub>CHC), 3.85 (3H, s, C(4)OCH<sub>3</sub>), 3.84 (6H, s, C(3)OCH<sub>3</sub> and C(5)OCH<sub>3</sub>), 3.34 (4H, d, J 7.0 Hz, CH<sub>2</sub>CHC), 1.80 (6H, d, H 1.0 Hz, CCH<sub>3</sub>) and 1.72 (6H, d, H 1.0 Hz, CCH<sub>3</sub>); **<sup>13</sup>C NMR** δ<sub>C</sub>(100 MHz, CDCl<sub>3</sub>) 150.1− (C3 and C5), 149.2− (C1), 140.3− (C4), 133.4− (C(CH<sub>3</sub>)<sub>2</sub>), 122.6+ (CH<sub>2</sub>CHC), 116.8− (C2 and C6), 61.1+ (C(3)OCH<sub>3</sub> and C(5)OCH<sub>3</sub>), 60.9+ (C(4)OCH<sub>3</sub>), 25.8+ (CCH<sub>3</sub>), 23.1− (CH<sub>2</sub>CHC) and 17.8+ (CCH<sub>3</sub>); **MS** (+ESI) m/z 321 (M+H<sup>+</sup>, 50 %); **HRMS** (+ESI) Found M+H<sup>+</sup>, 321.2066; C<sub>19</sub>H<sub>29</sub>O<sub>4</sub> requires M+H<sup>+</sup> 321.2066.
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7. APPENDICES

7.1. APPENDIX 1: BIOLOGICAL DATA

7,8-Dihydro-6H-[1,3]dioxolo[4,5-g]isoquinolin-5-one (144)
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/22/P
72h Exposure MTS 2h

![Chemical Structure](image)

**Graph**

- **OD**$_{490nm}$ vs Concentration (M)
- **IC$_{50}$ = 656μM
- **HC = 4.01

1% DMSO only
Points are means ± s.d
n = 4
6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (147)

EXPT KJ-1
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/19/P
72h Exposure MTS 4h

IC₅₀ = 715μM
H.C. = 0.904

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/19/P
72h Exposure MTS 2h

![Chemical Structure]

IC₅₀ = 1.1mM
HC = 0.74

1% DMSO only
Points are means ± s.d
n = 4
**EXPT KJ-1**

HT29 Human Colon Ca
MTS Cell Proliferation Assay

**Test Compound:** KJ2/61/P

72h Exposure MTS 4h

![Chemical Structure](image)

**Graph:**

- **OD$_{490\text{nm}}$** vs. KJ2/61/P Concentration (M)

- **IC$_{50}$ = 286µM**
- **H.C. = 1.18**

- 1% DMSO only
- Points are means ± s.d
- n = 4
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ4/60/P
72h Exposure MTS 2h

![Graph showing concentration vs. OD490 with IC50 = 487 μM and HC = 1.24]

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-3
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/31/P
72h Exposure MTS 2h

![Graph showing the concentration-response curve for KJ3/31/P. The graph includes a plot of OD490nm against KJ3/31/P Concentration (M), with data points and error bars. The IC50 is 511 μM, and HC is 2.08.]

Points are means ± s.d.
n = 4

1% DMSO alone
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ4/62/P
72h Exposure MTS 2h

\[ IC_{50} = 284 \mu M \]
\[ HC = 1.83 \]

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-3
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/79/P
72h Exposure MTS 2h

IC$_{50}$ = 80µM
HC = 1.35

Points are means ± s.d.
n = 4
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/79/P
72h Exposure MTS 2h

\[ \text{IC}_{50} = 136\mu M \]
\[ \text{HC} = 1.64 \]

Points are means ± s.d
n = 4

1% DMSO only
EXPT KJ-3
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/53/P
72h Exposure MTS 2h

[Graph showing OD at 490nm vs. KJ3/53/P Concentration (M)]

IC$_{50}$ = 49µM
HC = 1.39

1% DMSO alone
Points are means ± s.d.
n = 4

6,7-Dimethoxy-8-hydroxyisoquinolin-1(2H)-one (174)
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ5/56/P
72h Exposure MTS 2h

![Chemical Structure]

$\text{IC}_{50} = 94 \mu M$
$HC = 1.28$

$\text{OD}_{490\text{nm}}$

Concentration (M)

1% DMSO only
Points are means ± s.d
$n = 4$
2,3,4,9-Tetrahydro-β-carbolin-1-one (153)

**EXPT KJ-2**

HT29 Human Colon Ca  
MTS Cell Proliferation Assay  
**Test Compound:** KJ2/64/P  
72h Exposure MTS 2h

![Graph showing cell proliferation assay results with IC50 = 243μM](image)

- **OD**  
- **KJ2/64/P Concentration (M)**

- 1% DMSO alone
- Points are means ± s.d.  
- n = 4
EXPT KJ-10

HT29 Human Colon Ca

MTS Cell Proliferation Assay

Test Compound: KJ6/24/P

72h Exposure MTS 2h

\[ \text{IC}_{50} = 277\mu M \]
\[ \text{HC} = 1.79 \]

\[ \text{OD}_{490nm} \]

Concentration (M)

1% DMSO only

Points are means ± s.d

n = 4
EXPT KJ-2
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ2/68/P
72h Exposure MTS 2h

IC_{50} = 204\mu M

1% DMSO alone

Points are means ± s.d.
n = 4
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/30/P
72h Exposure MTS 2h

![Chemical Structure](Image)

![Graph](Image)

- $IC_{50} = 166\mu M$
- $HC = 1.77$

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-8
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound:  KJ6/32/P
72h Exposure MTS 2h

IC\textsubscript{50} = 144\mu M
HC = 1.17

1% DMSO only
Points are means \pm s.d
n = 4
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/32/P
72h Exposure MTS 2h

![Graph showing concentration vs. OD at 490nm with IC50 and HC values]

IC50 = 265[μM]
HC = 1.26

<table>
<thead>
<tr>
<th>Concentration (M)</th>
<th>OD_{490nm}</th>
</tr>
</thead>
<tbody>
<tr>
<td>10^{-6}</td>
<td>0.6</td>
</tr>
<tr>
<td>10^{-5}</td>
<td>0.4</td>
</tr>
<tr>
<td>10^{-4}</td>
<td>0.2</td>
</tr>
<tr>
<td>10^{-3}</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-3
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/84/P
72h Exposure MTS 2h

IC$_{50}$ = 64µM
HC = 1.05

1% DMSO alone
Points are means ± s.d.
n = 4
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/29/P
72h Exposure MTS 2h

![Graph showing concentration vs. OD490nm]

$IC_{50} = 107 \mu M$
$HC = 3.27$

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/31/P
72h Exposure MTS 2h

IC₅₀ = 106µM
HC = 1.45

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-13
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/31/P
72h Exposure MTS 2h

![Graph showing the effect of KJ6/31/P concentration on cell proliferation.](image)

$IC_{50} = 183.6 \mu M$

- Gray: 1% DMSO only
- Points are means ± s.d
- $n = 4$
2,9-Dimethyl-2,9-Dihydro-1H-pyrido[3,4-b]indol-1-one (177)

EXPT KJ-8
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/33/P
72h Exposure MTS 2h

![Chemical Structure](image)

\[ \text{OD}_{490nm} \]

<table>
<thead>
<tr>
<th>Concentration (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>$10^{-3}$</td>
</tr>
</tbody>
</table>

\[ IC_{50} = 108 \mu M \]
\[ HC = 1.45 \]

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/33/P
72h Exposure MTS 2h

![Chemical Structure](image)

IC$_{50} = 146 \mu$M
HC = 2.15

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-2
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/11/P
72h Exposure MTS 2h

IC₅₀ = 155μM

Points are means ± s.d.
n = 4
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/11/P
72h Exposure MTS 2h

![Chemical Structure](Image)

$IC_{50} = 126 \mu M$
$HC = 1.37$

$\text{OD}_{490\text{nm}}$

Concentration (M)

1% DMSO only
Points are means $\pm$ s.d
n = 4
EXPT KJ-2
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/15/P
72h Exposure MTS 2h

IC₅₀ = 275μM

1% DMSO alone
Points are means ± s.d.
n = 4
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/15/P
72h Exposure MTS 2h

![Chemical Structure](image)

**Graph:**
- **OD** at 490nm
- **Concentration (M):** $10^{-6}$ to $10^{-3}$
- **IC$_{50}$ = 329$\mu$M
- **HC = 1.15

**Legend:**
- 1% DMSO only
- Points are means ± s.d
- n = 4
2,10-Dimethyl-3,4,5,10-tetrahydro-2H-azeppino[3,4-b]indol-1-one (167)

EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ7/60/P
72h Exposure MTS 2h

IC₅₀ = 373μM
HC = 2.85

1% DMSO only
Points are means ± s.d
n = 4
8-Hydroxy-6,7-dimethoxy-1-oxo-1H-isoquinoline-2-carboxylic acid ethyl ester (178)

EXPT KJ-4
HT29 Human Colon Ca
MTS Cell Proliferation Assay
**Test Compound:** KJ4/82/P
72h Exposure MTS 2h

![Chemical Structure](image)

IC$_{50}$ = 83μM
HC = 1.27

**OD$_{490nm}$ vs. KJ4/82/P1 Concentration (M)**

- 1% DMSO alone
- Points are means ± s.d.
- n = 4
Benzyl 8-hydroxy-6,7-dimethoxy-1-oxoisooquinoline-2(1H)-carboxylate

(179)

EXPT KJ-5
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ5/17/P 1
72h Exposure MTS 2h

![Graph showing concentration response](image)

- $\text{IC}_{50} = 88 \mu M$
- $\text{HC} = 1.36$

1% DMSO only
Points are means ± s.d
n = 4
7-Hydroxy-8,9-dimethoxy-3,4,4a,5-tetrahydrophenanthridin-6(2H)-one

EXPT KJ-11
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/10/P
72h Exposure MTS 2h

![Chemical Structure](image)

$IC_{50} = 23 \mu M$
$HC = 3.71$

**Graph:**
- **OD$_{490nm}$** vs. Concentration (M)
- 1% DMSO only
- Points are means ± s.d
- n = 4
EXPT KJ-12
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/10/P
72h Exposure MTS 2h

\[ \text{IC}_{50} = 22.7 \mu M \]

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-11
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/15/P1
72h Exposure MTS 2h

IC₅₀ = 45µM
HC = 1.49

1% DMSO only
Points are means ± s.d
n = 4
EXPT KJ-12
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/15/P1
72h Exposure MTS 2h

\[ IC_{50} = 29.4 \mu M \]

1% DMSO only
Points are means ± s.d
n = 4
8,9-Dimethoxy-1,2,3,4-tetrahydrophenanthridin-6(5H)-one (240)

EXPT KJ-11
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/15/P2
72h Exposure MTS 2h
EXPT KJ-12
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/15/P2
72h Exposure MTS 2h

IC$_{50}$ = 19.2 µM

1% DMSO only
Points are means ± s.d
n = 4
7.2. APPENDIX 2: CRYSTALLOGRAPHIC DATA

7.2.1. 8-(Difluoroboryloxy)-6,7-dimethoxy-3,4-dihydroisoquinolin-(2H)-one (148)

Table 1. Crystal data and structure refinement for 1.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>k08farm2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C11 H12 B F2 N O4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>271.03</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
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<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.7930(1) Å  ( \alpha = 90^\circ )</td>
</tr>
<tr>
<td></td>
<td>b = 10.5440(2) Å  ( \beta = 102.540(1)^\circ )</td>
</tr>
<tr>
<td></td>
<td>c = 14.7380(4) Å  ( \gamma = 90^\circ )</td>
</tr>
<tr>
<td>Volume</td>
<td>1182.12(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.523 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.133 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>560</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.25 x 0.15 x 0.10 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.82 to 27.51 °</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-10≤h≤10; -13≤k≤13; -19≤l≤19</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>21708</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2705 [R(int) = 0.0399]</td>
</tr>
<tr>
<td>Reflections observed (&gt;2σ)</td>
<td>2171</td>
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<tr>
<td>Data Completeness</td>
<td>0.996</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.98 and 0.94</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2705 / 0 / 175</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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</tr>
<tr>
<td>Final R indices [I&gt;2σ(I)]</td>
<td>R1 = 0.0388  wR2 = 0.1003</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0531  wR2 = 0.1097</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.244 and -0.290 eÅ⁻³</td>
</tr>
</tbody>
</table>

Notes: H…F interactions generate 1-D chains in the lattice.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

<table>
<thead>
<tr>
<th>D-H</th>
<th>d(D-H)</th>
<th>d(H-A)</th>
<th>&lt;DHA</th>
<th>d(D-A)</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-H1</td>
<td>0.880</td>
<td>2.002</td>
<td>156.91</td>
<td>2.833</td>
<td>F2 [-x, y+1/2, -z+3/2]</td>
</tr>
<tr>
<td>N1-H1</td>
<td>0.880</td>
<td>2.616</td>
<td>142.91</td>
<td>3.360</td>
<td>F1 [-x, y+1/2, -z+3/2]</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates (x 10^5) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F(1)</td>
<td>1729(1)</td>
<td>93(1)</td>
<td>6650(1)</td>
<td>43(1)</td>
</tr>
<tr>
<td>F(2)</td>
<td>-363(1)</td>
<td>-483(1)</td>
<td>7428(1)</td>
<td>36(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>4451(1)</td>
<td>-2210(1)</td>
<td>11188(1)</td>
<td>33(1)</td>
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<tr>
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<td>4219(1)</td>
<td>-2528(1)</td>
<td>9361(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>2628(1)</td>
<td>-693(1)</td>
<td>8138(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>1222(1)</td>
<td>1381(1)</td>
<td>7846(1)</td>
<td>30(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>1110(2)</td>
<td>2700(1)</td>
<td>9020(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>2745(2)</td>
<td>-530(1)</td>
<td>9055(1)</td>
<td>22(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>3523(2)</td>
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<td>9681(1)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>3629(2)</td>
<td>-1269(1)</td>
<td>10631(1)</td>
<td>24(1)</td>
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<tr>
<td>C(4)</td>
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<tr>
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<td>-2145(2)</td>
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<td>40(1)</td>
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<td>9301(1)</td>
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<td>47(2)</td>
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<td>29(1)</td>
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Table 3. Bond lengths [Å] and angles [°] for 1.

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<th>Bond</th>
<th>Length [Å]</th>
<th>Angle [°]</th>
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<td>F(1)-B(1)</td>
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<tr>
<td>O(1)-C(3)</td>
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<td>1.4365(18)</td>
</tr>
<tr>
<td>O(2)-C(2)</td>
<td>1.3784(16)</td>
<td>1.4327(18)</td>
</tr>
<tr>
<td>O(3)-C(1)</td>
<td>1.3443(15)</td>
<td>1.4500(19)</td>
</tr>
<tr>
<td>O(4)-C(8)</td>
<td>1.3016(16)</td>
<td>1.4993(19)</td>
</tr>
<tr>
<td>N(1)-C(8)</td>
<td>1.3067(18)</td>
<td>1.4694(18)</td>
</tr>
<tr>
<td>N(1)-H(1)</td>
<td>0.8800</td>
<td>1.3905(18)</td>
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<tr>
<td>C(1)-C(9)</td>
<td>1.4062(18)</td>
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<tr>
<td>C(3)-C(4)</td>
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<tr>
<td>C(4)-H(4)</td>
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<tr>
<td>C(5)-C(6)</td>
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<tr>
<td>C(7)-H(7A)</td>
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<tr>
<td>C(11)-H(11C)</td>
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<tr>
<td>C(3)-O(1)-C(10)</td>
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<td>113.47(10)</td>
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<tr>
<td>C(1)-O(3)-B(1)</td>
<td>117.40(11)</td>
<td>118.40(11)</td>
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<td>C(8)-N(1)-C(7)</td>
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<tr>
<td>C(7)-N(1)-H(1)</td>
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<td>120.07(12)</td>
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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å² x 10³) for 1. The anisotropic displacement factor exponent takes the form: -2 gpi² [ h² a*² U11 + ... + 2 h k a* b* U ]

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<th>Atom</th>
<th>U11</th>
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<th>U33</th>
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<th>U13</th>
<th>U12</th>
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<td>30(1)</td>
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<td>3(1)</td>
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<tr>
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<td>1(1)</td>
<td>1(1)</td>
<td>2(1)</td>
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<tr>
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<td>22(1)</td>
<td>26(1)</td>
<td>1(1)</td>
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<td>4(1)</td>
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<tr>
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<td>22(1)</td>
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<td>2(1)</td>
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<tr>
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<td>0(1)</td>
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<td>-3(1)</td>
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<tr>
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<td>2(1)</td>
<td>6(1)</td>
<td>-4(1)</td>
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<tr>
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<td>25(1)</td>
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<td>5(1)</td>
<td>-4(1)</td>
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### Table 5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 1.

<table>
<thead>
<tr>
<th>Atom</th>
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<th>y</th>
<th>z</th>
<th>U(eq)</th>
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</thead>
<tbody>
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<td>H(1)</td>
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<tr>
<td>H(4)</td>
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<td>H(6A)</td>
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<td>11277</td>
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<tr>
<td>H(6B)</td>
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<td>1796</td>
<td>10592</td>
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<tr>
<td>H(7A)</td>
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<td>3766</td>
<td>10119</td>
<td>33</td>
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<td>H(7B)</td>
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<td>3362</td>
<td>10163</td>
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<td>H(10A)</td>
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<td>H(10B)</td>
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<td>60</td>
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<td>H(10C)</td>
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<td>H(11C)</td>
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<td>65</td>
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### Table 6. Dihedral angles [°] for 1.

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<tr>
<th>Atom1 - Atom2 - Atom3 - Atom4</th>
<th>Dihedral</th>
</tr>
</thead>
<tbody>
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<td>159.26(12)</td>
</tr>
<tr>
<td>B(1) - O(3) - C(1) - C(9)</td>
<td>-21.87(17)</td>
</tr>
<tr>
<td>C(11) - O(2) - C(2) - C(1)</td>
<td>-101.17(15)</td>
</tr>
<tr>
<td>C(11) - O(2) - C(2) - C(3)</td>
<td>80.74(16)</td>
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<tr>
<td>O(3) - C(1) - C(2) - O(2)</td>
<td>1.91(18)</td>
</tr>
<tr>
<td>C(9) - C(1) - C(2) - O(2)</td>
<td>-176.97(11)</td>
</tr>
<tr>
<td>O(3) - C(1) - C(2) - C(3)</td>
<td>-179.96(11)</td>
</tr>
<tr>
<td>C(9) - C(1) - C(2) - C(3)</td>
<td>1.16(18)</td>
</tr>
<tr>
<td>C(10) - O(1) - C(3) - C(2)</td>
<td>-173.73(12)</td>
</tr>
<tr>
<td>C(10) - O(1) - C(3) - C(4)</td>
<td>6.28(19)</td>
</tr>
<tr>
<td>O(2) - C(2) - C(3) - O(1)</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>179.78(11)</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>C(2) - C(3) - C(4) - C(5)</td>
<td>-2.95(19)</td>
</tr>
<tr>
<td>C(3) - C(4) - C(5) - C(9)</td>
<td>1.32(19)</td>
</tr>
<tr>
<td>C(3) - C(4) - C(5) - C(6)</td>
<td>178.70(11)</td>
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Table 1. Crystal data and structure refinement for 1.

<table>
<thead>
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<th>Identification code</th>
<th>h08farm1</th>
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<tr>
<td>Empirical formula</td>
<td>C23 H21 Cl3 N4 O2</td>
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<tr>
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<td>Temperature</td>
<td>150(2) K</td>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>( a = 12.5260(2)\AA \quad 90^\circ )</td>
</tr>
<tr>
<td></td>
<td>( b = 12.9790(2)\AA \quad 107.493(1)^\circ )</td>
</tr>
<tr>
<td></td>
<td>( c = 15.0540(2)\AA \quad 90^\circ )</td>
</tr>
<tr>
<td>Volume</td>
<td>2334.22(6) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.399 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
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<tr>
<td>F(000)</td>
<td>1016</td>
</tr>
<tr>
<td>Crystal size</td>
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</tr>
<tr>
<td>Theta range for data collection</td>
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</tr>
<tr>
<td>Index ranges</td>
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</tbody>
</table>

7.2.2. 2,3,4,9-Tetrahydro-β-carbolin-1-one (153)

Table 1. Crystal data and structure refinement for 1.
<table>
<thead>
<tr>
<th>Reflections collected</th>
<th>33937</th>
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<tbody>
<tr>
<td>Independent reflections</td>
<td>5345 [R(int) = 0.0743]</td>
</tr>
<tr>
<td>Reflections observed (≥2σ)</td>
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<tr>
<td>Data Completeness</td>
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</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.95 and 0.88</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>5345 / 0 / 31</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
<td>1.036</td>
</tr>
<tr>
<td>Final R indices [I&gt;2σ(I)]</td>
<td>R1 = 0.0667  wR2 = 0.1741</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1011  wR2 = 0.2000</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.604 and -0.692 eÅ^-3</td>
</tr>
</tbody>
</table>

Notes: The asymmetric unit contains 2 molecules and 1 molecule of solvent of recrystallization (CHCl₃). The latter exhibited disorder of the chlorines which was modeled as a 65:35 ratio. The gross structure consists of hydrogen-bonded tapes.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

\[
\begin{align*}
\text{D-H} & \quad \text{d(D-H)} \quad \text{d(H..A)} \quad \text{<DHA} \quad \text{d(D..A)} \quad \text{A} \\
N1-H1 & \quad 0.880 \quad 1.963 \quad 169.68 \quad 2.834 \quad \text{O1A} \ [ x, -y+1/2, z+1/2 ] \\
N2-H2 & \quad 0.880 \quad 1.967 \quad 170.12 \quad 2.838 \quad \text{O1A} \\
N1A-H1A & \quad 0.880 \quad 2.056 \quad 161.07 \quad 2.903 \quad \text{O1} \\
N2A-H2A & \quad 0.880 \quad 2.029 \quad 172.88 \quad 2.904 \quad \text{O1} \ [ x, -y+1/2, z-1/2 ]
\end{align*}
\]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

<table>
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<tr>
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<th>z</th>
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<tr>
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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å² x 10³) for 1. The anisotropic displacement factor exponent takes the form: -2 gpi² / h² a*² U11 + ... + 2 h k a* b* U

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Table 5. Hydrogen coordinates (x $10^4$) and isotropic displacement parameters (Å$^2$ x $10^3$) for 1.