Oxepine-Pyrimidinone Natural Products: The Total Synthesis of (±)-Janoxepin

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Thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy

The University of York

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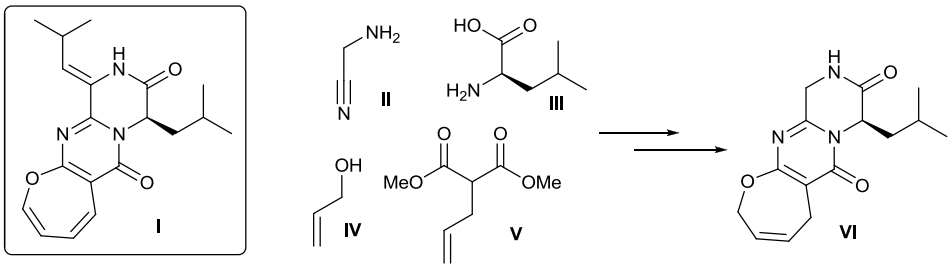
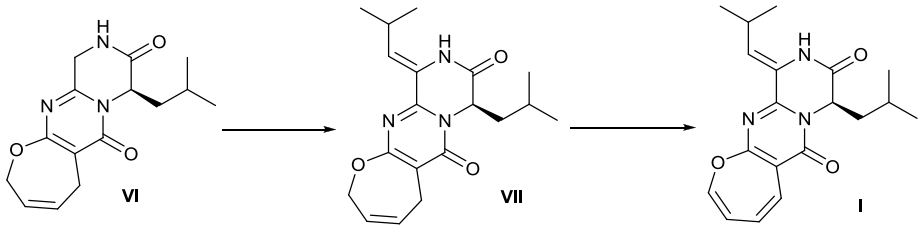
March 2012

Abstract

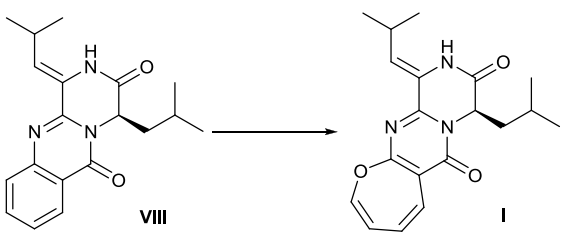
The first total synthesis of (±)-janoxepin **I**, an antiplasmodial oxepine-pyrimidinone natural product isolated from the fungus *Aspergillus janus* is described herein. Chapter 1 provides an introduction to janoxepin **I** and related natural products that have been reported in the literature. In Chapter 2, the available methods for the synthesis of oxepines and pyrimidinones are reviewed, before the preparation of dihydro-oxepine **VI** from readily available starting materials **II**-**V** is described.



The enamine side-chain seen in janoxepin **I** was introduced by way of aldol-addition to the ketopiperazine ring. The development of methodology to achieve this efficiently, and its application to the synthesis of dihydro-janoxepin **VII** is described in Chapter 3. The synthesis of janoxepin **I** was completed by way of a novel dihydro-oxepine elaboration to construct the oxepine ring. This transformation was the subject of much investigation as discussed in Chapter 4.



The proposed biosynthesis of janoxepin **I** from pyrazino[2,1-*b*]quinazoline-3,6-dione **VIII** was identified as an alternative strategy for oxepine synthesis. Chapter 5 first briefly reviews pyrazino[2,1-*b*]quinazoline-3,6-dione-containing natural products and the available methods for their synthesis. It then describes the preparation of the putative biosynthetic precursor of janoxepin **VIII** with a view to further investigation of biomimetic methods for oxepine synthesis.



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Acknowledgements

It goes without saying that nothing recorded herein would have been possible without the experienced guidance of an excellent supervisor. I would like to begin by thanking Richard Taylor for his trust and patience in allowing me to carry out my studies with independence, and yet, still be immediately on hand to advise and direct. It is much appreciated, and will not be forgotten.

Every member of the Taylor group has made my time in the lab unforgettable. I hope I will be forgiven for particularly mentioning the following: René S., for being an excellent addition to team janoxepin; Mike E., for knowing everything and teaching me how to run a column; Alan B., for sound advice, based upon solid morals; Russ K., for being on another wavelength; David P., for being indispensable; Dan H., for a ridiculous sense of humour, not dissimilar to mine, perhaps slightly worse; Katie G., for some very random chats having sensed I needed a beer; Cat M., keep on caving; Dave B., for listening lots, but never judging; Phil C., for giving plenty of monthly report notice; Jon O., responsible for my now impressive knowledge of golf; and Vil F., who rejuvenated my CV!

I would like to pay particular thanks to Will Unsworth and James Cuthbertson, not only for proof reading this thesis, but for whose ideas and suggestions have been such an inspiration. A special thank-you also goes to Graeme McAllister for everything he has done to help me over the last 3 years – too much to record here. Those reckless Sunday/midweek pub sessions were much enjoyed, and will hopefully continue for many years to come….maybe on Saturdays from now on.

My thanks go to all the technical staff in the Chemistry Department, in particular, Heather and Amanda (NMR), Trevor and Karl (mass spec.), Adrian and Rob (X-ray crystallography), Phil and Graeme (CHN) and Mike and Steve (stores).

Finally I would like to thank all my family for their unerring support over the last 3 years, through good times and bad. I am also indebted to Aneika, who, although times have moved on, has been the source of much support and self-confidence. None of this will be forgotten!

Declaration

The research in this Thesis was carried out at the University of York between October 2008 and January 2012. The work is, to the best of my knowledge, original except where due reference has been made to other workers.

Richard G. Doveston
March 2012

Chapter 1. Introduction: Oxepine-Pyrimidinone-Containing Natural Products – Janoxepin

1.1 Isolation

Janoxepin (**1**) is a novel tricyclic oxepine-containing secondary metabolite isolated from the fungus *Aspergillus janus* in 2005 by Sprogøe and co-workers (Figure 1.1).[1] Also isolated from the same ethyl acetate extract was brevicompanine B (**2**) which has been isolated from other sources[2] and was the subject of a total synthesis in 2001.[2,3] *Aspergillus janus* was first reported in 1940 by Raper and Thom;[4] a component of the Panamanian microflora, it is so named because it possesses two distinct conidial head types.

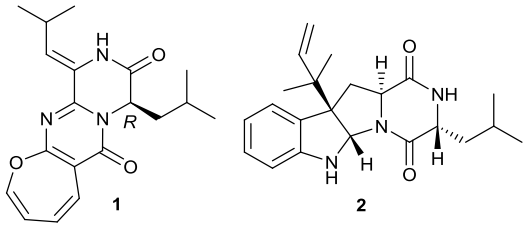


Figure 1.1. Janoxepin (**1**) and brevicompanine B (**2**).

1.2 Structural Features and Assignment

Sprogøe and co-workers describe janoxepin (**1**) as an orange crystalline powder with a melting point of 88-89 °C.[1] The structure was determined through ^{1}H and ^{13}C-NMR spectroscopy (in conjunction with COSY, HMBC and nOe experiments) together with mass spectrometry.[1] Key features include an unsaturated enamine side chain in the *Z*-configuration (confirmed by nOe data),[1] and a D-leucine derived stereocentre which was determined as (*R*) by Marfey's method - derivatisation with 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (FDAA) and HPLC analysis.[5]

1.3 Biological Activity

In a radio-isotope assay, janoxepin (**1**) was found to demonstrate antiplasmodial activity against the malaria parasite *Plasmodium falciparum* 3D7, exhibiting an IC_{50} value of 28 mg/mL. It is suggested that the actual IC_{50} value is lower, as the compounds were observed to precipitate in the test media.[1]

1.4 Structurally Related Natural Products

The oxepine-pyrimidinone system incorporated in janoxepin (**1**) is highly unusual, only found in a small family of closely related natural products. Before focussing on this small class of compound, a brief overview of natural products bearing the oxepine moiety is insightful. First however, the nomenclature of oxepines needs to be clarified.

1.4.1 Oxepine Nomenclature

The most recent reviews of the literature surrounding the synthesis of oxepines[6-8] have classified any seven-membered ring containing a single oxygen atom as an 'oxepine', 'oxepene' or 'oxepin'. Given the differing levels of saturation that are possible in such structures, the different properties they exhibit, and the very different challenges that their synthesis presents, here 'oxepines' have been categorised and named according to this characteristic:

- An 'oxepine' herein is defined as a fully unsaturated seven membered ring bearing a single oxygen atom. Therefore, three carbon-carbon double bonds will be present in the heterocycle (Figure 1.2, **3**).
- A 'dihydro-oxepine' has a higher level of saturation, bearing two double bonds in the ring (Figure 1.2, **4**).
- A 'tetrahydro-oxepine' bears a single double bond as part of the heterocycle (Figure 1.2, **5**).
- An 'oxepane' is defined as a fully saturated seven membered ring bearing a single oxygen atom. No carbon-carbon double bonds will be present in the heterocycle (Figure 1.2, **6**).

Figure 1.2. 'Oxepines' defined according to the level of saturation.

Where an aromatic group is fused to the heterocycle, the same definitions will apply (Figure 1.3).

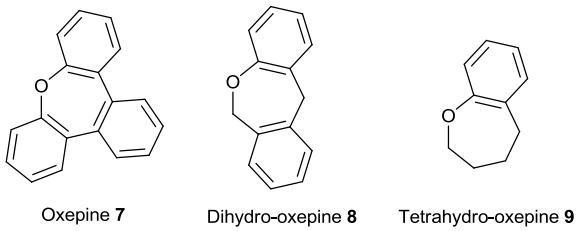


Figure 1.3. 'Oxepine' definition applied to substrates with fused aromatic groups.

1.4.1 Oxepine-Containing Natural Products

Whilst numerous natural products containing dihydro- and tetrahydro-oxepine as well as oxepane moieties have been reported such as brevitoxin B,[9] gambierol,[10] ptilomycalin A,[11] aranotin[12] and psammaplysin I,[13] compounds based on an oxepine are less common. Dibenzo-oxepine compounds represent the largest class of oxepine-containing natural product which includes artoristilbene (**10**),[14] artocarpol A (**11**),[15] bauhinoxepin A (**12**)[16] and bauhiniastatin 1 (**13**)[17] as shown in Figure 1.4.

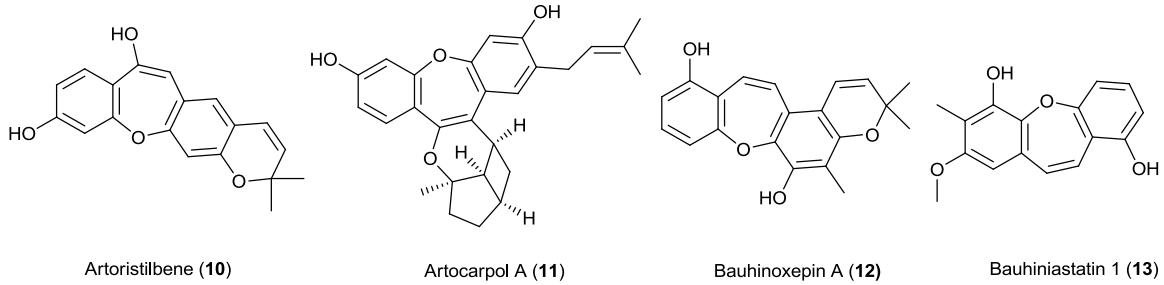


Figure 1.4. Dibenzo-oxepine-containing natural products.

Few oxepine-containing natural products lacking dibenzo-annelation (excluding the oxepine-pyrimidinone family) have been reported. Tenual (**14**) and tenucarb (**14a**),[18] perilloxin (**15**) and dehydroperilloxin (**16**),[19] fusidienol (**17**),[20] fusidienol A (**18**),[21] isofusidienol A-B (**19-20**)[22] and microsphaeropsone C (**21**)[23] remain the only examples (Figure 1.5), none of which bear the 2,3-disubstituted oxepine seen in janoxepin (**1**).

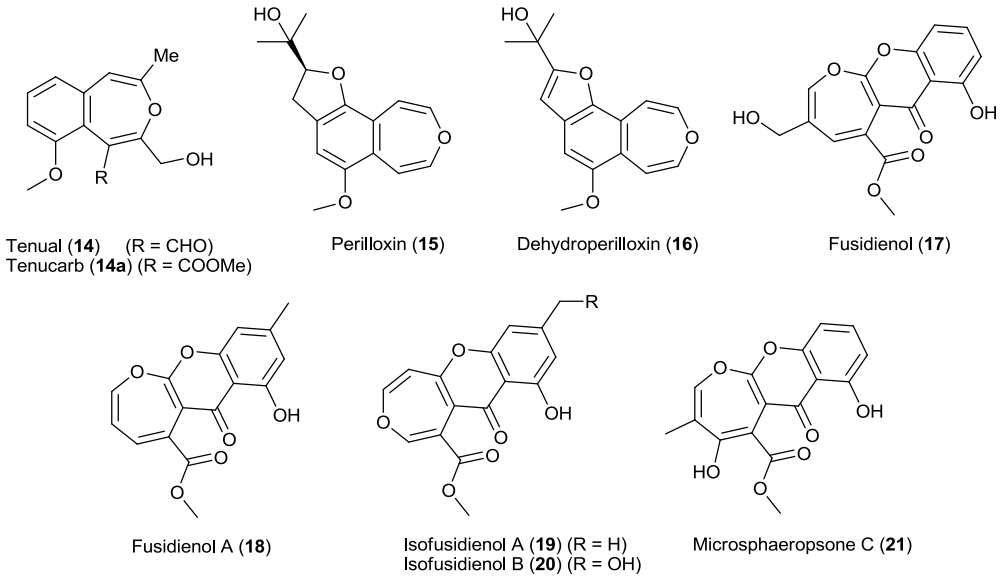


Figure 1.5. Oxepine-containing natural products.

1.4.2 Oxepine-Pyrimidinone-Containing Natural Products

Although small, the number of oxepine-pyrimidinone compounds isolated from natural sources is ever growing (Figure 1.6).

Cinereain (**22**) was isolated by Cutler and co-workers from the fungus *Botrytis cinerea* in 1988 and its structure confirmed by X-ray crystallography.[24] Structurally, it differs from janoxepin (**1**) only by the possession of a valine-derived saturated side chain which was subsequently reported to be derived from L-valine,[1] although the absolute stereochemistry was not defined in the original publication.[24] In bioassays, cinereain (**22**) demonstrated growth inhibition of wheat coleoptiles in the 10^{-4} – 10^{-3} M range, indicating wider potential as a plant growth regulator.[24]

Belofsky, Köck and co-workers reported the isolation of oxepinamides A-C (**23-25**) from the culture broth and mycelia of an *Acremonium sp*. fungus found on the surface of the Caribbean tunicate *Ecteinascidia turbinata* in 2000.[25] These compounds all possess an 11-methoxy substituent on the oxepine ring as well as an alanine-derived saturated side-chain (only relative stereochemistry reported). Oxygenated substituents were observed in place of the enamine moiety seen in janoxepin (**1**). Only oxepinamide A (**23**) showed notable biological activity, demonstrating good anti-inflammatory activity in a topical resiniferatoxin-induced mouse ear oedema assay.[25]

Oxepinamide D (**26**) was reported in 2011, isolated from the fungus *Aspergillus puniceus* obtained from a Chinese soil sample.[26] Whilst oxepinamide D (**26**) contains a related oxepine-pyrimidinone-ketopiperazine core to that seen in janoxepin (**1**), the closely related oxepinamides E-G (**27-29**) contain a 13-oxygenated dihydro-oxepine ring and a different pattern of conjugation through the pyrimidinone-ketopiperazine bicyclic system. The structure of oxepinamide E (**27**) was confirmed by X-ray crystallography. Oxepinamides D-G (**26-29**) were shown to be novel liver X receptor agonists with potential use in the treatment of atherosclerosis, diabetes and Alzheimer's disease.[26]

Zhang and co-workers isolated brevianamides O-P (**30-31**) from the harmful fungus *Aspergillus versicolor* in 2009/2010.[27] Like oxepinamide D, these compounds have a close relative in brevianamide L (**32**)[28] which contains a 13-oxygenated dihydro-

oxepine ring. None of the brevianamides showed any notable activity in cytotoxicity assays.

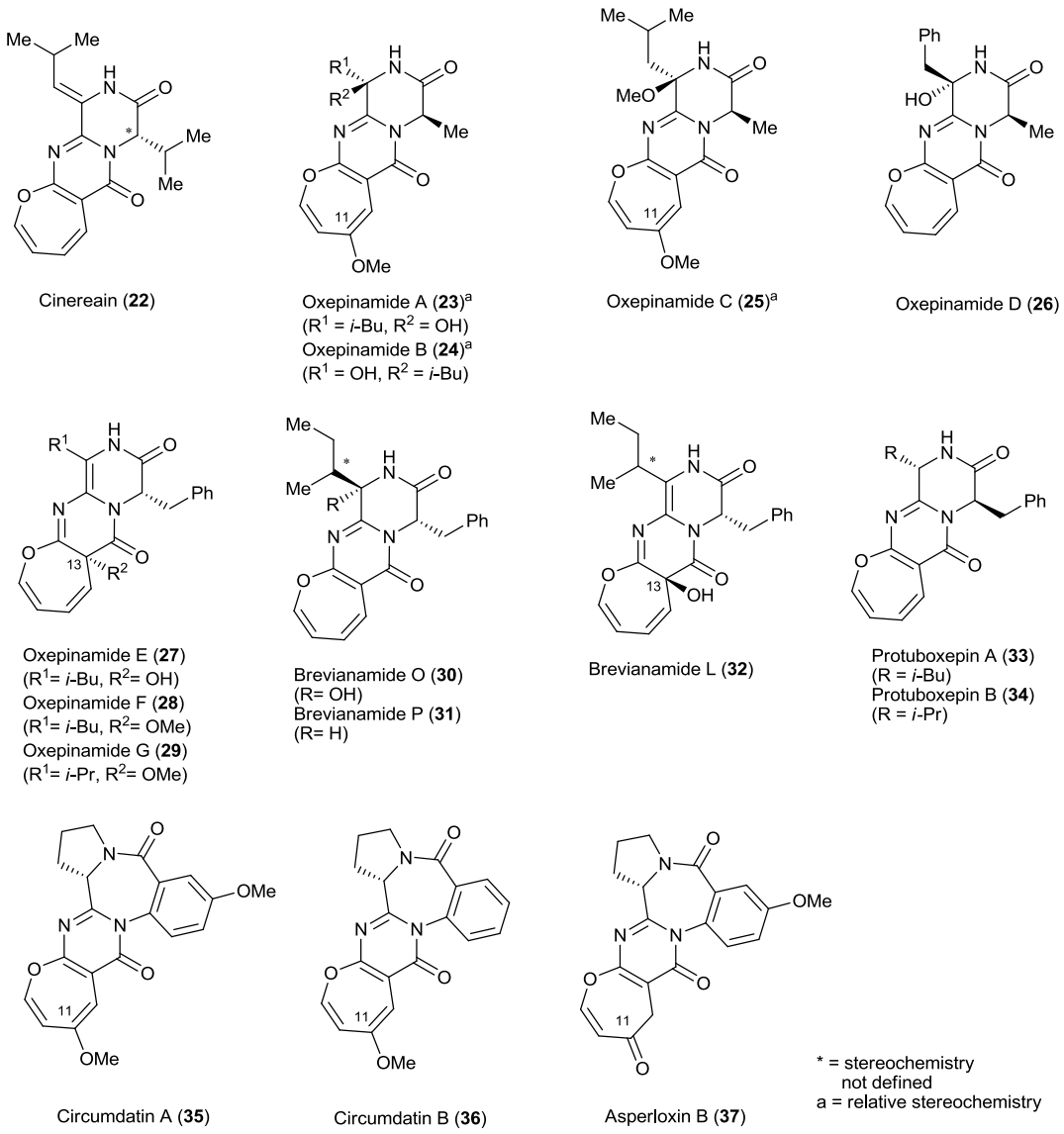


Figure 1.6. Oxepine-pyrimidinone-containing natural products.

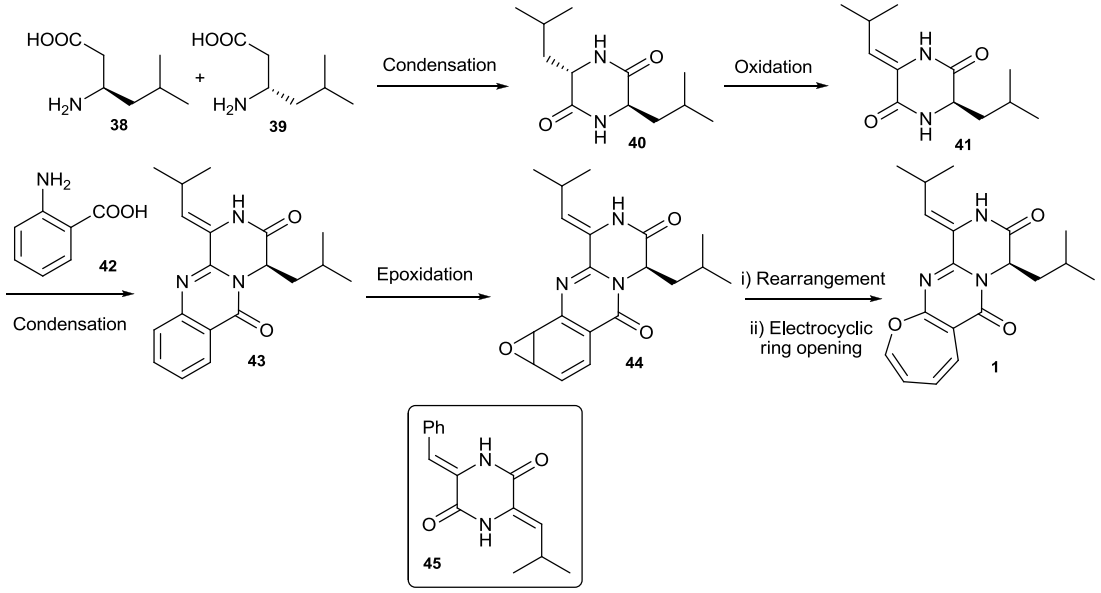
Protuboxepin A (**33**) and protuboxepin B (**34**) are very close relatives of brevianamide P (**31**) and were isolated by Oh and co-workers from the *Aspergillus* species SF-5044 found in a Korean sediment sample.[29] Protuboxepin A (**33**) displayed weak cell growth inhibition properties against a panel of cell lines.[29]

The benzodiazepine oxepine alkaloids, circumdatin A[30,31] [asperloxin A (**35**)[32]] and circumdatin B (**36**)[30] also possess the oxepine-pyrimidinone system seen in janoxepin (**1**). First isolated from the fungus *Aspergillus ochraceus* in 1999, they were only identified as oxepine-containing compounds following subsequent isolation of

circumdatin A (**35**) (also from *Aspergillus ochraceus*) by Zeeck and co-workers in 2002[32] and a structural revision by Kusumi and co-workers in 2008.[33] The isolation of asperloxin B (**37**)[32] was reported with that of circumdatin A (**35**) and it was found to possess a dihydro-oxepine bearing ketone functionality at the 11-position.

1.5 Proposed Biogenesis

It was proposed by Sprogøe,[1] Kiyota[26] and Zeeck[32] that janoxepin (**1**) (as well as the other oxepine-pyrimidinone-ketopiperazine containing natural products **22-37** in Figure 1.6) might be derived from diketopiperazine **40**, the product of the condensation of two amino acid residues. Cyclic dipeptide oxidase catalysed oxidation would then follow (as required) in analogy with the proposed biosynthesis of albonoursin (**45**) which occurs *via* the diketopiperazine (DKP) biosynthetic pathway.[34] It is proposed that condensation with anthranilic acid **42** would then occur to form arene-derivative **43** which could undergo an intriguing epoxidation, rearrangement and electrocyclic ring opening sequence to form the oxepine ring (Scheme 1.1).

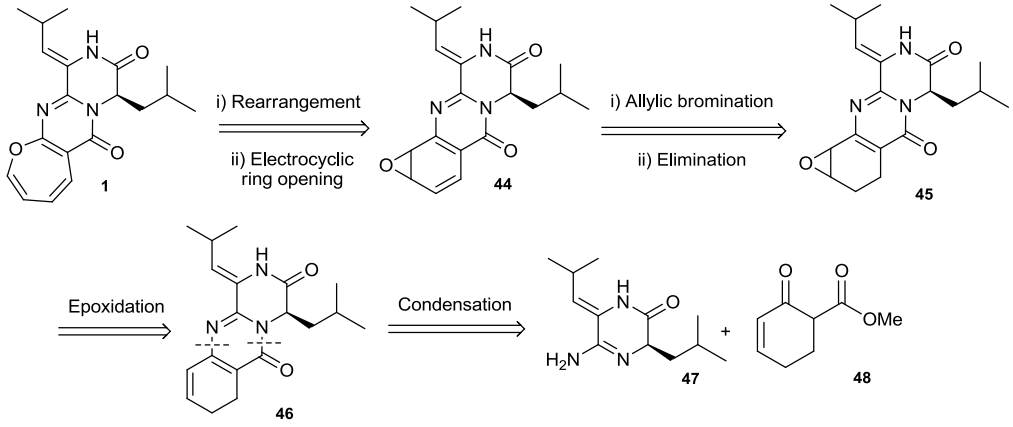


Scheme 1.1. Proposed biogenesis of janoxepin (**1**).

1.6 Strategy

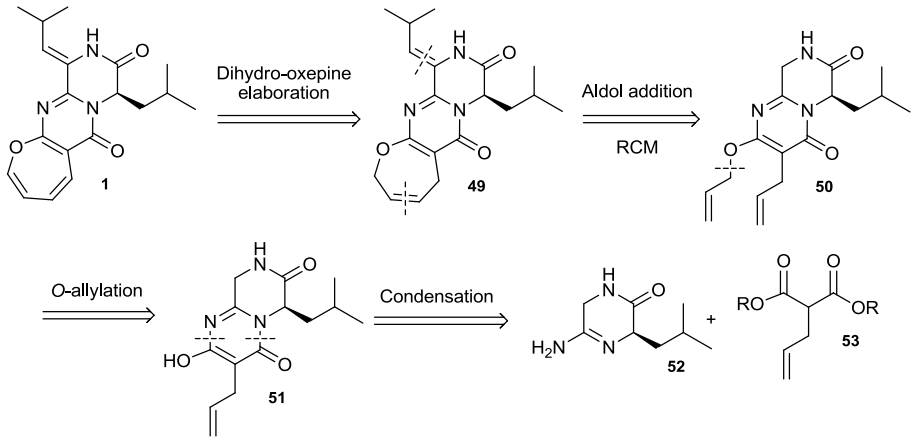
To the best of our knowledge there have been no reports of synthetic routes to janoxepin (**1**) or any of the aforementioned oxepine-containing natural products (**14-37**) that lack dibenzo-annelation. Furthermore, there have been no reported methods for the preparation of the unusual oxepine-pyrimidinone system incorporated in janoxepin (**1**). Focusing on the development of a synthetic route to janoxepin (**1**), preliminary studies

carried out by Jones in 2008 utilised a biosynthetically inspired retrosynthetic analysis of the oxepine-pyrimidinone system (Scheme 1.2).[35] This relied on rearrangement and electrocyclic ring opening of epoxide **44** to form the oxepine ring. The alkene in epoxide **44** would be installed by allylic bromination of pyrimidinone **45** followed by elimination. A cyclocondensation between a suitable amidine such as **47** and cyclohexene carboxylate **48** would be used to generate the key pyrimidinone intermediate **46**.



Scheme 1.2. Initial retrosynthetic analysis of janoxepin (**1**).

However, the synthetic challenges encountered in the preparation of model compounds of pyrimidinone **46** could not be overcome, and the alternative approach shown in Scheme 1.3 was devised. This strategy relied upon late stage elaboration of a dihydro-oxepine such as **49** to construct the oxepine ring.[35] It was proposed that the enamine side chain could be installed by means of an aldol addition to the ketopiperazine ring at a convenient point in the synthesis, whilst the dihydro-oxepine would be prepared by ring-closing metathesis (RCM) of advanced diallyl intermediate **50**. Diallyl intermediate **50** would be constructed by *O*-allylation of pyrimidinone **51**, itself prepared from the condensation of amidine **52** and malonate **53** in analogy with the original strategy.



Scheme 1.3. Revised retrosynthetic analysis of janoxepin (**1**).

1.7 Aims of the Project

The core project aim was to develop a synthetic route to janoxepin (**1**) to enable a more thorough evaluation of its biological activity. Not only this, janoxepin (**1**) represents an excellent target for the elucidation of novel strategies to access the other oxepine-pyrimidinone natural products (**22-37**) shown in Figure 1.6, some of which are of notable biological interest.

Initial investigations would be focussed on developing methods for the construction of the oxepine-pyrimidinone system and the synthesis of a model compound. Attention would then turn to utilising the developed methodology to incorporate the ketopiperazine ring and synthesise the tricyclic core of janoxepin (**1**) before exploring the introduction of the enamine moiety by way of aldol addition to the ketopiperazine ring.

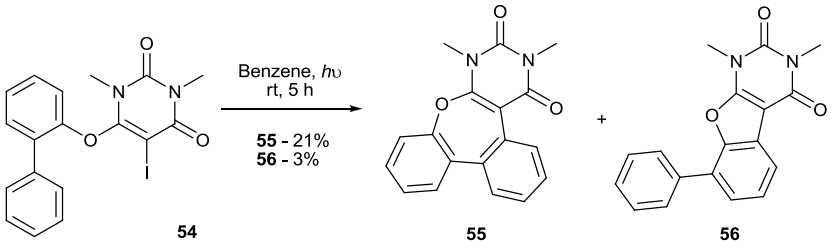
Chapter 2. Oxepine-Pyrimidinone Ring System Construction

2.1 Oxepine-Pyrimidinone Synthesis: Literature Routes

In order to highlight all the relevant literature examples that are available, the synthesis of oxepine-, dihydro-oxepine-, tetrahydro-oxepine- and oxepane-pyrimidinones is covered in this review.

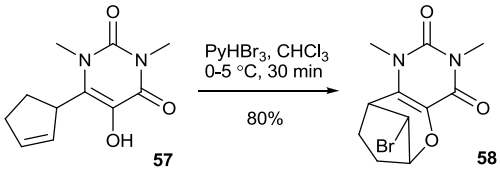
2.1.1 Intramolecular Cyclisation Strategies

To the best of our knowledge Weisz and co-workers reported the only synthesis of an oxepine-pyrimidinone system in 1973. They observed the intramolecular cyclodehydrohalogenation of barbituric acid derived iodide **54** to dibenzo-oxepine **55** in low yield under photochemical conditions (Scheme 2.1).[36]



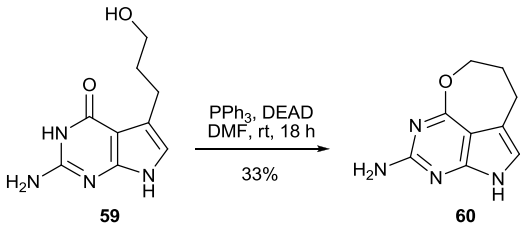
Scheme 2.1. Photocyclodehydrohalogenation of iodide **54** to dibenzo-oxepine **55**.

There is more precedent for the intramolecular cyclisation of barbituric acid derivatives to furnish dihydro- or tetrahydro-oxepine-pyrimidinones. Majumdar and co-workers reported the 6-endo-trig cyclisation of cyclo-pentene **57** to bridged tetrahydro-oxepine **58** upon treatment with a brominating agent such as pyridine hydrotribromide (Scheme 2.2).[37]



Scheme 2.2. 6-endo-trig cyclisation of cyclo-pentene **57**.

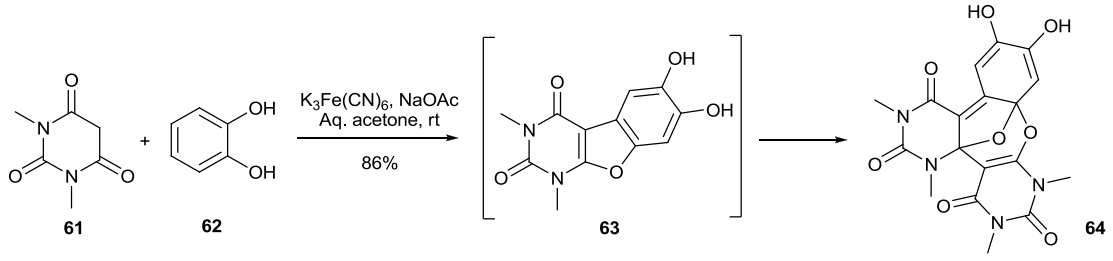
Williams and co-workers utilised an intramolecular Mitsunobu reaction to construct the oxepane ring in *O*-methyl guanine derivative **60** (Scheme 2.3).[38]



Scheme 2.3. Oxepane-pyrimidinone construction utilising Mitsunobu chemistry.

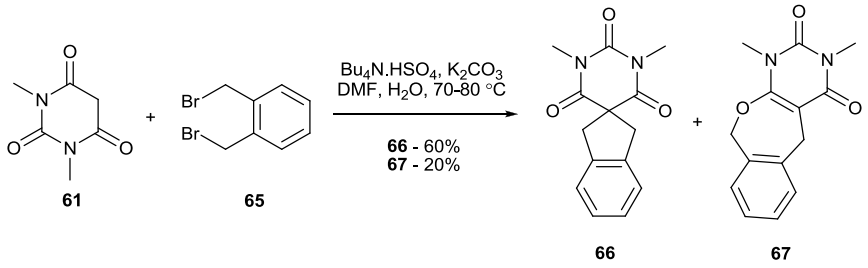
2.1.2 Intermolecular Strategies

The intermolecular cyclisation of barbituric acid derivatives to provide dihydro-oxepine-pyrimidinone compounds has also been reported. Zoorob and co-workers observed the formation of bridged dihydro-oxepine **64** upon treatment of catechol **62** with an excess of *N,N'*-dimethylbarbituric acid **61** in the presence of potassium ferricyanide, presumably *via* the intermediate furan **63** (Scheme 2.4).[39]



Scheme 2.4. Intermolecular cyclisation of *N,N'*-dimethylbarbituric acid **61** and catechol **62**.

Building on earlier work by Zoorob and co-workers,[40] Singh and Paul observed the cyclisation of *N,N'*-dimethylbarbituric acid **61** with alkyl dihalides such as **65** under basic phase transfer conditions. In this case dihydro-oxepine **67** was isolated as the minor product, the spirocyclic barbituric acid derivative **66** predominating (Scheme 2.5).[41]



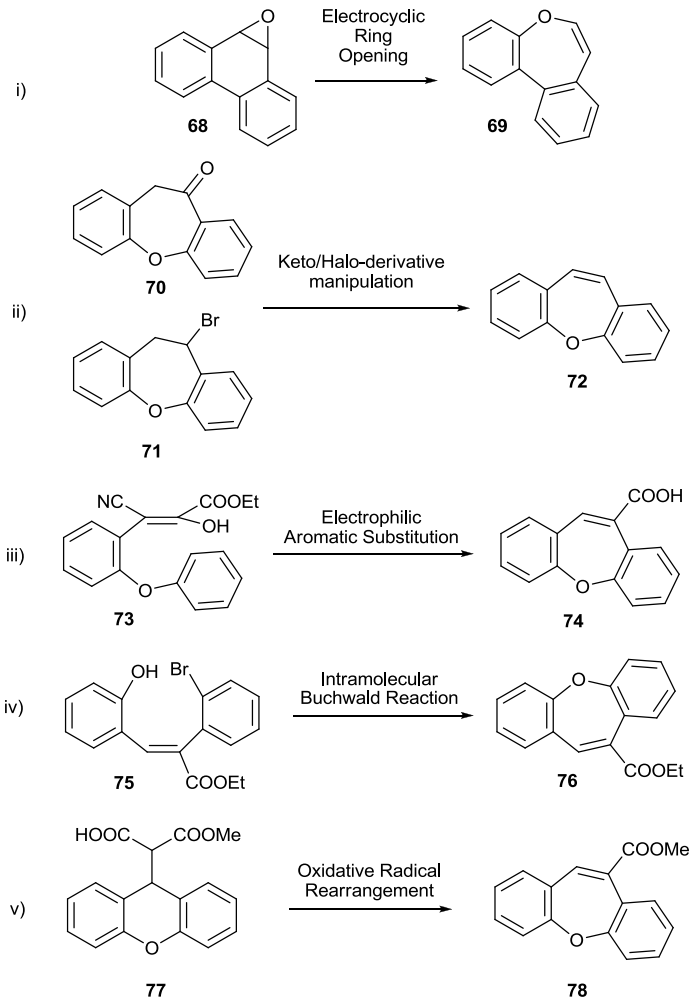
Scheme 2.5. Intermolecular cyclisation of *N,N'*-dimethybarbituric acid **61** and alkyl dihalide **65**.

The substitution patterns of the oxepine-, dihydro-oxepine, tetrahydro-oxepine and oxepane-pyrimidinone products seen in these literature examples, as well as the

synthetic methods employed were clearly not applicable to the synthesis of janoxepin (**1**). It was therefore necessary to develop a novel approach having considered literature precedent for the synthesis of oxepines and pyrimidinones in isolation.

2.2 Dibenzo-Oxepine Synthesis: Literature Examples

The proposed synthetic strategy for construction of the oxepine ring of janoxepin (**1**) involved an uncommon elaboration of a dihydro-oxepine, the literature surrounding the synthesis of which will be reviewed in detail later (2.4). The reported methods for the direct synthesis of oxepines, including dibenzo-oxepines, are first summarised. The literature surrounding methods for dibenzo-oxepine preparation is vast. Scheme 2.6 summarises the most common approaches, where arene-oxide ring expansion transformations have long been known to give access to their oxepine isomers (reaction i).[42] Synthetic strategies however have largely relied on the manipulation of keto-[43,44] or halo-derivatives[42,45] (reaction ii) and electrophilic aromatic substitution (reaction iii).[43] More recently, intra-molecular Buchwald reactions (reaction iv)[46] and oxidative radical rearrangements[47] (reaction v) have also been reported as convenient methods.



Scheme 2.6. Strategies for dibenzo-oxepine synthesis.

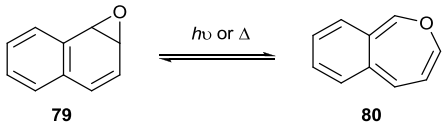
2.3 Oxepine Synthesis: Literature Routes

Only a limited number of strategies have been reported for the preparation of oxepines lacking dibenzo-annelation. Whilst most approaches rely upon the reversible isomerisation of arene-oxides to oxepines, a limited number of inter- and intramolecular cyclisation examples also exist. Of particular relevance to our planned strategy, the elaboration of dihydro-oxepines *via* eliminative transformations has also been reported, although such examples are rare.

2.3.1 Arene-Oxide – Oxepine Isomerisation

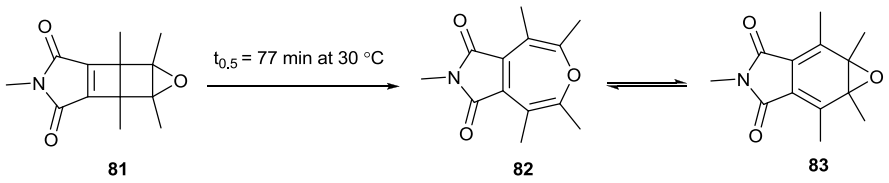
The reversible, photochemically or thermally-induced electrocyclic ring opening of arene-oxides to oxepines has been well documented.[48] In particular, the isomerisation of arene-oxides of polycyclic aromatic hydrocarbons[49] (including phenanthracene[50]) such as **79** as well compounds such as methyl benzoate derivatives[51] have been the subject of

much investigation (Scheme 2.7). Boyd and O'Kane reported that in the absence of light, the arene-oxide:oxepine ratio of an anthryl-oxepine remained constant at 43:57 as shown by NMR analysis. Upon irradiation with UV light for 30 minutes the ratio shifted to 10:90 in favour of the oxepine.[52]



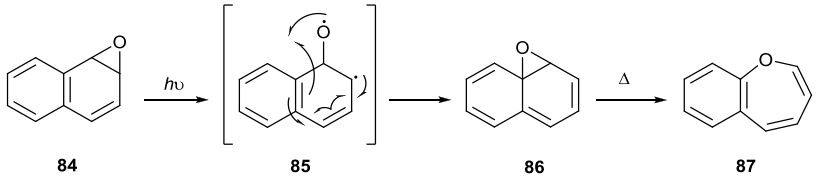
Scheme 2.7. A representative reversible electrocyclic ring opening of arene-oxide **79** to oxepine **80**.

The isolation of oxepines resulting from the isomerisation of Dewar-benzene epoxides has also been reported. Warrener and co-workers observed the isomerisation ($t_{0.5}$ = 77 min at 30 °C) of Dewar-benzene epoxide **81** to oxepine **82** which existed in equilibrium with arene-oxide **83** in solution, although they did not report the ratio of the two products obtained (Scheme 2.8).[53]

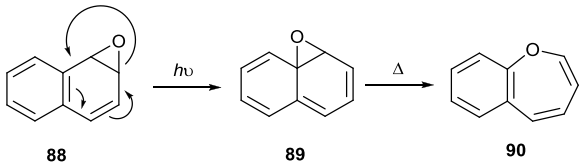


Scheme 2.8. Isomerisation of Dewar-benzene epoxide **81** to oxepine **82**/arene-oxide **83**.

Although a convenient method, the reversibility of the transformation can lead to low yields of isolated oxepine product. This is often compounded by light[54] or acid[55] induced aromatisation to phenol derivatives or oxygen rearrangement. It is proposed that the latter can occur *via* a diradical 'oxygen walk' (Scheme 2.9) or by [1,5]-sigmatropic (Scheme 2.10) pathways leading to the isolation of isomeric species.[52,53,56]

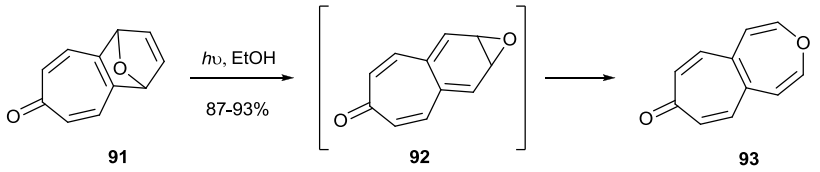


Scheme 2.9. Proposed 'oxygen walk' diradical mechanism for oxygen rearrangement.



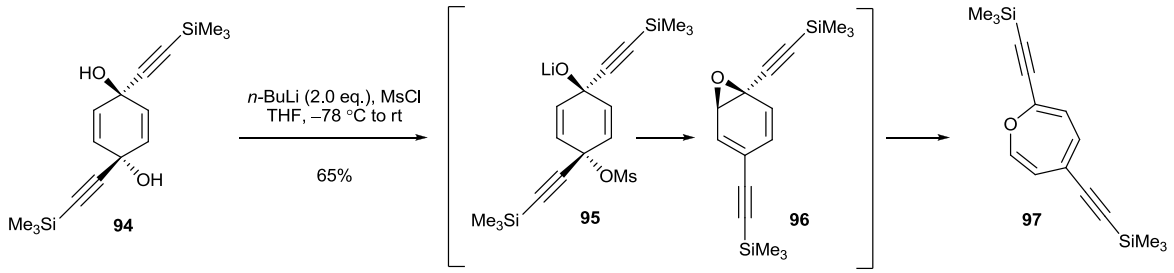
Scheme 2.10. Proposed [1,5]-sigmatropic mechanism for oxygen rearrangement.

Such transformations are well exemplified by the rearrangement followed by ring-opening of dihydro-furan **91** to oxepine **93** upon irradiation with a mercury lamp (Scheme 2.11). In this case the oxepine can be isolated in excellent yield, although it is sensitive to acidic conditions.[55]



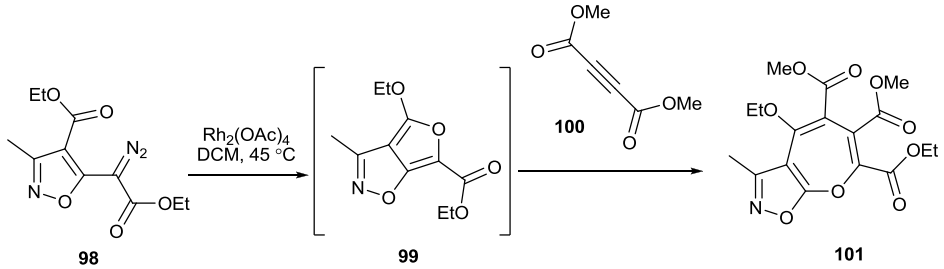
Scheme 2.11. Oxygen rearrangement and ring opening in the synthesis of oxepine **93**.

This study also serves to demonstrate that arene-oxide electrocyclic ring-opening is not just limited to benzannelated systems. Sankaraman and co-worker's synthesis of diethynyl oxepine **97** from its cyclohexadiene precursor **94** is another good example of this (Scheme 2.12).[57]



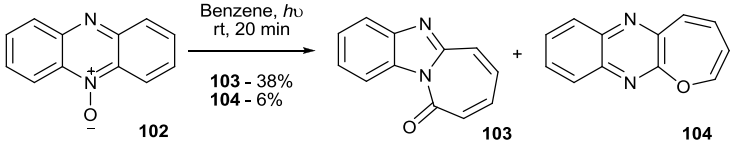
Scheme 2.12. Synthesis of diethynyl oxepine **97** *via* arene-oxide ring opening.

Friedrichsen and co-workers extended the scope of this methodology to the synthesis of more complex heterocyclces. They reported the synthesis of oxepine-isoxazole **101** from the rhodium(II) acetate mediated cyclisation of diazo-diester **98** to furan **99** with subsequent cycloaddition of dimethyl acetylenedicarboxylate **100** (Scheme 2.13). The oxygen rearrangement required to generate a suitable epoxide for ring-opening is remarkable, and thus unambiguous proof of the products structure was provided by X-ray crystallographic analysis.[58] No comment is made on yield however, although Yamazaki and co-workers utilised the same approach for oxepine formation in the preparation of benzoxepines from benzofurans achieving 42-62% yields.[59]



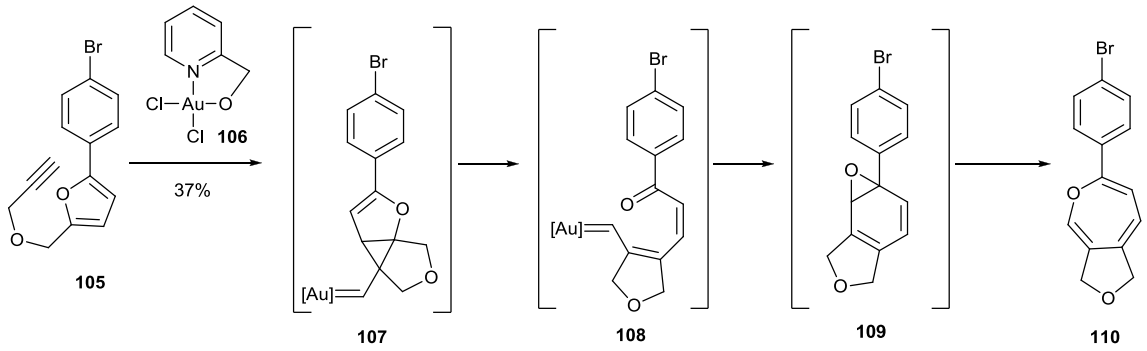
Scheme 2.13. Synthesis of oxepine-isoxazole **101**.

Albini and co-workers reported the photochemical rearrangement of phenazine-5-oxide **102** to the pyrazine-containing oxepine **104** in 1972. In this case, the yield of oxepine **104** obtained was very low (6%), with greater quantities of azepinone **103** being isolated (38%) (Scheme 2.14).[60] Similar observations were subsequently made by Niizuma and co-workers in 1985.[61]



Scheme 2.14. Rearrangement of phenazine-5-oxide **102** to azepinone **103** and oxepine **104**.

A final example of the synthesis of oxepines in complex heterocyclic systems is the gold-catalysed synthesis of oxepine **110** from ω-alkynyl furan **105**, first reported by Hashmi and co-workers in 2007 (Scheme 2.15).[62] Subsequent mechanistic studies followed in 2008.[63] It is proposed that the reaction proceeds *via* cyclopropyl carbenoid **107** which undergoes ring-opening to intermediate **108**. Cyclisation to arene-oxide **109** followed by ring-opening to form oxepine **110** then occurs.

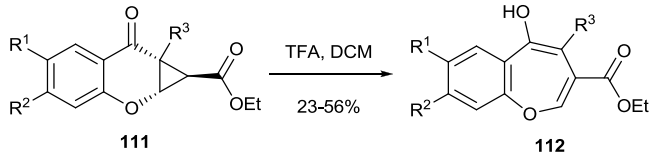


Scheme 2.15. Gold catalysed synthesis of oxepine **110** *via* arene-oxide **109**.

The literature examples outlined above demonstrate that an arene-oxide electrocyclic ring-opening strategy could be applied to the synthesis of 2,3-disubstitued oxepines such as janoxepin (**1**). However, the challenges associated with preparing suitable substrates for such transformations, frequent requirement for poly-substitution around the oxepine ring and low yields do not make it an attractive synthetic option.

2.3.2 Other Intramolecular Pathways to Oxepines

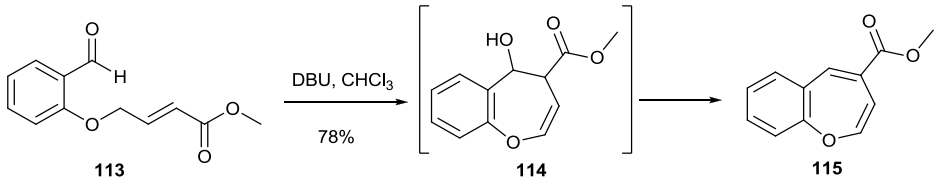
Examples of intra-molecular events leading to oxepine formation (not involving arene-oxide ring-opening) are extremely rare. Langer and co-workers reported the synthesis of oxepines in low to moderate yields by the ring-opening of cyclopropane **111** under acidic conditions (Scheme 2.16).[64] However, there is a requirement for an electron-withdrawing group on the cyclopropane as well as ketone functionality on the pyran ring for this reaction to proceed. It is therefore hard to envisage the method being applicable to the synthesis of 2,3-disubstituted oxepines such as janoxepin (**1**).



111 **112**

Scheme 2.16. Oxepine synthesis by ring-enlargement of cyclopropanes.

The only other notable example is the intramolecular aldol condensation between the α,β-unsaturated ester and aldehyde functionalities of substrate **113** as reported by Zeitler and Mager in 2007 (Scheme 2.17).[65] The apparently facile dehydration of hydroxyl-intermediate **114**, which the reaction presumably passes through, is particularly interesting in terms of possible eliminative strategies for oxepine formation.

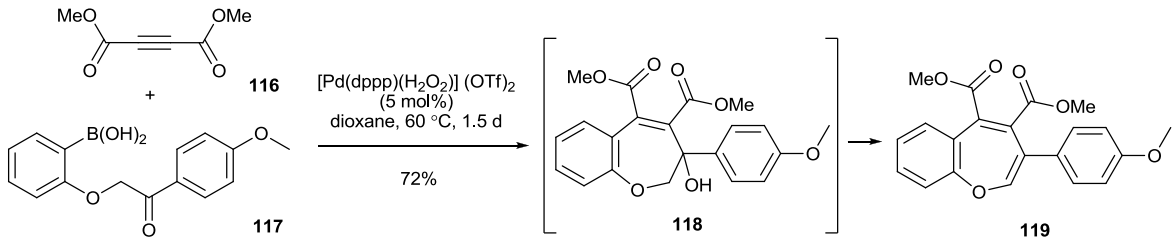


113 **114** **115**

Scheme 2.17. Formation of oxepine **115** by intra-molecular aldol condensation.

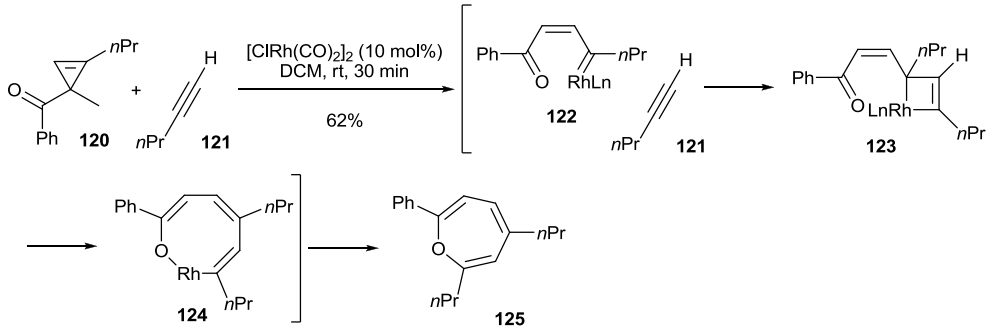
2.3.3 Intermolecular Cyclisation to Oxepines

Oxepines have also been prepared *via* intermolecular cyclisation events. Lu and Liu reported the fascinating palladium catalysed [5+2] annelation reaction between boronic acid **117** and alkyne **116** as shown in Scheme 2.18. This involves nucleophilic attack of an intermediate vinyl-palladium species onto the ketone. Oxepine **119** was isolated in good yield following the *in situ* dehydration of hydroxy-derivative **118**, a process which could be prevented by the addition of base to the reaction mixture.[66]



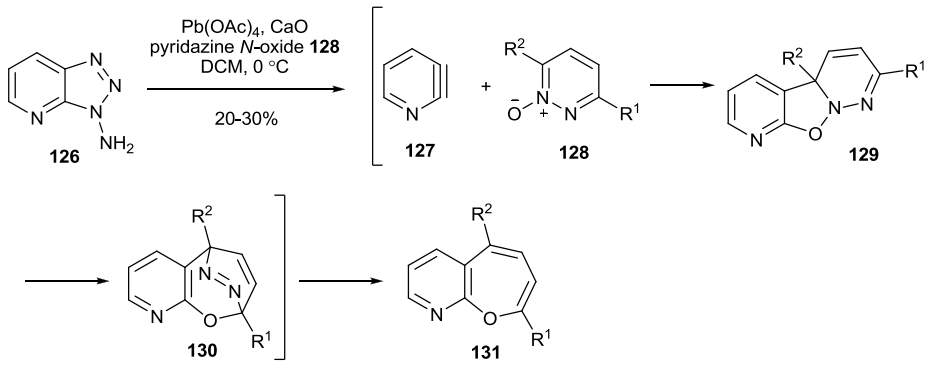
Scheme 2.18. [5+2] annelation reaction between boronic acid **117** and alkyne **116**.

The rhodium(I) catalysed reaction of alkyne **121** and cyclopropene **120** has also been reported as shown in Scheme 2.19. It is proposed that initial electrophilic attack of the rhodium(I) species on the cyclopropene gives metal carbene **122** which undergoes a [2+2]-cycloaddition with alkyne **121**. The resulting metallocyclic intermediate **123** then undergoes rearrangement followed by reductive elimination of the rhodium(I) species to give oxepine **125** in good yield. It was noted that treatment of oxepine **125** with acid induced aromatisation to a phenolic derivative.[67]



Scheme 2.19. Rhodium-catalysed cyclisation of cyclopropene **120** and alkyne **121**.

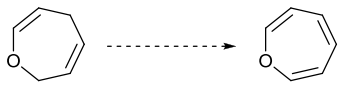
A final example of an intermolecular cyclisation leading to oxepine formation was reported by Tsuchiya and co-workers. In this reaction, pyridyne **127** is first generated from the treatment of aminotriazolopyridine **126** with lead tetra-acetate. This then undergoes cyclisation with pyridazine *N*-oxide **128** to afford oxepine **131**. Mechanistic studies indicated that the reaction proceeds *via* cycloadduct **129** which undergoes N-O bond fission and a [1,3]-shift to give intermediate **130**. The oxepine ring is then generated with the loss of nitrogen (Scheme 2.20).[68,69]



Scheme 2.20. Cyclisation of pyridazine *N*-oxide **128** and pyridine **126** to form oxepine **131**.

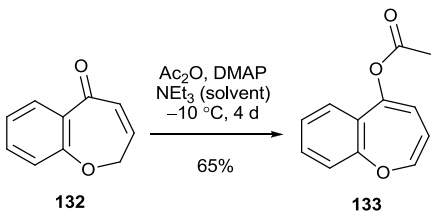
2.3.4 Dihydro-Oxepine Elaboration

The direct oxidation of dihydro-oxepines to oxepines (Scheme 2.21) either *via* radical (*e.g.* DDQ) or dehydrogenative (*e.g.* Pd/C) approaches has not been reported. However, two examples of the preparation of oxepines from dihydro-oxepines through an eliminative approach exist.



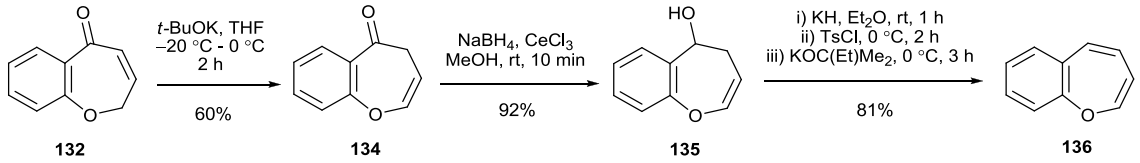
Scheme 2.21. Dihydro-oxepine elaboration.

Hoffman and Djafari reported the synthesis of oxepine **133** by trapping the enol-tautomer of enone **132** generated under basic conditions with acetic anhydride (Scheme 2.22).[70]



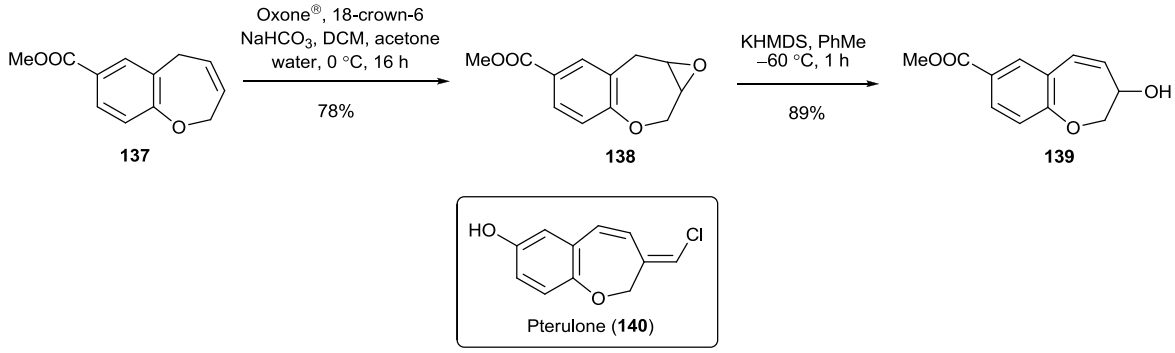
Scheme 2.22. Trapping enol tautomer of enone **132** as enol ester **133**.

They subsequently demonstrated that double bond migration of enone **132** followed by Luche reduction of the ketone gave alcohol **135**. This could then be eliminated following activation as a tosylate using potassium *tert*-amylate as base to generate oxepine **136** (Scheme 2.23).[71]



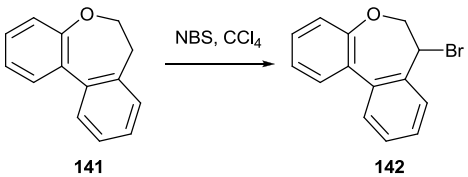
Scheme 2.23. Elaboration of enone **132** to oxepine **136**.

Apart from these examples, the dehydration of hydroxy-dihydro-oxepine intermediates **114** and **118** as seen in Schemes 2.17[66] and 2.18[65] respectively is also worthy of note. Given the potential utility of this eliminative approach, it is important to consider methods for the preparation of suitable dihydro-oxepine substrates. Again, few literature examples exist, however, epoxidation followed by base-induced ring-opening is one possible approach as demonstrated by the preparation of allylic alcohol **139** in Wijnberg and co-workers' synthesis of pterulone (**140**) (Scheme 2.24).[72] It is interesting to note that *m*-CPBA epoxidation was not possible in this case due to the *m*-chlorobenzoate anion formed during the reaction immediately opening epoxide **138**.



Scheme 2.24. Epoxidation followed by base-induced ring-opening to generate allylic alcohol **139**.

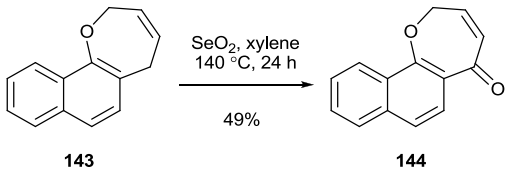
Allylic bromination of a dihydro-oxepine is also a reasonable strategy for preparing a substrate that could undergo dehydrobromination to an oxepine. However, this has only been reported on dibenzo-oxepine substrates such as **141**, and as long ago as 1973 (Scheme 2.25). No yield was reported for the reaction.[42]



Scheme 2.25. Allylic bromination of dibenzo-dihydro-oxepine **141**.

Similarly, allylic oxidation could provide a suitable substrate for elimination to an oxepine. Chattopadhyay and co-workers prepared enone **144** from selenium dioxide oxidation at the allylic-benzylic position of dihydro-oxepine **143** (Scheme 2.26). A

reduction – activation – E2' elimination sequence can be envisaged for subsequent elaboration to the corresponding oxepine.[73]



Scheme 2.26. Allylic oxidation of dihydro-oxepine **143**.

2.4 Dihydro-Oxepine Synthesis: Literature Routes

Synthetic approaches to the preparation of dihydro-oxepines have been well reviewed (alongside those of tetrahydro-oxepines) in recent years.[6,7,74] In particular, the 2006 review by Peczuh and co-workers covers an expansive cross-section of the literature, categorising syntheses according to carbon-carbon (C-C) and carbon-oxygen (C-O) bond-forming reactions (Figure 2.1).[8] Since then, there have been a number of advances in both these categories as well as in ring-enlargement approaches to dihydro-oxepines.

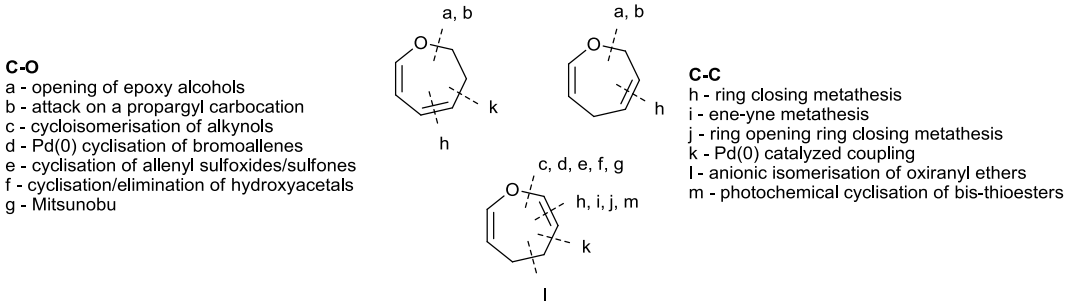
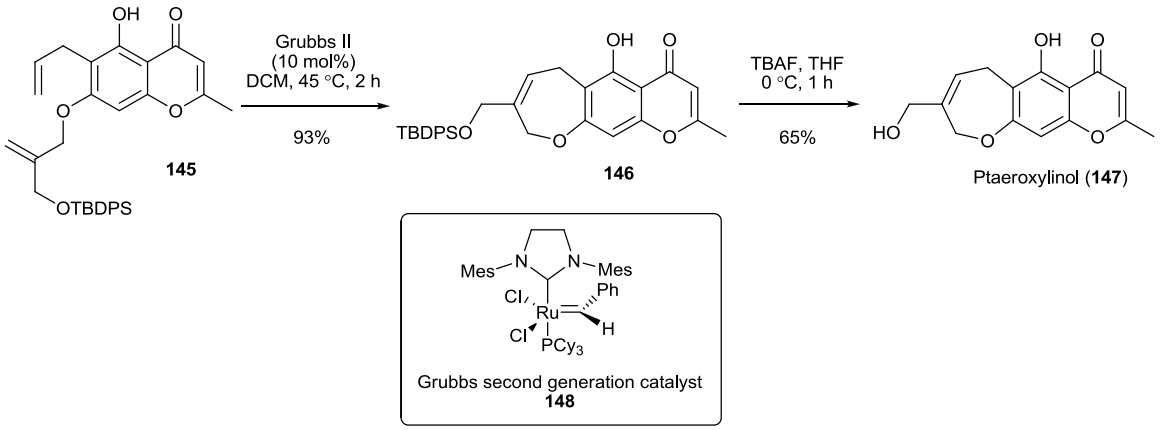


Figure 2.1. Categorisation of synthetic routes to dihydro-oxepines.[8]

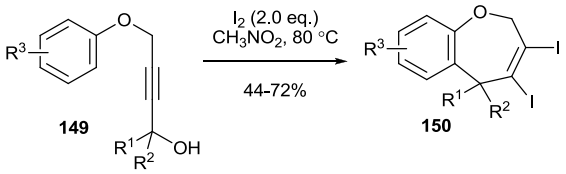
2.4.1 Carbon-Carbon Bond Forming Reactions

Ring-closing metathesis (RCM) has been used effectively in numerous settings since the Peczuh review. Whilst examples such as Widhalm and co-workers' synthesis of dihydro-oxepine-containing biheteroaryl compounds using RCM are notable,[75] the application of RCM in natural product synthesis is of particular relevance here. An example of this is the synthesis of ptaeroxylinol (**147**) as reported by Moody and co-workers in 2010. RCM of diallyl intermediate **145** using Grubbs second generation catalyst **148** followed by silyl deprotection completed the synthesis (Scheme 2.27). Another recent application of RCM in natural product synthesis is found in Yoshida's synthesis of radulanin H.[76]



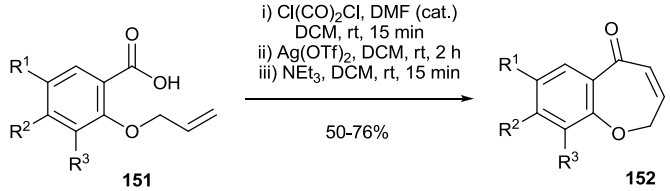
Scheme 2.27. RCM in the synthesis of dihydro-oxepine-containing ptaeroxylinol (**147**).

Another advance in C-C forming reactions is the electrophilic carbocyclisation of aryl propargylic alcohols as reported by Liang and co-workers. Diiodo-dihydro-oxepine derivatives **150** were prepared in 44-72% yields by treatment of aryl propargylic alcohol **149** with iodine in nitromethane at 80 °C (Scheme 2.28). Whilst the diiodides obtained might have application in subsequent coupling reactions, they have no direct utility in the synthesis of janoxepin (**1**).[77]



Scheme 2.28. Electrophilic carbocyclisation of aryl propargylic alcohols **149** to dihydro-oxepines **150**.

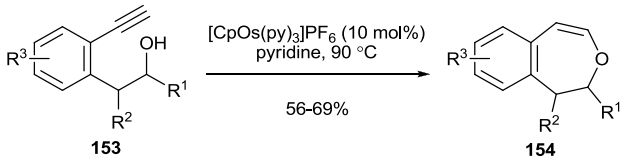
A final recent example of a dihydro-oxepine being prepared *via* a C-C bond forming reaction is the synthesis of benzoxepinones through a silver-mediated Kondakov-Darzens olefin acylation. Jarvo and Barczak reported that treatment of a range of *O*-allyl benzoic acids **151** with oxalyl chloride followed by silver(II) triflate gave access to benzo dihydro-oxepines **152** in 50-76% yields (Scheme 2.29).[78] The potential application of benzoxepinones in dihydro-oxepine elaboration to oxepines has already been discussed.



Scheme 2.29. Benzoxepinone synthesis *via* silver-mediated Kondakov-Darzens olefin acylation.

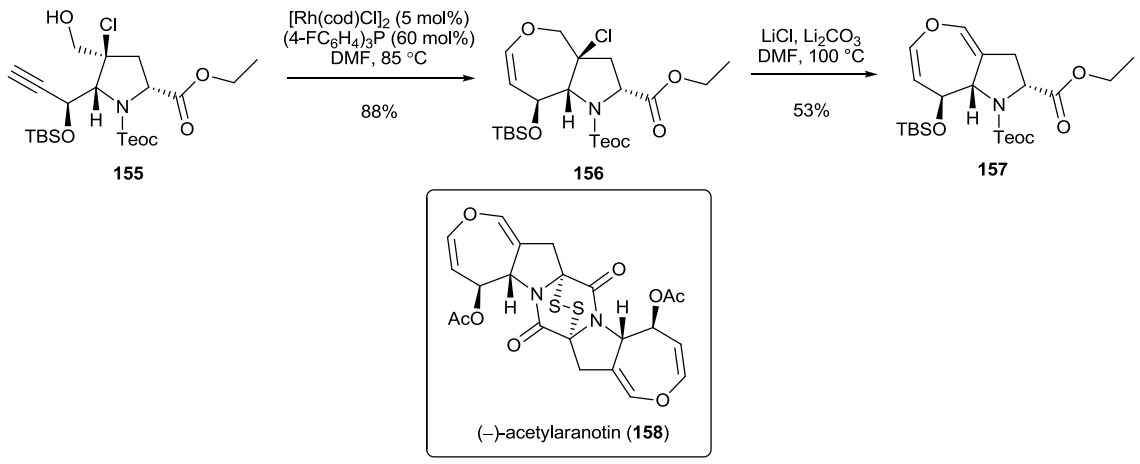
2.4.2 Carbon-Oxygen Bond Forming Reactions

The transition metal-catalysed cycloisomerisation of alkynols for the synthesis of dihydro-oxepines has been the focus of many studies since the Peczuh review. For example, Saá and co-workers reported the osmium-mediated cycloisomerisation of aromatic alkynols **153** to dihydro-oxepines **154** in 56-69% yields (Scheme 2.30).[79]



Scheme 2.30. Osmium-catalysed cycloisomerisation of alkynols.

This methodology has also been applied to natural product synthesis. Reisman and co-workers utilised a rhodium-catalysed cycloisomerisation of alkynol **155** to tetrahydro-oxepine **156**. A dehydrohalogenation then afforded the dihydro-oxepine **157** in their synthesis of the dihydro-oxepine epidithiodiketopiperazine natural product (–)-acetylaranotin (**158**) (Scheme 2.31).[80] These examples demonstrate that a wide substrate scope can be tolerated by such methodology making it a powerful C-O bond forming tool for the synthesis of dihydro-oxepines.

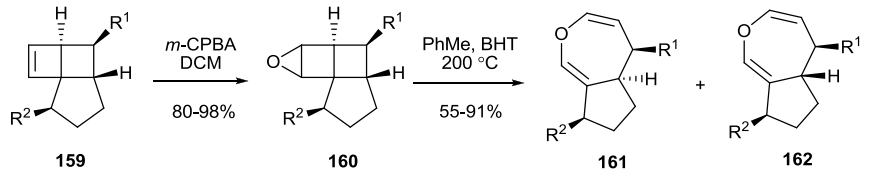


Scheme 2.31. Rhodium-catalysed cycloisomerisation of alkynol **155** to tetrahydro-oxepine **156** in the synthesis of (–)-acetylaranotin (**158**).

2.4.3 Ring-Expansion Methodology

A novel ring-expansion method for dihydro-oxepine synthesis has also been reported since the 2006 review. Snapper and Leyhane demonstrated that epoxidation of strained cyclobutenes **159** followed by thermally-induced ring-expansion gave access to

diastereomeric dihydro-oxepines **161** and **162** (Scheme 2.32).[81] The diastereomeric ratio obtained (believed to be due to fragmentation of the epoxide through diradical pathways) varies depending on the nature of the R^1 and R^2 substituents.

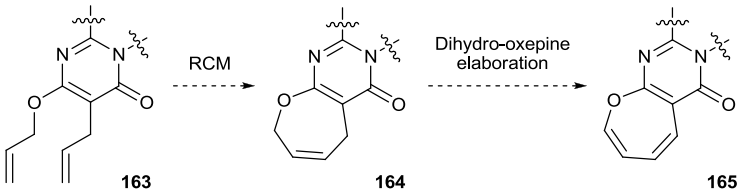


Scheme 2.32. Epoxidation and ring expansion of cyclobutenes **159**.

Having considered the many different strategies for preparing dihydro-oxepines outlined above, RCM was identified as the most suitable method for the synthesis of janoxepin (**1**) in accordance with the retrosynthetic analysis outlined in Scheme 1.3.

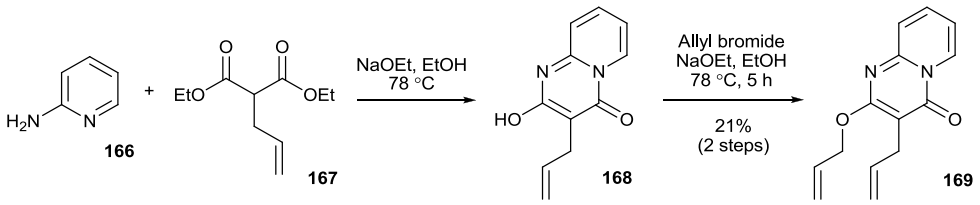
2.5 Pyrimidinone Synthesis: Literature Routes

The literature surrounding dihydro-oxepine elaboration to oxepines was not extensive, however the planned RCM - dihydro-oxepine elaboration strategy was still an attractive one (Scheme 2.33). An efficient method for the preparation of a suitable pyrimidinone such as **163** would therefore be required.



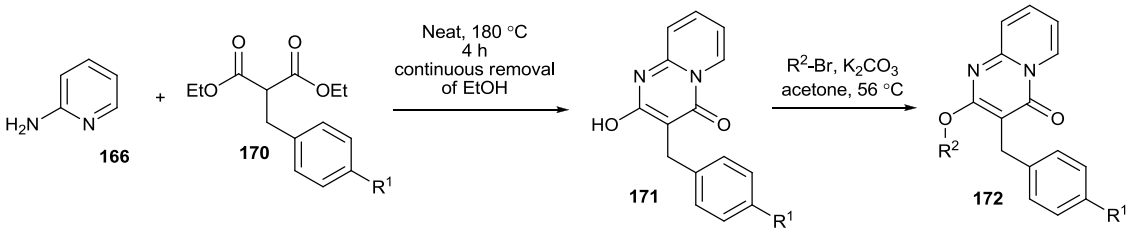
Scheme 2.33. Proposed strategy for oxepine construction.

Reported approaches to the synthesis of this class of pyrimidinone utilise a narrow range of reactions. They exclusively rely on condensation of an amidine/amino-pyridine and a dicarbonyl compound to form the pyrimidinone ring. A subsequent substitution reaction to install the *O*-alkyl chain is then performed. For example, Urban and co-workers prepared pyrimidinone **168** from the condensation of 2-aminopyridine **166** and commercially available malonate **167** using NaOEt as base. They then utilised the nucleophilic nature of the hydroxyl of the isolated enol tautomer **168** to perform an *O*-allylation with allyl bromide (Scheme 2.34).[82]



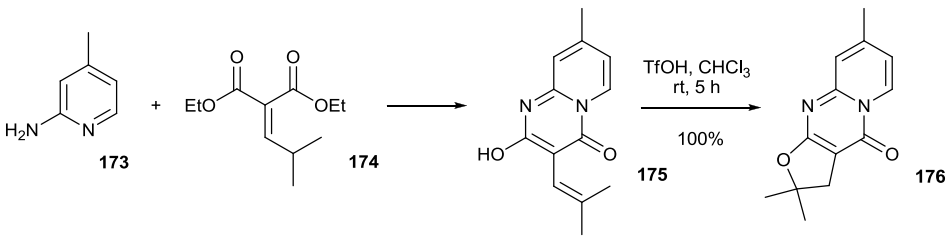
Scheme 2.34. Condensation-*O*-allylation sequence to synthesis diallyl pyrimidinone **169**.

An almost identical approach was applied using a range of alkyl bromides by Venkatesan and co-workers in their synthesis of pyrimidinone **172**.[83] In this case the condensation reaction was performed in the absence of base but at high temperature with the continuous removal of ethanol (Scheme 2.35).[83] No yields are reported for the reaction sequence, however Utley and co-workers demonstrated the efficient nature of such condensation reactions, achieving 74-96% yields on a range of substrates.[84]



Scheme 2.35. Pyrimidinone preparation through condensation at high temperature in the absence of base followed by *O*-alkylation with alkyl bromides.

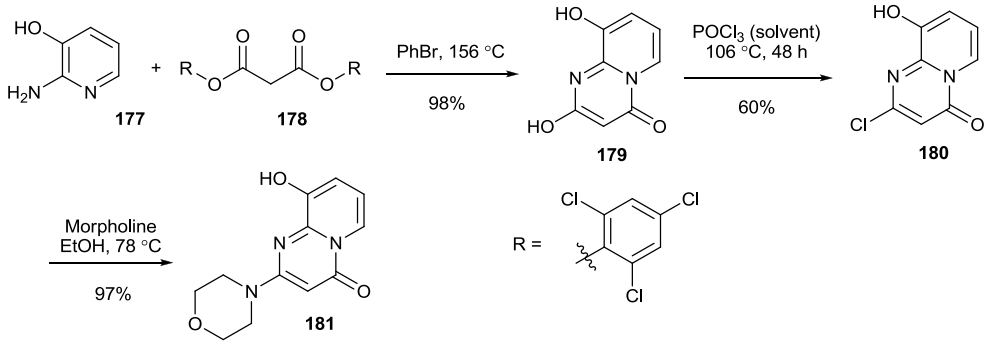
The synthesis of dihydro-furan **176** is another interesting example highlighting the nucleophilicity of the enol-oxygen. Under acidic conditions pyrimidinone **175** (prepared from condensation of amino-pyridine **173** and malonate **174** but not discussed) is seen to readily cyclise to dihydro-furan **176** (Scheme 2.36).[85]



Scheme 2.36. Preparation of pyrimidinone **175** and subsequent acid-mediated cyclisation to dihydro-furan **176**.

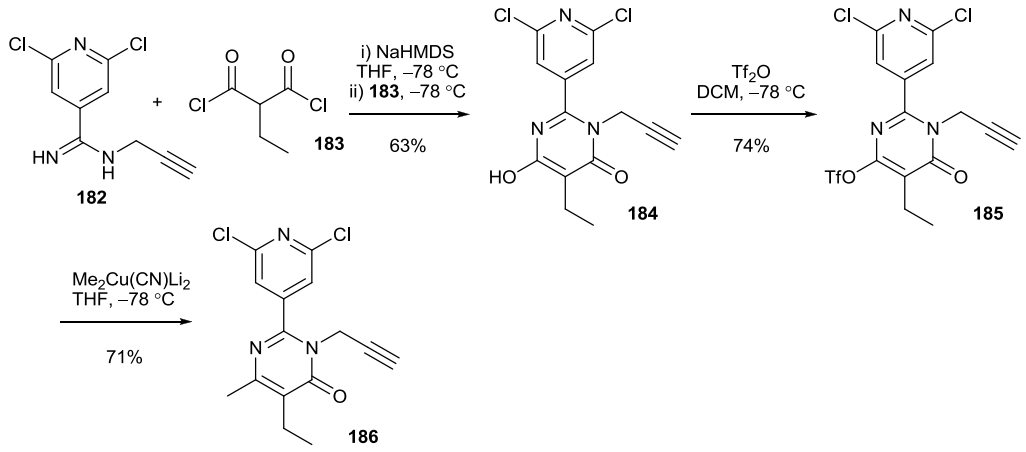
An alternative strategy commonly used also relies on a condensation reaction to form the pyrimidinone ring. However, the polarity of the hydroxyl functionality is reversed by installing a good leaving group, thereby generating an electrophilic centre. Alkylation is then possible by nulceophilic attack. One such example shown in Scheme

2.37 uses $POCl_3$ to generate chloride **180** from pyrimidinone **179** which is readily displaced by morpholine to furnish amine **181**.[56]



Scheme 2.37. Condensation followed by alkylation by addition of a nucleophile.

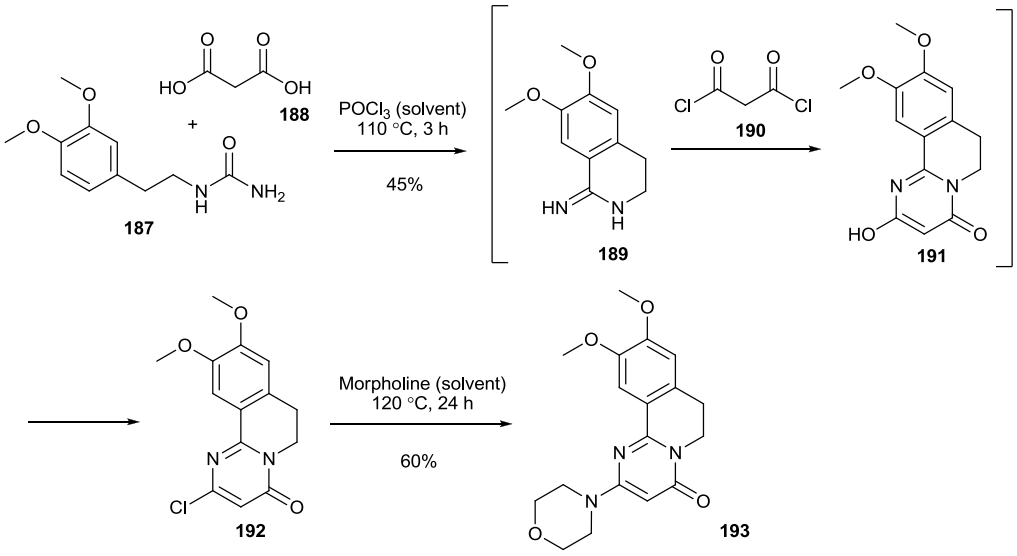
E. Taylor and co-workers expanded on early work by Dox and Yoder,[86] demonstrating that amidines and not just amino-pyridines could be used to prepare pyrimidinones *via* condensation with malonate derivatives. They employed malonyl dichloride **183** as an alternative to the commonly used malonate ester substrates in the synthesis of pyrimidinone **184**. In this case the hydroxyl group is activated for elimination by forming triflate **185**. This is then displaced by nucleophilic attack of a cyanocuprate to furnish the desired alkylated product **186** (Scheme 2.38).[87]



Scheme 2.38. Condensation of amidine **182** and malonyl dichloride **183** followed by alkylation with a cyanocuprate.

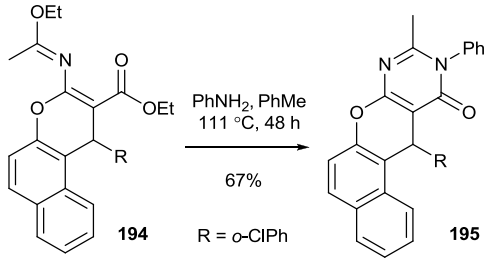
Ureas have also been employed to prepare pyrimidinones in condensation reactions. Lal and co-workers used a one-pot process to synthesise pyrimidinone chloride **192** from urea **187** and malonic acid **188** in moderate yield (Scheme 2.39).[88] It is proposed that initial cyclisation of urea **187** to cyclic amidine **189** is followed by condensation with the $POCl_3$ activated malonic acid **190**. Although an interesting transformation, the requirement of an activated aromatic species for cyclisation to

occur does limit its application. Morpholine was again used to demonstrate that nucleophilic substitution of chloride **192** was possible in good yield.



Scheme 2.39. One pot synthesis of pyrimidinone **191** from urea **187** and malonic acid **188** followed by nucleophilic substitution with morpholine.

Methods for pyrimidinone synthesis are not limited to the condensation of an amino-pyridine or amidine with a malonate derivative. This is exemplified by the cyclisation of imidate **194** with aniline to furnish pyrimidinone **195** (Scheme 2.40).[89] In this case, the required *O*-substitution was already installed whilst a range of primary alkyl amines were successfully used.

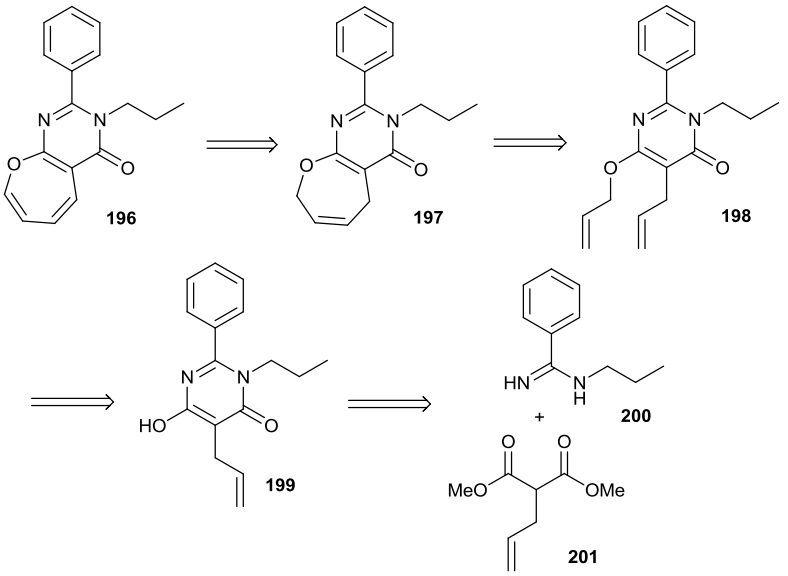


Scheme 2.40. Pyrimidinone **195** preparation by condensation of aniline and imidate **194**.

2.6 Pyrimidinone-Oxepine Model Study

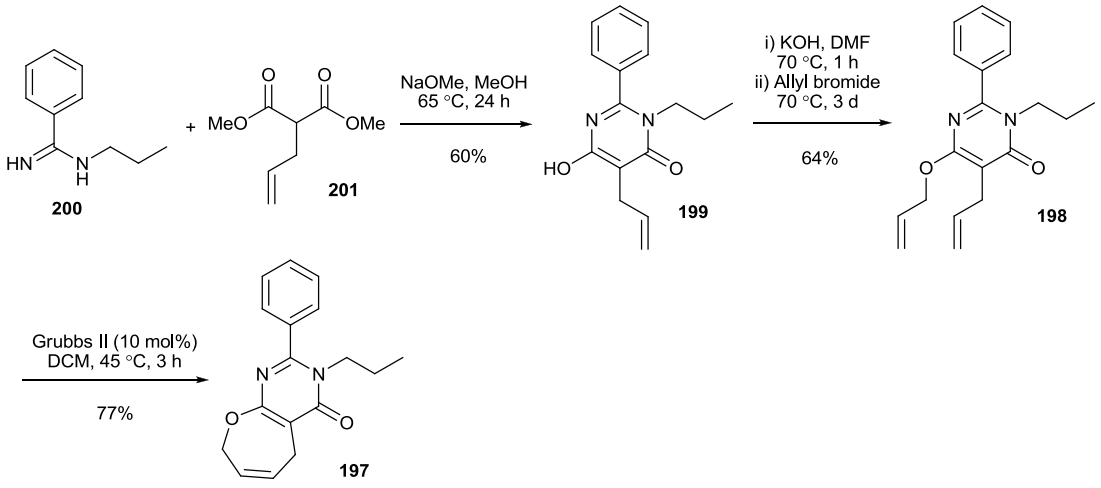
In order to prove the viability of the planned strategy initial investigations were focussed on repeating the synthesis of a compound to model the oxepine-pyrimidinone system seen in janoxepin (**1**). The novel oxepine-pyrimidinone **196** had been identified as a suitable target molecule by Jones in 2008, a retrosynthetic analysis of which is shown in Scheme 2.41.[35] As with the retrosynthetic analysis of janoxepin (**1**) (Scheme 1.3) the oxepine ring would be generated through elaboration of dihydro-oxepine **197**,

itself prepared by RCM of diallyl pyrimidinone **198**. This key intermediate would be synthesised by condensation of amidine **200** and malonate **201**.



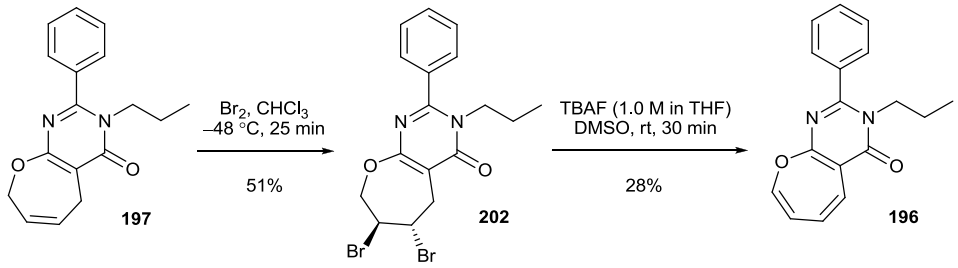
Scheme 2.41. Retrosynthetic analysis of model compound **196**.

Jones' synthesis[35] first required known amidine **200**[90] which was readily prepared from reaction of benzonitrile and *n*-propylamine in the presence of $AlCl_3$.[91] This underwent condensation with the commercially available malonate **201** in the presence of NaOMe to provide pyrimidinone **199** in moderate, but acceptable yield. *O*-Allylation was effected by treatment of pyrimidinone **199** with KOH followed by the addition of allyl bromide to afford the diallyl pyrimidinone intermediate **198**. This underwent a very efficient RCM with Grubbs second generation catalyst **148** to furnish the dihydro-oxepine **197** (Scheme 2.42). Pleasingly when this was repeated the yields achieved compared very well with those reported by Jones.[35]



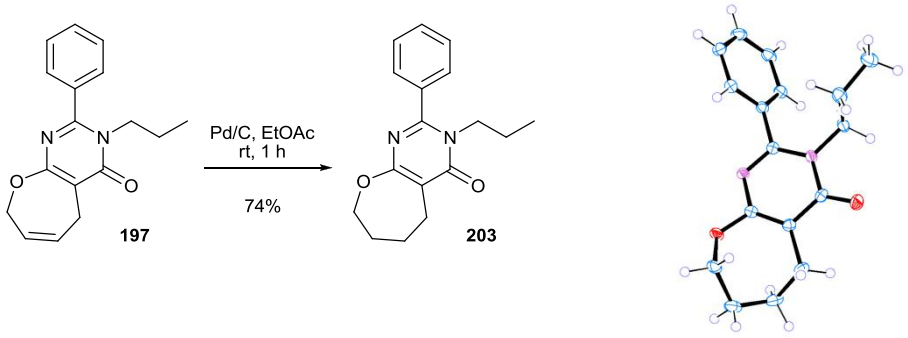
Scheme 2.42. Synthesis of dihydro-oxepine **197**.

Earlier attempts to elaborate dihydro-oxepine **197** to the desired oxepine *via* allylic bromination followed by dehydrobromination had been unsuccessful.[35] Therefore Jones elected to convert dihydro-oxepine **197** to the racemic vicinal dibromide **202**. A number of bases failed to mediate subsequent dehydrobromination to the desired oxepine **196**. The screened bases comprised DBU, NaOMe, MTBD and *t*-BuOK, all in THF.[35] Elimination was eventually achieved by treatment of dibromide **202** with TBAF (1.0 M solution in THF) in DMSO at room temperature, affording the desired oxepine-pyrimidinone **196** in an excellent 87% yield.[35] Disappointingly though, this result could not be replicated in subsequent attempts. A consistently reproduced yield of 28-30% was instead achieved (Scheme 2.43).



Scheme 2.43. Dihydro-oxepine elaboration: bromination – dehydrobromination.

The structure of oxepine-pyrimidinone **196** was assigned by ^{1}H and ^{13}C-NMR spectroscopy in conjunction with HSQC and COSY experiments. Relevant signals for the spectra obtained compared favourably to those of janoxepin (**1**) but to provide unambiguous structural proof it was desirable to obtain an X-ray crystal structure. Dihydro-oxepine **197**, dibromide **202** and oxepine **196** were not crystalline solids and therefore were unsuitable substrates for analysis. However, the study was expanded and hydrogenation of dihydro-oxepine **197** afforded tetrahydro-oxepine **203** as a colourless crystalline solid for which an X-ray crystal structure was obtained (Scheme 2.44).

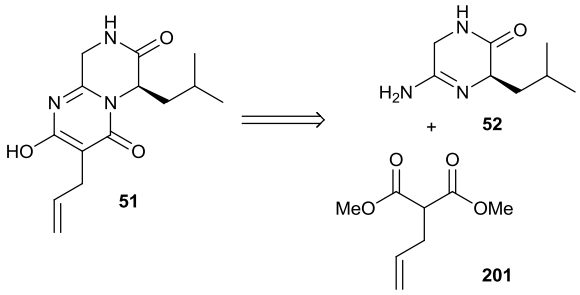


Scheme 2.44. Tetrahydro-oxepine **203**: synthesis and X-ray crystal structure. ORTEP representation shown with ellipsoids at 50% probability. CCDC 862141.

Despite the low yield associated with dihydro-oxepine elaboration, the model study did demonstrate that the planned strategy for oxepine-pyrimidinone synthesis was viable. Attention now turned to investigation of ketopiperazine ring construction and subsequent incorporation into the developed methodology.

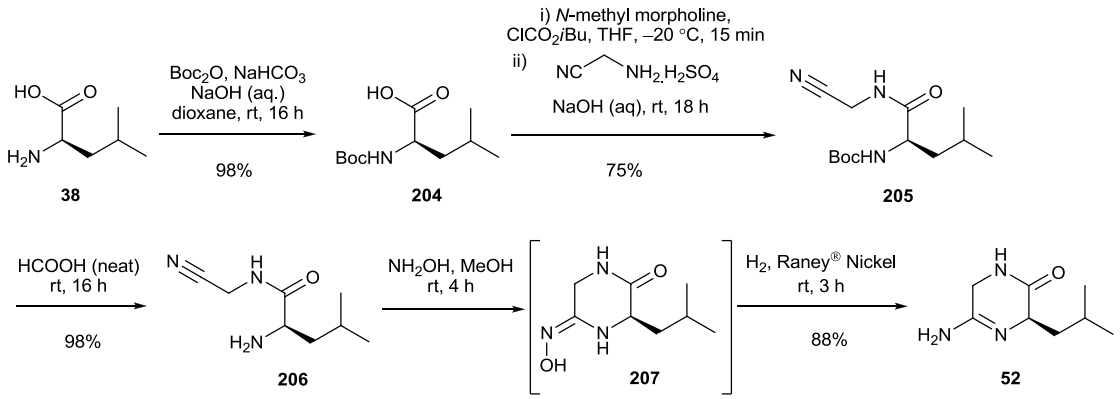
2.7 Cyclic Amidine Synthesis

As outlined in the retrosynthetic analysis of janoxepin (**1**) (Scheme 1.3), it was proposed that the key ketopiperazine-pyrimidinone **51** could be prepared from the condensation of cyclic amidine **52** and malonate **201** (Scheme 2.45).



Scheme 2.45. Retrosynthetic analysis of pyrimidinone **51**.

Using a synthetic route reported by Isobe and co-workers,[92] cyclic amidine **52** was efficiently prepared. Employing D-leucine **38** as the chiral starting material, Boc protection followed by coupling with aminoacetonitrile bisulfate *via* a mixed anhydride and then formic acid deprotection provided amine **206**. This underwent a one-pot oximation – cyclisation – hydrogenation sequence to afford the desired novel cyclic amidine **52** on multi-gram scale in just 4 steps and 63% yield from D-leucine **38** (which compared favourably to that obtained by Isobe and co-workers (61%) for a similar reaction sequence) (Scheme 2.46).[92]



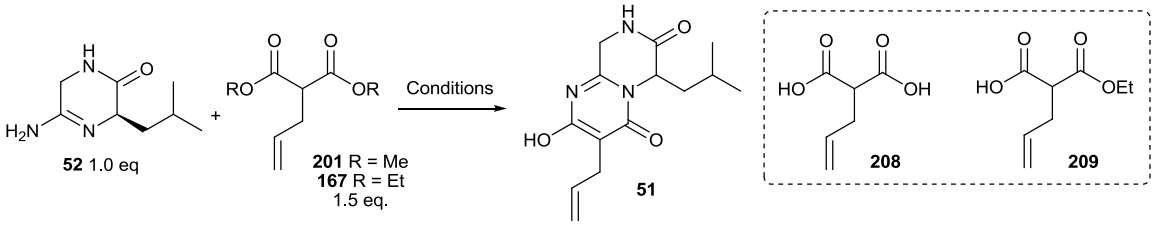
Scheme 2.46. Synthesis of cyclic amidine **52**.

The poor solubility of amidine **52** meant that chiral HPLC analysis to ascertain its ee could not be undertaken. However, optical rotation measurements ($[\alpha]_D^{22}$ –47 *c* = 1.0, MeOH) suggested that the configuration of the stereocentre may have been retained.

2.8 Preparation of Pyrimidinone **51**

Cyclic amidine **52** was first subjected to the condensation conditions successfully used in the model study. Pleasingly, reaction of amidine **52** and dimethyl malonate **201** with NaOMe in refluxing MeOH furnished the desired pyrimidinone **51** in 58% yield (Table 2.1, entry 1). However, it was desirable to improve the reaction efficiency for this critical step. Allowing for higher reaction temperatures, diethyl malonate **167** and ethanol as solvent were next investigated (Table 2.1, entry 2). Disappointingly, the yield achieved fell to just 32% of the desired pyrimidinone **51** with substantial quantities of malonate hydrolysis products **208** and **209** observed in the ^{1}H-NMR spectrum of the crude product. The side-products also led to a difficult purification by flash column chromatography, further reducing the isolated yield.

Steendam (an Erasmus visitor) investigated ways to minimise this problem in 2010.[93] He reported that using dimethyl malonate **201** in MeOH with a greater excess of Na could drastically reduce the reaction time. Together with implementing strictly anhydrous conditions - MeOH was dried over $Mg(OMe)_2$,[94] glassware was flame-dried under vacuum and activated 3 Å molecular sieves were added to the reaction mixture - a much improved 72% yield of pyrimidinone **51** was achieved (Table 2.1, entry 3).[93]

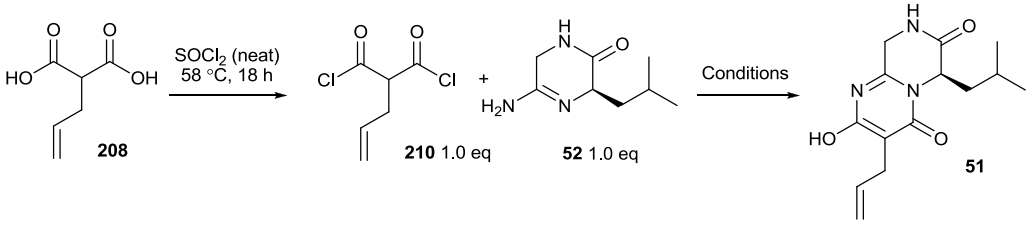


Entry	Malonate	Conditions	Yield 51
1	**201**	Na (3.0 eq.), MeOH, 66 °C, 18 h	58%
2	**167**	Na (3.0 eq.), EtOH, 78 °C, 18 h	32%
3	**201**	Na (6.0 eq.), MeOH, 3Å mol. sieves, 66 °C, 3 h	72%

Table 2.1. Optimisation study for the condensation of cyclic amidine **52** with allyl malonates.[93]

Steendam also explored the reaction of malonyl-dichloride **210** with cyclic amidine **52**.[93] Dichloride **210** was prepared from the commercially available malonic acid **208** by heating with thionyl chloride and was used without purification. Two condensation

conditions were investigated. The use of triethylamine as base in THF at –78 °C to room temperature returned only a 17% yield of pyrimidinone **51** (Table 2.2, entry 1). Using NaHMDS as base furnished only 14% of the desired product (Table 2.2, entry 2).[93] It is proposed that the low yields are associated with the facile hydrolysis of malonyl dichloride **210** back to malonic acid **208** under the reaction conditions.



Entry	Conditions	Yield 51
1	NEt_3 (2.0 eq.), THF, –78 °C - rt	17%
2	NaHMDS (2.0 eq.), THF, –78 °C - rt	14%

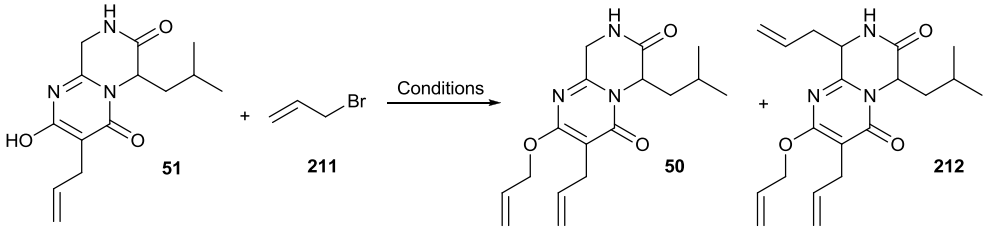
Table 2.2. Optimisation study for the condensation of cyclic amidine **52** with malonyl dichloride **210**.[93]

Again, the poor solubility of pyrimidinone **51** prevented chiral HPLC analysis to evaluate the *ee* of the product obtained. The optical rotation measurement observed ($[\alpha]_D^{22}$ +0.8 *c* = 1.0, MeOH) suggested that racemisation of the substrate had occurred during the condensation step, however. An unambiguous evaluation of the *ee* of a subsequent intermediate was therefore critical.

2.9 Preparation of Diallyl Pyrimidinone **50**

The conditions for *O*-allylation used in the model study were investigated first. Treatment of pyrimidinone **51** with KOH in DMF followed by the addition of allyl bromide **211** and heating provided diallyl pyrimidinone **50** but in a low 42% yield (Table 2.3, entry 1). Whilst this result produced material for investigation of subsequent steps, it was clear that such a low yield in a linear synthesis would not be sustainable. An extensive optimisation study was undertaken by Steendam[93] who first investigated using allyl bromide **211** with K_2CO_3 as base in refluxing acetone. Diallyl pyrimidinone **50** was isolated in 35% yield, whilst 7% of the intriguing *bis*-allylated compound **212** was also isolated (Table 2.3, entry 2). The addition of TBAI in order to increase the rate of reaction by a Finkelstein-type mechanism offered a slight improvement in overall yield at lower temperatures (Table 2.3, entry 3). In order to minimise the amount of *bis*-allylation observed using just one equivalent of allyl bromide **211** was investigated. This had the desired effect with respect to over alkylation – no *bis*-allylated compound

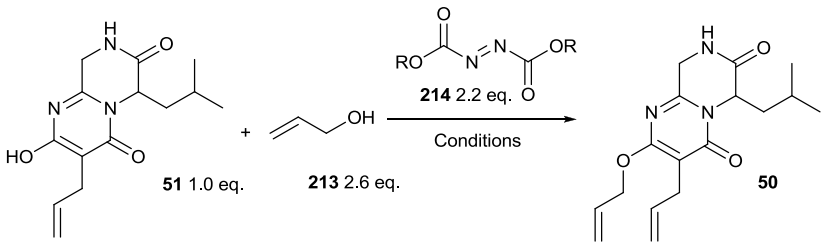
212 was isolated – but resulted in a small drop in yield of **50** (Table 2.3, entry 4). Changing the iodide source to NaI had a significant detrimental effect on yield (Table 2.3, entry 5) whilst changing the solvent to THF offered a slight improvement (Table 2.3, entry 6). Experimentation with Cs_2CO_3, Ag_2CO_2 and NaOMe as bases typically resulted in no reaction at all (Table 2.3, entries 7-10) whilst a formal deprotonation of pyrimidinone **51** with NaH in THF at –78 °C followed by addition of the alkylating agent was also unsuccessful.[93]



Entry	Equiv. 211	Base (1.5 eq.)	Additive (1.5 eq.)	Conditions	Yield 50
1	1.5	KOH	-	DMF, 60 °C, 2 d	41%
2	1.5	K_2CO_3	-	Acetone, 56 °C, 16 h	35% + **212** 7%
3	1.5	K_2CO_3	TBAI	Acetone, 0 °C – rt, 2 h	41% + **212** 7%
4	1.0	K_2CO_3	TBAI	Acetone, –78 °C – 0 °C, 18 h	37%
5	1.0	K_2CO_3	NaI	Acetone, 0 °C – rt, 3 d	21%
6	1.0	K_2CO_3	TBAI	THF, –78 °C – rt, 3 d	42%
7	1.0	Cs_2CO_3	TBAI	Acetone, 60 °C, 4 d	7%
8	1.0	Cs_2CO_3	TBAI	DMF, 60 °C, 4 d	-
9	1.0	Ag_2CO_3	TBAI	Acetone, 60 °C, 6 d	-
10	1.0	NaOMe	TBAI	MeOH, rt, 3 d	-
11	1.0	NaH	TBAI	THF, –78 °C – rt, 2 d	-

Table 2.3. Optimisation study for *O*-allylation with allyl bromide **211**.[93]

It was clear that a different approach was required in order to achieve selectivity for *O*-allylation and an acceptable yield for this transformation. Steendam proposed the Mitsunobu reaction of pyrimidinone **51** and allyl alcohol **213** with an azodicarboxylate **214** and a phosphine as an alternative strategy.[93] Initial experiments using diethyl azodicarboxylate (DEAD) with PPh_3 and PBu_3 returned similar yields to those achieved in the allyl bromide study (Table 2.4, entries 1-2). Using the sterically hindered di-*tert*-butyl azodicarboxylate (DBAD) resulted in lower yields (Table 2.4, entry 3) whilst the more readily available di-*iso*-propyl azodicarboxylate (DIAD) was used with great success. With the addition of NEt_3 as a base and a higher reaction temperature, diallyl pyrimidinone **50** was isolated in 73% yield after just 2 hours (Table 2.4, entry 4). This result could be reliably reproduced on an 8 g scale.



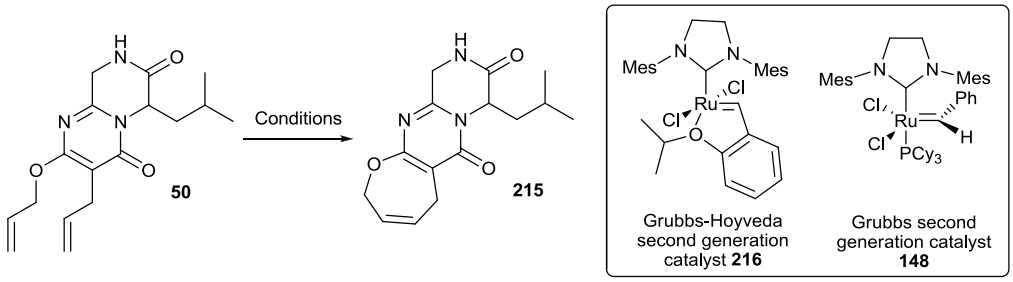
Entry	Phosphine (2.2 eq.)	Azodicarboxylate 214	Additive	Conditions	Yield 50
1	PPh_3	DEAD (R = Et)	-	THF, 10 °C – rt, 2 d	32%
2	PBu_3	DEAD (R = Et)	-	THF, 10 °C – rt, 2 d	30%
3	PPh_3	DBAD (R = *t*-Bu)	-	THF, 10 °C – rt, 2 d	21%
4	PPh_3	DIAD (R = *i*-Pr)	NEt_3 (1.0 eq.)	THF, 10 °C – 60 °C, 2 h	73%

Table 2.4. Optimisation study for *O*-allylation using Mitsunobu conditions.[93]

Chiral HPLC analysis (Chiralpak AD-H column) of diallyl pyrimidinone **50** was undertaken and confirmed that the material was essentially racemic (53:47 *er*). Optical rotation measurements ($[\alpha]_D^{22}$ +0.5 *c* = 1.0, MeOH) were in agreement with this outcome which is presumably a result of racemisation during the cyclocondensation step.

2.10 Preparation of Dihydro-Oxepine **215**

Pleasingly, RCM of diallyl pyrimidinone **50** was as efficient as that observed in the model study. Initial experiments utilised the more thermally stable Grubbs-Hoyveda second generation catalyst **216**, with dropwise addition of the catalyst in a single batch to the substrate **50** at high dilution. An acceptable 70% yield was achieved (Table 2.5, entry 1). This yield was considerably improved (88%) by addition of the catalyst in two batches separated by 2 h (Table 2.5, entry 2). Continuing to use this addition technique, it was shown that Grubbs second generation catalyst **148** not only gave similar yields (Table 2.5, entry 3) but also allowed for much reduced reaction times (Table 2.5, entry 4).



Entry	Catalyst (10 mol%)	Catalyst addition (dropwise over 30 min)	Conditions	Yield 215
1	**216**	1 batch	DCM (2.5 mM), 45 °C, 18 h	70%
2	**216**	2 batches, 1 h apart	DCM (2.5 mM), 45 °C, 18 h	88%
3	**148**	2 batches, 1 h apart	DCM (2.5 mM), 45 °C, 18 h	90%
4	**148**	2 batches, 1 h apart	DCM (2.5 mM), 45 °C, 4 h	91%

Table 2.5. Optimisation study for RCM of diallyl pyrimidinone **50**.

X-ray crystallography confirmed the structural assignment of dihydro-oxepine **215** and gave an insight into the conformation of the molecule (Figure 2.2). A planar central pyrimidinone ring can be clearly seen flanked by the dihydro-oxepine ring adopting a pseudo-boat conformation, and the ketopiperazine also adopting a boat conformation. Two enantiomers were present in the unit cell providing further evidence that racemisation had indeed occurred.

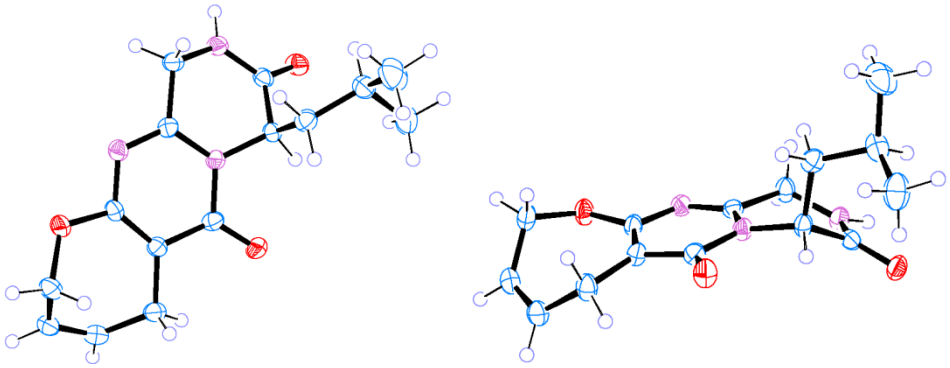
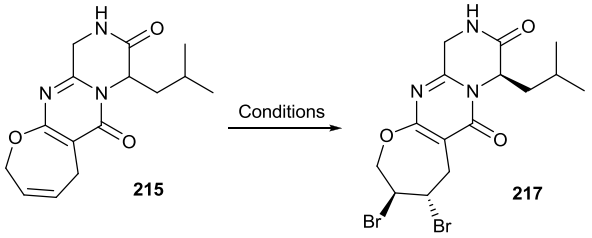


Figure 2.2. X-ray crystal structure of dihydro-oxepine **215**. Only a single (*R*) enantiomer is shown for clarity. ORTEP representations shown with ellipsoids at 50% probability. CCDC 848130, Appendix **V**.

2.11 Dihydro-Oxepine Elaboration

The elaboration of dihydro-oxepine **215** to its corresponding oxepine using the bromination – dehydrobromination methodology developed in the model study was investigated next. Bromination of dihydro-oxepine **215** proceeded in moderate yield using molecular bromine (Table 2.6, entry 1). This yield was much improved by using the easily handled pyridine hydrotribromide as a brominating agent (Table 2.6, entry 2).

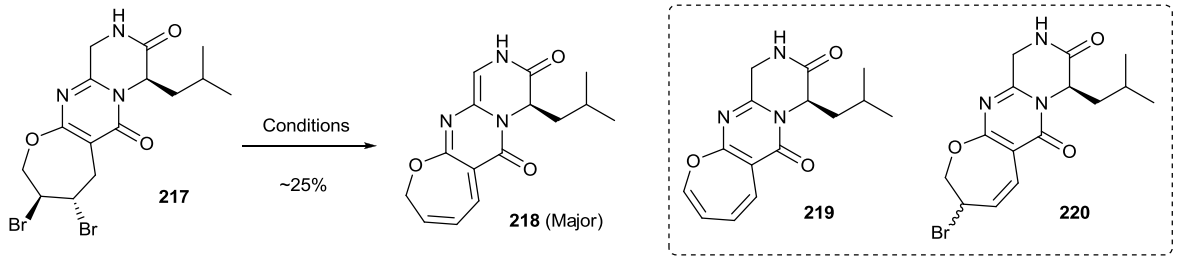
Dibromide **217** was isolated as a racemic mixture of *trans*-diastereomers which could not be separated.



Entry	Brominating Agent	Conditions	Yield 217
1	Br_2	DCM, –48 °C, 40 min	55%
2	$PyHBr_3$	DCM, rt, 1.5 h	85%

Table 2.6. Optimisation study for the bromination of dihydro-oxepine **215** (single diastereomer shown).

Unfortunately dehydrobromination to oxepine **218** could not be achieved. Treatment of dibromide **217** with a range of bases (Table 2.7) gave a complex mixture of products. Whilst the presence of trace amounts of oxepine **219** could not be ruled out, analysis of the ^{1}H-NMR spectrum of the unpurified product identified the isomer **218** as the major compound (approx. 25% yield in each case). A new singlet in the alkene region and loss of the ketopiperazine methylene proton signals indicated that deprotonation of the ketopiperazine had occurred to afford this conjugated isomer. Mass spectrometry also identified the mono-elimination product bromide **220**.



Entry	Base (2.1 eq.)	Conditions
1	TBAF (1.0 M in THF)	DMSO, rt, 30 min
2	TBAF (1.0 M in THF)	THF, –78 °C – rt, 4 h
3	DBU	THF, –78 °C – rt, 4 h
4	*t*-BuOK	THF, –78 °C – rt, 4 h
5	*t*-BuOK (1 M in *t*-BuOH)	DMF, 0 °C – rt, 4 h

Table 2.7. Dehydrobromination conditions explored.

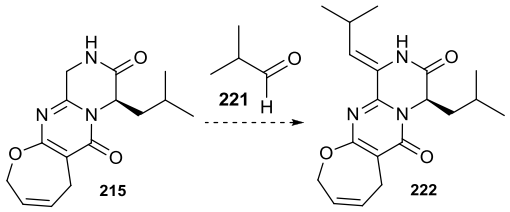
Given the apparently facile deprotonation of the ketopiperazine it was clear that an elaboration of dihydro-oxepine **215** involving a base-induce elimination was not going to be an efficient transformation.

2.12 Summary

Using methodology developed through the synthesis of the model compound **196** the tricyclic core of janoxepin (**1**) was efficiently constructed using condensation, Mitsunobu and RCM transformations. However, the acidic nature of the ketopiperazine methylene unit prevented thorough investigation of oxepine synthesis by elaboration of the dihydro-oxepine **215**. It was proposed that this problem could be addressed by first installing the enamine side-chain required at this position. The investigation of this is described in Chapter 3.

Chapter 3. Enamine Installation: Ketopiperazine Substitution

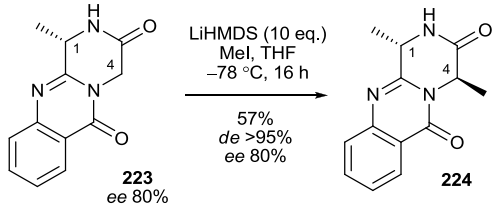
It was proposed that installation of the unsaturated enamine side-chain seen in janoxepin (**1**) could be achieved *via* an aldol-like condensation of *iso*-butyraldehyde **221** and dihydro-oxepine **215** (Scheme 3.1).



Scheme 3.1. Proposed aldol condensation.

3.1 Ketopiperazine Substitution: Literature Examples

Whilst the condensation of unprotected ketopiperazines (bearing an amide N-H) with aromatic aldehydes has been reported, a large excess of base and long reaction times were required.[95] This is thought to be due to deprotonation of the amide rendering the neighbouring methylene protons much less acidic. Avendaño and co-workers demonstrated this through the alkylation of ketopiperazine-pyrimidinone **223** where, crucially, no epimerisation of the C-1 stereocentre was observed (80% *ee* matches the *ee* of the starting material), and instead alkylation occurs α- to the carbonyl (C-4). A large excess of LiHMDS (10 eq.) was required to achieve a moderate yield of the *trans*-diastereomer **224** (95% *de*) (Scheme 3.2).[96]

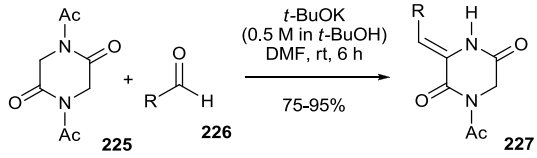


Scheme 3.2. No epimerisation at C-1 indicates poor reactivity of methylene protons to base when adjacent to amide N-H.

Protection of the amide is therefore a requirement for efficient substitution at the ketopiperazine C-1 position. *N*-Acyl-, *N*-carbamate-, *N*-alkyl- and imidate-protection strategies have all been successfully used in aldol and alkylation approaches, whilst Mannich-Hoffmann and Horner-Wadsworth-Emmons (HWE) methodologies have also been applied.

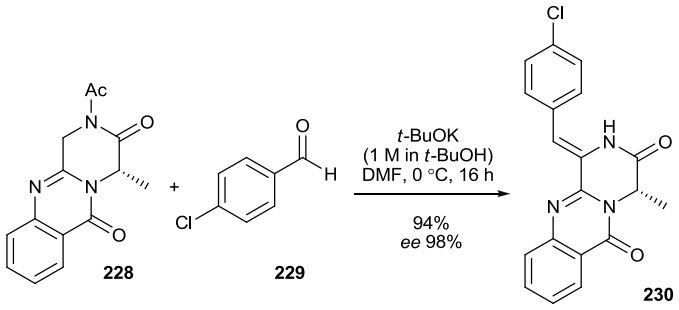
3.1.1 Aldol Approaches Utilising *N*-Acyl- and *N*-Carbamate Protecting Groups

Liberato and Gallina reported the efficient condensation of *N*-acyl-diketopiperazine **225** with a number of aliphatic and aromatic aldehydes in 1973 (Scheme 3.3).[97] They observed loss of the acyl group due to a kinetically favourable intra-molecular acyl transfer mechanism, resulting in the intermediate aldol addition species undergoing elimination to predominantly *Z*-alkenes (ratio not disclosed). Since then, this methodology has been used successfully in the synthesis of the structurally related natural product albonoursin (**45**)[98] and a novel flutimide isomer.[20]



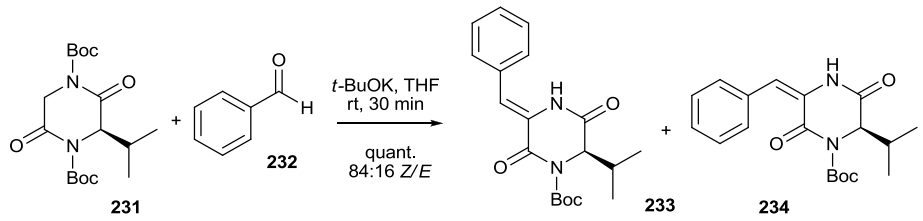
Scheme 3.3. Aldol condensation of aliphatic and aromatic aldehydes with *N*-acyl-diketopiperazine **225**.

Of particular relevance to the synthesis of janoxepin (**1**), Menéndez and co-workers recently described the condensation of *N*-acyl-ketopiperazine-pyrimidinone **228** with 4-chlorobenzaldehyde **229** using potassium *tert*-butoxide as base. A high yield of the de-acylated *Z*-enamine **230** was achieved in excellent *ee* with the *N*-acyl group being removed during the reaction (Scheme 3.4).[99]



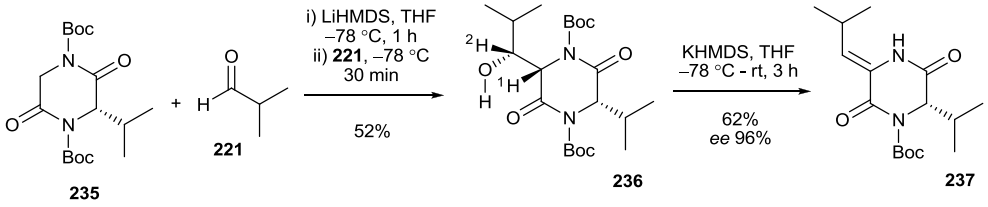
Scheme 3.4. Aldol condensation of *N*-acyl-ketopiperazine-pyrimidinone **228** with 4-chlorobenzaldehyde **229**.

Nishiyama and co-workers demonstrated that the condensation of *N*-Boc-protected ketopiperazines with benzaldehyde **232** also proceeded with great efficiency. As seen with *N*-acyl derivatives, the adjacent Boc group was lost through an acyl transfer mechanism to furnish an 84:16 mixture of *Z/E* enamine products **233** and **234** (Scheme 3.5).[100]



Scheme 3.5. Aldol condensation of *N*-Boc-diketopiperazine **231** with benzaldehyde **232**.

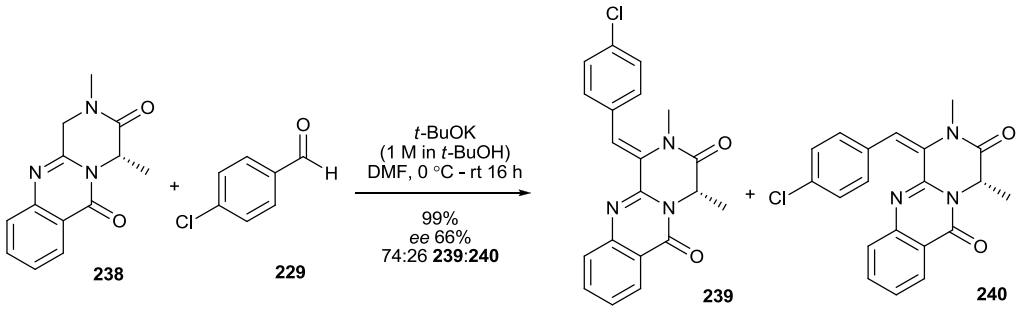
Working with the similar substrate **235**, Davies and co-workers reported that condensation with *iso*-butyraldehyde **221** using LiHMDS as the base at low temperature is also possible; the aldol adduct **236** was isolated in 52% yield as a single diastereomer (Scheme 3.6). The *cis*-configuration of substituents on the ketopiperazine ring was established by nOe studies, whilst the diastereoselective *syn*-aldol addition was tentatively assigned based upon a coupling constant between H-1 and H-2 of 2.4 Hz. This assignment assumed restriction of rotation about the new bond due to hydrogen bonding between the hydroxyl and carbonyl groups. Subsequent deprotonation with KHMDS effected elimination with acyl-transfer to furnish the *Z*-enamine **237** in 62% yield and excellent *ee* (Scheme 3.6).[101]



Scheme 3.6. Aldol condensation using LiHMDS as base.

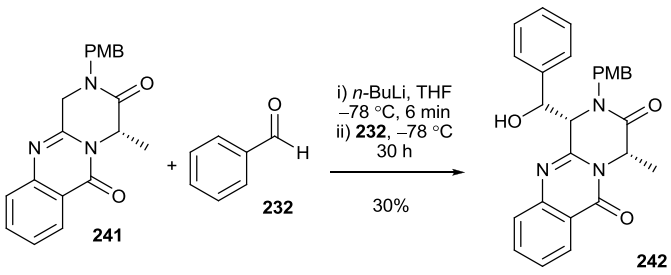
3.1.2 Aldol Approaches Utilising *N*-Alkyl Protecting Groups

N-Alkyl protecting groups have been widely used in the aldol condensation of aldehydes with ketopiperazine-containing substrates. Menéndez and co-workers described the condensation of *N*-methyl-ketopiperazine-pyrimidinone **238** with 4-chlorobenzaldehyde **229** to furnish a mixture of enamines **239** and **240** (74:26) in a near quantitative yield (Scheme 3.7). In this case, however, partial epimerisation of the stereocentre is observed during the reaction.[99]



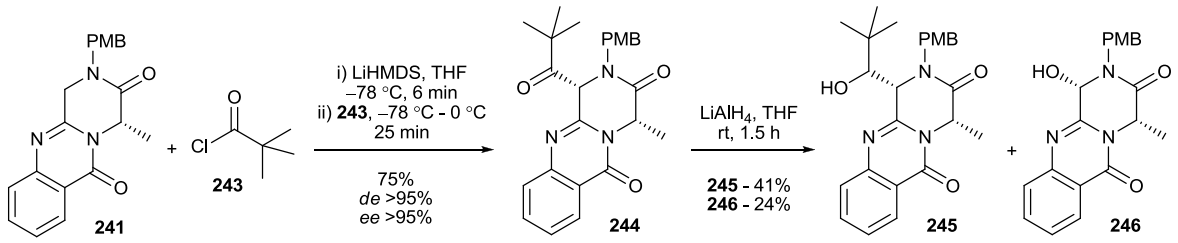
Scheme 3.7. Aldol condensation of *N*-methyl-ketopiperazine-pyrimidinone **238** and 4-chlorobenzaldehyde **229**.

The *para*-methoxybenzyl (PMB) protecting group has also been widely used, and has the advantage of its (usually) facile removal using DDQ or CAN. One such example, as reported by Bartolomé and co-workers, is the addition of benzaldehydye **232** to *N*-PMB-ketopiperazine-pyrimidinone **241** which led to the isolation of aldol adduct **242** in low yield (Scheme 3.8). Despite an extensive optimisation study, the yield could not be improved, possibly due a competing retro-aldol reaction. What is more, whilst giving good selectivity for relative *syn*-substitution across the ketopiperazine ring, the long reaction times required resulted in racemisation of the C-4 stereogenic centre. No comment as to the diastereoselectivity of aldol addition was made.[102] Elimination to the enamine was not observed under these reaction conditions, although alcohol activation-elimination has been reported as an efficient method for achieving this transformation (see Scheme 3.10).



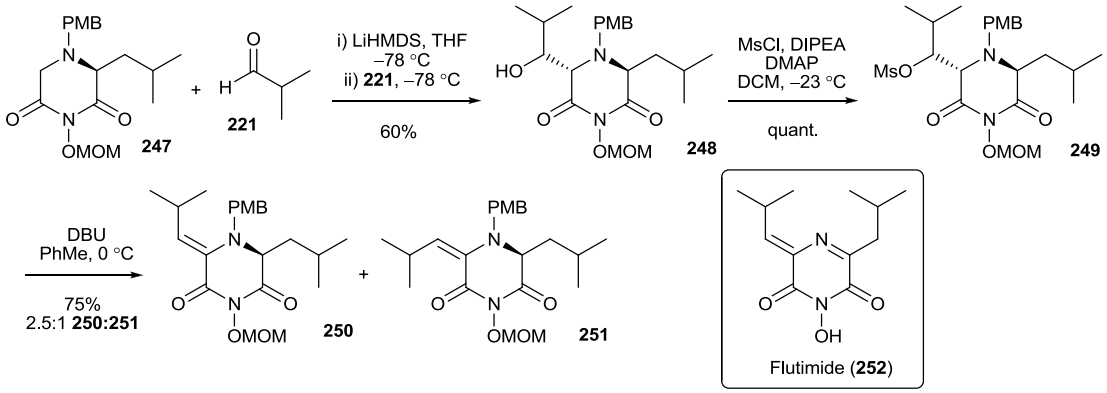
Scheme 3.8. Aldol addition of benzaldehyde **232** to *N*-PMB-ketopiperazine-pyrimidinone **241**.

Bartolomé and co-workers also reported an alternative approach for accessing similar aldol adducts. Treatment of *N*-PMB-ketopiperazine **241** with LiHMDS followed by the addition of pivaloyl chloride **243** provided ketone **244** in 80% yield, >95% *de* (in favour of the *cis*-isomer) and >95% *ee*. Subsequent reduction to the desired alcohol **245** was inefficient however, with substantial quantities of the decomposition product **246** also being isolated as a result of an auto-oxidation process (Scheme 3.9).[102]



Scheme 3.9. Addition of pivaloyl chloride **243** to *N*-PMB-ketopiperazine-pyrimidinone **241**.

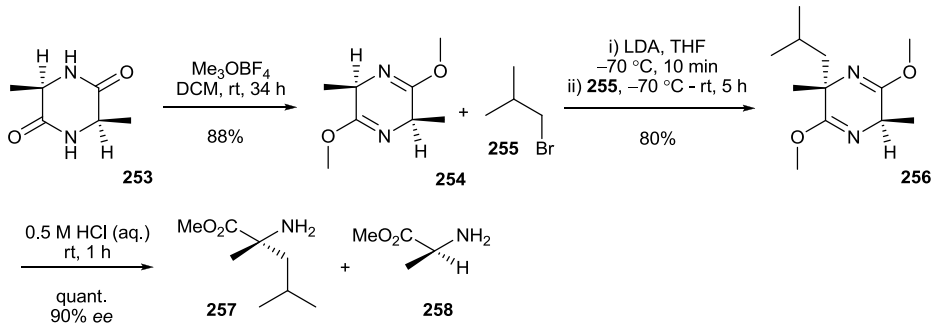
Aldol addition to *N*-PMB-protected ketopiperazines has also had utility in natural product synthesis. The efficient aldol addition of *iso*-butyraldehyde **221** to *N*-PMB-diketopiperazine **247** in the presence of LiHMDS was reported by Singh in the synthesis of flutimide (**252**) (Scheme 3.10). In this case, the enamine double bond was installed by activating the alcohol **248** as mesylate **249** followed by DBU-mediated elimination to afford a 2.5:1 mixture of *Z/E* alkenes **250** and **251**.[103]



Scheme 3.10. Aldol addition – alcohol activation – elimination in the synthesis of flutimide (**252**).

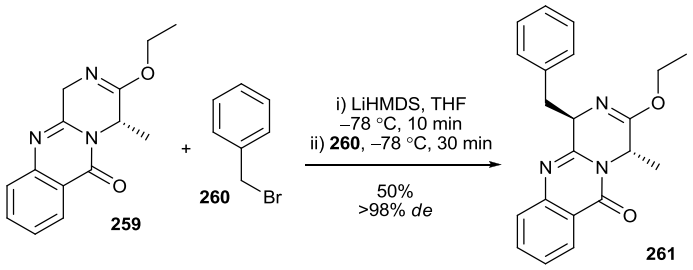
3.1.3 Ketopiperazine Substitution Using Imidate Amide Protection

The alkylation of *bis*-imidates such as **254** was first described by Schöllkopf and co-workers in their diastereoselective synthesis of α-methyl-α-aminoesters **257** and **258** as shown in Scheme 3.11. The *bis*-imidate **254** was readily prepared from diketopiperazine **253** by treatment with either triethyloxonium or trimethyloxonium tetrafluoroborate salts ('Meerwein's salt'). Imidates are readily hydrolysed under acid conditions.[104]



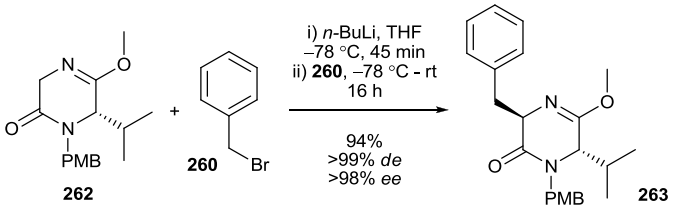
Scheme 3.11. Schöllkopf's synthesis of α-methyl-α-aminoesters **257** and **258** using imidate-protected ketopiperazines.

There are no examples of direct carbon-carbon double bond formation to imidate-protected ketopiperazines at the C-1 position, but there are a number of procedures describing efficient alkylation and aldol addition reactions. Avendaño and co-workers reported the benzylation of ketopiperazine-pyrimidinone **259** in moderate yield in 2005 (Scheme 3.12). In this case, the reaction was diastereoselective for the *trans*-product but smaller alkyl-halides (*e.g.* methyl iodide) gave poorer selectivity. The authors comment that epimerisation under the reaction conditions did not occur as readily as with *N*-alkyl substituted ketopiperazines, but was observed following prolonged work-up or chromatographic processes.[105]



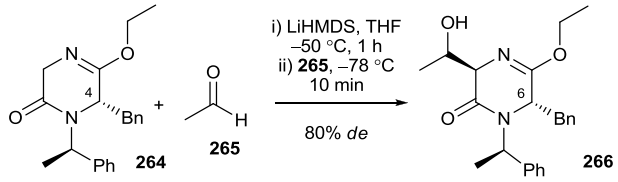
Scheme 3.12. Alkylation of imidate-protected ketopiperazine-pyrimidinone **259**.

Davies and co-workers utilised imidate protection for the alkylation of diketopiperazine substrates in 2007. Diastereoselective alkylation of imidate **262** by treatment with *n*-BuLi followed by the addition of benzyl bromide **260** proceeded in excellent *de* and *ee* (Scheme 3.13). As reported by Avendaño,[105] smaller alkyl halides were found to result in a lower *de*.[106]



Scheme 3.13. Chiral diastereoselective alkylation of imidate-protected diketopiperazine **262**.

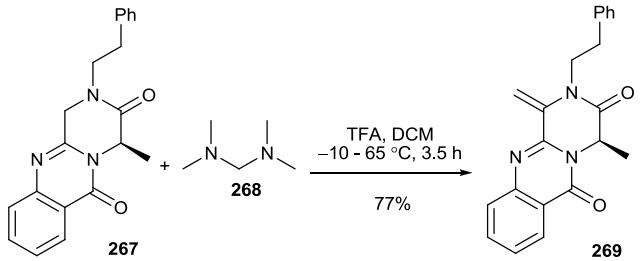
Only a single report describes aldol addition of an aldehyde to an imidate-protected ketopiperazine. Sandri and co-workers demonstrated that addition of acetaldehyde **265** to imidate **264**, in the presence of LiHMDS, proceeded with modest diastereoselectivity for the *trans*-isomers (Scheme 3.14). In this case, the steric bulk of the benzyl group present at the ketopiperazine C-4 position is crucial for good diastereoselectivity – methyl substitution at this position significantly lowers the *de* achieved. No comment is made on the reaction yield, the diastereoselectivity of aldol addition, or on the *ee* of the products isolated.[107] Application of an activation-elimination approach (as utilised by Singh[103]) to access the corresponding enamine can be envisaged.



Scheme 3.14. Aldol addition of acetaldehyde **265** to imidate-protected diketopiperazine **264**.

3.1.4 Other Approaches

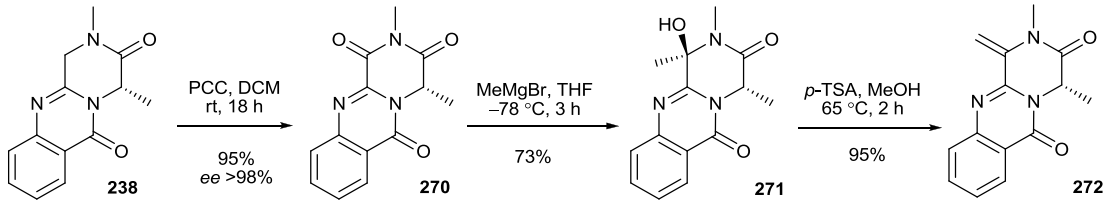
The Mannich-Hofmann reaction was used efficiently by Avendaño and co-workers to introduce a carbon-carbon double bond onto ketopiperazine-pyrimidinones at the C-1 position. As shown in Scheme 3.15, treatment of *N*-alkyl-ketopiperazine-pyrimidinone **267** with diamine **268** in the presence of TFA furnished enamine **269** in high yield and *ee* (as shown by chiral HPLC analysis, although no figure is quoted).[108]



Scheme 3.15. Mannich-Hofmann reaction of diamine **268** and *N*-alkyl-ketopiperazine-pyrimidinone **267**.

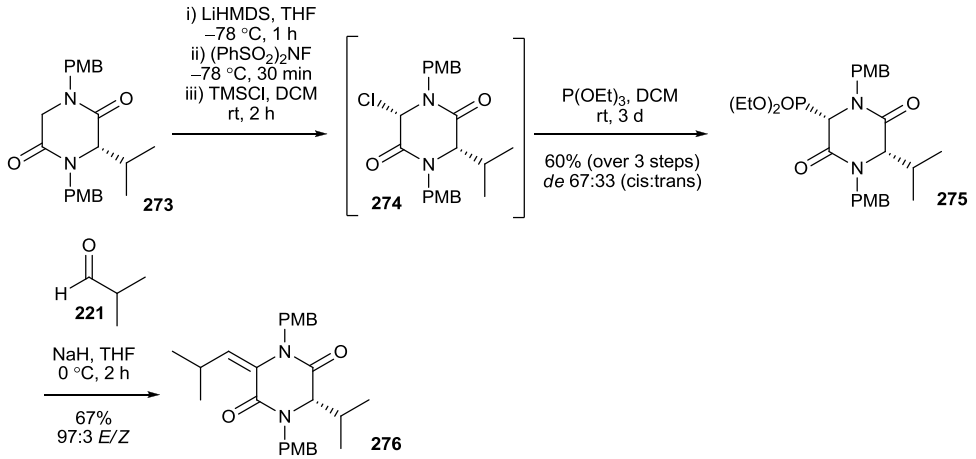
In the same report, the PCC-mediated oxidation of *N*-methyl-ketopiperazine-pyrimidinone **238** is also described. Subsequent addition of methyl magnesium bromide occurs with regioselectively for the newly introduced, more electrophilic carbonyl and with good *syn*-diastereoselectivity. Treatment of alcohol **271** with *p*-TSA in refluxing methanol then mediated dehydration to provide enamine **272** in excellent yield (Scheme 3.16).[108] This methodology may not only have utility in the synthesis of janoxepin (**1**),

but also in the synthesis of the oxepine-pyrimidinone natural products bearing hydroxyl substitution on the ketopiperazine ring (*e.g.* oxepinamides A-C **23-25**).



Scheme 3.16. Ketopiperazine oxidation – Grignard addition – dehydration approach.

The HWE reaction has also been used to introduce a carbon-carbon double bond to ketopiperazine substrates at C-1. Starting with *N*-PMB-diketopiperazine **273**, Davies and co-workers first performed an electrophilic fluorination followed by trans-halogenation to provide chloride **274**. This was then converted into phosphonate **275** (as a mixture of diastereomers) upon treatment with triethylphosphite in an Arbuzov reaction. The *cis*-phosphonate **275** was isolated by chromatography and underwent HWE olefination with *iso*-butyraldehyde **221** to furnish the *E*-enamine **276** in good yield (Scheme 3.17).[101]



Scheme 3.17. HWE approach for installing carbon-carbon double bonds onto ketopiperazines.

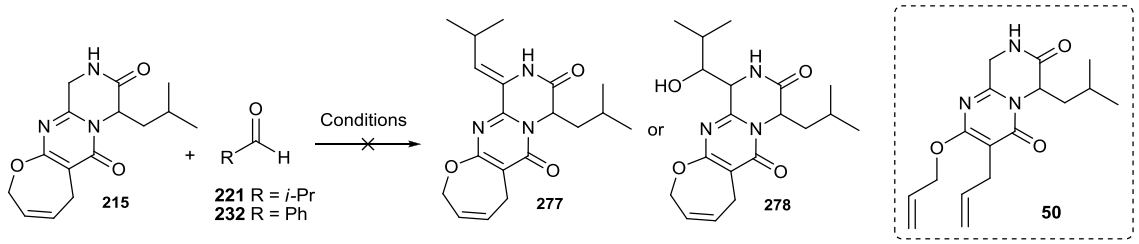
3.2 Aldol Condensation/Addition: Strategy

It was proposed to first establish whether amide protection was indeed required for successful aldol addition/condensation of *iso*-butyraldehyde **221** to either diallyl pyrimidinone **50** or dihydro-oxepine **215**. This was important to ascertain as, if found to be successful, it would negate the need for extra protecting group manipulation steps. Subsequent investigations then focussed on finding the optimal method of amide protection:

1. *N*-Acyl/*N*-carbamate protecting groups.
2. *N*-Alkyl protecting groups.
3. Imidate protection.

3.2.1 Aldol Addition/ Condensation Without Amide Protection

Dihydro-oxepine **215** was the first substrate to be investigated, but on treatment with potassium *tert*-butoxide (as a solution in *tert*-butanol) and *iso*-butyraldehyde **221** in DMF at 0 °C, only aldehyde self-condensation and decomposition of the substrate occured (Table 3.1, entry 1). In order to eliminate the problem of aldehyde self-condensation, the non-enolisable benzaldehyde **232** was employed, however, under the same reaction conditions, only decomposition of the starting material was seen (Table 3.1, entry 2). When LiHMDS was used in THF at –78 °C with both *iso*-butyraldehyde **221** and benzaldehyde **232** no reaction was observed (Table 3.1, entries 3-4).



Entry	Aldehyde (4.0 eq.)	Base (2.1 eq.)	Conditions	Comment
1	**221**	*t*-BuOK (1.0 M in *t*-BuOH)	DMF, 0 °C – rt, 2 h	Self-condensed aldehyde and decomposition
2	**232**	*t*-BuOK (1.0 M in *t*-BuOH)	DMF, 0 °C – rt, 2 h	Self-condensed aldehyde and decomposition
3	**221**	LiHMDS (1.0 M in THF)	THF, –78 °C – 0 °C, 18 h	rsm
4	**232**	LiHMDS (1.0 M in THF)	THF, –78 °C – 0 °C, 18 h	rsm

Table 3.1. Investigation of aldol condensation using unprotected dihydro-oxepine **215**.

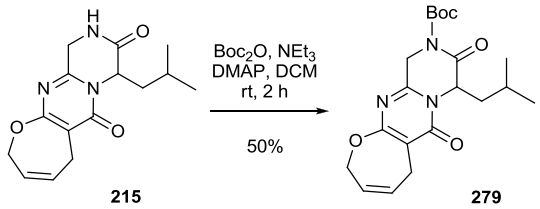
Based on a concern that instability of the dihydro-oxepine ring might be responsible for the observed decomposition, diallyl pyrimidinone **50** was also subjected to both sets of reaction conditions. However, the same results were obtained, leading to the conclusion that protection of the amide was indeed required.

3.3 Aldol Condensation using *N*-Boc Protection: The First Synthesis of 'Dihydro-Janoxepin' **49**

The *N*-Boc-substituted dihydro-oxepine **279** was first investigated as an alternative substrate for aldol addition/condensation. This was chosen in preference to the *N*-acyl-substitution as the Boc protecting group could be removed under mild conditions (should aldol addition occur without subsequent acyl-transfer and elimination).

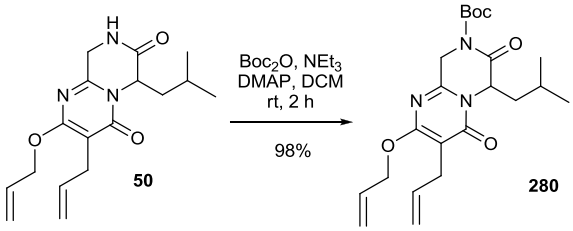
3.3.1 Preparation of *N*-Boc Substrates

Treatment of dihydro-oxepine **215** with di-*tert*-butyl dicarbonate in the presence of triethylamine and DMAP in DCM provided the desired Boc-protected substrate **279**, however, the yield obtained for this transformation was only 50% (Scheme 3.18).



Scheme 3.18. Boc-protection of dihydro-oxepine **215**.

Boc-protection of diallyl pyrimidinone **50** was found to be far more efficient (Scheme 3.19), and it is reasonable to assume that subsequent RCM would also be high yielding. The proposed explanation for this observation is discussed later (Chapter 4.8).

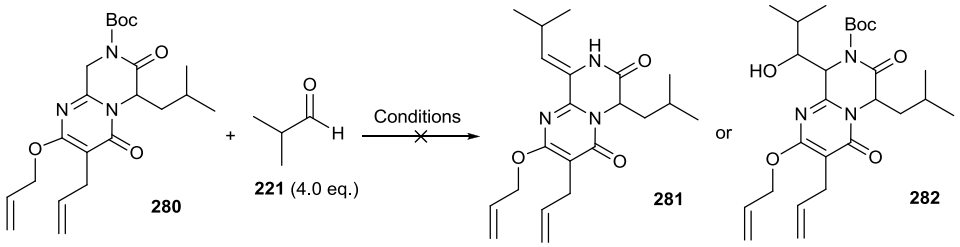


Scheme 3.19. Boc-protection of diallyl pyrimidinone **50**.

3.3.2 Aldol Condensation with *iso*-Butyraldehyde

Given the observed sensitivity of dihydro-oxepine **215** to the Boc-protection conditions, an initial investigation used *N*-Boc-diallyl pyrimidinone **280** as the substrate for condensation with *iso*-butyraldehyde **221**. However, when potassium *tert*-butoxide was used as base in DMF, decomposition of the substrate was observed (Table 3.2, entry 1).

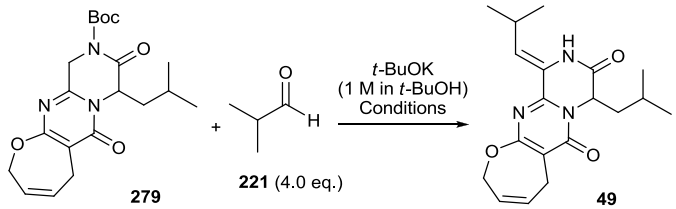
When LiHMDS was used as the base no reaction was observed, but the starting material was recovered (Table 3.2, entry 2).



Entry	Base (2.1 eq.)	Conditions	Comment
1	*t*-BuOK (1.0 M in *t*-BuOH)	DMF, 0 °C – rt, 3 h	Self-condensed aldehyde and decomposition
2	LiHMDS (1.0 M in THF)	THF, –78 °C – 0 °C, 18 h	rsm

Table 3.2. Investigation of aldol condensation using *N*-Boc-diallyl pyrimidinone **280**.

To our surprise, the condensation of *N*-Boc-dihydro-oxepine **279** with *iso*-butyraldehyde **221** was successfully mediated using potassium *tert*-butoxide in DMF. The reaction proceeded with cleavage of the Boc group, presumably due to an acyl-transfer process, to provide 'dihydro-janoxepin' **49** as a single enamine isomer (Table 3.3, entry 1). However, the transformation was low yielding and unreliable; performing the reaction at a lower temperature using THF as solvent (Table 3.3, entry 2), and using a single equivalent of base (Table 3.3, entry 3), only led to the recovery of starting material whilst experimentation with the rate and order of reagent addition also offered no improvement.

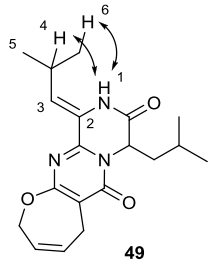


Entry	*t*-BuOK eq.	Conditions	Yield 49
1	2.1	DMF, 0 °C – rt, 3 h	21%
2	2.1	THF, –78 °C – rt, 6 h	rsm
3	1.1	DMF, 0 °C – rt, 3 h	rsm

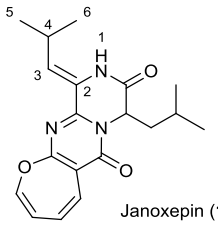
Table 3.3. Optimisation study for the aldol condensation of *N*-Boc-dihydro-oxepine **279** with *iso*-butyraldehyde **221**.

3.3.3 Characterisation of 'Dihydro-Janoxepin' **49**

The structure of dihydro-janoxepin **49** was confirmed by the comparison of key NMR data with those of janoxepin (**1**) (Table 3.4).[1] The *Z*-configuration of the enamine was confirmed by nOe experiments – nOe enhancements were seen between H-1 and H-4 and, to a lesser extent, between H-1 and H-5/6. No enhancement was seen between H-1 and H-3. All other characterisation data (mass spectrometry and IR) were also consistent with the structural assignment.



49



Janoxepin (**1**)

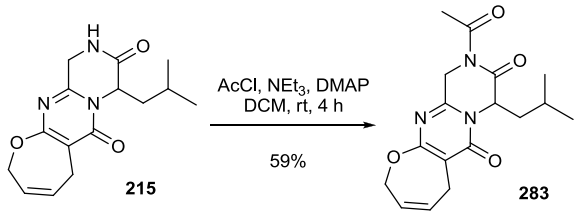
#	δ_H (ppm) (*J* in Hz)		δ_C (ppm)	
	49	**1**	**49**	**1**
1	8.98 (br s)	8.68 (br s)	-	-
2	-	-	123.8	123.9
3	6.31 (d, *J* 10.5)	6.31 (d, *J* 10.2)	127.9	129.0
4	2.73 (dsept. *J* 10.5, 6.5)	2.66 (dsept. *J* 10.2, 6.5)	26.1	26.3
5/6	1.11 (d, *J* 6.5)	1.08 (d, *J* 6.7)	22.2	21.9
5/6	1.10 (d, *J* 6.5)	1.07 (d, *J* 6.5)	21.2	21.1

Table 3.4. Selected NMR data for 'dihydro-janoxepin' **49** and janoxepin (**1**).[1] Arrows indicate nOe enhancements observed. See Appendix **I** for ^{1}H- and ^{13}C-NMR spectra.

3.4 Aldol Condensation Using *N*-Acyl Protection

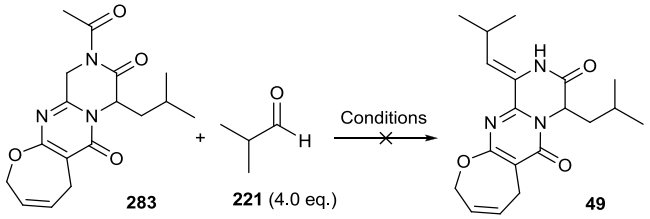
With the aim of improving the efficiency of the aldol condensation step, *N*-acyl protection was next investigated using a dihydro-oxepine derivative (based upon the previous success with *N*-Boc protection).

N-Acyl-dihydro-oxepine **283** was prepared by the treatment of dihydro-oxepine **215** with acetyl chloride in the presence of triethylamine and DMAP in DCM. As seen in the synthesis of *N*-Boc substrate **279** only a moderate yield was achieved (Scheme 3.20).



Scheme 3.20. *N*-Acyl protection of dihydro-oxepine **215**.

Disappointingly, condensation with, or the addition of *iso*-butyraldehyde **221** to *N*-acyl-dihydro-oxepine **283** was not possible. The successful conditions previously used resulted in the isolation of a complex mixture of side products (Table 3.5, entry 1). The same outcome was observed at a lower reaction temperature when THF was used as solvent (Table 3.5, entry 2) and when LiHMDS was used as the base (Table 3.5, entry 3). Reducing the number of equivalents of base again resulted in no reaction (Table 3.5, entry 4).



Entry	Base	Conditions	Comment
1	*t*-BuOK (2.1 eq.) (1.0 M in *t*-BuOH)	DMF, 0 °C – rt, 3 h	Self-condensed aldehyde and decomposition
2	*t*-BuOK (2.1 eq.) (1.0 M in *t*-BuOH)	THF, –78 °C – rt, 6 h	Self-condensed aldehyde and decomposition
3	LiHMDS (2.1 eq.) (1.0 M in THF)	THF, –78 °C – rt, 18 h	rsm
4	*t*-BuOK (1.1 eq.) (1.0 M in *t*-BuOH)	DMF, 0 °C – rt, 3 h	rsm

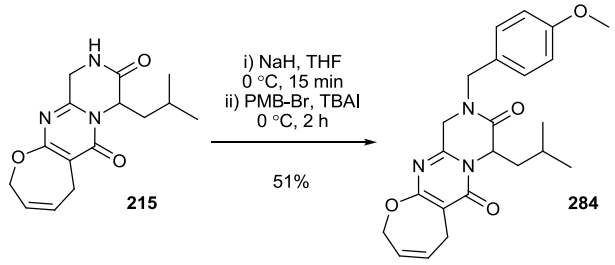
Table 3.5. Investigation of the aldol condensation of *N*-acyl-dihydro-oxepine **283** with *iso*-butyraldehyde **221**.

3.5 Aldol Addition Using *N*-PMB Protection

Based upon literature precedent for its successful application in aldol addition reactions, and subsequent removal under mild conditions, *N*-protection using the PMB group was investigated next.

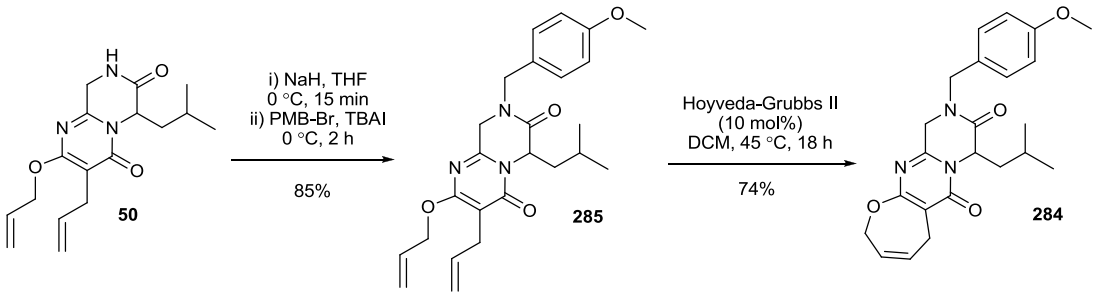
3.5.1 Preparation of *N*-PMB Dihydro-Oxepine **284**

As observed with *N*-Boc and *N*-acyl-protection, *N*-PMB-protection of dihydro-oxepine **215** was only possible in moderate yield (Scheme 3.21).



Scheme 3.21. Preparation of *N*-PMB dihydro-oxepine **284** from dihydro-oxepine **215**.

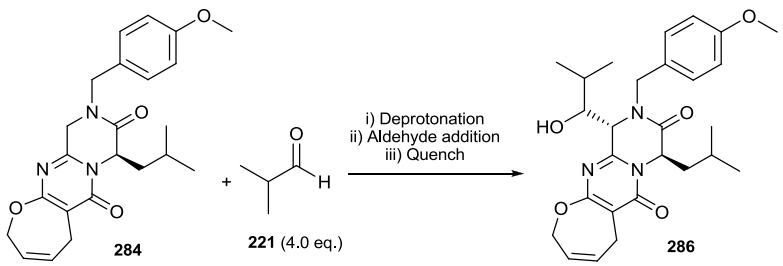
Protection of diallyl pyrimidinone **50** was found to be much more efficient, and subsequent RCM also proceeded in good yield (un-optimised), thus providing a much improved synthetic route to *N*-PMB-dihydro-oxepine **284** (Scheme 3.22).



Scheme 3.22. Preparation of *N*-PMB-dihydro-oxepine **284** from diallyl pyrimidinone **50**.

3.5.2 Aldol Addition Optimisation Study

An initial investigation of the conditions used for the successful aldol condensation of *iso*-butyraldehyde **221** with *N*-Boc-dihydro-oxepine **279** gave disappointing results. The treatment of *N*-PMB-dihydro-oxepine **284** with potassium *tert*-butoxide in both DMF and THF, followed by the addition of *iso*-butyraldehyde **221** gave only a complex mixture of decomposition products (Table 3.6, entries 1-2). However, the treatment of **284** with LiHMDS in THF at –78 °C, followed by addition of *iso*-butyraldehyde **221**, and quenching at –78 °C with AcOH furnished a promising 30% yield of the aldol adduct **286** (Table 3.6, entry 3). A modest increase in this yield was achieved following the *in situ* preparation of LiHMDS by the treatment of freshly distilled HMDS with *n*-BuLi (Table 3.6, entry 4). When KHMDS was used as the base only a trace of aldol adduct **286** (<5%) was isolated along with a complex mixture of decomposition products (Table 3.6, entry 5).

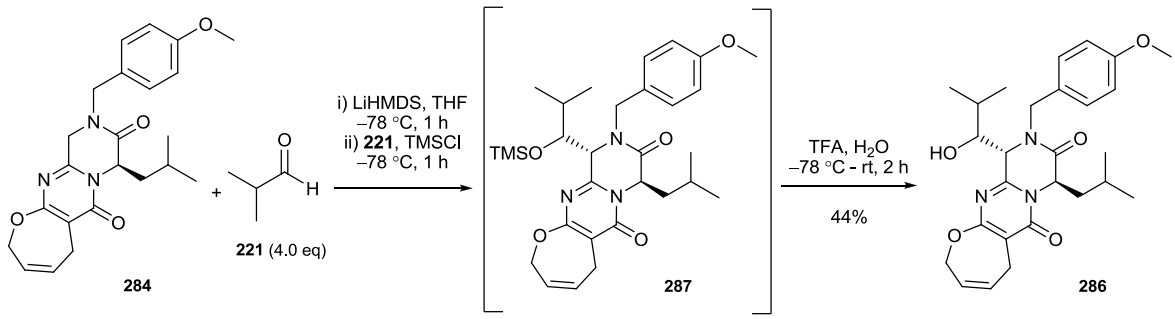


Entry	Deprotonation	Aldehyde Addition	Quench	Yield 286
1	*t*-BuOK (2.1 eq., 1.0 M in *t*-BuOH), DMF, 0 °C, 1 h	DMF, 0 °C – rt, 1 h	Sat. NH_4Cl (aq)	Decomposition products isolated
2	*t*-BuOK (2.1 eq., 1.0 M in *t*-BuOH), THF, 0 °C, 1 h	THF, 0 °C – rt, 1 h	Sat. NH_4Cl (aq)	Decomposition products isolated
3	LiHMDS (2.1 eq., 1.0 M in THF), THF, –78 °C, 1 h	THF, –78 °C, 1 h	AcOH, –78 °C – rt, 30 min	30%
4	LiHMDS (2.1 eq., generated *in situ*), THF, –78 °C, 1 h	THF, –78 °C, 1 h	AcOH, –78 °C – rt, 30 min	35%
5	KHMDS (2.1 eq., 1.0 M in PhMe), THF, –78 °C, 1 h	THF, –78 °C, 1 h	AcOH, –78 °C – rt, 30 min	<5%

Table 3.6. Optimisation study for the aldol addition of *iso*-butyraldehyde **221** to form *N*-PMB-dihydro-oxepine **284**. (Relative stereochemistry shown).

To ascertain if the poor yields were due to the self-condensation of *iso*-butyraldehyde **221**, benzaldehyde **232** was used under the optimal conditions. However, no reaction was observed, suggesting that the carbonyl centre of benzaldehye **232** was not sufficiently electrophilic to react with the intermediate ketopiperazine enolate.

Warming the reaction mixture slowly to room temperature following addition of the aldehyde led to any aldol product initially formed, as observed by TLC, appearing to be converted back to the starting material; presumably as a result of a retro-aldol reaction. It was proposed that the forward reaction could be promoted by trapping the intermediate alkoxide with an electrophile. Thus, it was found that addition of TMS-Cl together with the aldehyde prevented the retro-aldol reaction and the intermediate silyl-ether **287** was formed. This was not isolated, but hydrolysed in the same pot by the addition of TFA and water, with warming to room temperature, to reliably furnish the aldol adduct **286** in 44% yield (Scheme 3.23). Surprisingly, the addition of AcOH did not mediate the desired hydrolysis.

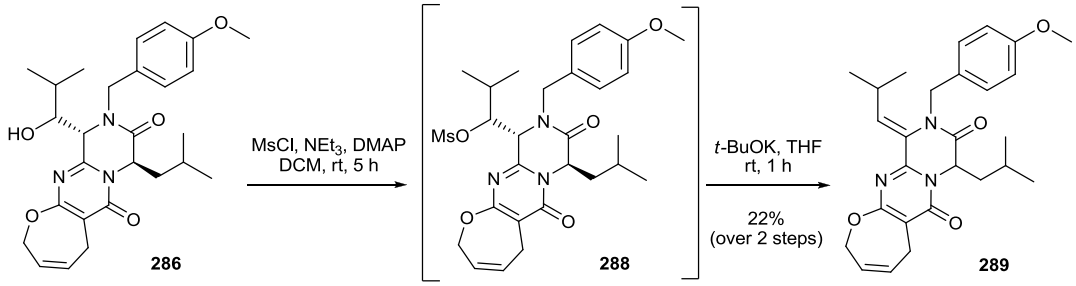


Scheme 3.23. Optimised synthesis of *N*-PMB aldol adduct **286**. (Relative stereochemistry shown).

Extensive experimentation with reaction time, as well as the order and rate of reagent addition, offered no improvement in the reliable, but moderate, 44% yield. This could be due to instability of the dihydro-oxepine under the harsh silyl-ether hydrolysis conditions used, but was not investigated further.

3.5.3 Activation – Elimination: The Synthesis of *N*-PMB-Dihydro-Janoxepin **289**

The direct acid-mediated dehydration of aldol adduct **286** to enamine **289** was not a desirable strategy. No dehydration was observed under the silyl-ether hydrolysis conditions, and the low yield obtained was associated with stability of the dihydro-oxepine in acidic media. Therefore, an activation-elimination approach was adopted. Aldol adduct **286** was treated with MsCl in the presence of triethylamine and DMAP to afford mesylate **288**. Following work-up, this was immediately treated with potassium *tert*-butoxide in THF to provide *N*-PMB-dihydro-janoxepin **289**, albeit in just 22% yield (Scheme 3.24).



Scheme 3.24. Activation – elimination of aldol adduct **286**. (Relative stereochemistry shown).

The *Z*-configuration of the enamine was confirmed by nOe experiments showing enhancements between benzylic protons H-1 and *iso*-propyl proton H-3. No nOe enhancement was observed between H-1 and the alkene proton H-2 (Figure 3.1).

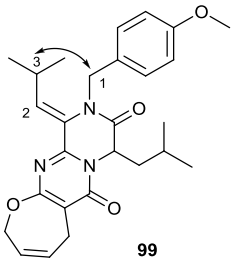
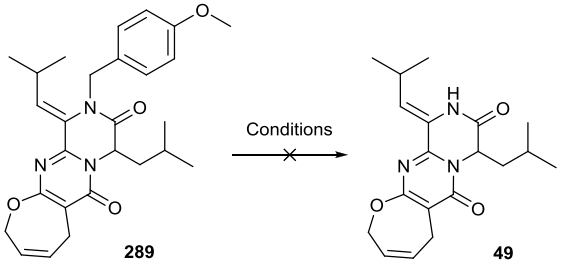


Figure 3.1. nOe enhancement observed for *N*-PMB-dihydro-janoxepin **289**.

The reaction sequence was not optimised further as it was first important to establish an efficient method for PMB group removal.

3.5.4 *N*-PMB Deprotection

To our disappointment, PMB group removal could not be achieved. A range of conditions were investigated as shown in Table 3.7, however only complex mixtures of side products were isolated.



Entry	Conditions	Comment
1	DDQ, PhMe, rt, 1 h	Decomposition
2	CAN, MeCN, H_2O 0 °C – rt, 2 h	Decomposition on warming
3	$AlCl_3$, anisole (solvent), rt, 1 h	Decomposition
4	TFA (solvent), anisole, rt, 1 h	Decomposition
5	H_2SO_4, TFA (solvent), rt, 30 min	Decomposition
6	NaI, DMF, rt – 110 °C, 16 h	Decomposition upon heating

Table 3.7. PMB group removal: reaction conditions screened.

Unable to remove the PMB protecting group, the *N*-alkyl protection strategy was abandoned, and an imidate protection approach was investigated.

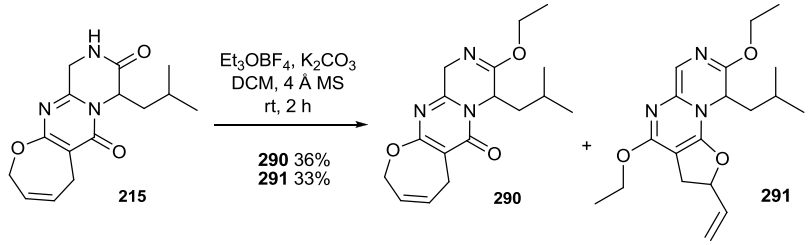
3.6 Aldol Addition to an Imidate-Protected Ketopiperazine

Although the literature precedent for aldol addition to imidate-protected ketopiperazines is limited (Chapter 3.1.3), it was proposed that such substrates would be suitable for

such a reaction. Furthermore, hydrolysis under mild conditions should provide a facile method for subsequent removal of this protecting group.

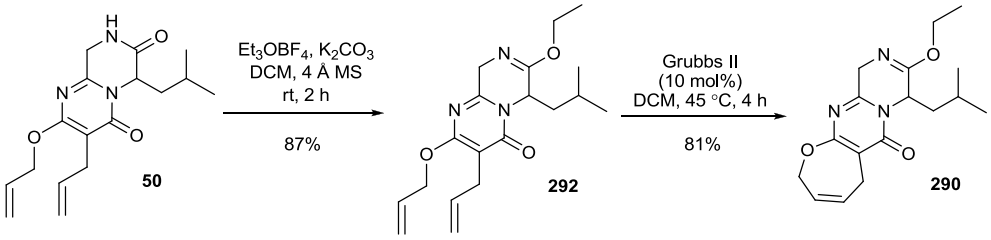
3.6.1 Imidate Preparation

Again, protection of dihydro-oxepine **215** directly was inefficient. When dihydro-oxepine **215** was treated with triethyloxonium tetrafluoroborate and potassium carbonate in the presence of 4 Å molecular sieves, the desired imidate **290** was isolated in just 36% yield (Scheme 3.25). A substantial quantity of the intriguing *bis*-alkylated rearrangement product dihydro-furan **291** was also isolated, the characterisation of which, alongside mechanistic proposals is discussed later (Chapter 4.8).



Scheme 3.25. Imidate protection of dihydro-oxepine **215**.

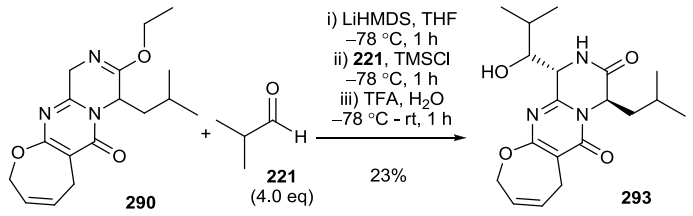
It was again found to be far more efficient to protect diallyl pyrimidinone **50** as imidate **292**. RCM then proceeded in excellent yield to provide the desired imidate-protected dihydro-oxepine **290** (Scheme 3.26).



Scheme 3.26. Optimised preparation of imidate-protected dihydro-oxepine **290**.

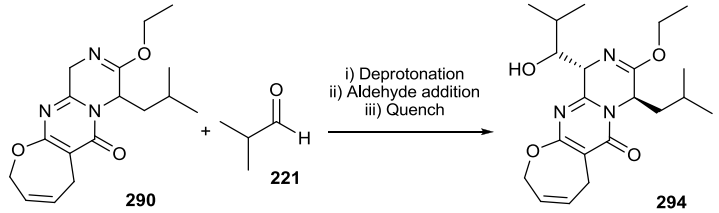
3.6.2 Aldol Addition Optimisation

Initial application of the optimal reaction conditions for the aldol addition of *iso*-butyraldehyde **221** to *N*-PMB dihydro-oxepine **284** gave disappointing results. The acidic conditions required for hydrolysis of the intermediate silyl-ether also led to hydrolysis of the imidate, leading to the isolation of aldol adduct **293** in poor yield (Scheme 3.27).



Scheme 3.27. Application of previously optimal aldol conditions. (Relative stereochemistry shown).

Performing the reaction at low temperature without the addition of TMS-Cl was found to be a more efficient strategy. Treatment of imidate **290** with LiHMDS (prepared *in situ*) at –78 °C for 1 h was followed by the addition of *iso*-butyraldehyde **221**. The reaction mixture was stirred at –78 °C for 1 h before the addition of AcOH and warming to room temperature. The desired aldol adduct **294**, with the imidate group intact, was isolated in a very promising 51% yield (Table 3.8, entry 1). The yield was further improved by reducing the reaction time for deprotonation and following aldehyde addition. At the same time, it was found that the number of equivalents of aldehyde used could be reduced without negative effect (Table 3.8, entry 2).



Entry	Deprotonation	Aldehyde addition	Quench	Yield 294
1	LiHMDS (2.1 eq.), (generated *in situ*), THF, –78 °C, 1 h	**221** (4.0 eq.), THF, –78 °C, 1 h	AcOH, –78 °C – rt, 1 h	51%
2	LiHMDS (2.1 eq.), (generated *in situ*), THF, –78 °C, 10 min	**221** (3.0 eq.), THF, –78 °C, 10 min	AcOH, –78 °C – rt, 30 min	70%

Table 3.8. Optimisation study for aldol addition to imidate **290**. (Relative stereochemistry shown).

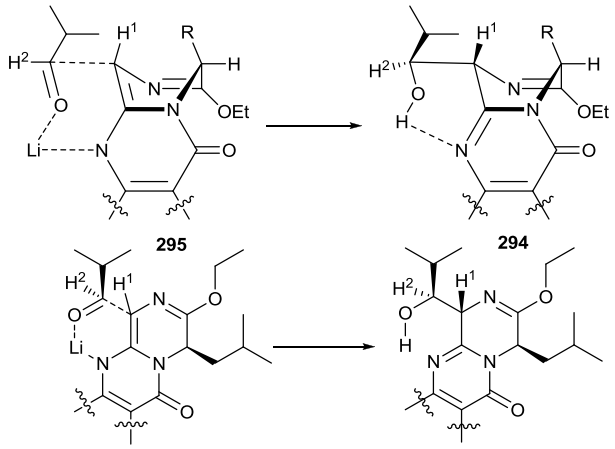
As previously observed, no reaction took place when 1.1 equivalents of base was used, or when these conditions were applied to imidate protected diallyl pyrimidinone **292**.

3.6.3 Diastereoselectivity of Aldol Addition

Aldol addition to both the *N*-PMB and imidate-protected ketopiperazines provided products as single diastereomers. It was assumed that addition in both cases occurred *trans*- to the bulky *iso*-butyl substituent at C-1 based upon steric considerations. However, further investigation involving nOe or X-ray crystallography experiments was not pursued.

A tentative assignment of whether *syn*- or *anti*-aldol addition had occurred was made based upon the ^{1}H-NMR coupling constant between H-1 and H-2, in analogy with an assignment made previously by Davies and co-workers as described in Chapter 3.1.1.[101]

In the case of the imidate-protected substrate **290** it is proposed that *anti*-aldol addition occurred (as expected) *via* an *E*-'enolate'. Scheme 3.28 shows how the *iso*-propyl group of the aldehyde is able to adopt the preferred, equatorial position in a Zimmerman-Traxler-like transition state **295**. Assuming restricted rotation about the new bond, due to a hydrogen bonding interaction between the hydroxyl group and pyrimidinone nitrogen, H-1 and H-2 must adopt an *anti*-periplanar arrangement. This is consistent with the higher than usual coupling constant of 8.5 Hz between the two protons. However, this is surprising given that only the *Z*-enamine was isolated upon elimination, where the expected product would be the *E*-enamine. This perhaps suggests that reversible isomerisation of the enamine occurs, the thermodynamic outcome of which is driven by steric factors.



Scheme 3.28. Imidate-protected ketopiperazine **295** undergoes *anti*-aldol addition based upon observed coupling constant between H-1 and H-2 (*J* 8.5 Hz). (Relative stereochemistry shown).

In the case of the *N*-PMB-protected substrate **286** the observed coupling constant between H-1 and H-2 was much smaller (2.5 Hz). Using the same model, this can be explained by the bulky PMB group forcing the *iso*-propyl group of the aldehyde to adopt an axial position in the transition state **296** (Figure 3.2).

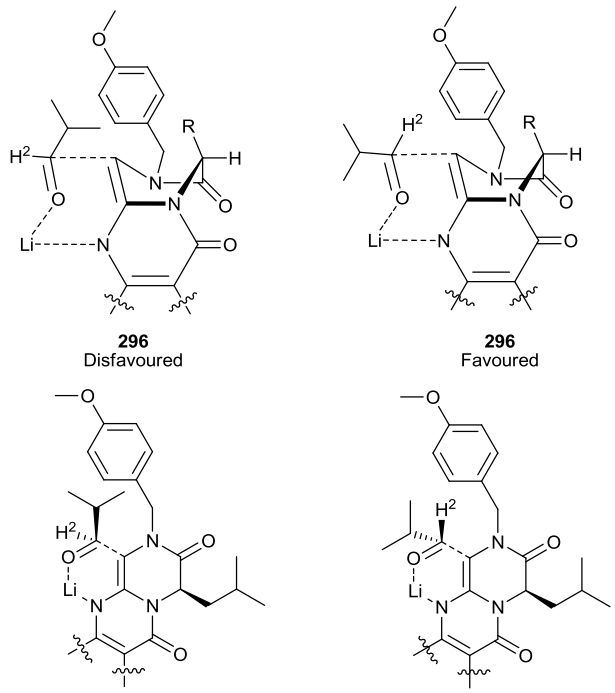
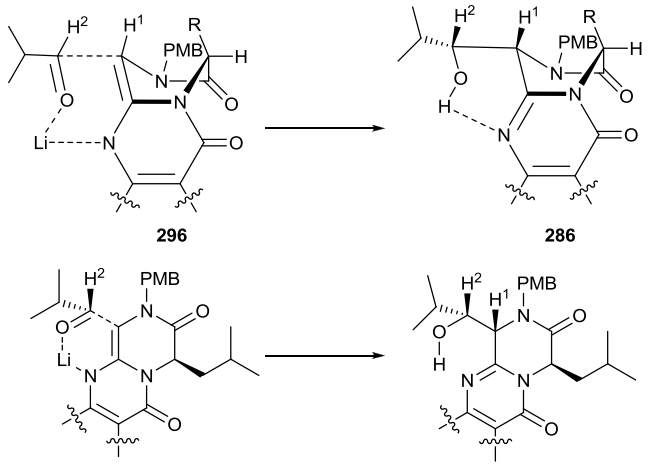


Figure 3.2. Bulky *N*-PMB group forces the *iso*-butyl chain of the aldehyde to adopt an axial position in the transition state. (Relative stereochemistry shown).

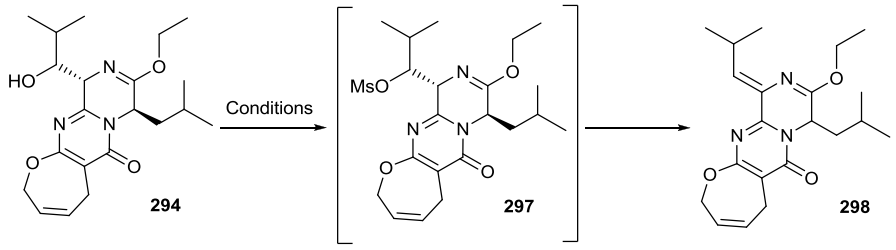
Thus, *syn*-aldol addition occured, resulting in H-1 and H-2 adopting an eclipsed arrangement in the product (Scheme 3.29). This is a plausible explanation for the observed difference in *J* values; indeed Davies and co-workers reported an almost identical coupling of 2.4 Hz in their example of *syn*-aldol addition (Chapter 3.1.1).[101] In this case of aldol adduct **286**, the *Z*-enamine isolated upon elimination is the expected product.



Scheme 3.29. *N*-PMB-protected ketopiperazine **284** undergoes *syn*-aldol addition based upon observed coupling constant between H-1 and H-2 (*J* 2.5 Hz). (Relative stereochemistry shown).

3.6.4 Enamine Synthesis: Activation – Elimination

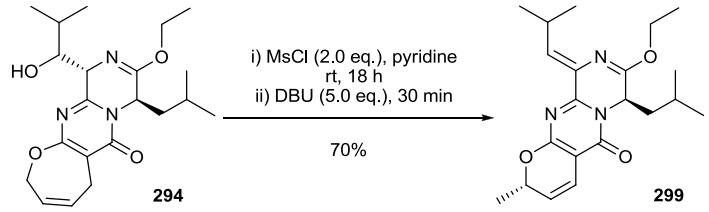
An activation – elimination strategy was again adopted, but application of the mesylation conditions previously used (MsCl, triethylamine and DMAP) gave a disappointing 31% yield of mesylate **297** (Table 3.9, entry 1). When pyridine was used as solvent, a mixture of mesylate **297** and enamine **298** was obtained. Addition of DBU, with heating to 50 °C, completed the elimination to furnish enamine **298** in a much improved 64% yield (Table 3.9, entry 2). Complete elimination could be achieved without the addition of DBU, but the prolonged reaction time required at 50 °C had a detrimental effect on the yield (Table 3.9, entry 3).



Entry	Conditions	Yield 298
1	MsCl (2.5 eq.), NEt_3 (2.5 eq.), DMAP (0.1 eq), DCM, rt, 2 h	31%
2	i) MsCl (2.0 eq.), pyridine (solvent), rt, 18 h ii) DBU (2.0 eq), 50 °C, 1 h	64%
3	MsCl (2.0 eq.), pyridine (solvent), 50 °C, 18 h	50%

Table 3.9. Mesylation – elimination optimisation study. (Relative stereochemistry shown).

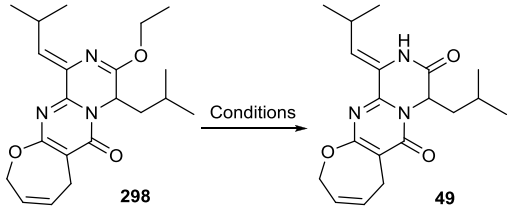
Further optimisation studies focussing on the reaction time and temperature offered no improvement in the yield of enamine **298**. However, an intriguing observation was made when a large excess of DBU was used to investigate if elimination at room temperature was possible. The fascinating ring-contracted dihydro-pyran **299** was isolated in high yield as a single diastereomer (Scheme 3.30). The proposed mechanism for this rearrangement will be discussed in Chapter 4.8.



Scheme 3.30. Unexpected rearrangement of dihydro-oxepine **294**. (Relative stereochemistry shown).

3.6.5 Imidate Hydrolysis: A Second Generation Synthesis of Dihydro-Janoxepin **49**

Initially, an aqueous HCl/EtOAc system (1:3) for the hydrolysis of the imidate protecting group was investigated. Hydrolysis proceeded quickly, with the starting material being consumed within 40 min, but the isolated yield of dihydro-janoxepin **49** was disappointing (Table 3.10, entry 1). Heating imidate **298** in AcOH and water (4:1) to 50 °C for 1 h was found to be the optimal conditions for hydrolysis, completing a second generation synthesis of dihydro-janoxepin **49** in 73% yield. The configuration of the enamine was again confirmed as *Z* by nOe experiments.

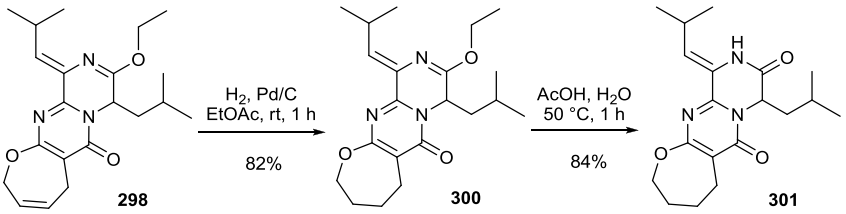


Entry	Conditions	Yield 49
1	3 M HCl, EtOAc (1:3), rt, 40 min	31%
2	AcOH, H_2O (4:1), 50 °C, 1 h	73%

Table 3.10. Optimisiation of imidate hydrolysis: preparation of dihydro-janoxepin **49**.

3.7 Dihydro-Oxepine Hydrogenation: The Synthesis of Tetrahydro-Janoxepin **301**

Tetrahydro-janoxepin **301** was identified as an interesting analogue of janoxepin (**1**), and the model study (Chapter 2.6) had shown dihydro-oxepine hydrogenation to be an efficient process. However, selectivity for hydrogenation of the cyclic alkene over the enamine olefin presented an additional challenge for the synthesis of tetrahydro-janoxepin **301** from either imidate **298** or dihydro-janoxepin **49**. However, when imidate **298** was treated with palladium on carbon under an atmosphere of hydrogen, selective dihydro-oxepine hydrogenation was indeed observed to furnish tetrahydro-oxepine **300**. Subsequent imidate hydrolysis using the previously developed conditions then afforded tetrahydro-janoxepin **301** in 69% yield for the two-step sequence (Scheme 3.31, see Appendix **II** for NMR spectra). A direct hydrogenation of dihydro-janoxepin **49** was not subsequently investigated.



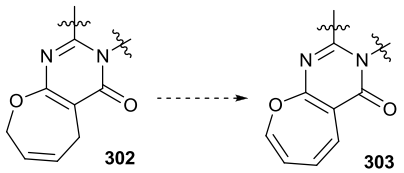
Scheme 3.31. Synthesis of tetrahydro-janoxepin **301**.

3.8 Summary

The enamine side chain seen in janoxepin (**1**) was successfully introduced by aldol addition of *iso*-butyraldehyde **221** to imidate-protected dihydro-oxepine **290**. Following extensive experimentation, a high and reliable yield of a single diastereomer was achieved which underwent elimination to exclusively the desired *Z*-enamine **298**. This allowed for the synthesis of the novel janoxepin analogue dihydro-janoxepin **49** and, following a selective alkene hydrogenation, tetrahydro-janoxepin **301**. The final transformation now required to complete the synthesis of janoxepin (**1**) was the elaboration of the dihydro-oxepine moiety to the required unsaturated oxepine. This is discussed in Chapter 4, alongside mechanistic proposals for the dihydro-oxepine rearrangements observed during this study.

Chapter 4. Dihydro-Oxepine Elaboration: The Synthesis of (±)-Janoxepin (1)

Literature precedent for the elaboration of dihydro-oxepines to oxepines (Scheme 4.1) is limited, as discussed in Chapter 2.3.4. However, a bromination followed by double dehydro-bromination sequence had been established as a viable method for effecting this transformation, and its utility demonstrated through the synthesis of the model compound, oxepine-pyrimidinone **196** (Chapter 2.6). This Chapter will first discuss the application of this methodology to the attempted synthesis of janoxepin (**1**) before describing alternative strategies that were subsequently explored.

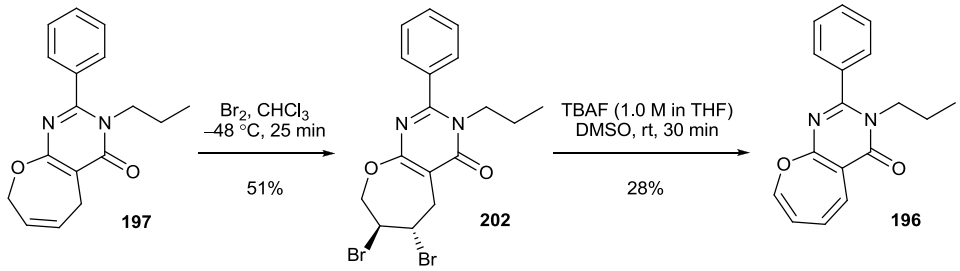


Scheme 4.1. Representative dihydro-oxepine **302** elaboration to oxepine **303**.

4.1 Bromination – Dehydrobromination

4.1.1 Re-Cap: Model Study

The bromination of dihydro-oxepine **197** to give dibromide **202**, followed by a TBAF mediated double dehydrobromination to furnish the model oxepine-pyrimidinone **196** (Scheme 4.2) was discussed in Chapter 2.6. Disappointingly, the elimination step was low yielding (28%) compared to the results initially reported by Jones in 2008 (87%),[35] and this yield could not be improved upon following a screen of different bases.

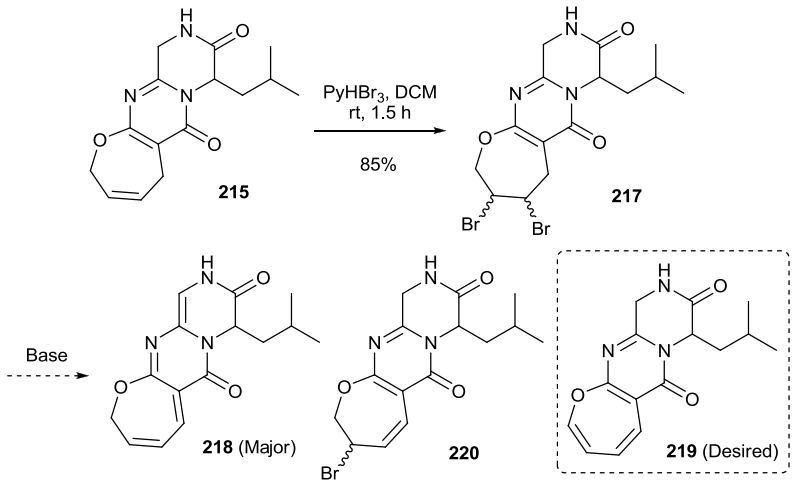


Scheme 4.2. Bromination – dehydrobromination: synthesis of model oxepine-pyrimidinone **196**. (Relative stereochemistry shown).

4.1.2 Re-Cap: Application to Dihydro-Oxepine **215**

As discussed in Chapter 2.11, the bromination of dihydro-oxepine **215** was achieved in good yield, but dehydrobromination was not successful (Scheme 4.3). A complex

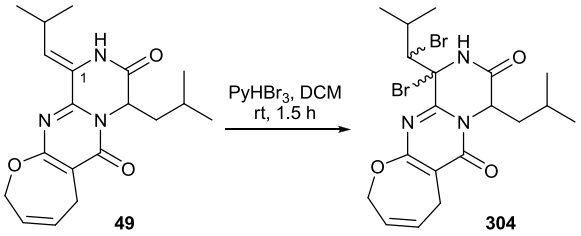
mixture of polar side-products was isolated, with the major product being identified as the isomeric species **218** which was formed as a result of deprotonation of the ketopiperazine. The mono-elimination product bromide **220** was also observed.



Scheme 4.3. Bromination – dehydrobromination: application to dihydro-oxepine **215**.

4.1.3 Application to Dihydro-Janoxepin **49**

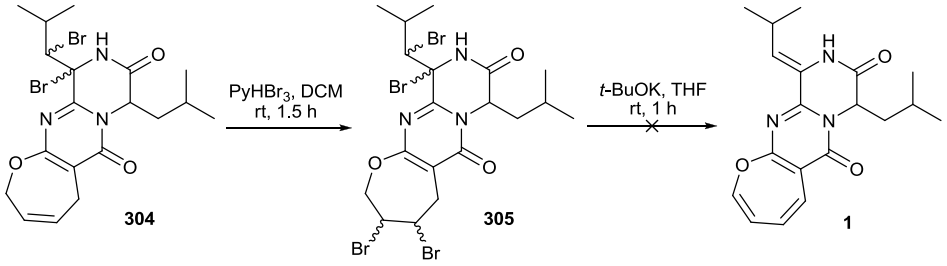
It was proposed that employing a dihydro-oxepine substrate bearing ketopiperazine substitution at C-1 would avoid deprotonation at this position as previously observed. Dihydro-janoxepin **49** was identified as the ideal substrate as, if successful, the synthesis of janoxepin (**1**) would be completed in just two further steps. However, bromination was favoured at the electron rich enamine double bond when a single equivalent of pyridine hydrotribromide was used. Dibromide **304** was isolated as a complex mixture of diastereomers which could not be separated and the mixture was not characterised (Scheme 4.4).



Scheme 4.4. Bromination of dihydro-janoxepin **49**.

Treatment of dibromide **304** with a further equivalent of pyridine hydrotribromide did lead to bromination of the dihydro-oxepine olefin. Tetrabromide **305** was not isolated, but immediately treated with potassium *tert*-butoxide in an attempt to effect an unlikely global dehydrobromination (Scheme 4.5). This was unsuccessful, and following a brief

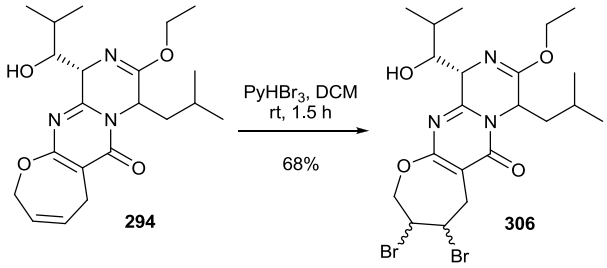
screen of different reaction conditions as described in Chapter 2.6, the approach was abandoned.



Scheme 4.5. Synthesis of tetrabromide **305** from dibromide **304**. Subsequent global elimination was unsuccessful.

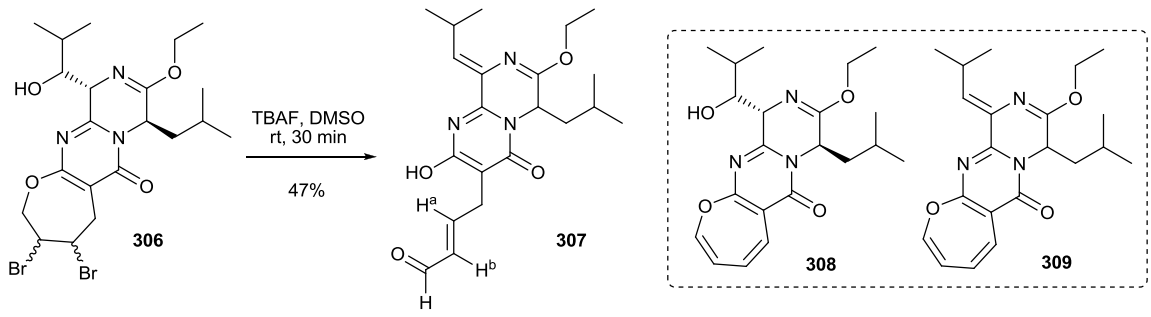
4.1.4 Application to Aldol Adduct **294**

Aldol adduct **294** was identified as a more suitable substrate for bromination–dehydrobromination as the selectivity issue previously encountered would be negated. Following treatment with pyridine hydrotribromide in DCM, dibromide **306** was isolated in 68% yield as a 1:1 mixture of diastereomers that could not be separated (Scheme 4.6).



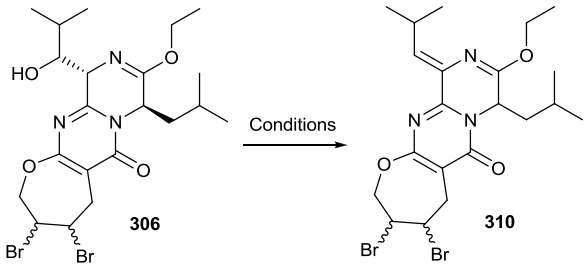
Scheme 4.6. Bromination of aldol adduct **294**.

Dibromide **306** was next subjected to the optimal dehydrobromination conditions previously identified – TBAF in DMSO (Scheme 4.7). It was expected to obtain a mixture of aldol adduct **308** and enamine **309** (resulting from base induced elimination of the aldol adduct **308**), but the isolation of aldehyde **307** in 47% yield was surprising. The characterisation of aldehyde **307**, a possible mechanism for its formation and attempts to promote a subsequent cyclisation to oxepine **309** are discussed later (Chapter 4.8.2).



Scheme 4.7. Dehydrobromination of dibromide **306**: isolation of aldehyde **307**. (Relative stereochemistry shown).

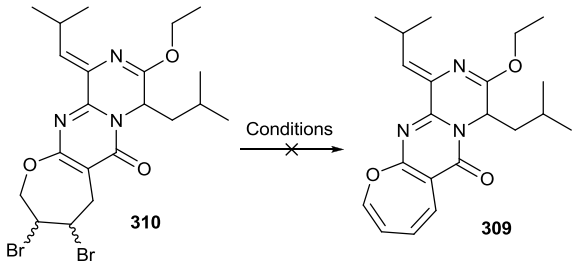
The dehydrobromination of dibromide **306** with DBU in DCM was also unsuccessful, but dehydration did occur and enamine **310** was isolated in moderate yield as a single diastereomer (Table 4.1, entry 1). The same transformation was also achieved in similar yield by treatment of dibromide **306** with mesyl chloride in pyridine as solvent (Table 4.1, entry 2).



Entry	Conditions	Yield 310
1	DBU, DCM, rt, 30 min	38%
2	MsCl, pyridine, 50 °C, 2 h	36%

Table 4.1. Dehydration of aldol adduct **306** to enamine **310**. (Relative stereochemistry shown).

It was postulated that dibromide **310** would be a simplified substrate for further investigation of the double elimination to an oxepine. Therefore, dibromide **310** was subjected to three different reaction conditions, but in each case, only poor recovery of a complex mixture of products could be obtained (Table 4.2). Surprisingly, not even aldehyde **307** was seen upon treatment of dibromide **310** with TBAF in DMSO as previously observed (Scheme 4.7).



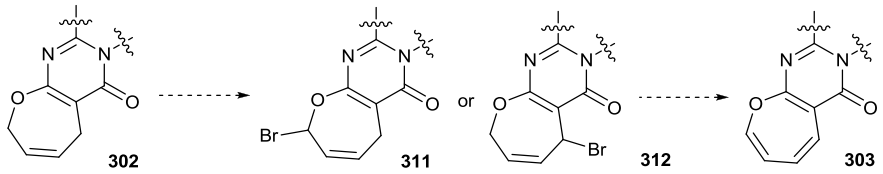
Entry	Base (3.1 eq.)	Conditions
1	TBAF (1.0 M in THF)	DMSO, rt, 30 min
2	DBU	PhMe, rt, 30 min
3	*t*-BuOK	THF, 0 °C – rt, 1 h

Table 4.2. Reaction conditions screened for the dehydrobromination of dibromide **310**.

The double dehydrobromination strategy for dihydro-oxepine elaboration was now abandoned altogether and an alternative strategy relying upon allylic bromination was investigated.

4.1.5 Allylic Bromination Strategy

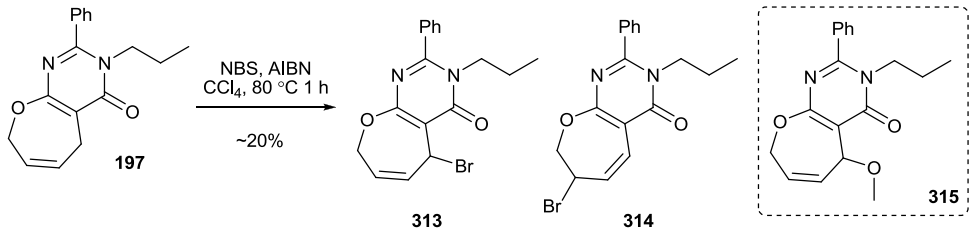
It was proposed that allylic bromination of a dihydro-oxepine **302** would be an efficient way to access an allylic bromide **311** or **312**, which would then require only a single elimination in order to access the desired oxepine **303** (Scheme 4.8). Indeed, this strategy has been utilised in the preparation of dibenzo-oxepines as described by Griffin and Brightwell.[42] The model dihydro-oxepine **197** was used for initial investigation owing to its relative ease of preparation.



Scheme 4.8. Proposed allylic bromination – dehydrobromination strategy.

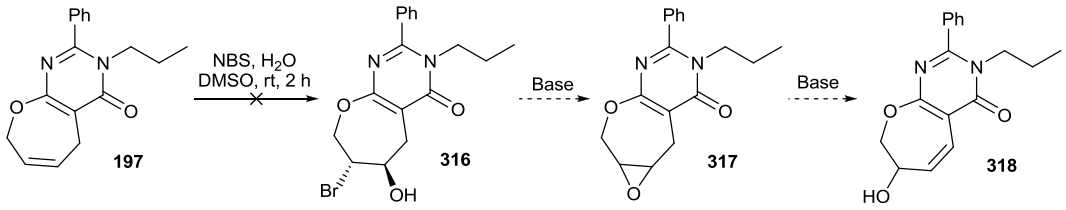
Dihydro-oxepine **197** was treated with NBS and AIBN in degassed CCl_4 at 80 °C for 1 h (no reaction was observed at room temperature) (Scheme 4.9). Despite the starting material being consumed in the reaction, only traces of two possible bromination products **313** and **314** could be identified in the ^{1}H-NMR spectrum of the unpurified material. Mass spectrometry was also inconclusive, as no $[MH]^+$ peak or characteristic bromine isotope peaks were present, as would be expected for an allylic bromide. Instead, the mass for the methoxy derivative **315** was observed. It is proposed that this

was a result of nucleophilic substitution of methanol, used to inject the sample into the spectrometer.



Scheme 4.9. Allylic bromination of dihydro-oxepine **197**.

An alternative approach was to prepare bromohydrin **316** and either: perform a double elimination following alcohol activation; or form epoxide **317** and open to allylic alcohol **318** upon treatment with base. Unfortunately, treatment of dihydro-oxepine **197** with NBS and water in DMSO led to the isolation of a complex mixture of side products (Scheme 4.10).

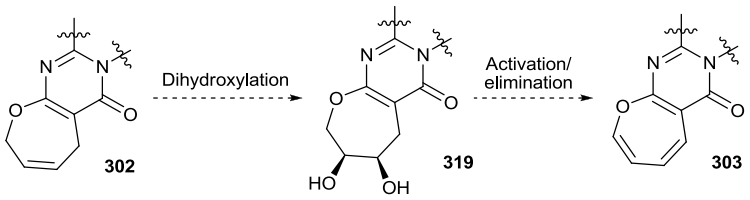


Scheme 4.10. Attempted bromhydrination of dihydro-oxepine **197** and proposed epoxide formation.

Despite success in the model study, dihydro-oxepine elaboration *via* any bromination – dehydrobromination sequence could not be achieved for ketopiperazine-pyrimidinone-containing substrates. A number of alternative approaches for dihydro-oxepine elaboration were therefore investigated.

4.2 Dihydro-Oxepine Dihydroxylation

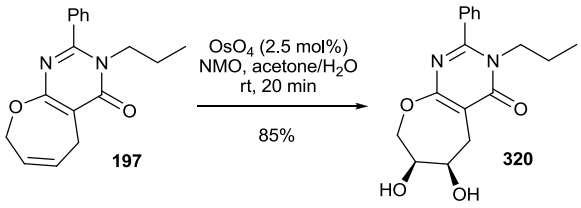
It was envisaged that the osmium-catalysed dihydroxylation of a dihydro-oxepine **302** followed by diol activation and elimination would provide an alternative method for elaboration to oxepines **303** (Scheme 4.11). Not only that, it was predicted that dihydroxylation would be selective for the least hindered dihydro-oxepine olefin, and therefore the strategy could be applied to advanced enamine-containing intermediates. A study using the model system was first undertaken to demonstrate the viability of the approach.



Scheme 4.11. Proposed dihydroxylation – elimination strategy. (Relative stereochemistry shown).

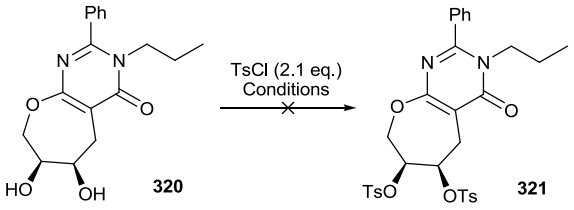
4.2.1 Model Study

Gratifyingly, application of standard Upjohn dihydroxylation conditions gave immediate success. Treatment of the model dihydro-oxepine **197** with osmium tetroxide (2.5 mol%) and *N*-methylmorpholine *N*-oxide (NMO) in acetone and water furnished the *cis*-diol **320** in excellent yield (Scheme 4.12).



Scheme 4.12. Dihydroxylation of dihydro-oxepine **197**. (Relative stereochemistry shown).

Activation of diol **320** as a disulfonate for double elimination to an oxepine was investigated next. Conditions for the tosylation of diol **320** were initially explored without success. The treatment of diol **320** with TsCl, NEt_3 and DMAP in DCM returned only starting material after a long reaction time at room temperature (Table 4.3, entry 1), whilst heating the reaction mixture also failed to promote any conversion to the desired ditosylate **321**. Using TsCl in pyridine as solvent gave the same outcome (Table 4.3, entry 2).

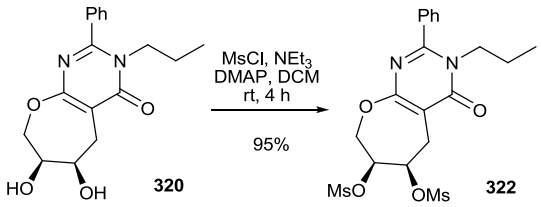


Entry	Conditions	Comment
1	NEt_3, DMAP, DCM, rt, 24 h	rsm
2	Pyridine (solvent), rt, 24 h	rsm

Table 4.3. Ditosylate **321** formation: reaction conditions screened. (Relative stereochemistry shown).

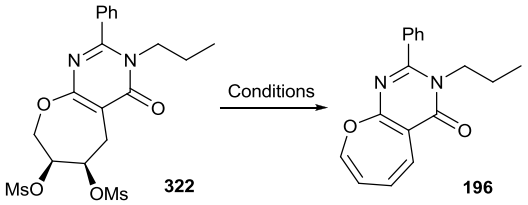
Mesylation was found to proceed efficiently, and dimesylate **322** was isolated in 95% yield following treatment with MsCl, NEt_3 and DMAP in DCM (Scheme 4.13). Why

tosylation could not be achieved is unclear, but could be due to unfavourable steric interactions or the reduced reactivity of TsCl compared to MsCl.



Scheme 4.13. Synthesis of dimesylate **322**. (Relative stereochemistry shown).

With dimesylate **322** in hand, a screen of elimination conditions was carried out. The successful dehydrobromination conditions previously described (TBAF in DMSO) gave optimal results, with the desired oxepine **196** being isolated in 30% yield (Table 4.4, entry 1). When DBU in DCM (Table 4.4, entry 2) and potassium *tert*-butoxide in THF (Table 4.4, entry 3) were employed, oxepine **196** was isolated in very low yields (<5%) from a complex mixture of other side-products.



Entry	Base (4.0 eq.)	Conditions	Yield 196
1	TBAF (1.0 M in THF)	DMSO, rt, 30 min	30%
2	DBU	DCM, 0 °C – rt, 16 h	<5%
3	*t*-BuOK	THF, 0 °C – rt, 16 h	<5%

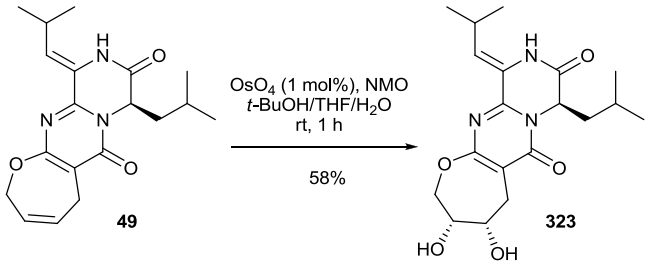
Table 4.4. Dimesylate **322** elimination to oxepine **196**: reaction conditions screened. (Relative stereochemistry shown).

Having demonstrated the viability of this strategy, no further optimisation studies were carried out on the model system. It was important to first ascertain that dihydroxylation of dihydro-janoxepin **49**, or its imidate derivative **298**, would proceed with the required selectivity.

4.2.2 Selective Dihydroxylation of Dihydro-Janoxepin **49**

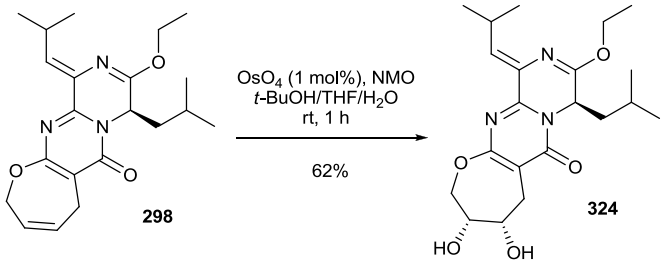
The dihydroxylation of dihydro-janoxepin **49** was indeed found to be selective for the dihydro-oxepine olefin. Following the treatment of dihydro-janoxepin **49** with 1.0 mol% of osmium tetroxide and a stoichiometric amount of NMO in a solvent system of *t*-BuOH/THF/water (as reported by Panek[109]), the desired diol **323** was isolated in good

yield as a 1:1 mixture of diastereomers with the *cis*-diol *syn* and *anti* to the *iso*-butyl group respectively (Scheme 4.14). Increasing the loading of osmium tetroxide or extending the reaction time was found to be detrimental to the yield.



Scheme 4.14. Dihydroxylation of dihydro-janoxepin **49**. (*Anti* diastereomer shown).

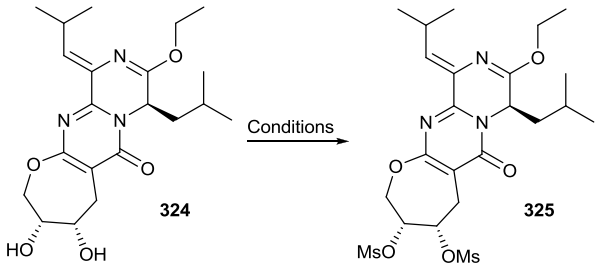
The same conditions were applied to the imidate **298** with similar results (Scheme 4.15).



Scheme 4.15. Dihydroxylation of imidate **298**. (*Anti* diastereomer shown).

4.2.3 Mesylation of Diols **323** and **324**

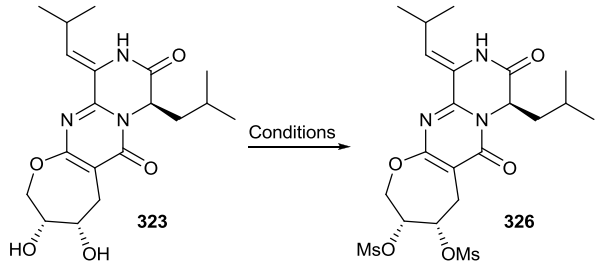
The dimesylation of both diols **323** and **324** was investigated in order to compare any differences in reactivity, and thus quickly identify the optimal substrate to use. Application of the mesylation conditions previously employed (MsCl, NEt_3, DMAP) gave disappointing results when applied to imidate-containing diol **324**: only traces of dimesylate **325** could be identified in a complex mixture of side-products as shown by the ^{1}H-NMR spectrum of the unpurified product (Table 4.5, entry 1). This problem was overcome by using MsCl in pyridine as solvent, which provided the desired dimesylate **325** in 76% yield (Table 4.5, entry 2).



Entry	Conditions	Yield 325
1	MsCl, NEt_3, DMAP, DCM, rt, 4 h	Trace – mainly decomposition products isolated
2	MsCl, pyridine, rt, 4 h	76%

Table 4.5. Synthesis of dimesylate **325**: reaction conditions screened. (*Anti* diastereomer shown).

Similar results were obtained when the dihydro-janoxepin derived diol **323** was subjected to the same reaction conditions (Table 4.6).

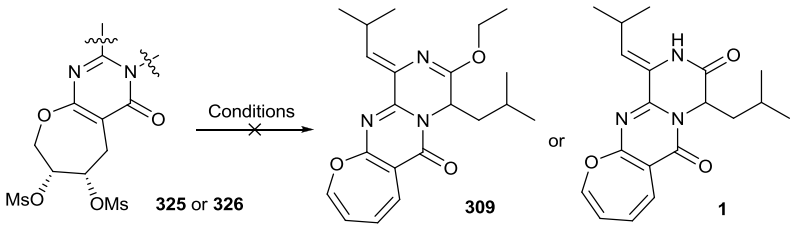


Entry	Conditions	Yield 326
1	MsCl, NEt_3, DMAP, DCM, rt, 4 h	Trace – mainly decomposition products isolated
2	MsCl, pyridine, rt, 4 h	98%

Table 4.6. Synthesis of dimesylate **326**: reaction conditions screened. (*Anti* diastereomer shown).

4.2.4 Dimesylate Elimination

The double elimination of both dimesylates **325** and **326** to the respective oxepines **309** and **1** was investigated next with the results obtained for each substrate being identical. When both the substrates were treated with TBAF in DMSO, no conversion to product was observed following prolonged reaction times with heating (Table 4.7, entry 1). The same outcome occurred when DBU was used in toluene (Table 4.7, entry 2) and NaOMe was used in DMF with heating (Table 4.7, entry 3). When stronger bases were employed, only a complex mixture of decomposition products was isolated: potassium *tert*-butoxide was used in both THF (Table 4.7, entry 4) and DMF (Table 4.7, entry 5) whilst potassium hydroxide in DMSO was also investigated (Table 4.7, entry 6).



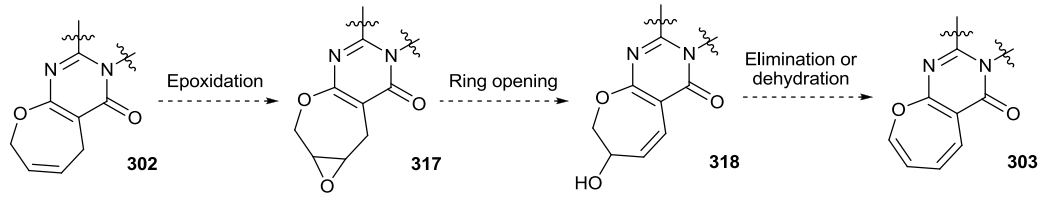
Entry	Base (3.1 eq.)	Conditions	Comment
1	TBAF (1.0 M in THF)	DMSO, rt – 60 °C, 2 h	rsm
2	DBU	PhMe, rt – 60 °C, 2 h	rsm
3	NaOMe	DMF, rt – 100 °C,	rsm
4	*t*-BuOK	THF, –78 °C – rt, 2 h	Decomposition of sm on warming to rt
5	*t*-BuOK	DMF, rt, 30 min	Decomposition of sm
6	KOH	DMSO, rt – 100 °C, 2 h	Decomposition of sm on heating

Table 4.7. Elimination of dimesylates **325** and **326** to oxepines **309** or **1**: reaction conditions screened.

Both dehydrobromination and dihydroxylation studies provided clear evidence of ketopiperazine-pyrimidinone-oxepine instability under basic conditions. Therefore, strategies that would require a single elimination event to install the oxepine ring under mild conditions became the focus of further investigation.

4.3 Epoxidation – Ring Opening Approach: Model Study

As discussed in Chapter 2.3.4, Wijnberg and co-workers reported that a dihydro-oxepine epoxidation followed by base induced ring-opening sequence could provide access to an allylic alcohol – in our case this would be **318**.[72] It was envisaged that an activation-elimination sequence, or indeed direct dehydration, would then provide access to the desired oxepine **303** under milder conditions to those required for a double elimination event (Scheme 4.16).



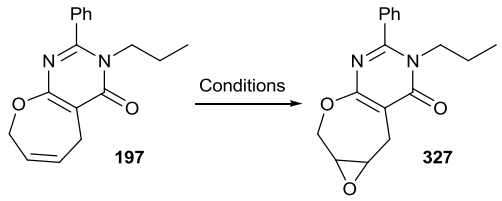
Scheme 4.16. Proposed epoxidation – ring-opening strategy.

A model study was undertaken to demonstrate that the approach would be viable for oxepine-pyrimidinone systems but, unfortunately, epoxidation of the model dihydro-oxepine **197** proved very difficult. When conditions requiring the *in situ* generation of

DMDO from acetone using Oxone® as reported by Wijnberg and co-workers were applied,[72] only a complex mixture of side-products was obtained (Table 4.8, entry 1). This poor result was attributed to the slow and unreliable formation of DMDO, and so Yang's conditions for TFDO generation from trifluoroacetone using Oxone® were investigated,[110] but with the same outcome (Table 4.8, entry 2).

A *m*-CPBA mediated epoxidation had been avoided due to concerns that the benzoate anion formed would immediately open the newly formed epoxide.[72] Indeed, when dihydro-oxepine **197** was treated with an excess of *m*-CPBA in DCM complete decomposition of the starting material was observed (Table 4.8, entry 3). It was proposed that the addition of an aqueous solution of $NaHCO_3$ to the reaction would minimise any unwanted interaction of the substrate with the benzoate anion or benzoic acid. However, this modification resulted in the same outcome as previously obtained (Table 4.8, entry 4).

Next, DMDO was prepared as a solution in acetone according the procedure of Singh and co-workers.[111] Treatment of dihydro-oxepine **197** with the DMDO solution did lead to the isolation of epoxide **327** in low yield (Table 4.8, entry 5), but this result could not be repeated. Traces of diol **320** were observed by mass spectrometry suggesting that the epoxide was susceptible to ring-opening in the presence of water. Repeating the reaction in the presence of the desiccant Na_2CO_3 offered no improvement however.



Entry	Epoxidising agent	Conditions	Comment
1	Oxone®/acetone	$NaHCO_3$, 18-crown-6, DCM, H_2O, 0 °C, 4 h	Decomposition of sm
2	Oxone®/trifluoroacetone	$NaHCO_3$, Na_2EDTA, MeCN, 0 °C, 10 min	Decomposition of sm
3	*m*-CPBA	DCM, 0 °C – rt, 16 h	Decomposition of sm
4	*m*-CPBA	Sat. $NaHCO_3$ (aq.), DCM, 0 °C – rt, 16 h	Decomposition of sm
5	DMDO	Acetone, –78 °C, 2.5 h	13% **327**

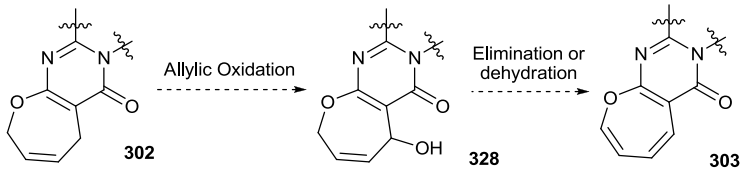
Table 4.8. Epoxidation of dihydro-oxepine **197**: reaction conditions screened.

The small quantities of epoxide **327** that could be isolated from the reaction of dihydro-oxepine **197** with DMDO made further investigation impossible. It was therefore

decided to abandon this route: it seemed reasonable to suggest that other epoxidation conditions (*e.g.* Shi or Jacobsen methods) would also fail. Not only that, but it was deemed unlikely that dihydro-janoxepin **49**, or a derivative, would prove a good substrate for epoxidation where the model system had already failed.

4.4 Allylic Oxidation Strategy

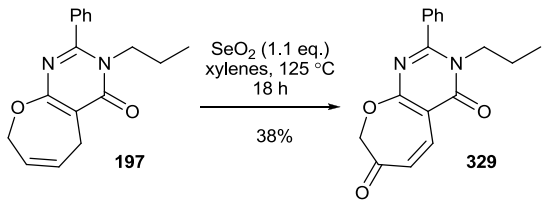
The allylic oxidation of a dihydro-oxepine **302** was identified as an alternative strategy for preparing an allylic alcohol **328**, for either activation-elimination, or direct dehydration to an oxepine **303** (Scheme 4.17).



Scheme 4.17. Proposed allylic oxidation strategy.

4.4.1 Allylic Oxidation: Model Study

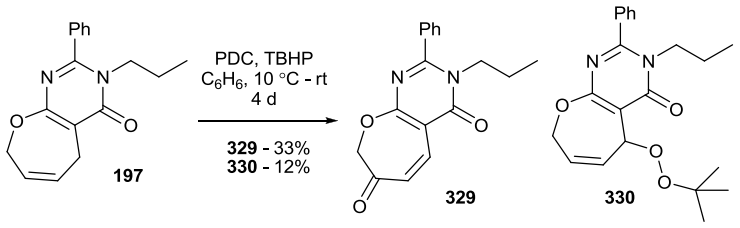
The allylic oxidation of dihydro-oxepines was described by Chattopadhyay and co-workers in 2007 (Chapter 2.3.4).[112] Following their procedure, the model dihydro-oxepine **197** was treated with 1.1 equivalents of selenium dioxide in xylenes, with heating at 125 °C for 18 h, to furnish the enone **329** in moderate yield (Scheme 4.18). The structure of enone **329** was assigned based upon the ^{1}H-NMR spectrum which showed a doublet and doublet of doublets for the two alkene protons respectively and a singlet at 4.70 ppm corresponding to the *O*-methylene protons. The regioselectivity observed was surprising: it was expected that oxidation would occur at the benzylic-allylic position. Instead, isomerisation of the alkene into conjugation with the pyrimidinone ring occured before oxidation at the now only available allylic position.



Scheme 4.18. Selenium dioxide-mediated allylic oxidation of dihydro-oxepine **197** in xylenes.

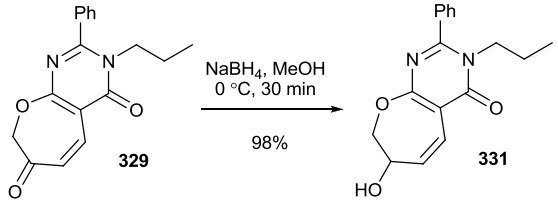
Enone **329** could also be prepared in comparable yield by pyridinium dichromate (PDC) and *tert*-butyl hydrogen peroxide (TBHP) mediated allylic oxidation of dihydro-oxepine **197**, a procedure previously used by the Taylor group (Scheme 4.19).[113] The interesting

peroxy-intermediate **330** was also isolated, where addition of the TBHP radical had occurred at the expected benzylic-allylic position but subsequent oxidation to the respective enone had not proceeded.



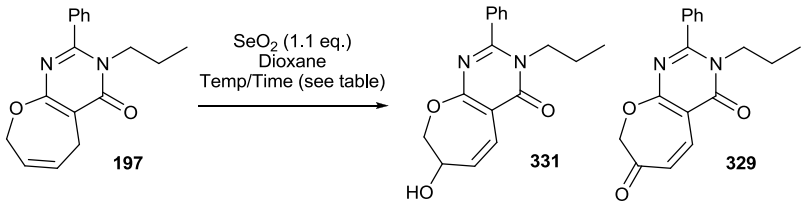
Scheme 4.19. PDC/TBHP-mediated allylic oxidation of dihydro-oxepine **197**.

Whilst enone **329** was a valuable intermediate, our initial interest was to utilise allylic alcohol **331**. Thus, enone **329** was readily reduced using sodium borohydride in MeOH at 0 °C in near quantitative yield (Scheme 4.20).



Scheme 4.20. Reduction of enone **329**.

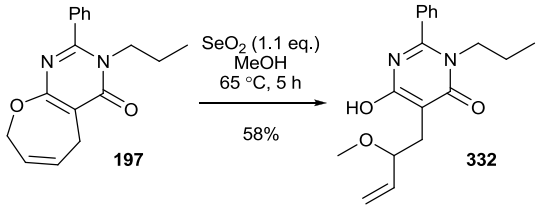
It was more desirable to access allylic alcohol **331** directly, without the need for a subsequent reduction step. Pleasingly, it was discovered that treatment of dihydro-oxepine **197** with selenium dioxide in dioxane as solvent at 100 °C for 30 min furnished the desired alcohol **331** in 39% yield and enone **330** in 14% yield (Table 4.9, entry 1). Reducing the reaction temperature to 75 °C with an increase in reaction time led to an improvement in the overall yield as well as the ratio of alcohol **331** to enone **329**, with alcohol **331** isolated in 52% yield, and enone **329** in 10% yield (Table 4.9, entry 2). These conditions were found to be optimal - any further reduction in temperature resulted in extremely slow oxidation of dihydro-oxepine **197** (Table 4.9, entries 3 and 4).



Entry	Temperature (°C)	Time (h)	Yield 331	Yield 329	Overall Yield
1	100	0.5	39%	14%	53%
2	75	1.0	52%	10%	62%
3	50	18	-	-	<10%
4	rt	18	-	-	rsm

Table 4.9. Selenium dioxide-mediated allylic oxidation of dihydro-oxepine **197** in dioxane: optimisation study.

When methanol was investigated as an alternative solvent during the optimisation study, only the intriguing ring opened methoxy derivative **332** was isolated (Scheme 4.21). [This observation was also made in the absence of selenium dioxide]. The sensitivity of dihydro-oxepines to nucleophiles is indeed noteworthy; mechanistic proposals and the characterisation of **332** are discussed later (Chapter 4.8.3).



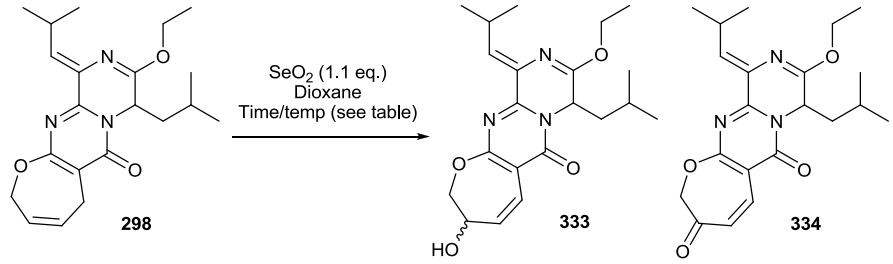
Scheme 4.21. Unexpected synthesis of ring-opened methoxy-derivative **332**.

4.4.2 Allylic Oxidation of Dihydro-Oxepine **298**

The dihydro-janoxepin **49** imidate-protected precursor **298** was identified as the most suitable substrate for the investigation of allylic oxidation to alcohol **333**. Its lower polarity compared to that of dihydro-janoxepin made it easier to handle, and amide nitrogen protection would preclude any complications arising from *N*-oxide formation.

Application of the optimum conditions identified in the model study gave encouraging results, with the desired allylic alcohol **333** being isolated as a 1:1 mixture of diastereomers in 35% yield and enone **334** in 11% yield (Table 4.10, entry 1). The disappointing overall yield was attributed to decomposition of dihydro-oxepine **298** under the reaction conditions. Increasing the reaction temperature to 90 °C, but halving the reaction time gave a much improved 58% yield of alcohol **333** and 13% yield of ketone **334** (Table 4.10, entry 2). A further increase in temperature to 100 °C had a

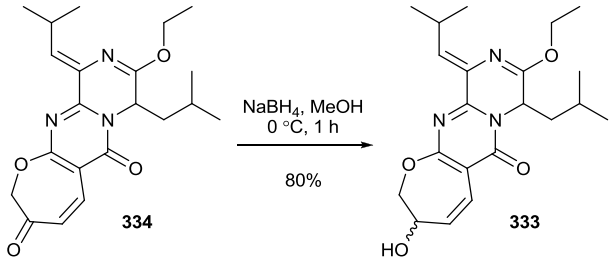
considerable detrimental effect on the overall yield (Table 4.10, entry 3), whilst lower temperatures gave very slow conversion to product (Table 4.10, entry 4).



Entry	Temperature (°C)	Time (h)	Yield 333	Yield 334	Overall Yield
1	75	1.0	35%	11%	46%
2	90	0.5	58%	13%	71%
3	100	0.5	26%	15%	41%
4	50	18	-	-	<10%

Table 4.10. Allylic oxidation of dihydro-oxepine **298**.

As found in the model study, enone **334** could be readily reduced to alcohol **333** using sodium borohydride (Scheme 4.22).



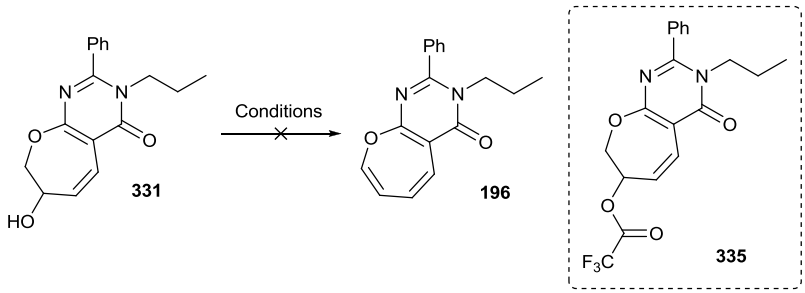
Scheme 4.22. Reduction of enone **334**.

With allylic alcohol **333** available in good yield directly from dihydro-oxepine **298**, an investigation of methods for dehydration or elimination to provide the desired oxepine was undertaken next. Reaction conditions were applied to the model allylic alcohol **331** in the first instance owing to its ready availability.

4.4.3 Allylic Alcohol Dehydration: Model Study

The acid-catalysed dehydration of alcohol **331** was initially investigated. Disappointingly, aqueous sulfuric acid (Table 4.11, entry 1) and *p*-toluenesulfonic acid (Table 4.11, entry 2) failed to promote any dehydration to oxepine **196**. When TFA was used (10% v/v in DCM), the trifluoroacetate derivative **335** was observed in both mass and ^{1}H-NMR spectra of the unpurified product. Following purification on silica gel

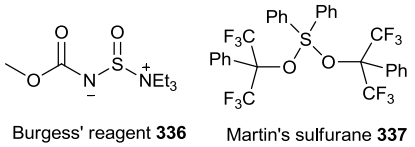
however, only a very poor recovery of the starting material was obtained (Table 4.11, entry 3).



Entry	Acid	Conditions	Comment
1	H_2SO_4 (5% aq. solution)	Dioxane, rt – 80 °C, 18 h	rsm
2	*p*TSA (0.5 eq.)	PhMe, rt – 110 °C, 18 h	rsm
3	TFA (10% v/v)	DCM, rt, 18 h	**335** present in unpurified material

Table 4.11. Acid-catalysed dehydration of alcohol **331**: reaction conditions screened.

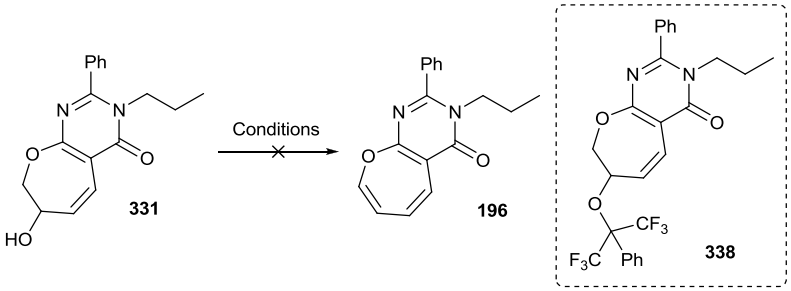
Having observed no conversion to oxepine **196** this approach was abandoned and the utility of sulfur-containing dehydrating agents such as Burgess' reagent[114] **336** and Martin's sulfurane[115] **337** (Figure 4.1) was investigated.



Burgess' reagent **336** Martin's sulfurane **337**

Figure 4.1. Structure of Burgess' reagent **336** and Martin's sulfurane **337**.

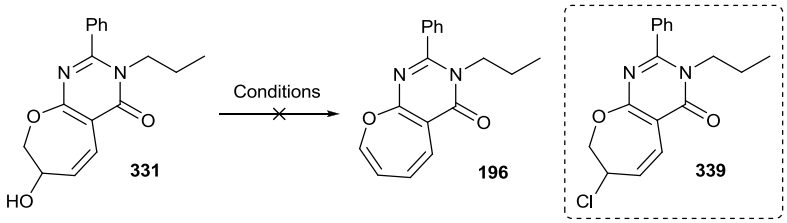
When alcohol **331** was heated with Burgess' reagent **336** in both DMF (Table 4.12, entry 1) and toluene (Table 4.12, entry 2), complete consumption of the starting material was observed by TLC, but to a complex mixture of baseline material. Using Martin's sulfurane **337** at room temperature also gave no conversion to the desired oxepine **196**, but the intermediate species **338** could be seen in both mass and ^{1}H-NMR spectra of the unpurified product (Table 4.12, entry 3). This indicated that initial activation of the alcohol was occurring, but that subsequent deprotonation of the α-proton with elimination was an unfavourable process - heating the reaction mixture was not sufficient to promote this.



Entry	Dehydrating Agent (2.0 eq.)	Conditions	Comment
1	Burgess' reagent **336**	DMF, 80 °C, 3 h	Decomposition
2	Burgess' reagent **336**	PhMe, 110 °C, 18 h	Decomposition
3	Martin's sulfurane **337**	DCM, rt, 2 h	Intermediate **338** observed in crude material

Table 4.12. Dehydrating agent-mediated dehydration of alcohol **331**: reaction conditions screened.

Two further alternative methods for the dehydration of alcohol **331** were investigated. Alcohol **331** was treated with Ph_3P and DIAD in THF, it being proposed that the loss of $Ph_3P(O)$ may provide a driving force for elimination, but only decomposition of the starting material was observed as the reaction mixture was warmed to room temperature (Table 4.13, entry 1). When alcohol **331** was treated with $SOCl_2$ in pyridine for 1 h, the allylic chloride **339** was isolated in 57% yield (Table 4.13, entry 2). Unfortunately, heating the reaction mixture was not sufficient to promote subsequent dehydrochlorination.

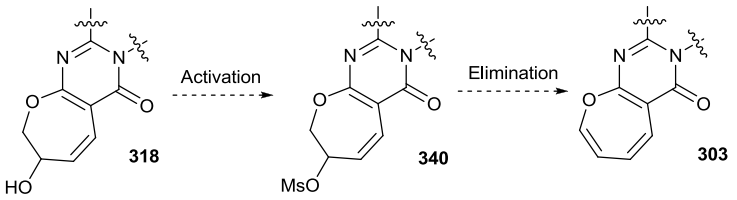


Entry	Conditions	Comment
1	PPh_3, DIAD, THF, 0 °C – rt, 1.5 h	Decomposition
2	$SOCl_2$, pyridine (solvent), 0 °C – rt, 1 h	57% **339**

Table 4.13. Alternative dehydration conditions investigated.

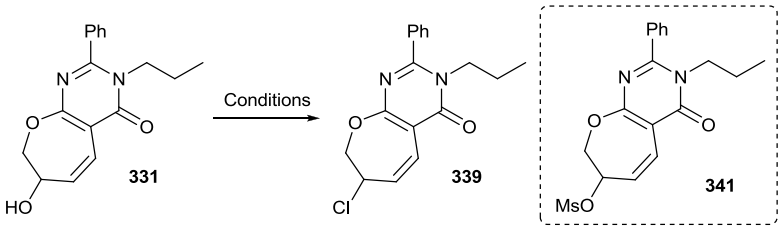
4.4.4 Chlorination – Dehydrochlorination: Model Study

An activation-elimination sequence for the conversion of an allylic alcohol **318** to an oxepine **303** was investigated next. It was proposed that a mesylate **340** would be a suitable intermediate for elimination (Scheme 4.23).



Scheme 4.23. Proposed activation – elimination sequence.

Surprisingly, treatment of alcohol **331** with MsCl in pyridine (as used to prepare dimesylates **325** and **326**) resulted in no conversion to product, with complete recovery of the starting material (Table 4.14, entry 1). When MsCl was used with NEt_3 and DMAP, complete conversion to a product was observed in 4 h, however, no singlet corresponding to the mesyl group protons was present in the ^{1}H-NMR spectrum. The product was eventually identified as chloride **339** (characterisation discussed below) which was isolated in 98% yield (Table 4.14, entry 2). When TsCl was used under the same reaction conditions, chloride **339** was again isolated, but a longer reaction time was required and a lower yield obtained (Table 4.14, entry 3).

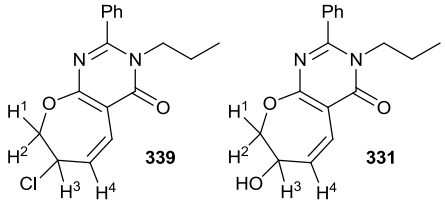


Entry	Conditions	Yield 339
1	MsCl, pyridine (solvent), rt, 18 h	rsm
2	MsCl, NEt_3, DMAP, DCM, rt, 4 h	98%
3	TsCl, NEt_3, DMAP, DCM, rt, 18 h	59%

Table 4.14. Synthesis of chloride **339**: reaction conditions screened.

The ESI mass spectrum of chloride **339** did show the corresponding molecular ion (with chlorine isotope peaks), but at low intensity. The major peak corresponded to that of alcohol **331**, presumably as a result of hydrolysis under the spectrometer conditions. IR spectroscopy of the product clearly showed the absence of an absorption band at a frequency corresponding to an O-H stretch, whilst NMR spectroscopy provided further evidence for the structural assignment. In the ^{1}H-NMR spectrum of chloride **339** the signal for H-3 had clearly shifted downfield with respect to alcohol **331** whilst the diastereotopic protons H-1 and H-2 had also shifted downfield and had very distinct chemical shifts (Table 4.15). In the ^{13}C-NMR spectrum the signal corresponding to the

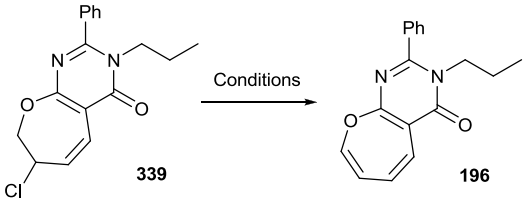
H-3 carbon had shifted upfield (Table 4.15). These observations were consistent with the predicted NMRs generated by ACD© and ChemDraw©.



#	δ_H (*J* in Hz)		δ_C	
	339	**331**	**339**	**331**
1	4.64 (ddd, *J* 12.0, 3.0, 1.0)	4.37 (ddd, *J* 11.5, 5.0, 1.0)	72.3	73.5
2	4.35 (dd, *J* 12.0, 7.0)	4.31 (dd, *J* 11.5, 2.0)		
3	4.86 (dddd, *J* 7.0, 4.0, 3.0, 1.5)	4.50 (app. td, *J* 5.0, 2.0, 1.0)	54.9	68.3
4	6.11 (ddd, *J* 12.0, 4.0, 1.0)	6.17 (dd, *J* 12.0, 5.0)	129.9	132.5

Table 4.15. Selected NMR data for chloride **339** and alcohol **331**.

With chloride **339** in hand, dehydrochlorination to oxepine **196** was investigated. The treatment of chloride **339** with TBAF in DMSO resulted in the isolation of oxepine **196** in 41% yield, an improvement on previous eliminations (Table 4.16, entry 1). A brief optimisation study was subsequently undertaken. When 1.1 equivalents of base were used, no reaction at all was observed. Changing the base to potassium *tert*-butoxide (used in THF), and DBU (used in DCM), resulted in decomposition of the substrate to a complex mixture of side-products (Table 4.16, entries 2-3). Heating chloride **339** in pyridine to 50 °C also failed to effect elimination (Table 4.16, entry 4).

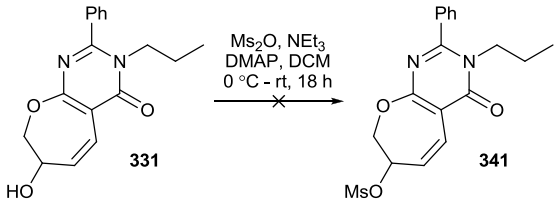


Entry	Base (2.1 eq.)	Conditions	Yield 196
1	TBAF (1.0 M in THF)	DMSO, rt, 30 min	44%
2	*t*-BuOK	THF, 0 °C – rt, 2 h	Decomposition
3	DBU	DCM, rt – 45 °C	Decomposition on heating
4	Pyridine (solvent)	50 °C, 18 h	rsm

Table 4.16. Elimination of chloride **339**: reaction conditions screened.

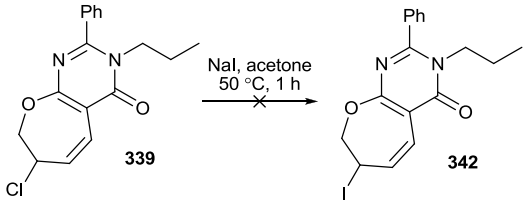
Although the yield for TBAF-mediated elimination was encouraging, it was still desirable to improve the efficiency of this key transformation. It was proposed that installing a better leaving group than chloride might achieve this and so alcohol **331** was treated with Ms_2O in place of MsCl to avoid rapid substitution of chloride (Scheme

4.24). Disappointingly, only alcohol **331** was isolated following work-up of the reaction mixture, suggesting that mesylate **341** was an unstable intermediate and not easily handled.



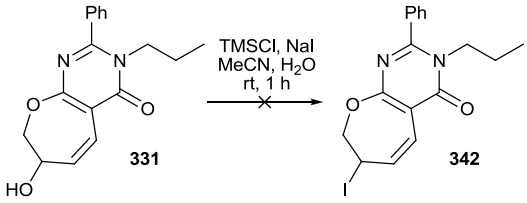
Scheme 4.24. Attempted synthesis of mesylate **341** with Ms_2O.

Another strategy was to use a Finkelstein reaction to install an iodide leaving group. However, when chloride **339** was treated with NaI in acetone only alcohol **331** was isolated following work-up of the reaction mixture (Scheme 4.25).



Scheme 4.25. Attempted Finkelstein reaction with chloride **339**.

An attempt was also made to prepare iodide **342** from alcohol **331** using TMSCl and NaI in a procedure reported by Kanai and co-workers (Scheme 4.26).[116] However, this too was unsuccessful, with only the starting material being recovered.

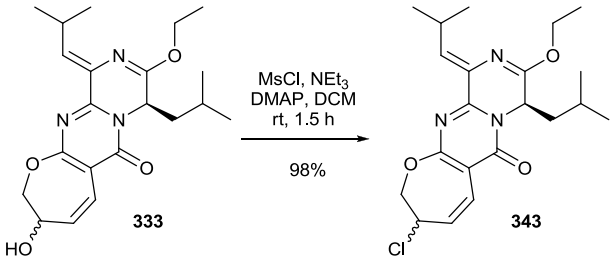


Scheme 4.26. Attempted preparation of iodide **342** from alcohol **331**.

Despite its moderate efficiency, chlorination of allylic alcohol **331** followed by dehydrochlorination was a viable alternative strategy for oxepine construction. The methodology was next applied to allylic alcohol **333** in order to focus further optimisation studies on that system.

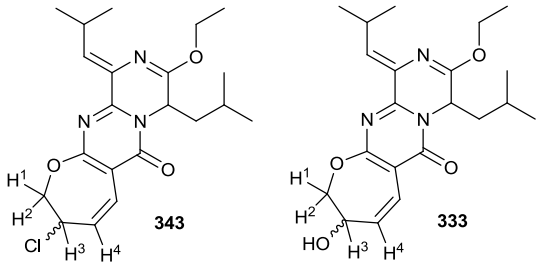
4.4.5 Chlorination – Dehydrochlorination of Allylic Alcohol **333**

Chloride **343** was readily prepared from alcohol **333** using MsCl, NEt_3 and DMAP in excellent yield, as a 1:1 mixture of inseparable diastereomers (Scheme 4.27).



Scheme 4.27. Synthesis of chloride **343**.

The characterisation of chloride **343** was found to be more challenging than in the case of the model study, as the $[MH]^+$ peak could not be seen in the ESI mass spectrum - only the mass of alcohol **333** was observed. This problem was overcome by the development of an APCI method whereby the substrate was injected in acetonitrile. In the absence of water and methanol the expected $[MH]^+$ was then observed. IR spectroscopy showed the loss of an absorption band at a frequency corresponding to an O-H stretch from alcohol **333** to chloride **343**, whilst NMR experiments again provided further evidence for the structural assignment. The data showed in Table 4.17 compared well with those of the model study despite the complex nature of the ^{1}H-NMR spectrum as a result of the two diastereomers present.

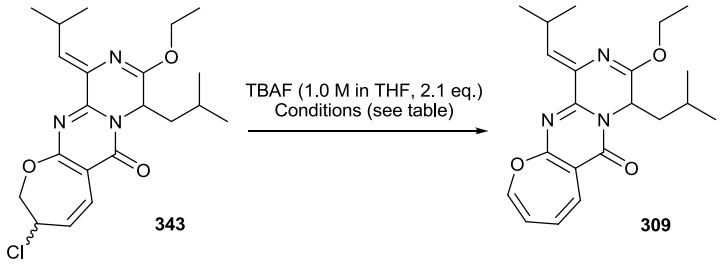


#	δ_H (*J* in Hz)		δ_C	
	343	**333**	**343**	**333**
1	4.61 (dd, *J* 12.0, 3.0)	4.38-4.21 (m)	72.4	73.4
2	4.41 (dd, *J* 12.0, 6.0)	4.38-4.21 (m)		
3	4.87-4.82 (m)	4.51-4.44 (m)	54.8	68.3
4	6.06-6.00 (m)	6.11 (dd, *J* 12.0, 4.0)	129.1	131.4

Table 4.17. Selected NMR data for chloride **343** and alcohol **333**. Data corresponds to that of a single diastereomer.

To our delight, treatment of chloride **343** with TBAF in DMSO effected elimination to oxepine **309** (Table 4.18, entry 1), the structure of which was confirmed by comparison of relevant NMR data with that of janoxepin (**1**). Unfortunately, the transformation occurred in just 10% yield and this could not be improved by extending the reaction time (Table 4.18, entry 2) or heating the reaction mixture (Table 4.18, entry 3). No

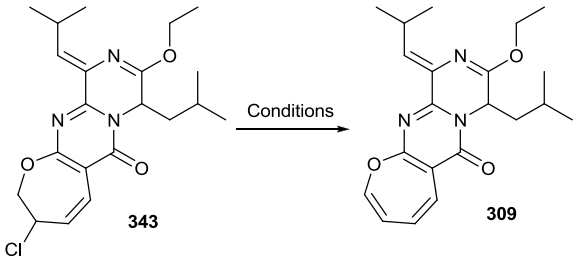
reaction was observed at low temperatures using DMF (Table 4.18, entry 4) or THF (Table 4.18, entry 5) as solvent - conversion to product was only observed upon warming to room temperature. Again, using 1.1 equivalents of base resulted in no reaction at all.



Entry	Temperature (°C)	Time (min)	Solvent	Yield 309
1	rt	10	DMSO	10%
2	rt	60	DMSO	<5%
3	50	10	DMSO	Decomposition
4	–40 - rt	240	DMF	9%
5	–40 - rt	240	THF	<5%

Table 4.18. Dehydro-chlorination to of chloride **343** using TBAF: optimisation study.

An extensive screen of alternative reaction conditions for the elimination of chloride **343** to oxepine **309** followed, as outlined in Table 4.19. In summary, the only improvement in yield was achieved by using the dehydrochlorination conditions as described by Reisman and co-workers, whereby heating chloride **343** with $LiCO_3$ and LiCl in DMF furnished oxepine **309** in 13% yield (Table 4.19, entry 1).[80] The only other successful reaction conditions used DBU as base in DCM, returning oxepine **309** in just 5% yield (Table 4.19, entry 2). All other attempts resulted in decomposition of the starting material (Table 4.19, entries 3-10).



Entry	Base (2.1 eq.)	Conditions	Yield 309
1	$LiCO_3$	LiCl, DMF, 100 °C, 2 h	13%
2	DBU	DCM, rt, 30 min	5%
3	DBU	DMF, rt, 30 min	-
4	*t*-BuOK	THF, –78 °C, 30 min	-
5	*t*-BuOK	*t*-BuOH, rt, 30 min	-
6	*t*-BuOK	DMF, rt, 30 min	-
7	Pyridine (solvent)	rt – 50 °C, 1 h	-
8	LiHMDS	THF, –78 °C, 30 min	-
9	NEt_3	$AgBF_4$, DCM, rt, 30 min	-
10	NaH	DMSO, rt, 30 min	-

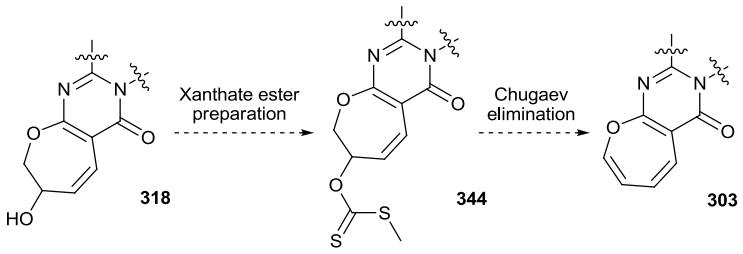
Table 4.19. Dehydrochlorination of chloride **343**: optimisation study.

To ascertain if one diastereomer was preferentially undergoing elimination, the two diastereomers of allylic alcohol **333** were separated (the diastereomers of chloride **343** were inseparable by column chromatography). Unfortunately, when the two diastereomers were independently subjected to the chlorination conditions, chloride **343** was again isolated as a 1:1 mixture of diastereomers.

The preparation of oxepine **309** represented a significant milestone in the synthesis of janoxepin (**1**), however, the low yield achieved for the elimination step was disappointing. An extensive study of alternative methods for dihydro-oxepine elaboration *via* an allylic alcohol now ensued.

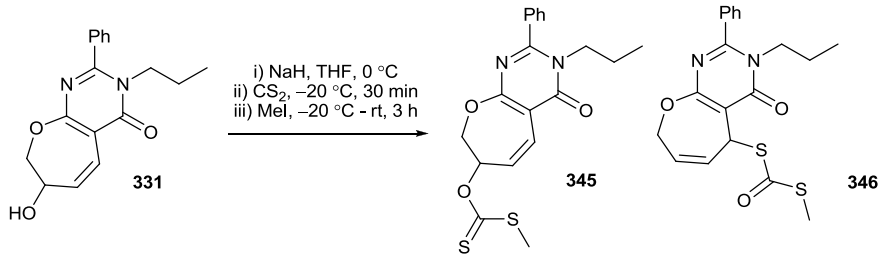
4.4.6 Chugaev Elimination: Model Study

It was proposed that oxepine **303** could be generated *via* Chugaev elimination of a xanthante ester **344** (Scheme 4.28), itself prepared in a single step from an allylic alcohol **318**.



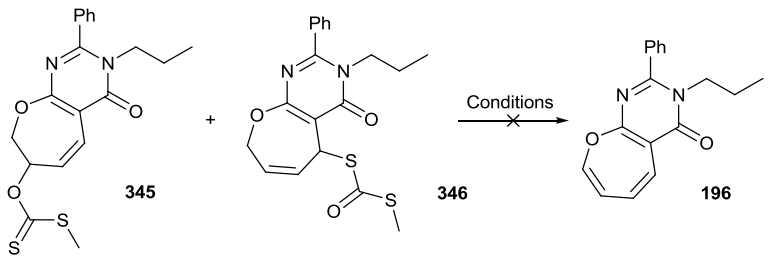
Scheme 4.28. Proposed Chugaev elimination strategy.

Using a procedure reported by Ball and co-workers, alcohol **331** was deprotonated with sodium hydride before the addition of carbon disulfide and methyl iodide (Scheme 4.29).[117] Unfortunately, an inseparable mixture of xanthate ester **345** and dithioate **346** was obtained, the latter a result of [2,3]-rearrangement of the intermediate sulfur anion, a process that has been observed previously in allylic systems.[118]



Scheme 4.29. Preparation of xanthate ester **345**.

Attempts to utilise the uncharacterised mixture of products in a subsequent elimination step were unsuccessful. Thermolysis in toluene at 110 °C for 3 d as described by Ball and co-workers[117] failed to provide any oxepine **196**, with the same mixture of products being recovered (Table 4.20, entry 1). When the mixture of xanthate ester **345** and dithioate **346** was heated in xylenes at 138 °C for 24 h, only approx. 50% recovery of the starting material was obtained, presumably as a result of decomposition under the reaction conditions (Table 4.20, entry 2). Finally, the palladium(0)-mediated elimination of xanthate esters to alkenes as described by Kanematsu and co-workers was investigated, but again without success (Table 4.20, entry 3).[118]

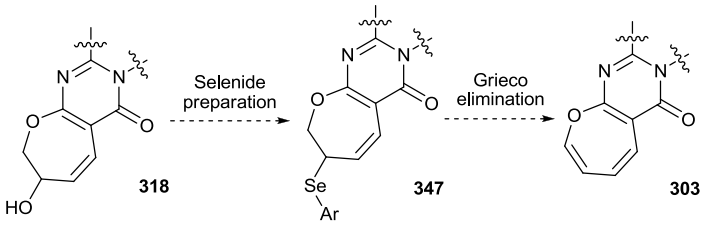


Entry	Conditions	Comment
1	PhMe, 110 °C, 3 d	rsm
2	Xylenes, 138 °C, 24 h	rsm (~50%)
3	$Pd(PPh_3)_4$, DCM, rt, 18 h	rsm

Table 4.20. Attempted Chugaev elimination: reaction conditions screened.

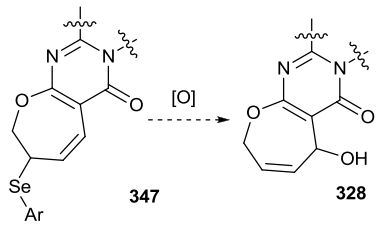
4.4.7 Grieco Elimination: Model Study

The elimination of a selenide to an alkene following oxidation, as reported by Grieco and co-workers,[119] was another possible strategy for preparing an oxepine **303** from an alcohol **318** (Scheme 4.30).



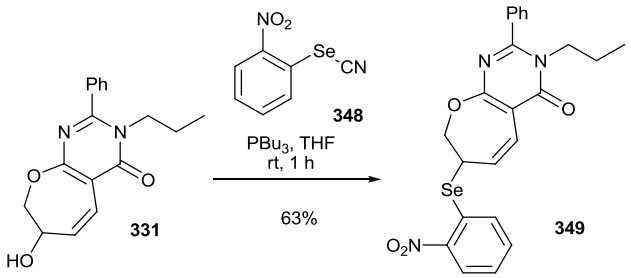
Scheme 4.30. Proposed Grieco elimination strategy.

However, it is well known that oxidation of a selenide in an allylic system can result in a [2,3]-rearrangement to furnish the regioisomer **328** as opposed to effecting elimination to an alkene (Scheme 4.31).[120,121] Nevertheless, this strategy was investigated as a regiomeric alcohol **328** was an interesting alternative substrate for the investigation of dehydration or E2' elimination strategies.



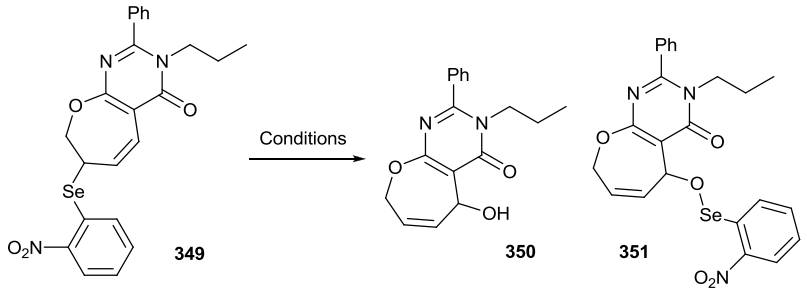
Scheme 4.31. [2,3] Selenide rearrangement in allylic systems.

Selenide **349** was prepared in 63% yield according to the Grieco procedure whereby alcohol **331** was treated with *o*-nitrophenyl selenocyanate **348** and tributylphosphine (Scheme 4.32).[119]



Scheme 4.32. Synthesis of selenide **349**.

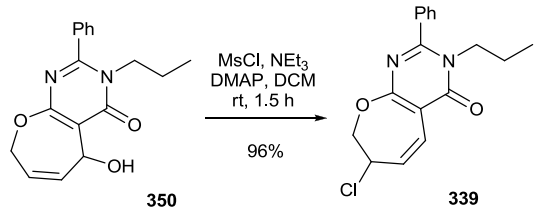
No elimination to oxepine **196** was observed upon oxidation of selenide **349**. When *m*-CPBA was used as the oxidant at low temperature (as described by Bonjoch and co-workers),[121] a mixture of the regiomeric alcohol **350** and intermediate selenate **351** was obtained (Table 4.21, entry 1). Complete conversion to alcohol **350** was observed when hydrogen peroxide was used as the oxidant in the presence of pyridine, in accordance with a procedure reported by Zakarian and co-workers (Table 4.21, entry 2).[120]



Entry	Oxidant	Conditions	Yield
1	*m*-CPBA	DCM, –78 °C, 1 h	15% **350**, 33% **351**
2	H_2O_2	Pyridine, H_2O, THF, 0 °C, 3 h	70% **350**

Table 4.21. Attempted Grieco elimination: conditions screened.

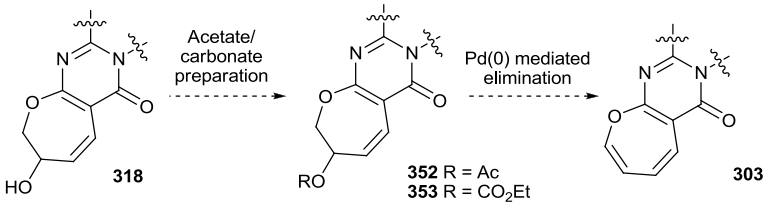
Alcohol **350** was next subjected to the screen of dehydration conditions previously described in Chapter 4.4.3, but without success. However, it was proposed that activation followed by elimination in an E2' fashion may be possible. Unfortunately, when alcohol **350** was treated with MsCl, NEt_3 and DMAP, chloride **339** was isolated in near quantitative yield as a result of conjugate addition of chloride to the alkene, with elimination of the activated hydroxyl group (Scheme 4.33).



Scheme 4.33. Attempted activation of alcohol **350** with MsCl.

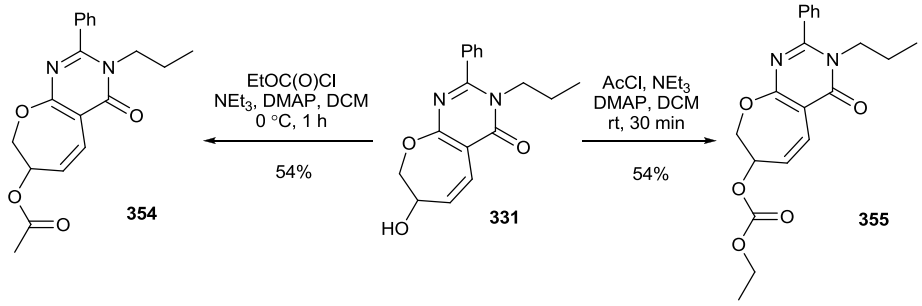
4.4.8 Palladium-Mediated Acetate/Carbonate Elimination: Model Study

Tsuji and Trost reported that 1,3-dienes such as that present in an oxepine **303** could be formed by the treatment of allylic acetates **352** or carbonates **353** with a palladium(0) species, providing a β-hydrogen was available for elimination and no suitable nucleophiles were present.[122,123] This was more recently utilised in the synthesis of a germination stimulant reported by Stick and co-workers.[124] As the necessary substrates could be readily prepared from an allylic alcohol **318**, this methodology was investigated for the preparation of an oxepine **303** (Scheme 4.34).



Scheme 4.34. Proposed palladium mediated elimination of acetate/carbonate **352** or **353**.

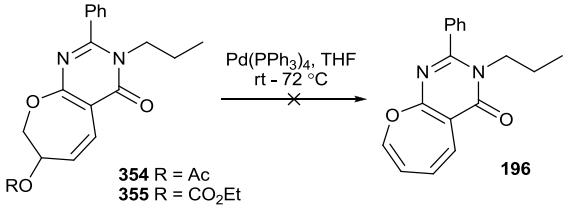
Acetate **354** was prepared in 54% yield by treating alcohol **331** with AcCl, NEt_3 and DMAP. The same conditions were used with ethyl chloroformate to synthesise ethyl carbonate **355** (Scheme 4.35). These transformations were not further optimised.



Scheme 4.35. Synthesis of acetate **354** and carbonate **355**.

Both acetate **354** and carbonate **355** were next treated with $Pd(PPh_3)_4$ (20 mol%) in THF. In both cases, no reaction was observed at room temperature and the starting material could be recovered. When the reaction mixture was heated at reflux, slow

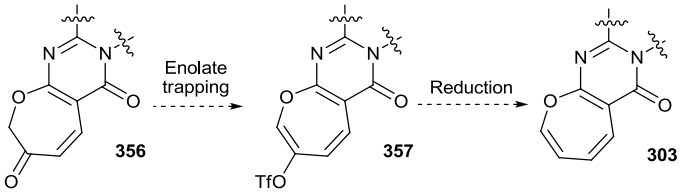
decomposition of the substrates to a complex mixture of baseline material occurred (Scheme 4.36). This approach was abandoned rather than committing further time and resource to a ligand and solvent screen.



Scheme 4.36. Attempted palladium mediated acetate/carbonate elimination.

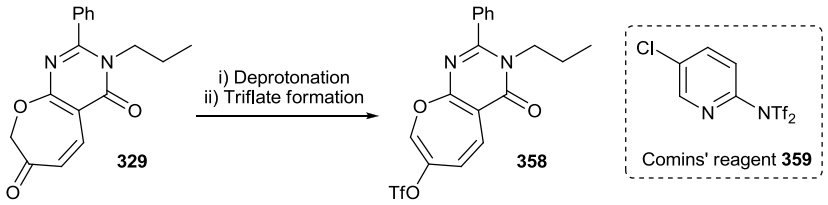
4.4.9 Utilising Enone **329**: Alkenyl Triflate Reduction

It was postulated that deprotonation of an enone **356** α- to the oxygen would be more likely than for an allylic alchol-derived substrate. Trapping the resulting enolate as a triflate **357**, followed by reduction to oxepine **303** was therefore worthy of investigation (Scheme 4.37).



Scheme 4.37. Proposed alkenyl triflate reduction strategy.

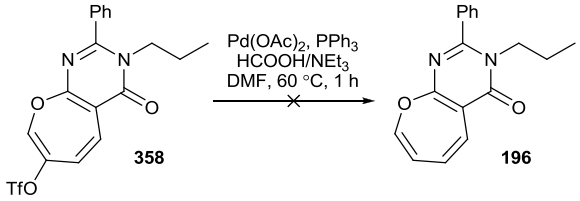
Formation of triflate **358** was not straightforward, however. Deprotonation of enone **329** with LiHMDS at –78 °C followed by the addition of Comins' reagent **359** as reported by Minehan and co-workers, resulted in complete recovery of the starting material (Table 4.22, entry 2).[125] Instead, enone **329** was treated with KHMDS at –20 °C with subsequent addition of Tf_2O, according to a procedure previously reported by the Taylor group.[126] Triflate **358** was observed in small quantities by mass spectrometry and ^{1}H-NMR spectroscopy of the unpurified product, but the compound quickly decomposed upon purification (Table 4.22, entry 2).



Entry	i) Deprotonation conditions	ii) Triflation conditions	Comment
1	LiHMDS, THF, –78 °C, 40 min	Comins' reagent **359**, DMPU, –78 °C, 1 h	rsm
2	KHMDS, DME, –20 °C, 30 min	Tf_2O, –20 °C, 2 h	Trace **358**

Table 4.22. Triflate **358** formation: reaction conditions investigated.

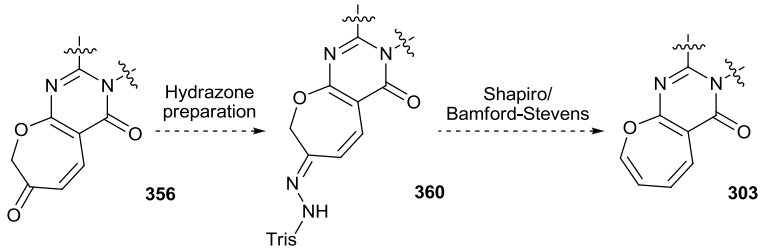
The unpurified product was therefore immediately subjected to the palladium-mediated triethylammonium formate reduction conditions as reported by Ortar and co-workers (Scheme 4.38).[127] Unfortunately, this resulted in complete decomposition of the starting material and the approach was abandoned.



Scheme 4.38. Attempted reduction of triflate **358**.

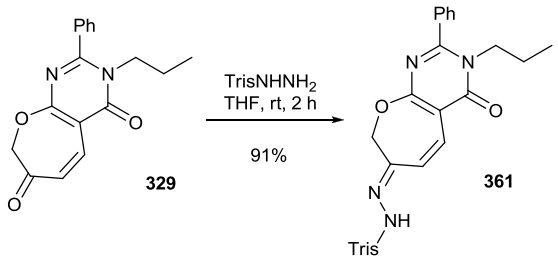
4.4.10 Utilising Enone **329**: Shapiro and Bamford-Stevens Reactions

The Shapiro or Bamford-Stevens reaction of a hydrazone **360** to access an oxepine **303** was also investigated (Scheme 4.39).



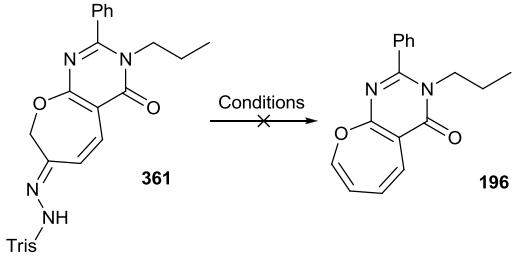
Scheme 4.39. Proposed Shapiro/Bamford-Stevens approach.

Hydrazone **361** was prepared in excellent yield by treatment of enone **329** with trisyl-hydrazine according to a procedure reported by Quayle and co-workers (Scheme 4.40).[128]



Scheme 4.40. Preparation of hydrazone **361**.

Unfortunately, subsequent attempts to effect a Shapiro reaction by treatment of hydrazone **361** with *n*-BuLi in hexane/TMEDA as reported by Heathcock and co-workers (Table 4.23, entry 1)[129] and in THF/TMEDA (Table 4.23, entry 2) resulted in complete decomposition of the substrate to a complex mixture of polar side-products. When Na in ethylene glycol was used in order to promote a Bamford-Stevens reaction (as reported by Quayle and co-workers) the same outcome was again observed (Table 4.23, entry 3).[128]



Entry	Base (3.0 eq.)	Conditions	Comment
1	*n*-BuLi (1.6 M in hexanes)	*n*-Hexane, TMEDA, –78 – 0 °C, 1.5 h	Decomposition
2	*n*-BuLi (1.6 M in hexanes)	THF, TMEDA, –78 – 0 °C, 1.5 h	Decomposition
3	Na	Ethylene glycol, rt – 100 °C, 3 h	Decomposition

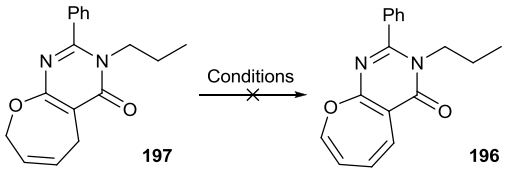
Table 4.23. Shapiro and Bamford-Stevens reaction of hydrazone **361**: conditions explored.

Having explored a number of different approaches for converting allylic alcohol **331** or enone **329** into an oxepine without improvement on the chlorination-dehydrochlorination method, two alternative approaches for dihydro-oxepine elaboration were explored. These involved the direct dehydrogenation of a dihydro-oxepine and installing the vinyl ether alkene by isomerisation or *O*-vinylation with subsequent elaboration to an oxepine.

4.5 Dihydro-Oxepine Dehydrogenation

It was proposed that dihydro-oxepine dehydrogenation may provide direct access to an oxepine. DDQ or CAN have been known to mediate such an oxidative transformation,

whilst Pd/C in anisole was also successfully used by Martin and co-workers in their synthesis of cribrostatin 6.[130] However, dehydrogenation is typically accompanied by aromatisation which provides a thermodynamic driving force for the reaction to proceed. When dihydro-oxepine **197** was treated with DDQ in toluene at room temperature no conversion into oxepine **196** was observed, whilst heating the reaction mixture resulted in decomposition of the substrate (Table 4.24, entry 1). When dihydro-oxepine **197** was heated with Pd/C in anisole only the starting material was recovered (Table 4.24, entry 2).

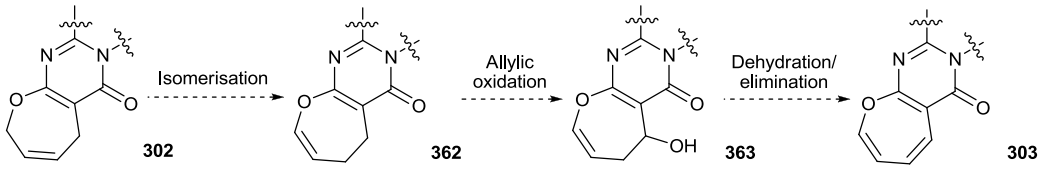


Entry	Conditions	Comment
1	DDQ, PhMe, rt – 90 °C, 4 h	Decomposition upon heating
2	Pd/C, anisole, 90 °C, 3 d	rsm

Table 4.24. Direct dehydrogenation approach: reaction conditions explored.

4.6 Alkene Isomerisation

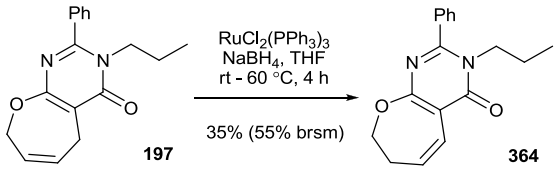
The isomerisation of allyl ether species to vinyl ethers is well known, and formed the basis of an alternative strategy for installing the double bond adjacent to oxygen before elaboration to an oxepine (Scheme 4.41). The isomerisation of both dihydro-oxepine **197** and diallyl pyrimidinone **198** was investigated.



Scheme 4.41. Proposed isomerisation – allylic oxidation – elimination strategy.

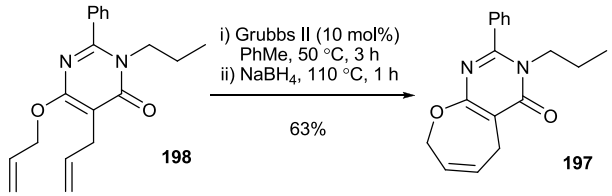
4.6.1 Dihydro-Oxepine Allyl Ether Isomerisation

Given the instability of dihydro-oxepines under basic conditions, the transition metal-catalysed isomerisation of dihydro-oxepine **197** was initially explored. When $RuCl_2(PPh_3)_3$ was employed as the catalyst in the presence of $NaBH_4$ using a procedure reported by Frauenrath and Runsink,[131] undesired isomerisation of the alkene into conjugation with the pyrimidinone ring occurred to furnish dihydro-oxepine **364** (Scheme 4.42).



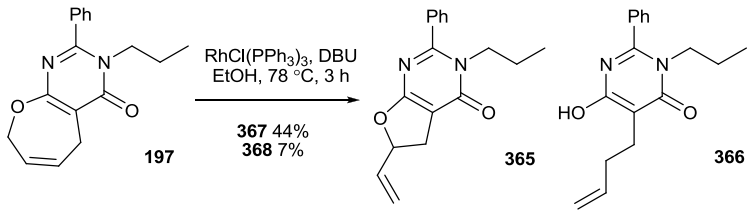
Scheme 4.42. Ru catalysed alkene isomerisation.

Ruthenium catalysts have also been employed in one pot RCM – isomerisation processes. For example, Schmidt reported that isomerisation could be induced following RCM by the addition of $NaBH_4$ to the reaction mixture.[132] When these conditions were applied to diallyl pyrimidinone **198** no isomerisation was observed, although the RCM product dihydro-oxepine **197** was isolated in moderate yield (Scheme 4.43).



Scheme 4.43. Attempted one-pot RCM – isomerisation sequence.

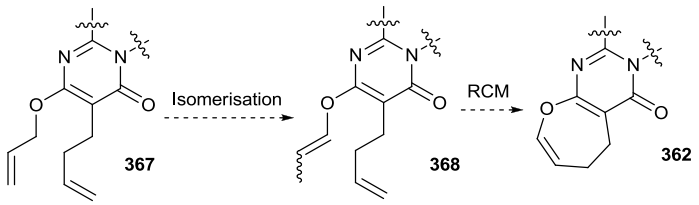
Wilkinson's catalyst ($RhCl(PPh_3)_3$) and a sub-stoichiometric quantity of DBU (0.3 eq.) was used to mediate allyl ether isomerisation by Rainier and co-workers when working with tetrahydro-oxepine substrates.[133] When these conditions were applied to dihydro-oxepine **197** a fascinating rearrangement to dihydro-furan **365** and pyrimidinone **366** occured, but with no isomerisation to the desired vinyl ether (Scheme 4.44). The characterisation of these compounds and proposed mechanisms for their synthesis will be discussed later (Chapter 4.8.1).



Scheme 4.44. Rhodium-catalysed isomerisation.

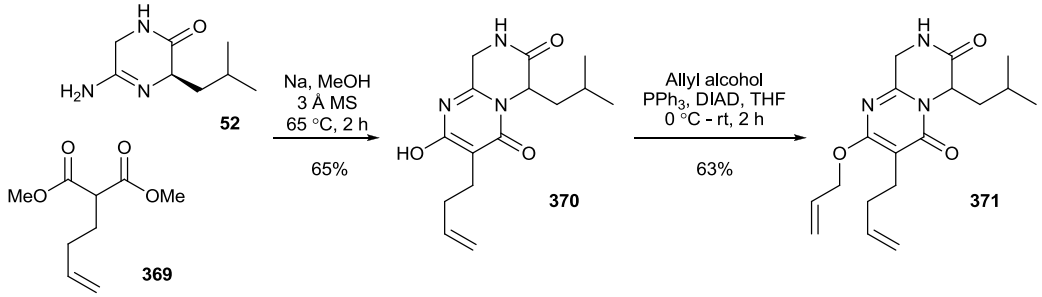
4.6.2 Allyl Ether Isomerisation

To avoid dihydro-oxepine rearrangement, the isomerisation of a diallyl pyrimidinone substrate was explored next. For this, a butenyl pyrimidinone **367** would be required for subsequent RCM of vinyl ether **368** to a dihydro-oxepine **362** (Scheme 4.45).



Scheme 4.45. Proposed allyl ether isomerisation – RCM sequence.

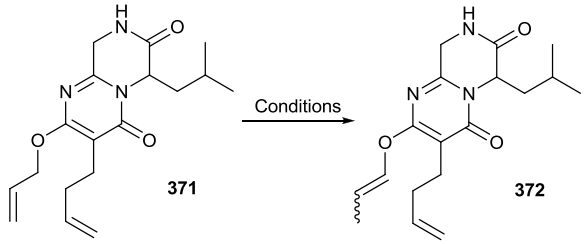
The proposed reaction sequence was investigated using the 'real' ketopiperazine-pyrimidinone system. Butenyl pyrimidinone **370** was prepared by the condensation of cyclic amidine **52** with known butenyl malonate **369**, itself prepared from dimethyl malonate and 4-bromo-1-butene according to a procedure reported by Poli and co-workers.[134] *O*-Allylation using the previously developed Mitsunobu procedure then followed to furnish the desired allyl-butenyl pyrimidinone **371** in an efficient process, which further demonstrated the utility of this methodology (Scheme 4.46).



Scheme 4.46. Preparation of allyl-butenyl pyrimidinone **373**.

The conditions previously investigated for dihydro-oxepine isomerisation were applied first. When Wilkinson's catalyst was used with DBU in refluxing ethanol, complete decomposition of the substrate was observed (Table 4.25, entry 1). The ruthenium-catalysed isomerisation conditions did give some conversion to the isomerised product as shown by ^{1}H-NMR spectroscopy of the unpurified product (Table 4.25, entry 2). However, the overall recovery of material was low (46%) due to decomposition of the substrate, and the product could not be efficiently purified. Most importantly, the observed transformation was not repeatable and therefore other conditions for the isomerisation of allyl ethers were explored. Crivello and Kong reported that efficient isomerisation could be achieved using sub-stoichiometric quantities of iron pentacarbonyl and sodium hydroxide.[135] However, when allyl-butenyl pyrimidinone **371** was subjected to these conditions, only a trace of the desired isomerised product was observed in the ^{1}H-NMR spectrum of the unpurified product (Table 4.25, entry 3). Attempts to promote further conversion by heating the reaction mixture were

unsuccessful. A base-induced isomerisation using potassium *tert*-butoxide in DMSO (as reported by Langlois and co-workers)[136] was also investigated, but no conversion to vinyl ether **372** was observed at room temperature and complete decomposition of the substrate occurred upon heating (Table 4.25, entry 4).

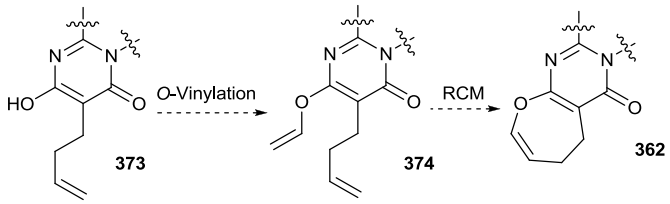


Entry	Conditions	Comment
1	$RhCl(PPh_3)_3$ (0.1 eq.), DBU (0.3 eq.), EtOH, 78 °C, 3 h	Decomposition
2	$RuCl_2(PPh_3)_3$ (0.02 eq.), $NaBH_4$ (0.1 eq.), THF, rt, 1.5 h	46% recovery; some conversion to vinyl ether **372**. Result not repeatable
3	$Fe(CO)_5$ (0.05 eq.), NaOH (0.1 eq.), EtOH/H_2O, rt, 1.5 h	Trace of vinyl ether **372**
4	*t*-BuOK (0.2 eq.), DMSO, rt – 80 °C, 18 h	Decomposition upon heating

Table 4.25. Allyl ether isomerisation: reaction conditions explored.

4.7 *O*-Vinylation Strategy

The *O*-vinylation of a pyrimidinone **373** was explored as an alternative strategy for installing a vinyl ether that would be suitable for subsequent RCM to a dihydro-oxepine **362** (Scheme 4.47). Both transetherification and eliminative approaches were investigated.

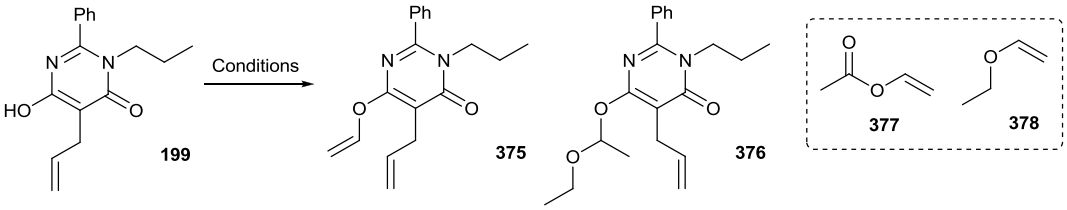


Scheme 4.47. Proposed vinylation – RCM strategy.

4.7.1 Vinylation by Transetherification

Three different transetherification conditions were explored using the model pyrimidinone **199**. The iridium-catalysed methodology developed by Ishii and co-workers was first investigated.[137] Pyrimidinone **199** was treated with $[Ir(cod)Cl]_2$ and sodium carbonate in vinyl acetate **377** as solvent, but no reaction was observed despite heating the reaction mixture as high as 100 °C (Table 4.26, entry 1). A more common

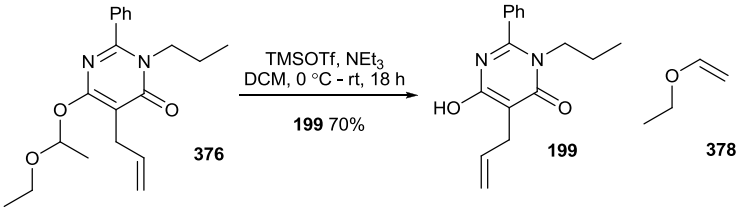
approach (such as that reported by Williams and co-workers in the synthesis of lankacyclinol) requires the treatment of an alcohol with ethyl vinyl ether **378** in the presence of mercuric triflate.[138] When these conditions were applied to pyrimidinone **199**, no vinyl ether **375** was isolated with acetal **376**, an intermediate in the reaction, isolated in 37% yield with pyrimidinone **199** also being recovered in 12% yield (Table 4.26, entry 2). A similar result was obtained when the gold-catalysed reaction reported by Tokunaga and Nakamura was utilised.[139] When pyrimidinone **199** was treated with ethyl vinyl ether **378** in the presence of $AuCl(PPh_3)_3$ and $Ag(O_2CCF_3)_2$ at room temperature, acetal **376** was isolated in 42% yield and pyrimidinone **199** recovered in 9% yield (Table 4.26, entry 3).



Entry	Catalyst	Conditions	Yield
1	$[Ir(cod)Cl]_2$ (0.1 eq.)	**377** (solvent), Na_2CO_3, PhMe, 50 – 100 °C, 3 h	rsm
2	$Hg(O_2CCF_3)_2$ (0.5 eq.)	**378** (solvent), NEt_3 (0.6 eq.), 33 °C, 18 h	37% **376** (49% brsm)
3	$AuCl(PPh_3)_3$ (0.05 eq.)	**378** (solvent), $Ag(O_2CCF_3)_2$ (0.05 eq.), rt, 18 h	42% **376** (51% brsm)

Table 4.26. Transetherification: reaction conditions screened.

Despite the mixed acetal **376** failing to undergo elimination to vinyl ether **375** under these reaction conditions, it was thought possible to effect elimination using a procedure reported by Brown and co-workers.[140] Thus, acetal **376** was treated with TMSOTf and NEt_3 in the expectation that elimination of EtOTMS would be favoured to furnish the desired vinyl ether **375**. Unfortunately, elimination of the substrate was observed, and pyrimidinone **199** was isolated in 70% yield along with ethyl vinyl ether **378** (Scheme 4.48).

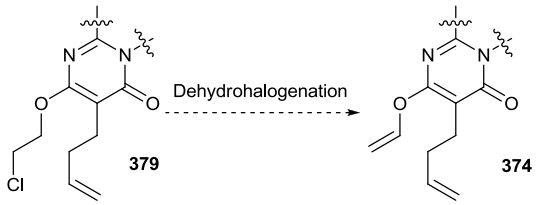


Scheme 4.48. Unwanted conversion of acetal **376** to pyrimidinone **199**.

Heating acetal **376** in toluene at 110 °C for 6 h also failed to effect any elimination to the desired vinyl ether.

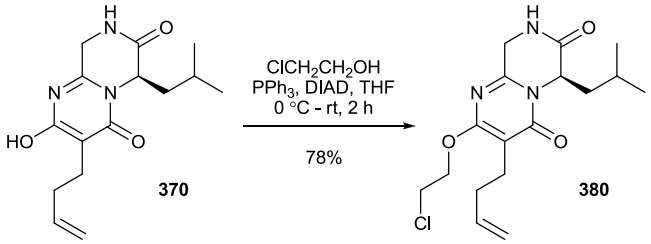
4.7.2 Vinylation by Dehydrohalogenation

Another proposed strategy for introducing a vinyl ether was by dehydrohalogenation of a suitable alkyl halide **379** (Scheme 4.49).



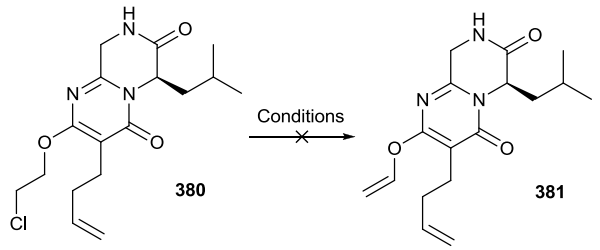
Scheme 4.49. Proposed dehydrohalogenation strategy to introduce a vinyl ether.

The previously prepared pyrimidinone **370** was used for this investigation and was first subject to a Mitsunobu reaction with chloroethanol which proceeded in excellent yield (Scheme 4.50).



Scheme 4.50. Preparation of chloride **380**.

The dehydrochlorination of chloride **380** to vinyl ether **381** was not possible. When potassium *tert*-butoxide was used in both DMF (Table 4.27, entry 1) and THF (Table 4.27, entry 2) at –10 °C no reaction was observed, with decomposition of the substrate occurring upon warming to room temperature. The milder phase transfer conditions reported by Otsuji and co-workers were investigated next.[141] However, when chloride **380** was treated with aqueous NaOH in the presence of *n*-Bu_4NHSO_4 no elimination was observed, with only slow decomposition of the substrate occurring over longer reaction times or upon heating (Table 4.27, entry 3).



Entry	Conditions	Comment
1	*t*-BuOK, DMF, –10 °C – rt, 3 h	Decomposition upon warming to rt
2	*t*-BuOK, THF, –10 °C – rt, 3 h	Decomposition upon warming to rt
3	NaOH (aq.), *n*-Bu_4NHSO_4, C_6H_6, rt, 8 d	Slow decomposition

Table 4.27. Dehydrochlorination to vinyl ether **381**: reaction conditions explored.

Having thoroughly investigated seven novel strategies for the elaboration of dihyro-oxepines to oxepines, only a single route had been identified that was applicable to the synthesis of janoxepin (**1**): allylic oxidation – chlorination – dehydrochlorination. Despite the low yield associated with this transformation, it had been shown to be a reliable method, and no further research was carried out in this area.

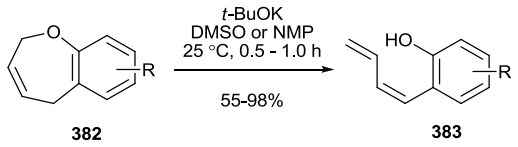
This Chapter will now summarise the many examples of dihydro-oxepine rearrangement that have already been highlighted. It will then describe the 'end-game' with respect to the synthesis of janoxepin (**1**).

4.8 Dihydro-Oxepine Rearrangement Products

A number of fascinating products have been isolated during the course of dihydro-oxepine elaboration and enamine installation (Chapter 3) research. Such observations have largely been made following exposure of a dihydro-oxepine to excess base, but also as a result of reaction with nucleophiles.

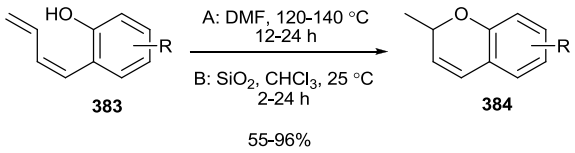
4.8.1 Dihydro-Oxepines: Base Sensitivity

The base sensitivity of dihydro-oxepines is not unknown. Ramachary and co-workers reported the base-induced ring-opening (BIRO) of a range of dihydro-oxepines **382** to phenols **383** in 2008 (Scheme 4.51).[142]



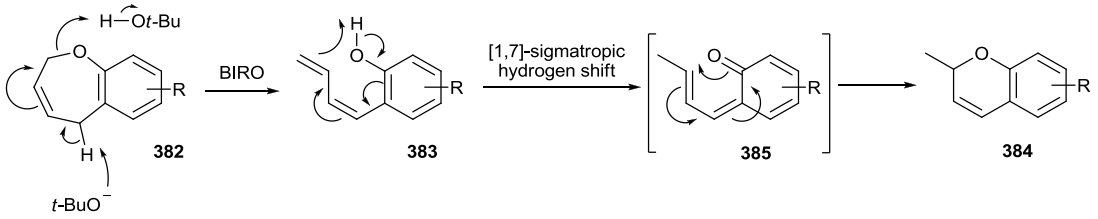
Scheme 4.51. Base-induced ring-opening of dihydro-oxepines.

Furthermore, they observed a thermal (A) or silica-induced (B) rearrangement of these products to corresponding chromenes **384** (Scheme 4.52).[142] This methodology was later utilised in the synthesis of a range of highly functionalised chromenes *via* a multi-catalysis cascade sequence.[143]



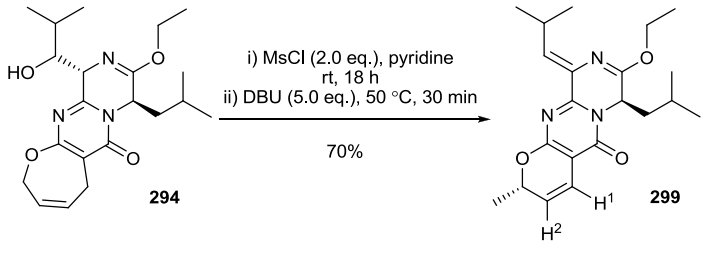
Scheme 4.52. Rearrangement to chromenes.

The proposed mechanism for these transformations is shown in Scheme 4.53 and involves initial BIRO of the dihydro-oxepine **382** to the ring-opened *cis*-diene **383**. A [1,7]-sigmatropic hydrogen shift would then proceed to give intermediate **385** which immediately undergoes a rapid cyclisation to chromene **384** (Scheme 4.53).[142]



Scheme 4.53. Proposed mechanism for BIRO and cyclisation to chromenes.

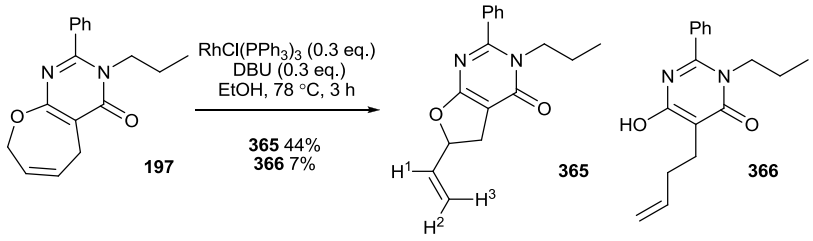
It is proposed that the same mechanism applies in the base-induced rearrangement of dihydro-oxepine **294** to pyran **299** which was isolated as a single diastereomer, where elimination to form the enamine occurs independently (Scheme 4.54). This was observed whilst investigating methods for preparing enamine **298** as described in Chapter 3.6.3.



Scheme 4.54. Dihydro-oxepine **294** rearrangement to pyran **299**. (Relative stereochemistry shown).

The ^{1}H-NMR spectrum of pyran **299** was key to its characterisation. A doublet (δ 1.50 ppm, *J* 6.5 Hz) clearly corresponded to the new methyl group whilst the position of the alkene was assigned based upon the signals for H-1 and H-2 which were a doublet and doublet of doublets, respectively. ^{13}C-NMR spectroscopy along with HSQC and COSY experiments provided further confirmation of the structural assignment.

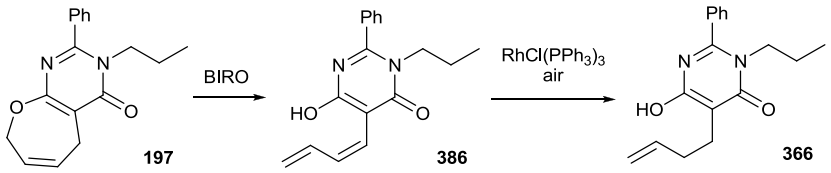
Dihydro-furan **365** and pyrimidinone **366** were isolated following treatment of dihydro-oxepine **197** with DBU in the presence of Wilkinson's catalyst (Scheme 4.55). This discovery was made whilst investigating methods to promote isomerisation of the dihydro-oxepine alkene (Chapter 4.6).



Scheme 4.55. Isolation of furan **365** and pyrimidinone **366**.

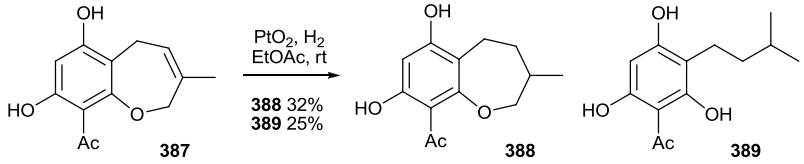
The characterisation of pyrimidinone **366** was not straightforward. Mass spectrometry showed that hydrogenation of dihydro-oxepine **197** had occurred but IR spectroscopy showed an absorption band at 3061 cm^{-1} indicating the presence of a hydroxyl group, thus ruling out hydrogenation to a tetrahydro-oxepine. The ^{1}H-NMR spectrum of **366** showed signals characteristic of a terminal alkene, as well as two complex CH_2 alkane signals which coupled to each other and the alkene. Following analysis of ^{13}C-NMR, DEPT, HSQC and COSY spectroscopic data, a firm assignment as to the structure of pyrimidinone **366** could be made.

The formation of pyrimidinone **366** is intriguing, and could be the result of hydrogenation of the BIRO intermediate **386**. The presence of Wilkinson's catalyst under an atmosphere of air could explain alkene hydrogenation, however, the selectivity for the *cis*-1,2-disubstituted alkene over the terminal alkene is surprising (Scheme 4.56). It could be argued that rhodium coordination to the electron rich *cis*-alkene is favoured initially but hydrogenation of terminal alkenes is typically favoured.



Scheme 4.56. Proposed mechanism for the generation of pyrimidinone **366**.

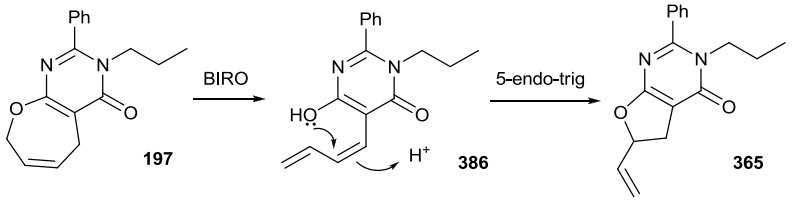
An alternative explanation may lie in the previously described formation of acyclic alkanes by hydrogenation of dihydro-oxepines in the absence of base, as reported by Kawase and co-workers. When dihydro-oxepine **387** was treated with Adams' catalyst (PtO_2) under an atmosphere of hydrogen, both tetrahydro-oxepine **388** and triphenol **389** were isolated in similar yields (Scheme 4.57).[144] Although no mechanistic proposals are made, this may suggest that the observed reaction could proceed *via* an alternative mechanism not involving the intermediate *cis*-diene **386**.



Scheme 4.57. Hydrogenation of dihydro-oxepine **389** to tetrahydro-oxepine **388** and triphenol **389**.

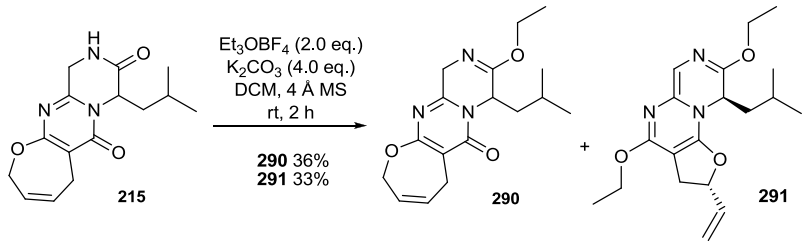
The ^{1}H-NMR spectrum of dihydro-furan **365** provided conclusive evidence for its structure. Signals at 6.10 ppm (1 H, ddd, *J* 17.0, 10.5, 6.0), 5.26 (1 H, dd, *J* 10.5, 1.0) and 5.42 (1 H, dd, *J* 17.0, 1.0) corresponded clearly to the terminal alkene protons H-1, 2 and 3 respectively, whilst a signal at 5.34 (1 H, ddd, *J* 10.0, 7.0, 6.0) related to the proton α- to the oxygen in the five-membered ring (H-4). This showed coupling to 'roofing' signals at 3.36 ppm and 2.95 ppm corresponding to the diastereotopic protons at the unsubstituted position on the dihydro-furan ring. The structural assignment was further confirmed by the ^{13}C-NMR spectrum along with DEPT, HSQC and COSY experiments.

A highly speculative mechanism for the generation of dihydro-furan **365** first involves BIRO (in the presence of DBU) to provide the intermediate *cis*-diene **386**. An unusual, 5-endo-trig cyclisation (disfavoured according to Baldwin's rules) would then be required to afford dihydro-furan **365** (Scheme 4.58). Whilst this seems highly unlikely, it is hard to envisage how a cationic species that would undergo the desired cyclisation can be derived from the intermediate *cis*-diene **386**.



Scheme 4.58. A speculative mechanism for the generation of dihydro-pyran **365**.

No mechanistic studies have been undertaken, but it can be deduced that rhodium is not essential as a similar cyclisation has been observed in the absence of any transition metal species. When dihydro-oxepine **215** was treated with triethyloxonium tetrafluoroborate and excess potassium carbonate, the fascinating dihydro-furan **291** was isolated as a single diastereomer in 33% yield, together with imidate **290** in 36% yield (Scheme 4.59). This observation was made whilst developing methods for installing the enamine moiety by aldol addition (Chapter 3.6.1).

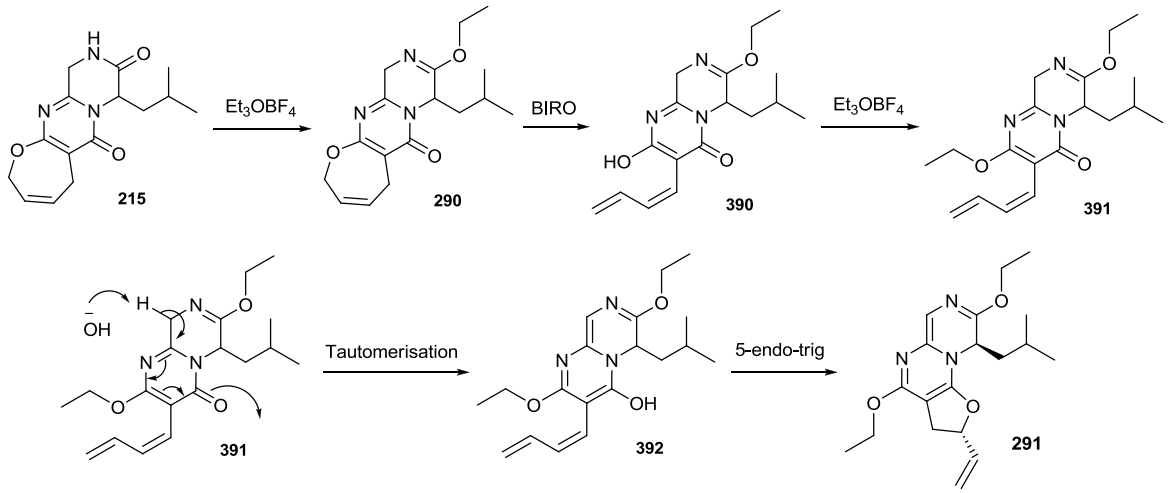


Scheme 4.59. Isolation of dihydro-furan **291**. (Relative stereochemistry shown).

In this case, the mass spectrum showed that *bis*-alkylation had occurred, whilst the ^{1}H-NMR spectrum was again instructive. Disappearance of the diastereotopic ketopiperazine CH_2 protons seen in the spectrum of dihydro-oxepine **215**, and appearance of a singlet in the alkene region (5.87 ppm) indicated that deprotonation at this position had occurred. Signals corresponding to a terminal alkene and diastereotopic protons at the unsubstituted position on the 5-membered ring compared extremely closely with those seen in the spectrum of dihydro-furan **291**. The only anomaly was that the signal corresponding to the proton α- to the oxygen was considerably more up-field compared to that for dihydro-furan **365** (2.47 ppm c.f. 5.34 ppm), however, ^{13}C-NMR spectroscopy with DEPT, HSQC and COSY experiments provided sufficient further evidence for firm structural assignment.

The proposed mechanism for this transformation is again highly speculative. It is suggested that following initial formation of imidate **290**, BIRO of the dihydro-oxepine takes place to afford the pyrimidinone intermediate **390**. This would then undergo

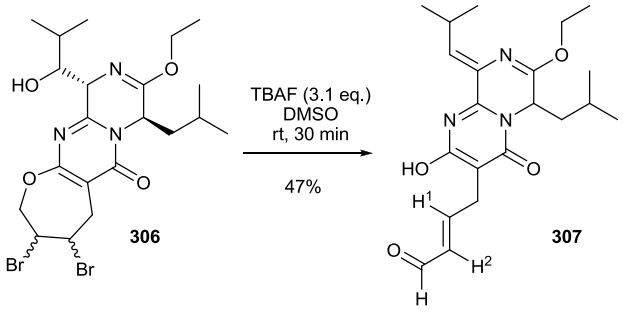
alkylation in the presence of a second equivalent of triethyloxonium tetrafluoroborate to give the *cis*-diene intermediate **391**. It is speculated that ketopiperazine deprotonation effects tautomerisation to **392** which, based upon the mechanistic proposal for the formation of dihydro-furan **365**, would undergo a disfavoured 5-endo-trig cyclisation to dihydro-furan **291** (Scheme 4.60). Why **390** does not undergo a [1,7]-sigmatropic hydrogen shift followed by cyclisation to a pyran in this case is unclear.



Scheme 4.60. A speculative mechanism for the generation of dihydro-furan **291**.

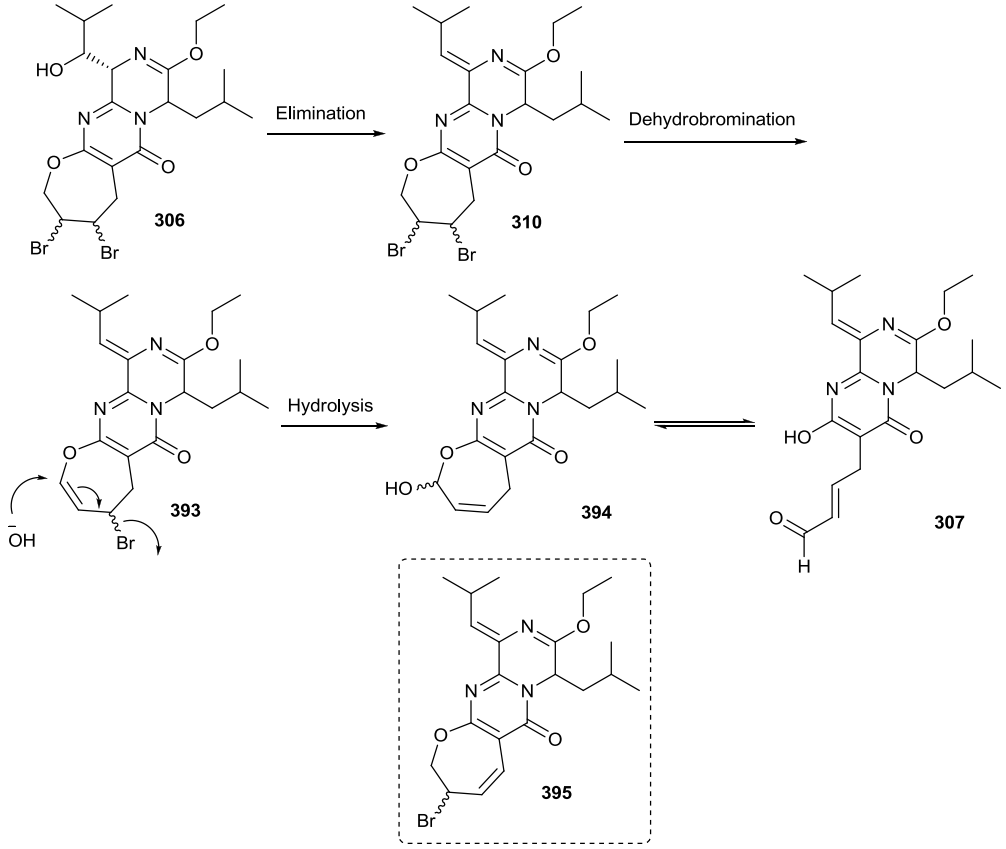
4.8.2 Dihydro-Oxepines: Hydrolysis

Not all unexpected reactions of dihydro-oxepines are as a result of a BIRO processes. For example, whilst investigating the double dehydrobromination of dibromide **306** using TBAF in DMSO (Scheme 4.61, see also, Chapter 4.1.4) aldehyde **307** was isolated in 47% yield (Scheme 4.61). Key to the characterisation of aldehyde **307** was the ^{1}H-NMR spectrum which showed a low field doublet indicative of an aldehyde proton (9.49 ppm, d, *J* 8.0 Hz), and two alkene signals (H-1 and H-2) at 6.93 and 6.11 ppm as a dt and dd, respectively. A coupling constant of 15.5 Hz between the alkene protons led to assignment of the *E*-configuration of the alkene.



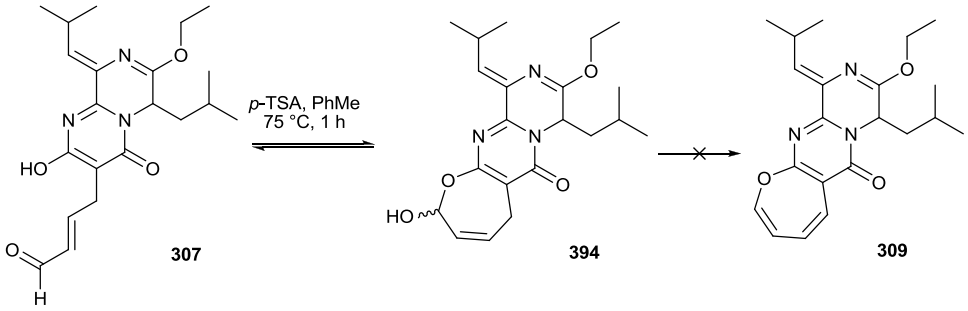
Scheme 4.61. Isolation of aldehyde **307**. (Relative stereochemistry shown).

It is proposed that elimination to afford enamine **310** occurs independently to the ring-opening event. While it would be expected to observe dehydrobromination to allylic bromide **395**, the corresponding chloride **343** was found to be a reasonably stable compound, with only slow hydrolysis to allylic alcohol **333** observed when exposed to water or the air. It is therefore speculated that dehydrobromination to allylic bromide **393** is rapidly followed by conjugate addition of water to give hemi-acetal **394** which exists in an equilibrium weighted in favour of aldehyde **307** (Scheme 4.62).



Scheme 4.62. Proposed mechanism for the generation of aldehyde **307**.

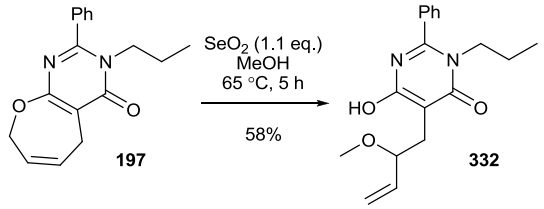
It was envisaged that under mild acidic conditions, aldehyde **307** would undergo cyclisation followed by elimination to oxepine **309**. Unfortunately, upon treatment with *p*-TSA in toluene only decomposition of aldehyde **307** was observed (Scheme 4.63).



Scheme 4.63. Attempted cyclisation of aldehyde **307** followed by elimination to afford oxepine **309**.

4.8.3 Dihydro-Oxepines: Nucleophilic Addition

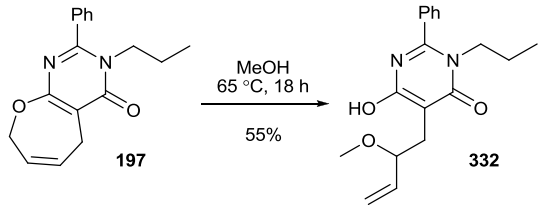
When methanol was used as a solvent during a study to optimise the allylic oxidation of dihydro-oxepine **197** (Chapter 4.4.1), the methoxy derivative **332** was unexpectedly isolated in 58% yield (Scheme 4.64).



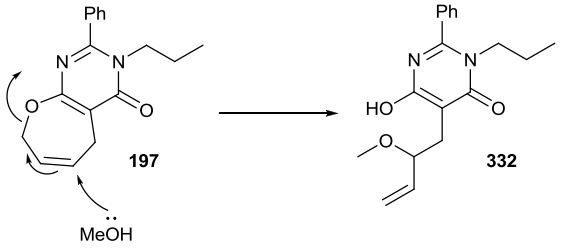
Scheme 4.64. Synthesis of methoxy-derivative **332**.

The structure of the compound was assigned based upon mass spectrometry, which clearly indicated the addition of methanol, and the ^{1}H-NMR spectrum. This contained characteristic signals for a terminal alkene as well as a singlet integrating for three protons at 3.36 ppm corresponding to a methyl ether group. IR spectroscopy was also informative, with a broad absorption band at 3040 cm^{-1} indicating the presence of a hydroxyl group.

In order to probe the mechanism of the reaction, dihydro-oxepine **197** was subject to the same reaction conditions but in the absence of selenium dioxide. The methoxy derivative **332** was again isolated, in similar yield following 18 h at reflux, demonstrating that methanol was the only reactant (Scheme 4.65). It is proposed that conjugate addition of methanol into the dihydro-oxepine alkene occurs with ring-opening to furnish the observed methoxy-derivative **332** (Scheme 4.66). When ethanol was used in place of methanol only very slow conversion (approx. 10%) to the corresponding ethoxy-derivative was observed following 24 h at reflux.



Scheme 4.65. Synthesis of methoxy-derivative **332** in the absence of SeO_2.



Scheme 4.66. Proposed mechanism for the synthesis of methoxy-derivative **332**.

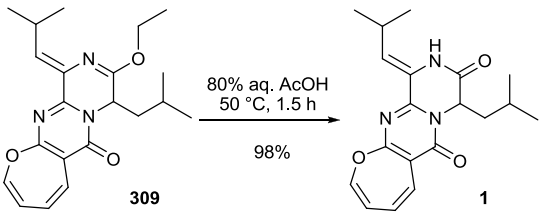
The novel transformations described here are worthy of further investigation, not only to establish mechanisms and potential applications of the transformations, but also to better understand the reactivity of dihydro-oxepines.

4.9 'End-Game': The First Synthesis of (±)-Janoxepin (**1**)

Despite the failure to achieve efficient dihydro-oxepine elaboration to oxepines, at least in part due to the instability of dihydro-oxepines in basic media, and their susceptibility to hydrolysis and nucleophilic attack, a reliable (if low-yielding) method had been established. All that remained to complete the synthesis was hydrolysis of the imidate protecting group.

4.9.1 Imidate Hydrolysis

The conditions previously developed for completing the synthesis of dihydro- and tetrahydro-janoxepin **49** and **301** were applied to imidate **309**. Pleasingly, imidate hydrolysis proceeded in excellent yield (98%) to complete the first total synthesis of (±)-janoxepin (**1**) in 14 steps from D-leucine **38** (Scheme 4.67).



Scheme 4.67. Imidate hydrolysis to complete the synthesis of (±)-janoxepin (**1**).

4.9.2 Characterisation of (±)-Janoxepin (**1**)

The ^{1}H- and ^{13}C-NMR spectral data for synthetic (±)-janoxepin (**1**) matched exactly with those reported by Sprogøe and co-workers for the isolated compound – see Appendix **III** for a detailed comparison and copies of NMR spectra.[1] The only anomaly

between the two sets of data was that the melting point of the synthetic material (179-180 °C) did not match the reported value (88-89 °C).[1] This was attributed to polymorphism and the presence of two different oxepine conformers in the solid state as shown by X-ray crystallography (Figure 4.2).

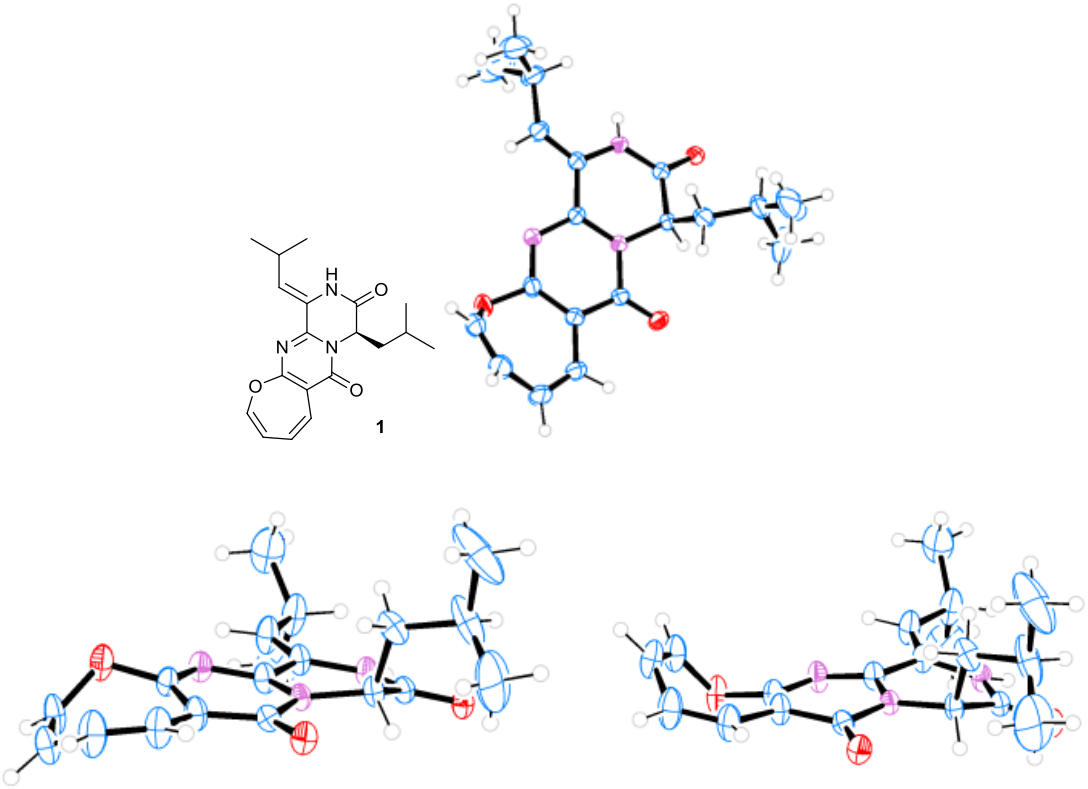
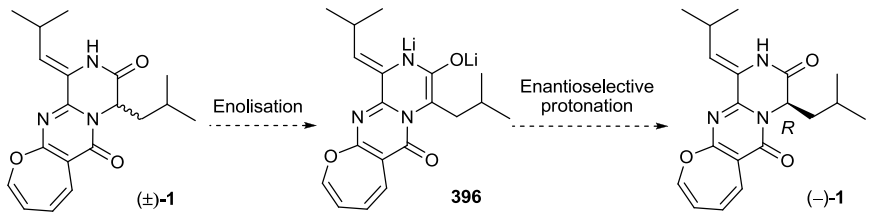


Figure 4.2. X-ray crystal structure of (±)-janoxepin (**1**). Only a single enantiomer (*R*) is shown for clarity. ORTEP representations shown with ellipsoids at 50% probability. CCDC 848130, see Appendix **V**.

4.10 De-Racemisation Studies

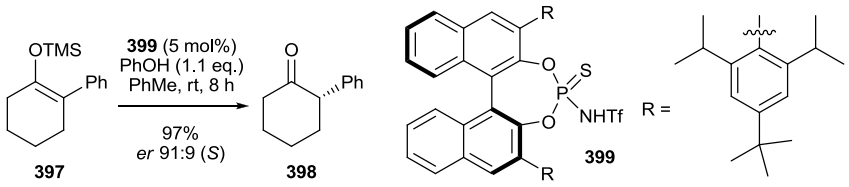
Enantioselective protonation of enolate **396** was identified as a possible strategy for accessing the naturally occuring *R*-enantiomer of janoxepin (**1**) directly from the racemic material already prepared (Scheme 4.68).



Scheme 4.68. Proposed de-racemisation of (±)-janoxepin (**1**).

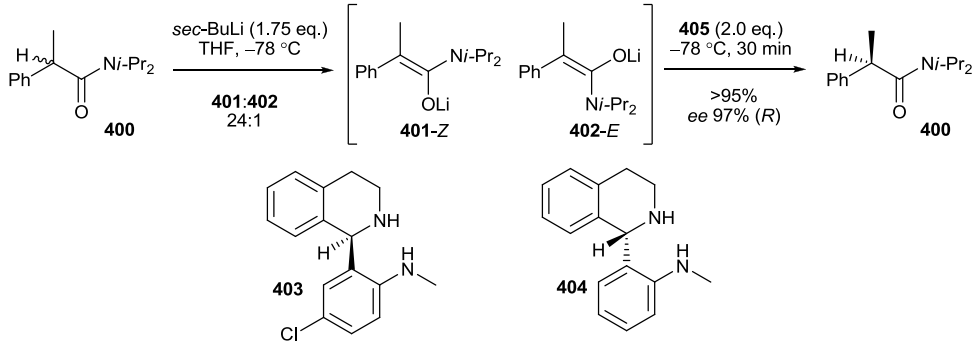
4.10.1 Enantioselective Protonation: Literature Examples

The de-racemisation of ketones, carboxylic acids, amino acid derivatives and esters by enantioselective protonation of their enolates has been the subject of much study; the work of Fehr,[145] Eames[146] and Plaquevent[147] is particularly noteworthy. More recently, catalytic methods have been developed. For example, Yamamoto and co-workers reported the de-racemisation of silyl enol ether **397** using a sub-stoichiometric quantity of the novel *N*-triflyl thiophosphoramide **399** in the presence of a stoichiometric amount of phenol as an achiral proton source (Scheme 4.69).[148]



Scheme 4.69. Catalytic enantioselective protonation of silyl enol ether **399**.

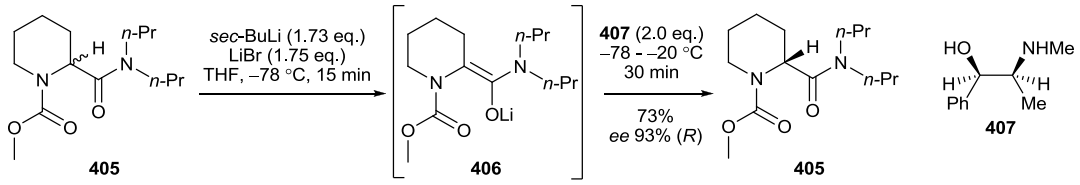
The available methods for the de-racemisation of amides are limited, largely due to the harsh enolisation conditions required. Vedejs and co-workers reported that, following enolisation of di-*iso*-propyl amide **400** (which required an excess of *sec*-BuLi), enantioselective protonation using chiral aniline **404** gave access to the *R*-enantiomer of **400** in excellent *ee.* The corresponding *S*-enantiomer could be accessed with similar efficiency and optical purity using aniline **404** (Scheme 4.70).[149]



Scheme 4.70. De-racemisation of di-*iso*-propyl amide **400**.

Lasne and co-workers had previously utilised chiral aniline **403** in the de-racemisation of pipecolic acid derived amides but also employed ephedrine derivatives effectively as the chiral proton source.[150] They subsequently expanded this study to investigate the effect of nitrogen substituents and identify optimal reaction conditions. Enolisation of amide **405** was found to be most efficient using an excess of *sec*-BuLi and lithium bromide in THF at –78 °C. Enantioselective protonation was then achieved in good *ee*

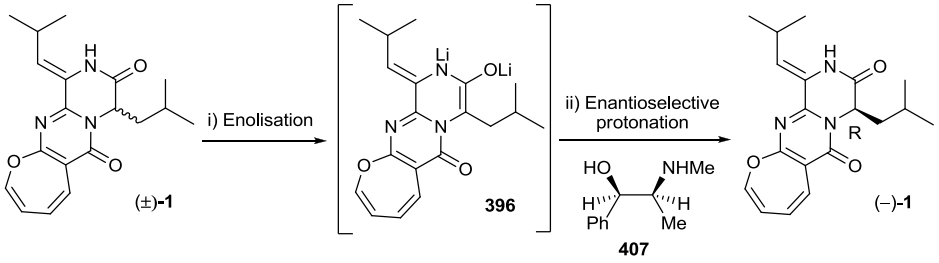
(93%) using (–)-ephedrine **407** (as well as other derivatives) to furnish the *R*-enantiomer of **405** (Scheme 4.71).[151]



Scheme 4.71. De-racemisation of pipecolic acid derived amide **405** using (–)-ephedrine **407**.

4.10.2 De-Racemisation of (±)-Janoxepin (**1**)

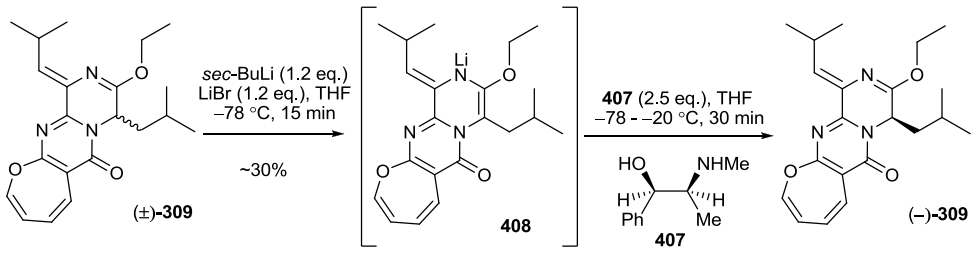
The conditions reported by Lasne and co-workers were chosen to investigate the de-racemisaton of (±)-janoxepin (**1**), mindful that two equivalents of *sec*-BuLi would be required to effect enolisation due to the presence of the amide functionality. When (±)-janoxepin (**1**) was treated with *sec*-BuLi and lithium bromide in THF at –78 °C, however, complete decomposition of the substrate was observed (Table 4.28, entry 1). The same outcome was obtained when *n*-BuLi was used as the base (Table 4.28, entry 2).



Entry	i) Enolisation	ii) Protonation	Comment
1	*sec*-BuLi (2.1 eq.), LiBr (2.1 eq.), THF, –78 °C, 15 min	**407** (4.0 eq.), THF, –78 °C - –20 °C, 30 min	Decomposition
2	*n*-BuLi (2.1 eq.), LiBr (2.1 eq.), THF, –78 °C, 15 min	**407** (4.0 eq.), THF, –78 °C - –20 °C, 30 min	Decomposition

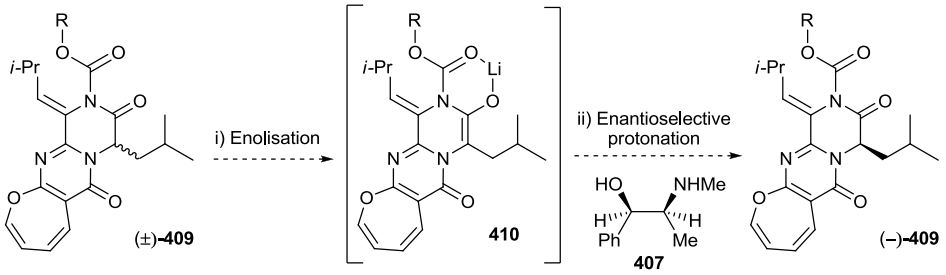
Table 4.28. De-racemisation of (±)-janoxepin (**1**): reaction conditions explored.

To establish that the excess of base required was responsible for the decomposition, imidate **309** was subjected to the same reaction conditions, where only 1.2 equivalents of *sec*-BuLi were required. In this case, approx. 30% material recovery was achieved following the addition of (–)-ephedrine **407**, however, this was still in racemic form (Scheme 4.72).



Scheme 4.72. Attempted de-racemisation of imidate **309**.

The limited availability and base-sensitivity of (±)-janoxepin (**1**) and precursors led to the decision to halt further investigation into methods for its de-racemisation. Any future work would screen a range of alternative lithium bases (*e.g.* LiHMDS, LDA) and also prepare the *N*-carbamate substrate **409** in analogy to the pipecolic acid derived substrates used by Lasne and co-workers (Scheme 4.71). Thus, it could be established if enolate **410** is stabilised by the formation of a six-membered chelate and therefore reduce the level of substrate decomposition observed (Scheme 4.73).



Scheme 4.73. Proposed de-racemisation of carbamate **409**.

4.11 Summary and Future Work

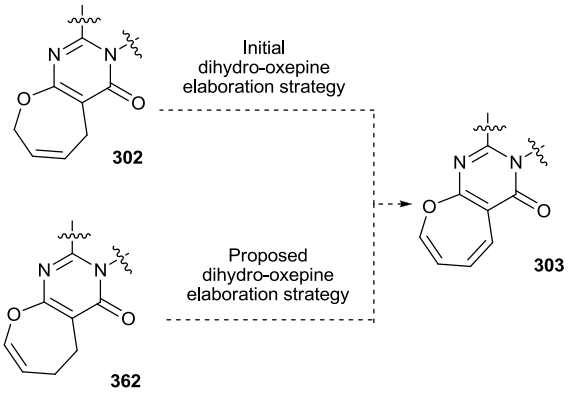
The elaboration of dihydro-oxepine **298** to oxepine **309** *via* an allylic oxidation – chlorination – elimination sequence enabled the first total synthesis of (±)-janoxepin (**1**) to be completed in 14 steps from D-leucine **38**; this was reported in a recent publication (see Appendix **VI**).[152] Unfortunately, this transformation was found to be low-yielding and could not be improved despite a thorough investigation of alternative strategies. The utilisation of a biomimetic approach for oxepine construction is discussed in Chapter 5, whilst future work will focus on developing an alternative oxepine synthesis by way of alkyne cycloisomerisation (see Chapter 4.11.1).

Attempts to de-racemise (±)-janoxepin (**1**) by enantioselective protonation of an enolate intermediate were unsuccessful owing to the instability of the oxepine substrates to the

conditions required for enolisation. The development of a chiral synthesis of the natural product and its derivatives will also be the subject of future work.

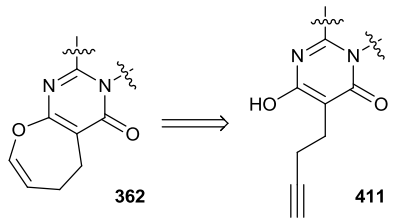
4.11.1 Future Work: Alkyne Cycloisomerisation Route

As already discussed, it was proposed that preparing a dihydro-oxepine substrate **362** with the vinyl ether alkene in place before elaboration to the oxepine **303** would represent a more efficient synthetic route to janoxepin (**1**) (Scheme 4.74).



Scheme 4.74. Dihydro-oxepine elaboration strategies.

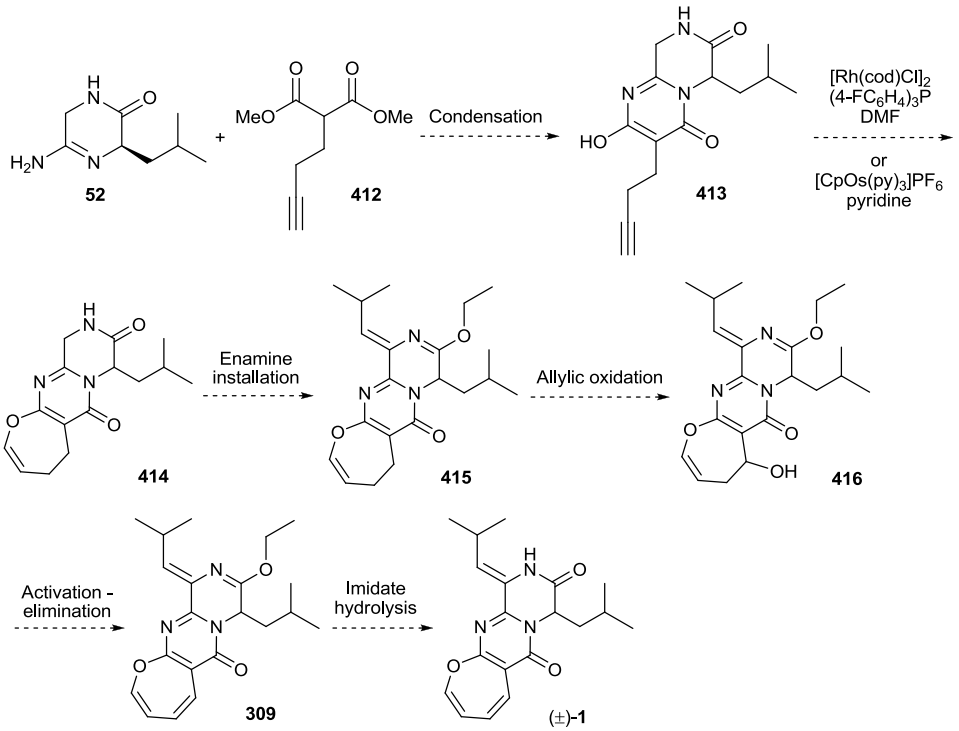
Attempts to implement this strategy by alkene isomerisation (Chapter 4.6) and *O*-vinylation (Chapter 4.7) were unsuccessful, however, an alternative retrosynthesis of a dihydro-oxepine **362** constructed the vinyl ether alkene by cycloisomerisation of an alkyne **411** (Scheme 4.75). This methodology has recently been used in the synthesis of such dihydro-oxepines by both Reisman[80] and Saá[79] groups as described in Chapter 2.4.2.



Scheme 4.75. Alternative retrosynthetic analysis of dihydro-oxepine **362**.

The proposed route would therefore commence with the condensation cyclic amidine **52** and known alkynyl malonate **412**[153] to access pyrimidinone **413**. Cycloisomerisation would then be effected by rhodium (Reisman)[80] or osmium (Saá)[79] catalysis to provide the vinyl ether-containing dihydro-oxepine **414**. Aldol condensation of *iso*-butyraldehyde **221** using the imidate protection methodology described in Chapter 3 would then follow to provide enamine **415**. Dihydro-oxepine elaboration *via* allylic

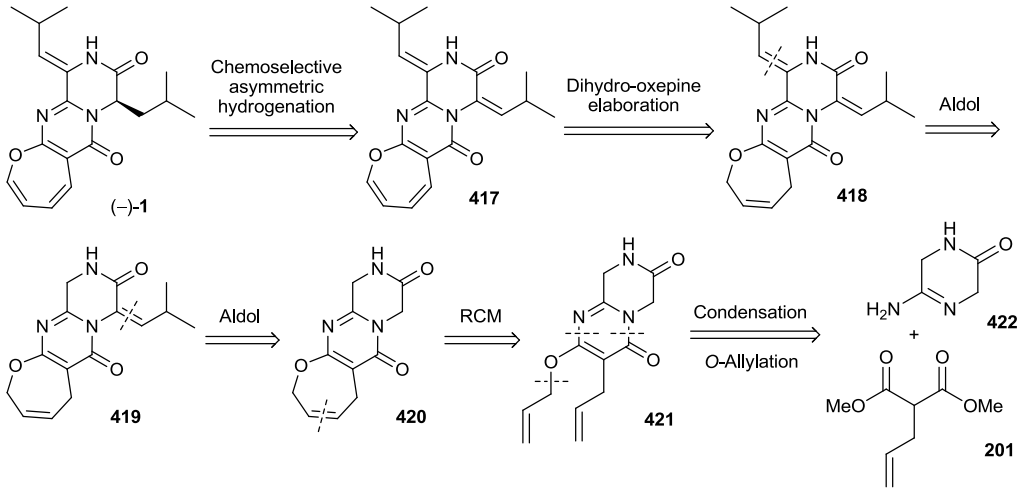
oxidation – activation – elimination would then install the final alkene to give oxepine **309**, with imidate hydrolysis completing the second generation synthesis of (±)-janoxepin (**1**) (Scheme 4.76).



Scheme 4.76. Proposed alkyne cycloisomerisation route.

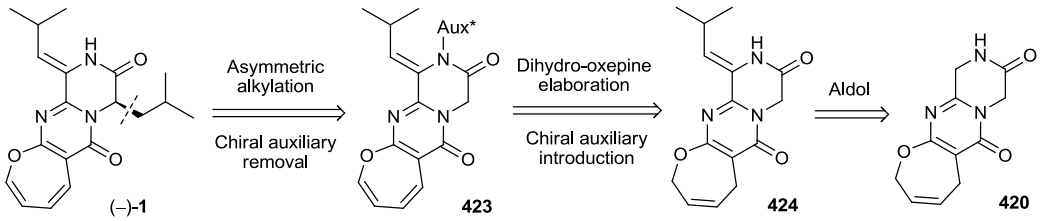
4.11.2 Future Work: Asymmetric Routes to (–)-Janoxepin (**1**)

In addition to the further investigation of chiral protonation methodology as outlined in Chapter 4.10, the development of a novel chiral synthesis of (–)-janoxepin (**1**) may be worthy of consideration. For example, introduction of the stereocentre by a chemoselective asymmetric hydrogenation of the conjugated alkene of ketopiperazine-pyrimidinone-oxepine **417** may be possible as a final step in the synthesis. [It has already been shown that selective hydrogenation of a dihydro-oxepine in the presence of an enamine is possible (Chapter 3.7), although how the oxepine ring would be affected is unknown]. Elaboration of dihydro-oxepine **418** (or an isomer) would follow double aldol condensation of *iso*-butyraldehyde **221** to the unsubstituted ketopiperazine-pyrimidinone **419**, itself constructed using the condensation – *O*-allylation sequence already developed. Thus, the unsubstituted cyclic amidine **422** and malonate **201** would be employed as the starting materials (Scheme 4.77).



Scheme 4.77. Retrosynthetic analysis of (–)-janoxepin (**1**): proposed asymmetric hydrogenation route.

Alternatively, introduction of the stereocentre *via* late stage asymmetric alkylation of the enamine-containing ketopiperazine-pyrimidinone-oxepine **423** can also be envisaged, with approach of the electrophile directed by a chiral auxiliary appended to the amide nitrogen. The key alkylation substrate **423** would be prepared by elaboration of dihydro-oxepine **424** followed by introduction of the auxiliary. Enamine installation would again be achieved by aldol addition of *iso*-butyraldehyde **221** to the unsubstituted ketopiperazine-pyrimidinone **420**, a common intermediate to both proposed chiral syntheses (Scheme 4.78). A crucial concern with this route would be the efficiency of dihydro-oxepine **424** elaboration to oxepine **423** in the presence of an acidic ketopiperazine proton and the distance of the auxiliary from the reactive site.

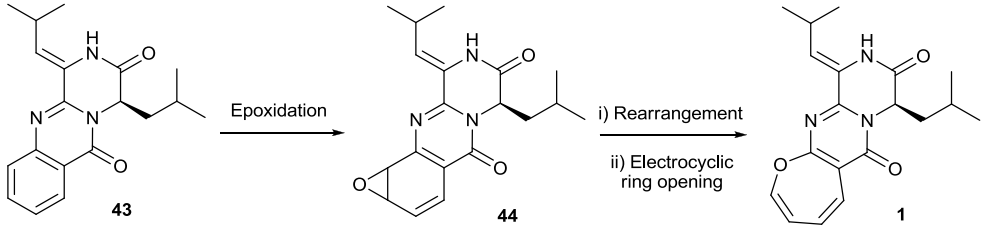


Scheme 4.78. Retrosynthetic analysis of (–)-janoxepin (**1**): proposed asymmetric alkylation route.

Chapter 5. Biomimetic Oxepine Construction: Synthesis of a Janoxepin Biosynthetic Precursor

5.1 Oxepine Biosynthesis: Recap

As described in Chapter 1.5, it is proposed that the biosynthesis of janoxepin (**1**), and similar natural products, proceeds *via* an intriguing enzymatic epoxidation of the pyrazino[2,1-*b*]quinazoline-3,6-dione intermediate **43**. This is followed by electrocyclic ring-opening of the resulting epoxide **44** to form the oxepine ring (Scheme 5.1).[1,26,27,32]



Scheme 5.1. Proposed oxepine biogenesis.

The electrocyclic ring-opening of arene-oxides to oxepines has been the subject of much study, as reviewed in Chapter 2.3.1. It was therefore decided to investigate the plausibility of using such a biomimetic approach as part of an on-going search for an efficient synthetic method of oxepine construction. Work would first focus on the synthesis of the pyrazino[2,1-*b*]quinazoline-3,6-dione intermediate **43** before investigating methods for its epoxidation to access **44**.

5.2 Pyrazino[2,1-*b*]quinazoline-3,6-dione-Containing Natural Products

The pyrazino[2,1-*b*]quinazoline-3,6-dione core of the novel, key intermediate **43** can be found in a number of natural products with interesting biological activity. Whilst many examples lacking an enamine side-chain on the ketopiperazine ring have been the subject of total syntheses, none bearing such a moiety have been prepared synthetically. Thus, the methodology used in the preparation of pyrazino[2,1-*b*]quinazoline-3,6-dione **43** may also have utility in natural product synthesis.

5.2.1 Natural Product Examples Without an Enamine Side-Chain

The isolation of numerous natural products bearing the pyrazino[2,1-*b*]quinazoline-3,6-dione core lacking an enamine side-chain have been reported. Many, including the fumiquinazolines A-I,[154-156] alantrypinone[157-159] and glyantrypine[156,160] have been

prepared synthetically, with 5-*N*-acetylardeemin (**425**),[161] fiscalin B (**426**)[155] and serantrypinone (**427**)[162] the subject of the most recent studies (Figure 5.1).

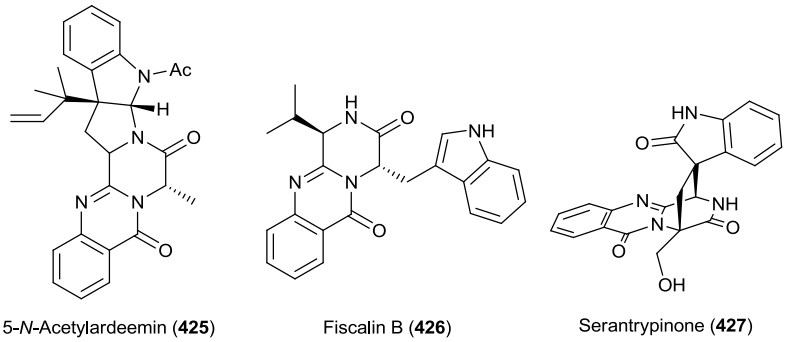


Figure 5.1. Pyrazino[2,1-*b*]quinazoline-3,6-dione-based natural product examples.

5-*N*-Acetylardeemin (**425**) was isolated from a strain of the fungus *Aspergillus fisheri* obtained from a Brazilian soil sample in 1993 by McAlpine and co-workers.[163] Its structure was determined using NMR spectroscopy and mass spectrometry, with further evidence for the assignment provided by X-ray crystallography. The compound was found to be a potent inhibitor of tumour cell 'multiple drug resistance' to anti-tumour agents such as vinblastine, taxol and doxorubicin.[164,165] It has been the subject of total syntheses by Danishefsky and co-workers,[166] Qin and co-workers and,[167,168] most recently, Kawasaki and co-workers.[161]

Fiscalin B (**426**) was first isolated from the fungus *Neosartorya fischeri* by Cooper and co-workers in 1993 and was found to inhibit the human neurokinin receptor (NK-1), thus having potential anti-depressant and anti-emetic properties.[169] The compound was subsequently also isolated from the ascomycete *Corynascus setosus* by Yamazaki and co-workers in 1996.[170] Its interesting biological activity has made fiscalin B (**426**) a popular synthetic target; Baldino and co-workers reported the most recent synthesis in 2005,[155] whilst Söllhuber and co-workers[156] and Ganesan and co-workers[171] have also completed total syntheses of the compound.

The spirooxindole-containing, pyrazino[2,1-*b*]quinazoline-3,6-dione serantrypinone (**427**) was first isolated from the fungus *Penicillium thymicola* in 2001 by Barrero and co-workers.[172] Its interesting structure was assigned based upon spectral similarities with the closely related natural product alantrypinone. In 2004, Ozoe and co-workers isolated the compound from the fungus *Aspergillus terreus* and reported it to have

insecticidal properties.[173] Serantrypinone (**427**) is the subject of a single total synthesis by Hart and Oba as reported in 2007.[162]

5.2.2 Natural Product Examples Bearing an Enamine Side-Chain

Only three natural product examples bear an enamine moiety at the C-1 position of the pyrazino[2,1-*b*]quinazoline-3,6-dione core, none of which have been prepared synthetically. These comprise aurantiomide C (**428**),[174] verrucine F (**429**),[175] and quinadoline A (**430**) (Figure 5.2).[176]

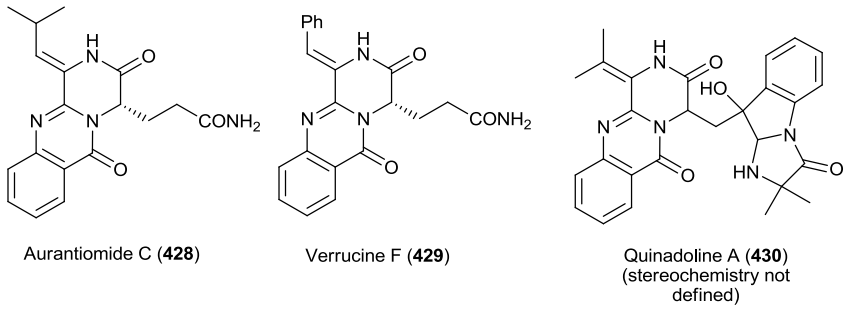


Figure 5.2. Pyrazino[2,1-*b*]quinazoline-3,6-dione natural product examples bearing an enamine moiety.

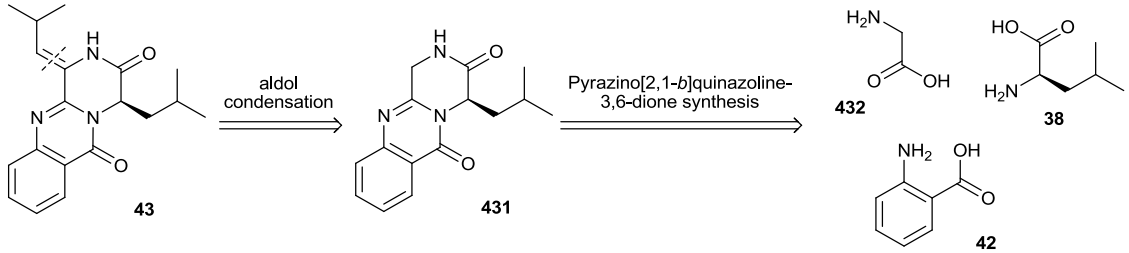
The L-glutamine derived pyrazino[2,1-*b*]quinazoline-3,6-dione aurantiomide C (**428**) was isolated from the fungus *Penicillium aurantiogriseum* SP0-19, alongside two hydroxylated derivatives, aurantiomides B and C, by Zhu and co-workers in 2007.[174] Its structure was elucidated from ^{1}H- and ^{13}C-NMR spectroscopic data, in conjunction with mass spectrometry. Aurantiomide C (**428**) was shown to have moderate cytotoxic activity against a panel of cell lines.

Verrucine F (**429**) is also derived from L-glutamine, differing to aurantiomide C (**428**) only in its phenyl-substituted enamine side-chain. Isolated in 2008 by Broberg and co-workers from the fungus *Penicillium verrucosum*, no investigation into the biological activity of the compound was undertaken.[175]

Quinadoline A (**430**) was isolated from the fungus *Aspergillus* sp. FKI-1746 by Tomoda and co-workers in 2008. Its structure was determined by ^{1}H- and ^{13}C-NMR spectroscopy in conjunction with COSY, HSQC and HMBC experiments, although the stereochemistry was not defined.[176] The compound was found to inhibit lipid droplet synthesis in mouse macrophages with no cytotoxic effects.

5.3 Strategy for the Preparation of the Janoxepin Biosynthetic Intermediate **43**

It was proposed that the enamine side-chain of the proposed biosynthetic intermediate **43** be installed using the aldol addition methodology described in Chapter 3. The known[177] pyrazino[2,1-*b*]quinazoline-3,6-dione **431** would be prepared from the readily available anthranilic acid **42**, glycine **432** and D-leucine **38** using a choice of established procedures which are reviewed below (Chapter 5.4) (Scheme 5.2).



Scheme 5.2. Retrosynthetic analysis of the janoxepin biosynthetic precursor **43**.

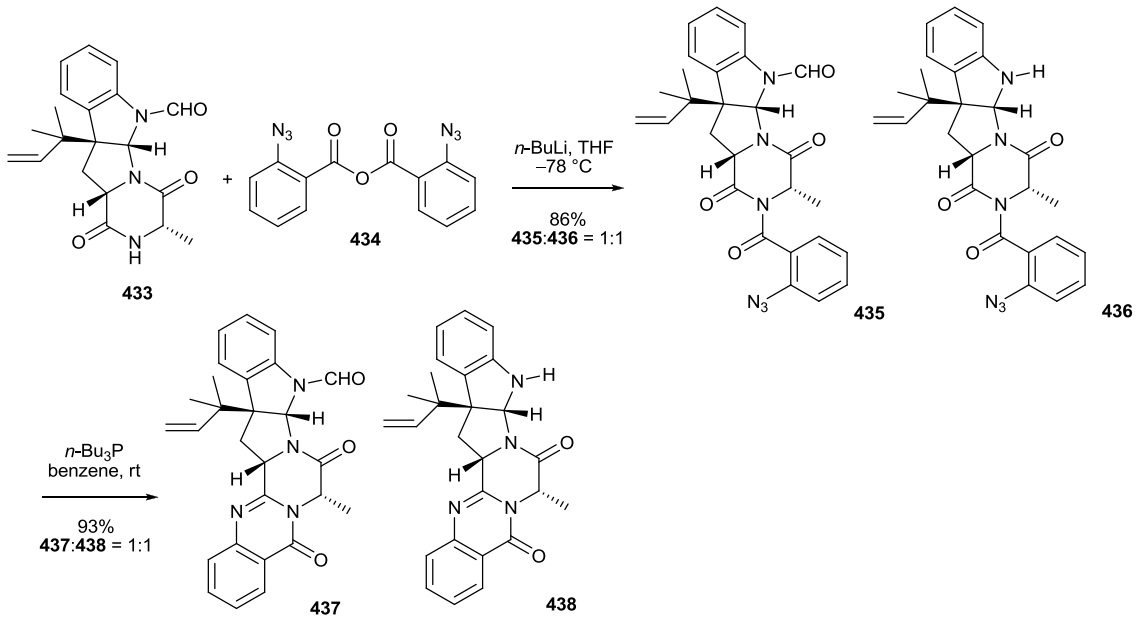
5.4 Literature Routes to Pyrazino[2,1-*b*]quinazoline-3,6-diones

Approaches to the synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones can be categorised into three areas:

- Aza-Wittig methods.
- Cyclodehydration approaches.
- Microwave-mediated cyclisations.

5.4.1 Aza-Wittig Approach

A number of syntheses of the natural products described above (Chapter 5.2.1) have relied upon an aza-Wittig-like reaction, as first developed by Eguchi and co-workers in 1989.[178] For example, Danishefsky and co-workers[166] and Qin and co-workers[167,168] both use this methodology at a late stage in their syntheses of 5-*N*-acetylardeemin (**425**) (Scheme 5.3). A 1:1 mixture of azido intermediates **435** and **436** is prepared by condensation of *ortho*-azidobenzoic anhydride **434** with diketopiperazine **433** in the presence of a strong base. Cyclisation is promoted by treatment of the mixture with tri-*n*-butylphosphine to furnish pyrazino[2,1-*b*]quinazoline-3,6-diones **437** and **438** as single diastereomers and in excellent yield (Scheme 5.3).

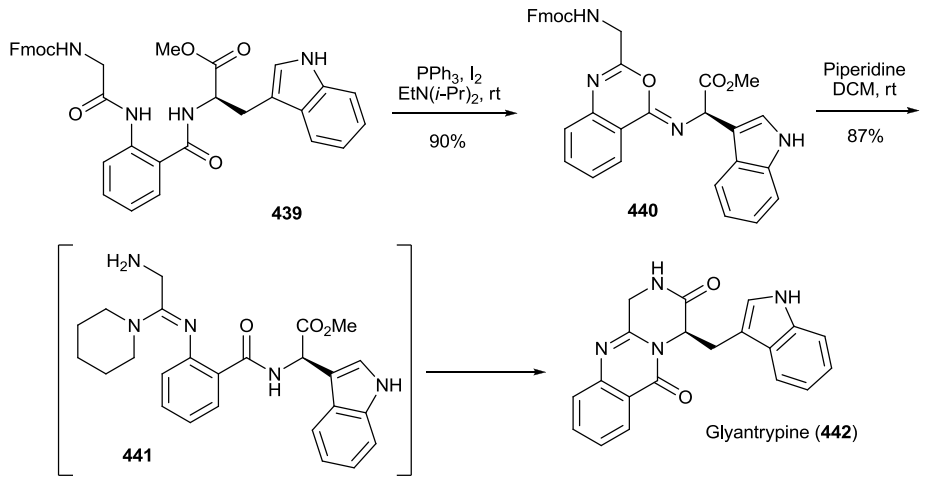


Scheme 5.3. Aza-Wittig approach to pyrazino[2,1-*b*]quinazoline-3,6-dione synthesis as applied to the synthesis of 5-*N*-acetylardeemin (**425**).

Söllhuber and co-workers,[96] Menéndez and co-workers[160] and Snider and co-workers[154] also apply this strategy to their syntheses of fiscalin B (**426**), glyantrypine (**442**) and the fumiquinazolines, respectively.

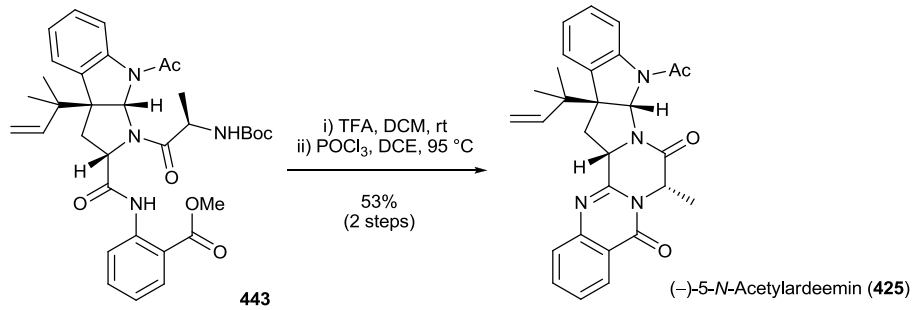
5.4.2 Cyclodehydration Approaches

Ganesan and Wang prepared the pyrazino[2,1-*b*]quinazoline-3,6-dione natural product glyantrypine (**442**), as well as the fumiquinazolines F-G and fiscalin B (**426**), by cyclodehydration of an amide intermediate.[179] As shown in Scheme 5.4, the treatment of amide **439** with triphenylphosphine and iodine (which are required in large excess) effects dehydration to oxazine **440**. The intermediate amidine **441** is then formed upon piperidine-mediated Fmoc cleavage, and readily cyclises to the pyrazino[2,1-*b*]quinazoline-3,6-dione natural product glyantrypine (**442**) upon heating in acetonitrile, with retention of configuration of the stereocentres (although no *ee* is reported). Ganesan and Wang developed this route into a solid phase procedure which was used to prepare the proposed pyrazino[2,1-*b*]quinazoline-3,6-dione **431**, a key intermediate in the retrosynthetic analysis of the target molecule **43** (Chapter 5.3).[177] The methodology has also been employed in Hart and Magomedov's[158] and Chen and co-workers'[157] syntheses of alantrypinone, and Sim and Wang's synthesis of verrucines A-B.[180]



Scheme 5.4. Cyclodehydration methodology as applied to the synthesis of glyantrypine (**442**).

An alternative procedure was reported by Kawasaki and co-workers in their synthesis of 5-*N*-acetylardeemin (**425**). A successive Boc-cleavage, followed by phosphorus oxychloride mediated double cyclisation of amide **443** is used to construct the pyrazino[2,1-*b*]quinazoline-3,6-dione core structure in moderate yield (Scheme 5.5).

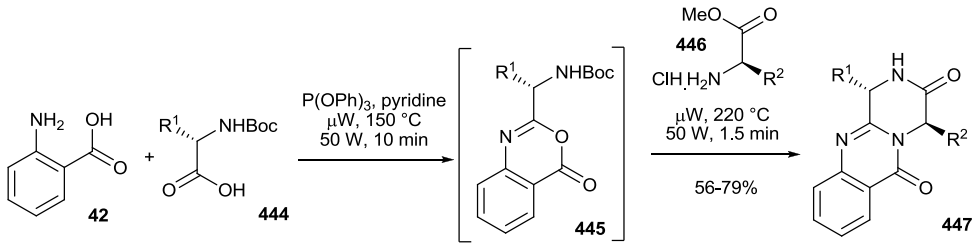


Scheme 5.5. $POCl_3$ mediated double cyclisation to construct the pyrazino[2,1-*b*]quinazoline-3,6-dione core of 5-*N*-acetylardeemin (**425**).

5.4.3 Microwave-Promoted Cyclisations

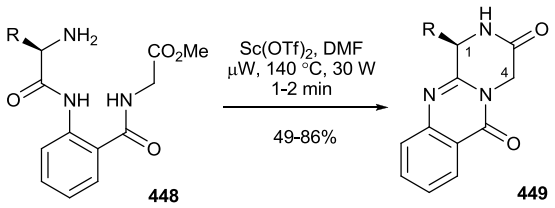
Liu and co-workers developed a microwave-promoted, three-component, one-pot procedure for pyrazino[2,1-*b*]quinazoline-3,6-dione construction, and applied this to the synthesis of fumiquinazoline F, fiscalin B (**426**) and glyantrypine (**442**).[181] Thus, treatment of anthranilic acid **42** and a Boc-protected amino acid **444** with $P(OPh)_3$ in pyridine, and microwave irradiation at 150 °C, 50 W for 10 min furnished an intermediate oxazine **445**. Addition of an amino acid hydrochloride **446** with further microwave irradiation at 220 °C, 50 W for 1.5 min then provided the desired pyrazino[2,1-*b*]quinazoline-3,6-diones **447**, with loss of the Boc-protecting group, in 56-79% yields (Scheme 5.6). Unfortunately, this process leads to epimerisation of the stereogenic centres and large R^2 groups are not well-tolerated, resulting in much lower

yields. Nishida and co-workers subsequently utilised this methodology in their synthesis of alantrypinone.[159]



Scheme 5.6. Microwave promoted, three-component, one-pot synthesis of pyrazino[2,1-*b*]quinazoline-3,6-diones.

A Lewis acid-mediated double cyclisation was developed by Chu and co-workers in 2010.[182] Thus, treatment of amine **448** with one equivalent of scandium triflate and microwave irradiation at 140 °C, 30 W for 1-2 min furnished a range of C-1 substituted pyrazino[2,1-*b*]quinazoline-3,6-diones **449** in 49-86% yield (Scheme 5.7). No racemisation of the stereocentre was observed under the reaction conditions, as shown by ^{1}H-NMR spectroscopy using a chiral shift reagent, although examples bearing a C-4 substituent were not investigated.



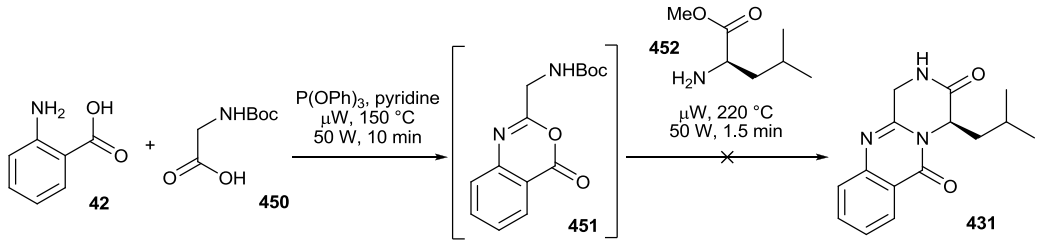
Scheme 5.7. Lewis acid-mediated, microwave promoted double cyclisation of amines **448**.

5.5 Synthesis of Pyrazino[2,1-*b*]quinazoline-3,6-dione 431: Liu Microwave Methodology

The solid-phase, dehydrative procedure for the synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** as reported by Ganesan required large excesses of triphenylphosphine and iodine, as well as long reaction times and thus was not an attractive synthetic strategy.[177] It was also desirable to avoid handling an azide intermediate. Our initial focus was therefore the microwave promoted, three-component, one-pot methodology reported by Liu and co-workers which had the virtues of brevity and its use of readily available, inexpensive starting materials.

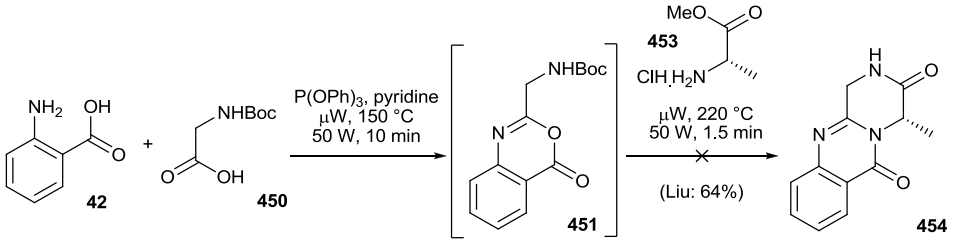
N-Boc-glycine **450** and anthranilic acid **42** were treated with $P(OPh)_3$ in DMF with microwave irradiation to 150 °C, 50 W for 10 min. As described by Liu and co-workers,

D-leucine methyl ester **452** was then added to the reaction mixture, with further microwave irradiation at 220 °C, 50 W for 1.5 min. Again, only a complex mixture of decomposition products was isolated (Scheme 5.8).



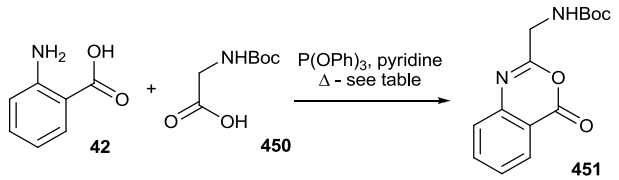
Scheme 5.8. Attempted synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** using Liu's procedure.

To establish if the bulky *iso*-butyl group of leucine was not well-tolerated, or if using a hydrochloride salt was essential, a reaction described in the Liu report, which proceeded in 64% yield, was repeated. Thus, *N*-Boc-glycine **450** and anthranilic acid **42** were treated with $P(OPh)_3$ in DMF with microwave irradiation at 150 °C, 50 W for 10 min before L-alanine methyl ester hydrochloride **453** was added, with further microwave irradiation at 220 °C, 50 W for 1.5 min.[181] However, only a complex mixture of products was isolated, with no trace of the desired pyrazino[2,1-*b*]quinazoline-3,6-dione **454** (Scheme 5.9).



Scheme 5.9. Unsuccessful repeat of the reaction of using L-alanine methyl ester hydrochloride as reported by Liu and co-workers.[155]

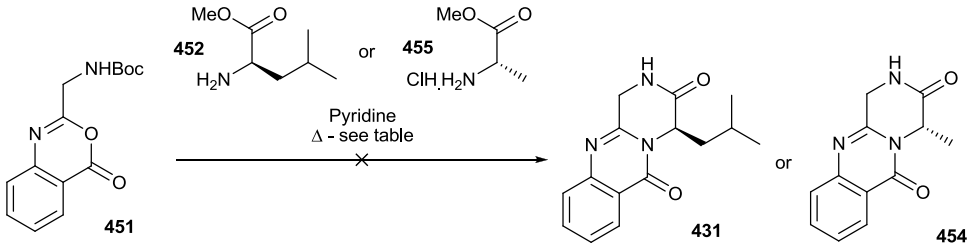
In order to establish why the reaction failed, the oxazine intermediate **451** was prepared in 55% yield using conventional heating at 70 °C for 18 h (Table 5.1, entry 1). Surprisingly, when the microwave conditions reported were used, no oxazine **451** was isolated, with only a complex mixture of products being obtained (Table 5.1, entry 2) indicating that the reaction was failing in the first step.



Entry	Conditions	Yield 451
1	70 °C (conventional), 18 h	55%
2	μW, 150 °C, 50 W, 10 min	Decomposition

Table 5.1. Synthesis of oxazine **451**: reaction conditions explored.

It was therefore decided to abandon the three-component, one-pot process and investigate using the previously prepared oxazine **451** in a sequential manner. However, when oxazine **451** was treated with D-leucine methyl ester **452** in pyridine with microwave irradiation as before, only decomposition of the substrates was observed (Table 5.2, entry 1). This was again the case using L-alanine methyl ester hydrochloride **455** (Table 5.2, entry 2, as reported by Liu). Furthermore, no reaction occurred upon conventional heating at reflux (Table 5.2, entry 3).



Entry	Amino methyl ester	Conditions	Comment
1	**452**	μW, 220 °C, 50 W, 1.5 min	Decomposition
2	**455**	μW, 220 °C, 50 W, 1.5 min	Decomposition
3	**452**	115 °C (conventional), 1.5 h	rsm

Table 5.2. Pyrazino[2,1-*b*]quinazoline-3,6-dione preparation from oxazine **451**: reaction conditions explored.

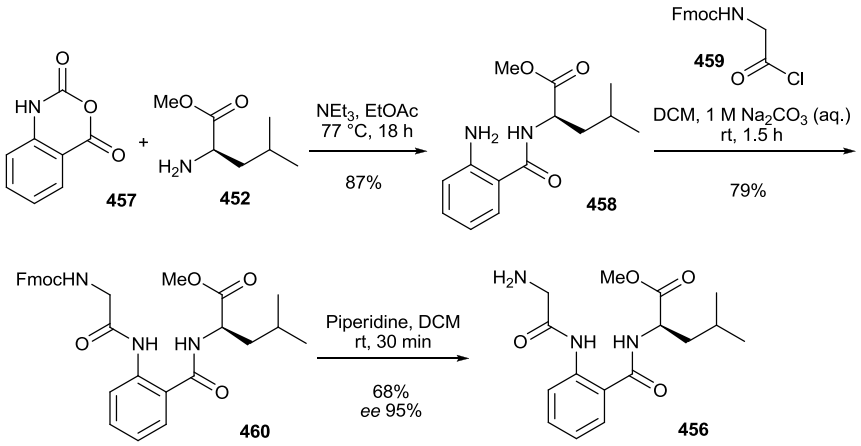
As we were unable to repeat the published procedures, or use conventional heating methods, this strategy was abandoned, and the Lewis acid-mediated cyclisation methodology reported by Chu and co-workers was investigated.

5.6 Synthesis of Pyrazino[2,1-*b*]quinazoline-3,6-dione 431: Chu Microwave Methodology

As outlined in Chapter 5.4.3, this strategy first required the synthesis of amine **456** which would undergo a double cyclisation to pyrazino[2,1-*b*]quinazoline-3,6-dione **431**.

5.6.1 Synthesis of Amine **456**

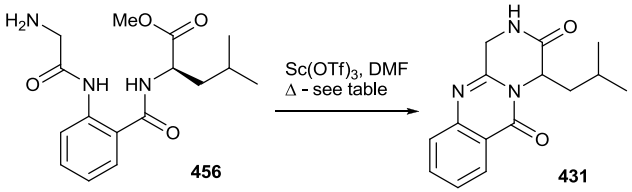
The synthesis of the novel amine **456** began with the coupling of isatoic anhydride **457** and D-leucine methyl ester **452** using a modified procedure (Scheme 5.10).[182] EtOAc was used as solvent in place of DMF, resulting in a much improved yield of 87% of the known amide **458**, compared to 32% previously reported.[183] Amide **458** was then coupled with Fmoc-protected glycine chloride **459** to furnish the novel *bis*-amide **460**, which was treated with piperidine to remove the Fmoc-protecting group and provide the required amine **456** in 47% yield over the three steps (Scheme 5.10). Chiral HPLC analysis (Chiralpak AD-H column) indicated that the configuration of the stereocentre had been retained, with the material being isolated in 95% *ee*.



Scheme 5.10. Synthesis of amine **456**.

5.6.2 Lewis Acid-Mediated Cyclisation

Pleasingly, the treatment of amine **456** with one equivalent of scandium triflate in DMF, with microwave irradiation at 140 °C, 50 W for 1.5 min, as according to the Chu procedure, did furnish pyrazino[2,1-*b*]quinazoline-3,6-dione **431**, but in low yield (Table 5.3, entry 1). Heating for 3.5 min led to an improved yield (Table 5.3, entry 2), whilst heating for 10 min was found to be optimal, providing pyrazino[2,1-*b*]quinazoline-3,6-dione **431** in 62% yield (Table 5.3, entry 3). When the reaction temperature was raised to 210 °C for 3.5 min, a complex mixture of decomposition products was obtained (Table 5.3, entry 4), whilst using conventional heating at 110 °C for 2.5 h provided a much lower yield of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** (Table 5.3, entry 5). Interestingly, it was found that a sub-stoichiometric amount (0.5 equivalents) of scandium triflate could be used with an increased reaction time at 140 °C, to obtain a 50% yield of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** (Table 5.3, entry 6).



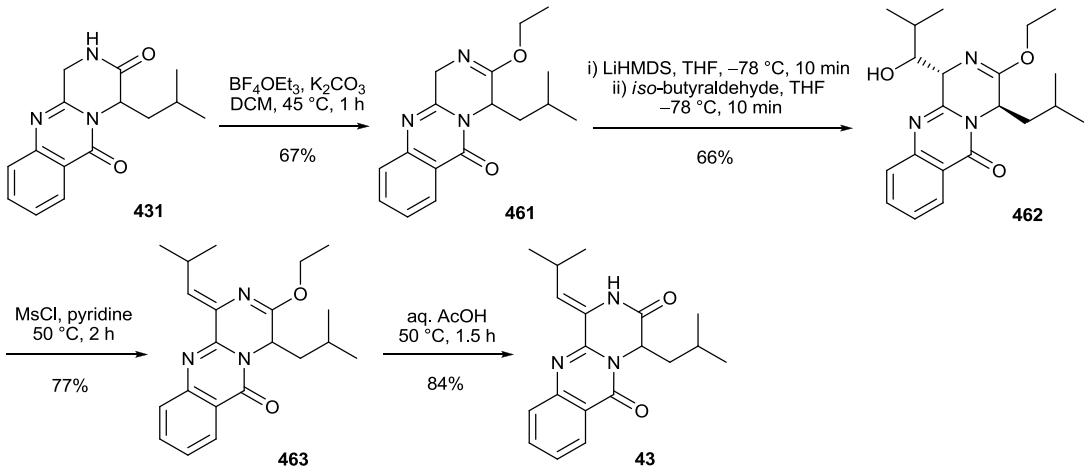
Entry	$Sc(OTf)_3$ eq.	Conditions	Yield 431
1	1.0	μW, 140 °C, 50 W, 1.5 min	18%
2	1.0	μW, 140 °C, 50 W, 3.5 min	35%
3	1.0	μW, 140 °C, 50 W, 10 min	62%
4	1.0	μW, 210 °C, 50 W, 3.5 min	Decomposition
5	1.0	110 °C (conventional), 2.5 h	20%
6	0.5	μW, 140 °C, 50 W, 15 min	50%

Table 5.3. Lewis acid-mediated cyclisation of amine **431**.

This demonstrated that the Chu methodology did tolerate substitution at the C-4 position, but that longer reaction times are required, and lower yields are obtained. Disappointingly, the reaction proceeded with racemisation of the stereogenic centre, as shown by chiral HPLC analysis (Chiralpak OD column). Although the overall yield for the preparation of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** from isatoic anhydride **457** (29%) is lower than for the solid-phase procedure reported by Ganesan (53%),[177] it is amenable to preparation on a 2 g scale. The ^{1}H- and ^{13}C-NMR spectroscopic data for pyrazino[2,1-*b*]quinazoline-3,6-dione **431** compared exactly with those previously reported.[177]

5.7 Aldol Introduction of the Enamine

It was proposed that the enamine side-chain of the janoxepin biosynthetic intermediate **43** be installed using the aldol methodology described in Chapter 3. Thus, pyrazino[2,1-*b*]quinazoline-3,6-dione **431** was first treated with triethyloxonium tetrafluoroborate and potassium carbonate with heating to reflux in DCM to furnish imidate **461** in 67% yield. Aldol addition was effected by deprotonation with LiHMDS (prepared *in situ*) in THF at –78 °C for 10 min followed by the addition of *iso*-butyraldehyde **221**. After 10 min, the reaction was quenched at –78 °C by the addition of acetic acid and the aldol adduct **462** was isolated in 66% yield without any further optimisation. Elimination to enamine **463** was achieved by treating aldol adduct **462** with MsCl in pyridine and heating to 50 °C for 1.5 h. Finally, imidate hydrolysis using aqueous acetic acid furnished the proposed janoxepin biosynthetic intermediate **43** in 28% yield for the four-step sequence, albeit in racemic form (Scheme 5.11).



Scheme 5.11. Synthesis of the proposed janoxepin biosynthetic intermediate **43**. (Relative stereochemistry shown).

5.8 Characterisation of Biosynthetic Intermediate **43**

The structure of the biosynthetic intermediate **43** was confirmed by ^{1}H- and ^{13}C-NMR spectroscopy in conjunction with COSY and HSQC experiments (see Appendix **IV** for NMR spectra). The *Z*-configuration of the enamine was established by nOe studies which showed enhancements betweem H-1 and H-2 and, to a lesser extent, H-1 and H-3 (Figure 5.3).

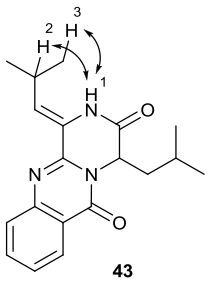


Figure 5.3. nOe enhancements for the janoxepin biosynthetic intermediate **43**.

Further evidence for the structural assignment was provided by X-ray crystallographic analysis of **43** (Figure 5.4).

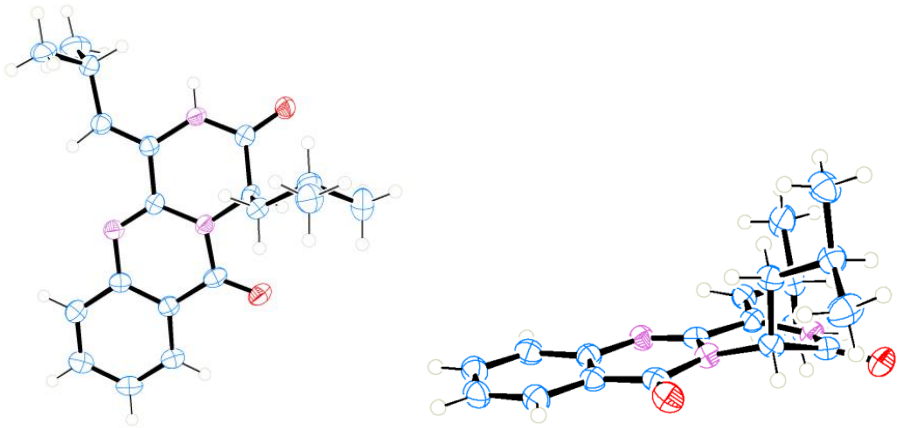
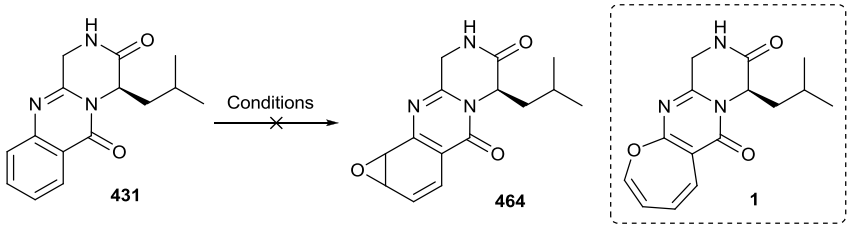


Figure 5.4. X-ray crystallography of (±)-**43**. ORTEP representations shown with ellipsoids at 50% probability. A single enantiomer (*R*) is shown for clarity. CCDC 862145; see Appendix **V**.

Unfortunately, attempts deracemise the product using an asymmetric protonation of an intermediate enolate species as described in Chapter 4.10 were again unsuccessful. As with janoxepin (**1**) and its imidate precursor **309**, treatment of **43** with *sec*-BuLi resulted in decomposition of the material and no further investigation was carried out.

5.9 Epoxidation – Ring-Opening: Preliminary Studies

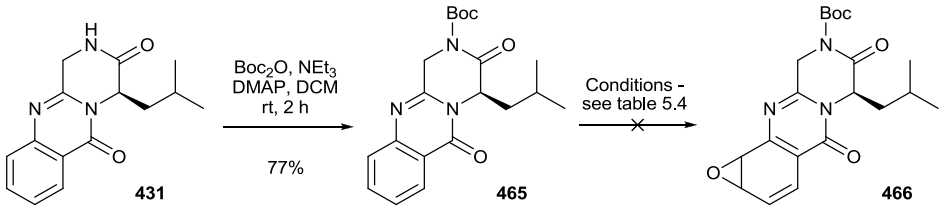
A preliminary investigation into the proposed biomimetic epoxidation – electrocyclic ring-opening strategy for oxepine synthesis was undertaken. It was decided to use pyrazino[2,1-*b*]quinazoline-3,6-dione **431** as the substrate for an initial epoxidation study, thus avoiding any selectivity issues arising from epoxidation of the enamine alkene in **43** or **463**. When pyrazino[2,1-*b*]quinazoline-3,6-dione **431** was treated with *m*-CPBA (Table 5.4, entry 1), sodium hypochlorite (Table 5.4, entry 2) and DMDO (Table 5.4, entry 3), no epoxide **464** (or oxepine **1**) was observed. Only a complex mixture of compounds including *N*-oxide species (as indicated by mass spectrometry and ^{1}H-NMR spectroscopy of the unpurified products), and decomposition products was isolated.



Entry	Oxidant	Conditions
1	*m*-CPBA	DCM/aq. $NaHCO_3$ (sat.), rt, 18 h
2	NaOCl	*n*-Bu_4NHSO_4, DCM, rt, 18 h
3	DMDO	acetone, 0 °C – rt, 18 h

Table 5.4. Attempted epoxidation of pyrazino[2,1-*b*]quinazoline-3,6-dione **431**: reaction conditions explored.

To inhibit competing *N*-oxidation, the *N*-Boc derivative **465** was prepared by treatment of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** with di-*tert*-butyl dicarbonate, triethylamine and DMAP. However, when this substrate was subjected to the same conditions shown in Table 5.4, again only complex mixtures of products were obtained (Scheme 5.12).



Scheme 5.12. Boc-protection of pyrazino[2,1-*b*]quinazoline-3,6-dione **431**. Subsequent epoxidation was not possible.

5.10 Summary and Future Work

In summary, the proposed janoxepin biosynthetic intermediate **43** has been prepared in an efficient eight-step synthesis in racemic form. The pyrazino[2,1-*b*]quinazoline-3,6-dione core was constructed using a Lewis acid-mediated double cyclisation of amine **456**, and the enamine side-chain was installed using the previously described aldol addition methodology (Chapter 3), demonstrating its broader scope. This synthetic approach not only has potential utility in the synthesis of enamine-containing pyrazino[2,1-*b*]quinazoline-3,6-dione natural products **428**-**430**, but has also allowed for preliminary investigations into the development of a biomimetic oxepine synthesis. This work has been the subject of a recent publication (see Appendix **VI**).[184]

Future work will first focus on investigating the chemical epoxidation of **43** itself, as well as other intermediates, before exploring the possibility of utilising an enzymatic

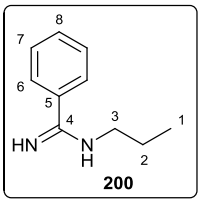
biotransformation. At the same time, further investigation using asymmetric protonation methods to afford optically pure material will then allow this methodology to be applied to enantiopure syntheses of enamine-containing pyrazino[2,1-*b*]quinazoline-3,6-dione natural products.

Chapter 6. Experimental

NMR spectra were recorded on a Jeol ECX-400 instrument at 400 MHz (^{1}H) and 100 MHz (^{13}C). A Bruker AV-500 instrument was used for recording nOe correlations at 500 MHz (^{1}H). Chemical shifts (δ) are quoted in parts per million (ppm) calibrated to residual non-deuterated solvent. Coupling constants (*J*) are quoted in Hertz. Structural assignment was verified by HSQC and COSY spectroscopy where necessary. Infrared (IR) spectra were recorded on a ThermoNicolet IR100 spectrometer with NaCl plates. Specific rotation values were measured on a JASCO DIP-370 digital polarimeter using a sodium lamp. High resolution electrospray ionisation (ESI) and atmospheric pressure chemical ionisation (APCI) mass spectra were recorded on a Brüker MicroTOF instrument. Elemental analysis was conducted on an Exeter Analytical, Inc. CE-440 Elemental Analyser with samples weighed using a Sartorius SE2 analytical balance. Melting points were recorded on a Gallenkamp apparatus and are uncorrected. Microwave reactions were performed in a CEM Discover system at the specified power. Thin layer chromatography was performed on aluminium plates coated with Merck Silica gel 60 F_{254}. Flash column chromatography was performed using Fluka flash silica gel 60 with the specified eluent. Petroleum ether (PE) refers to the fraction boiling in the range 40-60 °C. Where required, diethyl ether, DCM and toluene were obtained dry from an Innovative Technology Inc. PureSolv Purification System. THF was distilled from sodium benzophenone ketyl immediately before use. Methanol was dried according to the method of Lund and Bjerrum.[94] Degassed solvent refers to solvent which has been sparged with argon for at least 2 h. Except where specified, all reagents were purchased from commercial sources and used without further purification. Structural assignment was aided by the use of DEPT, COSY and HSQC spectroscopy. The atom numbering on structures is for assignment purposes and is independent of IUPAC nomenclature.

6.1 Chapter 2: Oxepine-Pyrimidinone Ring System Construction

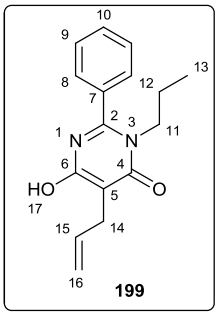
_N_-Propylbenzenecarboximidamide 200



A mixture of benzonitrile (6.85 g, 66.0 mmol, 1.0 eq.) and *n*-propylamine (3.96 g, 66.0 mmol, 1.0 eq.) was added dropwise over 30 min to $AlCl_3$ (8.93 g, 66.0 mmol, 1.0 eq.). A vigorous exotherm occurred on addition. The reaction mixture was heated at 200-220 °C for 45 min and then, while still molten, poured into an aqueous HCl solution (1.8% v/v, 170 mL). After being allowed to cool to room temperature the mixture was filtered through Celite®. The filtrate was poured into 4 M NaOH (aq.) (120 mL) and the organic component extracted with DCM (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish the crude product. Purification by distillation at reduced pressure gave the *title compound* **200** (6.58 g, 61%) as a colourless oil: bp 95-100 °C @ 0.45 mmHg (Lit.[185] 110-112 °C @ 7.0 mmHg); δ_H (400 MHz, MeOD) 7.62-7.39 (5 H, m, H-6, 7, 8), 3.22 (2 H, app. dd (dt), *J* 7.5, 7.0, H-3), 1.73-1.64 (2 H, m, H-2), 1.01 (3 H, t, *J* 7.5, H-1). Data consistent with those in the literature.[90]

Lab. Book: RD01/010/B1

5-Allyl-6-hydroxy-2-phenyl-3-propylpyrimidin-4(3*H*)-one 199

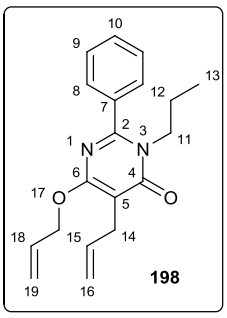


A solution of NaOMe was prepared by the portionwise addition of Na (1.32 g, 58.0 mmol, 2.3 eq.) to MeOH (80 mL). An exotherm occurred. Once the Na had completely reacted and the solution cooled to room temperature, dimethyl 2-allylmalonate **201** (5.01 g, 25.0 mmol, 1.0 eq.) in MeOH was added dropwise, over 5 min, followed by amidine **200** (4.89 g, 30.0 mmol, 1.2 eq.) in MeOH dropwise, over 5 min. The reaction mixture was heated at reflux for 24 h before quenching by the addition of water (300 mL), acidification to pH 1 (1 M HCl (aq.)) and extraction with DCM (3 × 150 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallisation from cyclohexane gave the *title compound* **199** (4.13 g, 60%) as colourless needles: mp 144-146 °C (Lit.[35] 142-143 °C); R_f 0.40 (1:1 PE/EtOAc); δ_H (400 MHz, $CDCl_3$) 11.55 (1 H, br s, H-17), 7.57-7.37 (5 H, m, H-8, 9, 10), 5.80 (1 H, ddt, *J* 17.0, 10.0, 7.0, H-15), 4.97 (1 H, dd, *J* 17.0, 2.0, H-16b), 4.92 (1 H, dd, *J* 10.0, 2.0, H-16a), 3.78 (2 H, t, *J* 7.5, H-11), 3.04 (2 H, d, *J* 7.0,

H-14), 1.59-1.51 (2 H, m, H-12), 0.72 (3 H, t, *J* 7.5, H-13). Data consistent with those previously reported.[35]

Lab. Book: RD01/018/B1

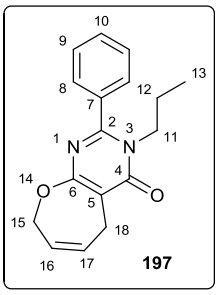
5-Allyl-6-(allyloxy)-2-phenyl-3-propylpyrimidin-4(3*H*)-one 198



To a solution of pyrimidinone **199** (2.00 g, 7.40 mmol, 1.0 eq.) in DMF (20 mL) was added KOH (0.560 g, 10.0 mmol, 1.4 eq.). The reaction mixture was heated at 70 °C for 2 h before a solution of allyl bromide (1.42 g, 11.8 mmol, 1.6 eq.) was added. The reaction mixture was heated at 70 °C for a further 3 d, cooled to room temperature and quenched by the addition of water (120 mL). The crude product was extracted with EtOAc (3 × 60 mL), the organic phase washed with water (3 × 75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 *n*-hexane/EtOAc) to furnish the *title compound* **198** (1.47 g, 64 %) as a pale yellow oil: R_f: 0.56 (1:1 PE/EtOAc); δ_H (400 MHz, $CDCl_3$) 7.51-7.41 (5 H, m, H-8, 9, 10), 6.03-5.90 (2 H, m, H-18, 15), 5.36-4.99 (4 H, m, H-16, 17), 4.80 (2 H, dt, *J* 5.0, 1.5, H-17), 3.85 (2 H, t, *J* 7.5, H-11), 3.29 (2 H, dt, *J* 6.5, 1.0, H-14), 1.65-1.55 (2 H, m, H-12), 0.73 (3 H, t, *J* 7.5, H-13). Data consistent with those previously reported.[35]

Lab. Book: RD01/012/B2

2-Phenyl-3-propyl-5,8-dihydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 197

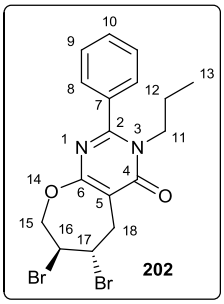


To a solution of diallyl pyrimidinone **198** (0.310 g, 1.00 mmol, 1.0 eq.) in degassed anhydrous DCM (400 mL) under an inert atmosphere was added a solution of Grubbs second generation catalyst **148** (0.0850 g, 0.100 mmol, 0.1 eq.) in degassed anhydrous DCM (20 mL) dropwise over 15 min. The reaction mixture was heated at reflux for 3 h, cooled to room temperature and before directly purified by flash column chromatography on silica gel (1:24 Et_2O/DCM) to furnish the *title compound* **197** (0.219 g, 77%) as a yellow oil: R_f 0.31 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3043 (aromatic C-H stretch), 2966 (C-H stretch), 2876 (C-H stretch), 1645 (C=O stretch), 1549 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.47-7.41 (5 H, m, H-8, 9, 10), 6.25 (1 H, dt, *J* 10.0, 6.0, H-17), 6.07-6.01 (1 H, m, H-16), 4.78 (2 H, d, *J* 6.5, H-

15), 3.83 (2 H, t, *J* 7.5, H-11), 3.55-3.53 (2 H, m, H-18), 1.59 (2 H, tq, *J* 7.5, 7.5, H-12), 0.73 (3 H, t, *J* 7.5, H-13). Data consistent with those previously reported.[35]

Lab. Book: RD01/024/B1

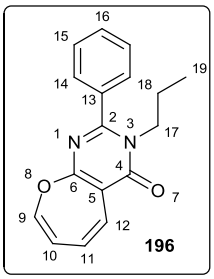
(6*S,7*S**)-6,7-Dibromo-2-phenyl-3-propyl-5,6,7,8-tetrahydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 202**



A solution of dihydro-oxepine **197** (0.190 g, 0.670 mmol, 1.0 eq.) in $CHCl_3$ was cooled to –48 °C (MeCN/CO_2 bath) before the dropwise addition of bromine (1.12 mL, 0.6 M solution in $CHCl_3$, 0.670 mmol, 1.0 eq.). The reaction mixture was stirred at –48 °C for 25 min and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (7:3 PE/EtOAc) to furnish the *title compound* **202** (0.142 g, 51%) as a yellow oil: R_f 0.54 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3059 (aromatic C-H stretch), 2966 (C-H stretch), 1657 (C=O stretch), 1592 (aromatic C=C stretch), 1541 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.52-7.46 (5 H, m, H-8, 9, 10), 4.72-4.68 (2 H, m, H-15a, 17), 4.65-4.63 (1 H, m, H-16), 4.46-4.41 (1 H, m, H-15b), 3.93-3.87 (2 H, m, H-11), 3.63-3.49 (2 H, m, H-18), 1.66-1.59 (2 H, m, H-12), 0.78-0.74 (3 H, m, H-13). Data consistent with those previously reported.[35]

Lab. Book: RD01/026/B1

2-Phenyl-3-propyloxepino[2,3-*d*]pyrimidin-4(3*H*)-one 196

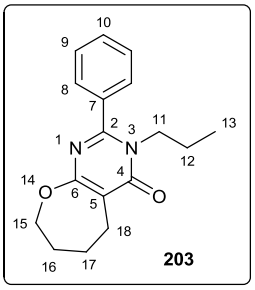


To a solution of dibromide **202** (0.0640 g, 0.160 mmol, 1.0 eq.) in DMSO (2.75 mL) at room temperature was added TBAF (0.610 mL, 1 M solution in THF, 0.610 mmol, 3.9 eq.) dropwise over 5 min. The reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10 mL) and the organic components extracted with EtOAc (3 × 10 mL). The combined organic phase was washed successively with sat. NH_4Cl (aq.) (2 × 10 mL), sat. $NaHSO_3$ (aq.) (2 × 10 mL), water (2 × 10 mL) and brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 PE/EtOAc) to furnish the *title compound* **196** (0.0110 g, 28%) as a yellow oil: R_f 0.51 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3046 (aromatic C-H stretch), 2963 (C-H stretch), 2919 (C-H stretch), 1665 (C=O stretch),

1529 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.52-7.46 (5 H, m, H-14, 15, 16), 6.81 (1 H, d, *J* 11.0, H-12), 6.17 (1 H, dd, *J* 11.0, 6.0, H-11), 6.07 (1 H, d, *J* 6.0, H-9), 5.62 (1 H, app. t, *J* 6.0, H-10), 3.92-3.88 (2 H, m, H-17), 1.63 (2 H, m, H-18), 0.76 (3 H, t, *J* 7.5, H-19). Data consistent with those previously reported.[35]

Lab. Book: RD01/029/C1, RD01/041/A1

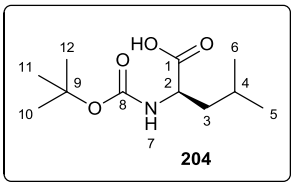
2-Phenyl-3-propyl-5,6,7,8-tetrahydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 203



To a solution of dihydro-oxepine **197** (0.0520 g, 0.180 mmol, 1.0 eq.) in EtOAc (5 mL) was added 10% Pd/C (0.0050 g, 0.0050 mmol, 2.5 mol%). The reaction mixture was placed under an atmosphere of hydrogen and stirred at room temperature for 1 h before being filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1:1 *n*-hexane/EtOAc) to furnish the *title compound* **203** (0.0380 g, 74%) as colourless needles: mp 103-104 °C; *Rf* 0.33 (1:1 *n*-hexane/EtOAc); Found: C, 71.55; H, 7.07; N, 9.79; $C_{17}H_{20}N_2O_2$ requires: C, 71.81; H, 7.09; N, 9.85%; υ_{max}/cm^{-1} 2963 (C-H stretch), 1650 (C=O stretch), 1586 (aromatic C=C stretch), 1542 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.48-7.43 (5 H, m, H-8, 9, 10), 4.35-4.32 (2 H, m, H-15), 3.87-3.83 (2 H, m, H-11), 2.82-2.79 (2 H, m, H-18), 2.04-1.98 (2 H, m, H-16), 1.93-1.87 (2 H, m, H-17), 1.61 (2 H, app. sext. (tq), *J* 7.5, H-12); 0.75 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 167.8 (C-4), 164.8 (C-6), 157.2 (C-2), 134.6 (C-7), 129.9 (C-10), 128.5 (C-9), 127.7 (C-8), 107.4 (C-5), 71.4 (C-15), 47.8 (C-11), 29.2 (C-16), 23.9 (C-17), 22.5 (C-18), 22.0 (C-12), 11.0 (C-13); *m/z* (ESI) 285 $[MH]^+$. Calcd. for $C_{17}H_{21}N_2O_2$: 285.1598. Found: $[MH]^+$, 285.1600 (0.2 ppm error). X-Ray crystallography: CCDC 862141 contains the supplementary crystallographic data for this compound, see Appendix **V**. Crystals were grown by slow diffusion (*n*-hexane/EtOAc).

Lab. Book: RD07/027/C1

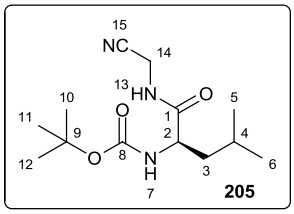
***N*-(*tert*-Butoxycarbonyl)-D-leucine 204**



D-Leucine **38** (9.45 g, 72.0 mmol, 1.0 eq.) and $NaHCO_3$ (6.05 g, 72.0 mmol, 1.0 eq.) were suspended in water (200 mL) and 1,4-dioxane (100 mL). Aqueous NaOH solution (2 M, 36 mL) was added to obtain a solution which was cooled to 0 °C (ice) before di-*tert*-butyl dicarbonate (20.5 g, 94.0 mmol, 1.3 eq.) was added. The reaction mixture was allowed to warm to room temperature with stirring over 16 h. After concentration *in vacuo* to half the volume, the solution was cooled to 0 °C (ice) and carefully acidified to pH 1 using 3 M HCl (aq.). The resulting white precipitate was extracted with EtOAc (3 × 100 mL) and the combined organic phase washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish the *title compound* **204** (16.4 g, 98%) as a colourless viscous oil which was used without further purification: R_f 0.18 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3323 (broad, O-H stretch), 2962 (C-H stretch), 1712 (broad, C=O stretch), 1517 (N-H bend); $[\alpha]_D^{24}$ +21 (*c* = 1.02, MeOH); δ_H (400 MHz, $CDCl_3$) 4.86 (1 H, d, *J* 8.0, H-7), 4.32-4.28 (1 H, m, H-2), 1.78-1.64 (2 H, m, H-3), 1.57-1.50 (1 H, m, H-4), 1.45 (9 H, s, H-10, 11, 12), 0.95 (6 H, d, *J* 6.0, H-5, 6). Data are consistent with those in the literature.[186, 187]

Lab. Book: RD03/040/A1

***N*^{2}-(*tert*-Butoxycarbonyl)-*N*-(cyanomethyl)-D-leucinamide 205**

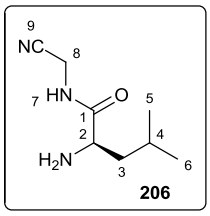


A solution of *N*-Boc-D-leucine **204** (16.4 g, 71.0 mmol, 1.0 eq.) in THF (250 mL) was cooled to –25 °C (CO_2/MeOH bath). *N*-Methyl morpholine (7.89 g, 78.0 mmol, 1.1 eq.) and *iso*-butylchloroformate (10.7 g, 78.0 mmol, 1.1 eq.) were added successively. A white precipitate formed immediately. After stirring for 15 min, solutions of aminoacetonitrile bisulfate (12.0 g, 78.0 mmol, 1.1 eq.) in water (15 mL) followed by 1 M aqueous NaOH (100 mL), pre-cooled to 0 °C (ice), were added. The reaction mixture was warmed to room temperature and stirred for 18 h. After concentration *in vacuo* to remove THF, the resulting aqueous solution was extracted with EtOAc (3 × 250 mL). The combined organic phase was washed with water (250 mL), sat. $NaHCO_3$ (aq.) (250 mL), brine (250 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a colourless oil, which solidified under vacuum. The crude product was suspended in PE and the *title compound* **205** (14.3 g, 75 %) isolated by filtration as colourless needles: mp 112–114 °C (Lit.[2] 114 – 116 °C); R_f 0.40 (1:1

PE/EtOAc); (Found: C, 57.9; H, 8.5; N, 15.5; $C_{13}H_{23}N_3O_3$ requires C, 57.9; H, 8.6; N, 15.6); $[\alpha]_D^{22}$ +26 (*c* = 0.99, MeOH); δ_H (400 MHz, $CDCl_3$) 7.34 (1 H, br s, H-7), 5.03 (1 H, d, *J* 5.5, H-13), 4.15 (2 H, d, *J* 5.5, H-14), 4.16-4.14 (1 H, m, H-2), 1.67-1.62 (2 H, m, H-3), 1.56-1.49 (1 H, m, H-4), 1.45 (9 H, s, H-10, 11, 12), 0.94 (3 H, d, *J* 6.0, H-5/6), 0.92 (3 H, d, *J* 6.0, H-5/6). Data are consistent with those reported in the literature.[188]

Lab. Book: RD03/055/C1

N-(Cyanomethyl)-D-leucinamide 206

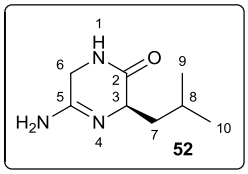


206

N^2-(*tert*-Butoxycarbonyl)-*N*-(cyanomethyl)-D-leucinamide **205** (14.1 g, 53.0 mmol, 1.0 eq.) was taken up in formic acid (neat, 150 mL) and stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* to furnish a colourless oil which was taken up in MeOH/aq. NH_3 (9:1) to neutralise, concentrated *in vacuo* and purified by flash column chromatography on silica gel (85:14:1 DCM/MeOH/aqueous NH_3) to furnish the *title compound* **206** (8.77 g, 98%) as a colourless oil: R_f 0.27 (90:9:1 DCM/MeOH/aqueous NH_3); υ_{max}/cm^{-1} (neat) 3358 (N-H stretch), 2958 (C-H stretch), 1660 (C=O stretch), 1525 (N-H bend); $[\alpha]_D^{22}$ –4 (*c* = 1.03, MeOH); δ_H (400 MHz, MeOD) 4.17 (1 H, d, *J* 17.5, H-8a), 4.16 (1 H, d, *J* 17.5, H-8b), 3.37-3.34 (1 H, m, H-2), 1.71 (1 H, tsept., *J* 8.0, 6.5, H-4), 1.53 (1 H, ddd, *J* 14.0, 8.0, 6.0, H-3a), 1.40 (1 H, ddd, *J* 14.0, 8.0, 6.0, H-3b), 0.96 (3 H, d, *J* 6.5, H-5/6), 0.93 (3 H, d, *J* 6.5, H-5/6); δ_C (100 MHz, MeOD) 178.6 (C-1), 117.6 (C-9), 54.4 (C-2), 45.5 (C-8), 27.9 (C-3), 25.8 (C-4), 23.4 (C-5/6), 22.4 (C-5/6); *m/z* (ESI) 170 $[MH]^+$. Calcd. for $C_8H_{16}N_3O$: 170.1288. Found: $[MH]^+$ 170.1286 (1.5 ppm error). Data are consistent with those in the literature.[189]

Lab. Book: RD03/061/B1

(3*R*)-5-Amino-3-*iso*-butyl-3,6-dihydropyrazin-2(1*H*)-one 52



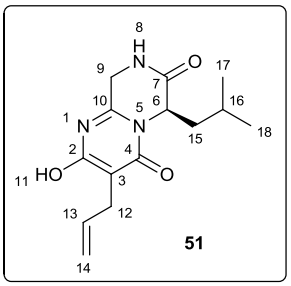
52

To a solution of *N*-(cyanomethyl)-D-leucinamide **206** (9.97 g, 59.0 mmol, 1.0 eq.) in MeOH (200 mL) was added hydroxylamine (4.52 mL, 50% w/w solution in water, 73.0 mmol, 1.25 eq.). After stirring at room temperature for 4 h, Raney® 2800 Nickel (slurry in water) (~ 5 g) was added and the reaction mixture placed under an atmosphere of hydrogen. After stirring at room temperature for 3 h the reaction mixture

was filtered through Celite® with MeOH washing and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (55:42:3 DCM/MeOH/aqueous NH_3) to furnish the *title compound* **52** (8.10 g, 81%) as a pale yellow solid: mp 94-96 °C; R_f 0.21 (80:19:1 DCM/MeOH/aqueous NH_3); υ_{max}/cm^{-1} (neat) 3333 (N-H stretch), 3201 (N-H stretch), 2953 (C-H stretch), 1660 (C=O stretch); $[\alpha]_D^{22}$ –47 (*c* = 1.00, MeOH); δ_H (400 MHz, DMSO *d*-6) 7.77 (1 H, br s, H-1), 3.78 (1 H, dd, *J* 16.5, 1.0, H-6a), 3.71 (1 H, dd, *J* 16.5, 1.0, H-6b), 3.58 (1 H, dd, *J* 9.5, 5.0, H-3), 1.88-1.78 (1 H, m, H-8), 1.47 (1 H, ddd, *J* 13.5, 8.5, 5.0, H-7a), 1.33 (1 H, ddd, *J* 13.5, 9.5, 5.5, H-7b), 0.87 (3 H, d, *J* 7.5, H-9/10), 0.85 (3 H, d, *J* 7.5, H-9/10); δ_C (100 MHz, DMSO *d*-6) 172.2 (C-2), 156.1 (C-5), 56.3 (C-3), 42.3 (C-7), 41.3 (C-6), 23.9 (C-8), 23.3 (C-9/10), 21.6 (C-9/10); *m/z* (ESI) 170 $[MH]^+$. Calcd. for $C_8H_{16}N_3O$: 170.1288. Found: $[MH]^+$, 170.1288 (0.7 ppm error).

Lab. Book: RD03/064/C1

(6*R)-3-Allyl-2-hydroxy-6-*iso*-butyl-8,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidine-4,7(6*H*)-dione 51**



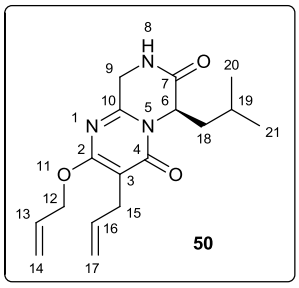
51

A solution of NaOMe was prepared by the portionwise addition of Na (6.66 g, 290 mmol, 6.0 eq.) to rigorously dried MeOH (100 mL) containing activated, powdered 3 Å molecular sieves (20.0 g, 0.500 g/mmol). An exotherm occurred. Once the Na had completely reacted the solution was cooled to room temperature and dimethyl 2-allylmalonate **201** (11.6 mL, 72.0 mmol, 1.5 eq.) followed by a solution of amidine **5** (8.10 g, 47.0 mmol, 1.0 eq.) in MeOH (40 mL) were added. The reaction mixture was heated at reflux for 3 h. After cooling to room temperature the reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (70:28:2 DCM/MeOH/aqueous NH_3) before recrystallisation from MeOH afforded the *title compound* **51** (9.38 g, 72%) as pale yellow needles: mp 240-242 °C; R_f 0.33 (70:28:2 DCM/MeOH/aqueous NH_3); υ_{max}/cm^{-1} (neat) 3211 (broad, O-H/N-H stretch), 2916 (C-H stretch), 1667 (C=O stretch), 1644 (C=O stretch), 1547 (C=C stretch); $[\alpha]_D^{22}$ +0.5 (*c* = 1.01, MeOH); δ_H (400 MHz, DMSO *d*-6) 11.50 (1 H, br s, H-11), 8.50 (1 H, d, *J* 5.0, H-8), 5.75 (1 H, ddt, *J* 16.0, 10.0, 6.0, H-13), 4.94-4.84 (3 H, m, H-6, 14), 6.67 (1 H, d, *J* 17.5, H-9a), 3.97 (1 H, dd, *J* 17.5, 5.0, H-9b), 2.99 (2 H, d, *J* 6.0, H-12), 1.72-1.57 (2 H, m, H-15a, 16), 1.44 (1 H, ddd, *J*

12.5, 8.0, 6.5, H-15b), 0.92 (3 H, d, *J* 6.5, H-17/18), 0.87 (3 H, d, *J* 6.5, H-17/18); δ_C (100 MHz, DMSO *d*-6) 167.7 (C-4/7), 164.4 (C-4/7), 161.1 (C-2), 152.0 (C-3/10), 135.3 (C-14), 97.5 (C-3/10), 53.5 (C-6), 43.5 (C-9), 39.5 (C-15), 26.9 (C-12), 24.4 (C-16), 22.1 (C-17/18), 21.6 (C-17/18); *m/z* (ESI) 278 $[MH]^+$. Calcd. for $C_{14}H_{20}N_3O_3$: 278.1499. Found: $[MH]^+$, 278.1500 (0.2 ppm error).

Lab. Book: RD05/094/C1

(6*R)-3-Allyl-2-(allyloxy)-6-*iso*-butyl-8,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidine-4, 7(6*H*)-dione 50**



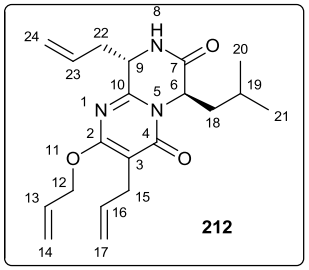
50

A suspension of pyrimidinone **51** (9.04 g, 33.0 mmol, 1.0 eq.) and PPh_3 (18.9 g, 72.0 mmol, 2.2 eq.) in THF (140 mL) was cooled to 0 °C (ice). To this was added allyl alcohol (5.83 mL, 86.0 mmol, 2.6 eq.), NEt_3 (4.59 mL, 33.0 mmol, 1.0 eq.) and DIAD (14.1 mL, 72.0 mmol, 2.2 eq.). The reaction mixture was allowed to warm to room temperature over 15 min before heating to 65 °C for 2 h. After cooling to room temperature, a 5% aq. HCl solution (180 mL) was added and the organic phase separated. The aqueous phase was further extracted with EtOAc (2 × 180 mL). The combined organic phase was washed with brine (180 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The $PPh_3(O)$ side product was removed by crystallisation from PE/EtOAc (3:2) and filtration. The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel (1:1 PE/EtOAc) to give the *title compound* **50** (7.70 g, 73%, *er* 53:47) as a pale yellow solid: mp 125-127 °C; R_f 0.23 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3230 (N-H stretch), 2959 (C-H stretch), 1666 (C=O stretch), 1602 (C=O stretch), 1542 (C=C stretch); $[\alpha]_D^{22}$ +1.0 (*c* = 1.01, MeOH); δ_H (400 MHz, $CDCl_3$) 7.48 (1 H, d, *J* 4.5, H-8), 5.99 (1 H, ddt, *J* 17.0, 10.5, 5.0, H-13), 5.89 (1 H, ddt, *J* 17.0, 10.0, 6.5, H-16), 5.40-5.33 (2 H, m, H-6, 14a), 5.24 (1 H, dd, *J* 10.5, 1.5, H-14b), 5.09 (1 H, dd, *J* 17.0, 1.5, H-17a), 4.99 (1 H, dd, *J* 10.0, 1.5, H-17b), 4.88-4.77 (2 H, m, H-12), 4.55 (1 H, d, *J* 17.5, H-9a), 4.33 (1 H, dd, *J* 17.5, 4.5, H-9b), 3.25 (2 H, d, *J* 6.5, H-15), 1.87-1.80 (1 H, m, H-19), 1.74 (1 H, ddd, *J* 14.0, 9.0, 6.0, H-18a), 1.65 (1 H, ddd, *J* 14.0, 9.0, 6.0, H-18b), 1.09 (3 H, d, *J* 6.5, H-20/21), 0.99 (3 H, d, *J* 6.5, H-20/21); δ_C (100 MHz, $CDCl_3$) 169.8 (C-4/7), 163.9 (C-4/7), 161.6 (C-2), 150.4 (C-10), 134.6 (C-16), 132.9 (C-13), 117.4 (C-14), 115.1 (C-17), 102.1 (C-3), 67.3 (C-12), 53.9 (C-6), 44.7 (C-9), 40.4 (C-15), 27.1 (C-18), 24.6 (C-19), 23.1 (C-20/21), 21.5 (C-20/21); *m/z* (ESI) 318 $[MH]^+$. Calcd. for

$C_{17}H_{23}N_3NaO_3$: 340.1632. Found: $[MNa]^+$, 340.1629 (0.7 ppm error); HPLC: Chiralpak AD-H (90:10 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 4.99 min (52.96%), 5.84 min (47.04%).

Lab. Book: RD05/096/C1

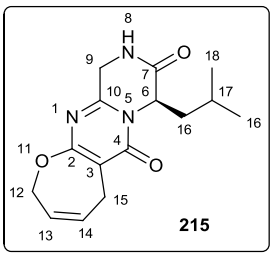
(6*R,9*S**)-3,9-Diallyl-2-(allyloxy)-6-*iso*-butyl-8,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidine-4,7(6*H*)-dione 212**



To a solution of pyrimidinone **51** (1.64 g, 5.90 mmol, 1.0 eq.) and K_2CO_3 (1.02 g, 7.40 mmol, 1.25 eq.) in acetone (30 mL) was added allyl bromide (0.89 g, 7.40 mmol, 1.25 eq.). The reaction mixture was heated at reflux for 16 h, cooled to room temperature, filtered through Celite® and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel (4:1 PE/EtOAc) to furnish diallyl pyrimidinone **50** (0.700 g, 35%) and the *title compound* **212** (0.140 g, 7%) as a pale yellow solid: mp 124-126 ^oC; R_f 0.43 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3247 (N-H stretch), 2958 (C-H stretch), 1676 (C=O stretch), 1442 (C=C stretch), 1398 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.94 (1 H, d, *J* 5.0, H-8), 5.71 (1 H, ddt, *J* 17.0, 10.5, 5.5, H-13), 5.58 (2 H, m, H-16, 23), 5.48 (1 H, d, *J* 5.0, H-9), 5.19-5.24 (3 H, m, H-6, 14), 4.98-5.15 (4 H, m, H-17, 24), 4.34 (2 H, d, *J* 5.5, H-12), 2.72 (2 H, m, H-15), 2.52 (2 H, d, *J* 7.5, H-22), 1.54-1.43 (3 H, m, H-19, 18), 0.92 (3 H, d, *J* 6.5, H-20/21), 0.91 (3 H, d, *J* 6.5, H-20/21); δ_C (100 MHz, $CDCl_3$) 167.4 (C-4/7), 167.1 (C-4/7), 166.5 (C-2), 132.6 (C-16/23), 131.4 (C-13), 130.8 (C-16/23), 120.5 (C-10), 120.1 (C-17/24), 119.5 (C-17/24), 117.7 (C-14), 95.7 (C-9), 56.7 (C-3), 52.6 (C-6), 45.9 (C-12), 42.9 (C-22), 39.6 (C-15), 38.9 (C-18), 23.9 (C-19), 22.7 (C-20/21), 22.0 (C-20/21); *m/z* (ESI) 358 $[MH]^+$. Calcd. for $C_{20}H_{28}N_3O_3$: 358.2125. Found: $[MH]^+$, 358.2121 (1.0 ppm error).

Lab. Book: RD03/072/B2

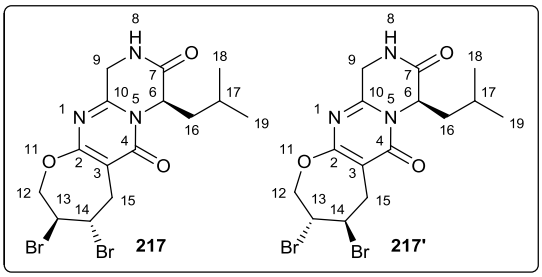
(8*R)-8-*iso*-Butyl-2,5,10,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione 215**



To a solution of diallyl pyrimidindione **50** (0.318 g, 1.00 mmol, 1.0 eq.) in degassed anhydrous DCM (400 mL) under an inert atmosphere was added a solution of Grubbs second generation catalyst **x** (0.0840 g, 0.100 mmol, 0.1 eq.) in degassed anhydrous DCM (20 mL) dropwise over 15 min in two 10 mL batches separated by 1 h. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, directly loaded onto a column of silica gel and purified by flash column chromatography (EtOAc). The *title compound* **215** (0.263 g, 91%) was isolated as an off-white solid: mp 159-160 °C decomposed; R_f 0.22 (EtOAc); υ_{max}/cm^{-1} (neat) 3258 (broad, N-H stretch), 2959 (C-H stretch), 1663 (C=O stretch), 1605 (C=O stretch), 1552 (C=C stretch); $[\alpha]_D^{23}$ -13 (1.01 gdL^{-1}, MeOH); δ_H (400 MHz, $CDCl_3$) 6.79 (1 H, d, *J* 5.0, H-8), 6.25 (1 H, dt, *J* 10.0, 6.0, H-14), 6.08-6.02 (1 H, m, H-13), 5.29 (1 H, ddd, *J* 9.0, 6.0, 1.0, H-6), 4.84 (1 H, dd, *J* 13.5, 6.5, H-12a), 4.77 (1 H, dd, *J* 13.5, 6.5, H-12b), 4.53 (1 H, d, *J* 17.0, H-9a), 4.30 (1 H, dd, *J* 17.0, 5.0, H-9b), 3.49 (2 H, d, *J* 6.0, H-15), 1.85-1.79 (1 H, m, H-17), 1.72 (1 H, ddd, *J* 13.5, 9.0, 6.0, H-16a), 1.61 (1 H, ddd, *J* 13.5, 9.0, 6.0, H-16b), 1.09 (3 H, d, *J* 6.5, H-18/19), 0.98 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 168.5 (C-4/7), 166.3 (C-4/7), 162.2 (C-2), 150.2 (C-10), 135.0 (C-14), 126.6 (C-13), 102.7 (C-3), 65.6 (C-12), 54.3 (C-6), 44.4 (C-9), 40.4 (C-16), 24.8 (C-17), 23.0 (C-18/19), 22.4 (C-15), 21.6 (C-18/19); *m/z* (ESI) 290 $[MH]^+$. Calcd. for $C_{15}H_{20}N_3O_3$: 290.1505. Found: $[MH]^+$, 290.1499 (2.2 ppm error). X-Ray crystallography: CCDC 848129 contains supplementary crystallographic data for this compound, see Appendix **V**. Crystals were grown by slow diffusion (DCM/*n*-hexane).

Lab. Book: RD03/074/B1

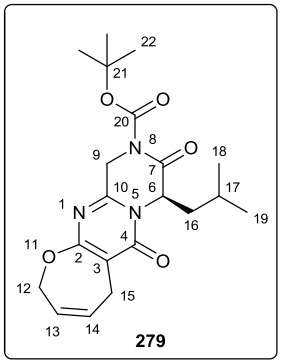
(3*S,4*S**,8*R**)-3,4-Dibromo-8-*iso*-butyl-2,3,4,5,10,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione 217**



To a solution of dihydro-oxepine **215** (0.0970 g, 0.330 mmol, 1.0 eq.) in DCM (5 mL) at room temperature was added pyridine hydrotribromide (0.113 g, 0.350 mmol, 1.05 eq.). The reaction mixture was stirred at room temperature for 1.5 h, quenched by the addition of sat. $NaHSO_3$ (aq.) (10 mL) and extracted with DCM (2 × 10 mL). The combined organic phase was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the *title compound* **217** (0.126 g, 85%) as a brown solid (1:1 mixture of diastereomers) which was used without further purification: mp 127-129 °C; R_f 0.36 (EtOAc); υ_{max}/cm^{-1} (neat) 3244 (broad, N-H stretch), 2960 (C-H stretch), 1665 (C=O stretch), 1602 (C=O stretch), 1555 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.60 (2 H, br s, H-8, 8'), 5.37-5.26 (2 H, m, H-6, 6'), 4.69-4.34 (12 H, m, H-9, 9', 12, 12', 13, 13', 14, 14'), 3.53-3.45 (4 H, m, H-15, 15'), 1.86-1.69 (4 H, m, H-17, 17'), 1.67-1.55 (4 H, m, H-16, 16'), 1.11-1.06 (6 H, m, H-18/19, 18'/19'), 1.00-0.98 (6 H, m, H-18/19, 18'/19'); δ_C (100 MHz, $CDCl_3$) 169.1 (C-4/7), 168.9 (C-4'/7'), 167.7 (C-4/7), 167.6 (C-4'/7'), 163.6 (C-2), 162.1 (C-2'), 152.7 (C-10), 151.4 (C-10'), 105.0 (C-3), 104.8 (C-3'), 70.5 (C-12), 70.4 (C-12'), 54.4 (C-6), 54.2 (C-6'), 53.7 (C-13/14), 52.9 (C-13'/14'), 52.6 (C-13/14), 49.7 (C-13'/14'), 44.4 (C-9), 44.3 (C-9'), 40.1 (C-16), 40.0 (C-16'), 27.4 (C-15), 27.1 (C-15'), 24.6 (d, C-17, 17'), 22.8 (C-18/19), 21.6 (C-18'/19'), 21.5 (C-18/19), 21.3 (C-18'/19'); *m/z* (ESI) 447 $[MH]^+$. Calcd. for $C_{15}H_{20}{}^{79}Br_2N_3O_3$: 447.9871. Found: $[MH]^+$, 447.9866 (0.3 ppm error).

Lab. Book: RD04/010/B1

tert-Butyl (8_R_*)-8-_iso_-butyl-6,9-dioxo-2,5,6,8,9,11-hexahydro-10_H_-oxepino[2,3-_d_]pyrazino[1,2-_a_]pyrimidine-10-carboxylate 279

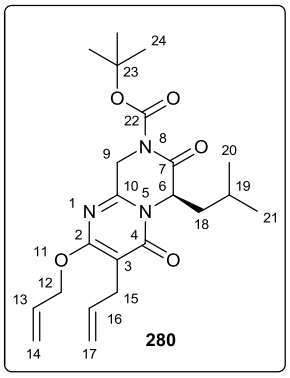


279

To a solution of dihydro-oxepine **215** (0.0680 g, 0.240 mmol, 1.0 eq.) in THF (3.5 mL) was added NEt_3 (0.0330 mL, 0.240 mmol, 1.0 eq.), Boc_2O (0.0630 g, 0.290 mmol, 1.2 eq.) and DMAP (0.0030 g, 0.0200 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 30 min before the addition of water (10 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with sat. NH_4Cl (aq.) (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (7:3 PE/EtOAc) to furnish the *title compound* **279** (0.0470 g, 50%) as a pale yellow film: R_f 0.71 (EtOAc); υ_{max}/cm^{-1} (neat) 2961 (C-H stretch), 1781 (C=O stretch), 1733 (C=O stretch), 1663 (C=O stretch), 1607 (C=C stretch), 1551 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.26 (1 H, dt, *J* 10.0, 6.0, H-14), 6.07 (1 H, app. dt (ddd), *J* 10.0, 6.5, H-13), 5.44 (1 H, dd, *J* 9.0, 6.5, H-6), 5.09 (1 H, d, *J* 17.0, H-9a), 4.82 (1 H, dd, *J* 13.5, 6.5, H-12a), 4.75 (1 H, dd, *J* 13.5, 6.5, H-12b), 4.54 (1 H, d, *J* 17.0, H-9b), 3.49 (2 H, d, *J* 6.0, H-15), 1.83-1.75 (2 H, m, H-16a, 17), 1.69-1.55 (1 H, m, H-16b), 1.53 (9 H, s, H-22), 1.08 (3 H, d, *J* 6.5, H-18/19), 1.01 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 166.5 (C-4/7), 165.5 (C-4/7), 161.8 (C-2), 149.9 (C-20), 149.7 (C-10), 134.9 (C-14), 126.6 (C-13), 103.2 (C-3), 85.2 (C-21), 65.7 (C-12), 55.8 (C-6), 46.8 (C-9), 40.3 (C-12), 27.8 (C-22, 23, 24), 24.8 (C-17), 22.8 (C-18/19), 22.3 (C-15), 21.6 (C-18/19); *m/z* (ESI) 390 $[MH]^+$. Calcd. for $C_{20}H_{28}N_3O_5$: 390.2023. Found: $[MH]^+$, 390.2031 (1.7 ppm error).

Lab. Book: RD03/095/C1

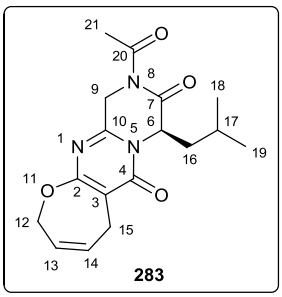
***tert*-Butyl (6*R**)-3-allyl-2-(allyloxy)-6-*iso*-butyl-4,7-dioxo-4,6,7,9-tetrahydro-8*H*-pyrazino[1,2-*a*]pyrimidine-8-carboxylate 280**



To a solution of diallyl pyrimidinone **50** (0.100 g, 0.310 mmol, 1.0 eq.) in THF (5 mL) was added NEt_3 (0.0430 mL, 0.310 mmol, 1.0 eq.), Boc_2O (0.137 g, 0.630 mmol, 2.0 eq.) and DMAP (0.0040 g, 0.0300 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 2 h before being quenched by the addition of water (10 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with sat. NH_4Cl (aq.) (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (17:3 PE/EtOAc) to furnish the *title compound* **280** (0.128 g, 98%) as a colourless oil: R_f 0.73 (EtOAc); υ_{max}/cm^{-1} (neat) 2961 (C-H stretch), 1783 (C=O stretch), 1733 (C=O stretch), 1669 (C=O stretch), 1606 (C=C stretch), 1544 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.00 (1 H, ddt, *J* 17.0, 10.5, 5.5, H-13), 5.87 (1 H, ddt, *J* 16.5, 10.0, 6.5, H-16), 5.51 (1 H, dd, *J* 9.0, 6.5, H-6), 5.38 (1 H, dd, *J* 17.0, 1.5, H-14a), 5.24 (1 H, dd, *J* 10.5, 1.5, H-14b), 5.08 (1 H, dd, *J* 16.5, 1.5, H-17a), 5.08 (1 H, d, *J* 17.0, H-9a), 4.98 (1 H, dd, *J* 10.0, 1.5, H-17b), 4.89-4.79 (2 H, m, H-12), 4.54 (1 H, d, *J* 17.0, H-9b), 3.23 (2 H, d, *J* 6.5, H-15), 1.83-1.73 (2 H, m, H-18a, 19), 1.66-1.60 (1 H, m, H-18b), 1.57 (9 H, s, H-24), 1.08 (3 H, d, *J* 6.5, H-20/21), 0.99 (3 H, d, *J* 6.5, H-20/21); δ_C (100 MHz, $CDCl_3$) 165.5 (C-4/7), 164.0 (C-4/7), 161.2 (C-2), 150.1 (C-22), 150.0 (C-10), 134.5 (C-16), 132.9 (C-13), 117.5 (C-14), 115.3 (C-17), 102.7 (C-3), 85.2 (C-23), 67.5 (C-12), 55.6 (C-6), 46.9 (C-9), 40.3 (C-18), 27.9 (C-24, 25, 26), 27.1 (C-15), 24.9 (C-19), 22.9 (C-20/21), 21.6 (C-20/21); *m/z* (ESI) 418 $[MH]^+$. Calcd. for $C_{22}H_{32}N_3O_5$: 418.2336. Found: $[MH]^+$, 418.2336 (0.7 ppm error).

Lab. Book: RD04/035/C1

(8*R)-10-Acetyl-8-*iso*-butyl-2,5,10,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione 283**



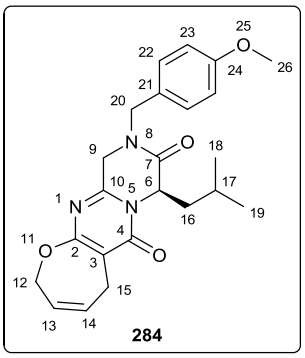
283

To a solution of dihydro-oxepine **215** (0.0770 g, 0.270 mmol, 1.0 eq.) in DCM (1.5 mL) was added NEt_3 (0.300 mL, 2.14 mmol, 8.0 eq.), acetyl chloride (0.152 mL, 2.14 mmol, 8.0 eq.) and DMAP (0.0060 g, 0.0500 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 4 h before being quenched by the addition of water (5 mL). The organic phase was separated and the aqueous phase extracted with DCM (2 × 10 mL). The combined organic phase was washed with sat. NH_4Cl (aq.) (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (3:2 *n*-hexane/EtOAc) to furnish the *title compound* **283** (0.0530 g, 59%) as a pale yellow film: R_f 0.57 (EtOAc); υ_{max}/cm^{-1} (neat) 2961 (C-H stretch), 1717 (C=O stretch), 1662 (C=O stretch), 1607 (C=C stretch), 1551 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.24 (1 H, dt, *J* 10.0, 6.0, H-14), 6.08-6.03 (1 H, m, H-13), 5.48 (1 H, dd, *J* 9.0, 6.0, H-6), 5.40 (1 H, d, *J* 17.5, H-9a), 4.84 (1 H, dd, *J* 13.5, 6.5, H-12a), 4.76 (1 H, dd, *J* 13.5, 6.5, H-12b), 4.34 (1 H, d, *J* 17.5, H-9b), 3.47 (2 H, d, *J* 6.0, H-15), 2.59 (3 H, s, H-21), 1.81-1.70 (2 H, m, H-16a, 17), 1.66-1.63 (1 H, m, H-16b), 1.08 (3 H, d, *J* 6.0, H-18/19), 1.00 (3 H, d, *J* 6.0, H-18/19); δ_C (100 MHz, $CDCl_3$) 171.3 (C-20), 167.5 (C-4/7), 166.6 (C-4/7), 161.7 (C-2), 150.0 (C-10), 134.9 (C-14), 126.6 (C-13), 103.1 (C-3), 65.6 (C-12), 55.8 (C-6), 44.4 (C-9), 40.2 (C-16), 27.0 (C-21), 24.8 (C-17), 22.7 (C-18/19), 22.2 (C-15), 21.5 (C-18/19); *m/z* (ESI) 332 $[MH]^+$. Calcd. for $C_{17}H_{22}N_3O_4$: 332.1605. Found: $[MH]^+$, 332.1606 (0.2 ppm error).

Lab. Book: RD04/063/C1

(8*R)-8-*iso*-Butyl-10-(4-methoxybenzyl)-2,5,10,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione 284**

- *N*-Substitution of Dihydro-Oxepine **215**:



284

A solution of dihydro-oxepine **215** (0.304 g, 1.05 mmol, 1.0 eq.) in THF (3.5 mL) was cooled to 0 °C (ice). To this was added NaH (0.046 g, 60% dispersion in mineral oil, 2.26 mmol, 1.1 eq.). The reaction mixture was stirred at 0 °C (ice) for 10 min before the addition of *para*-methoxy benzyl bromide (0.169 mL, 1.16 mmol, 1.1 eq.) and TBAI (0.428 g, 1.16 mmol, 1.1 eq.). After stirring at 0 °C for 2 h the reaction mixture was quenched by the addition of water (10 mL). The organic phase was separated and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (1:1 EtOAc/*n*-hexane) to furnish the *title compound* **284** (0.219 g, 51%) as a pale yellow waxy solid.

Lab. Book: RD05/025/C1

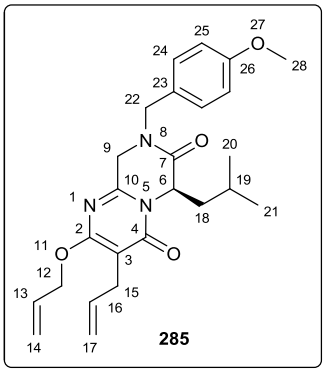
- Alternatively: RCM of *N*-PMB-Diallyl Pyrimidindione **285**:

To a refluxing solution of *N*-PMB-diallyl pyrimidindione **285** (0.437 g, 1.00 mmol, 1.0 eq.) in degassed anhydrous DCM (400 mL) under an inert atmosphere was added a solution of Hoveyda-Grubbs second generation catalyst **x** (0.0630 g, 0.100 mmol, 0.1 eq.) in degassed anhydrous DCM (20 mL) in two batches separated by 1 h, dropwise over 15 min. The reaction mixture was heated at reflux for 18 h before cooling to room temperature, direct loading onto a column of silica gel and purification by flash column chromatography (9:1 DCM/Et_2O). The *title compound* **284** (0.305 g, 74%) was isolated as a pale yellow waxy solid: R_f 0.25 (9:1 DCM/Et_2O); υ_{max}/cm^{-1} (neat) 2958 (C-H stretch), 1664 (broad, C=O stretch), 1608 (C=C stretch), 1552 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.17 (2 H, d, *J* 8.5, H-22), 6.86 (2 H, d, *J* 8.5, H-23), 6.24 (1 H, dt, *J* 10.0, 6.0, H-14), 6.06-6.00 (1 H, m, H-13), 5.37 (1 H, dd, *J* 9.0, 6.0, H-6), 4.77 (2 H, 2 × dd (overlapping), *J* 13.5, 6.5, H-12), 4.68 (1 H, d, *J* 14.5, H-20a), 4.49 (1 H, d, *J* 14.5, H-20b), 4.34 (1 H, d, *J* 17.5, H-9a), 4.11 (1 H, d, *J* 17.5, H-9b), 3.80 (3 H, s, H-26), 3.48 (2 H, d, *J* 6.0, H-15), 1.87-1.77 (1 H, m, H-17), 1.68-1.54 (2 H, m, H-16), 1.08 (3 H, d, *J* 6.5, H-18/19), 0.98 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 166.3 (C-4/7), 166.1 (C-4/7), 161.9 (C-2), 159.5 (C-24), 150.1 (C-10), 135.0 (C-14), 129.7 (C-22),

127.0 (C-21), 126.6 (C-13), 114.4 (C-23), 102.8 (C-3), 65.6 (C-12), 55.2 (C-26), 54.6 (C-6), 48.8 (C-20), 48.2 (C-9), 40.6 (C-16), 24.8 (C-17), 23.0 (C-15), 22.3 (C-18/19), 21.7 (C-18/19); *m/z* (ESI) 410 $[MH]^+$. Calcd. for $C_{23}H_{28}N_3O_4$: 410.2074. Found: $[MH]^+$, 410.2065 (2.7 ppm error).

Lab. Book: RD05/031/B1

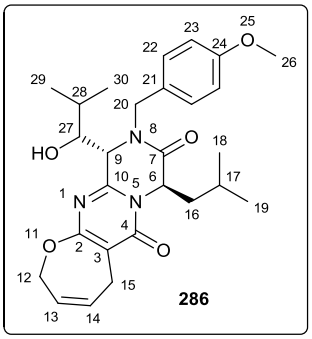
(6*R)-3-Allyl-2-(allyloxy)-6-*iso*-Butyl-8-(4-methoxybenzyl)-8,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidine-4,7(6*H*)-dione 285**



A solution of diallyl pyrimidindione **50** (1.00 g, 3.14 mmol, 1.0 eq.) in THF (20 mL) was cooled to 0 °C (ice). To this was added NaH (0.138 g, 60% dispersion in mineral oil, 3.46 mmol, 1.1 eq.). The reaction mixture was stirred at 0 °C for 10 min before the addition of *para*-methoxy benzyl bromide (0.504 mL, 3.46 mmol, 1.1 eq.) and TBAI (1.27 g, 3.46 mmol, 1.1 eq.). Following stirring at 0 °C for 2 h the reaction mixture was quenched by the addition of sat. NH_4Cl (aq.) (10 mL). The organic phase was separated and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (1:4 EtOAc/*n*-hexane) to furnish the *title compound* **285** (1.17 g, 85%) as a pale yellow oil: R_f 0.64 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2958 (C-H stretch), 1667 (broad, C=O stretch), 1605 (C=C stretch), 1542 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.20 (2 H, d, *J* 8.5, H-24), 6.89 (2 H, d, *J* 8.5, H-25), 5.95 (1 H, ddt, *J* 15.0, 9.5, 5.0, H-13), 5.87 (1 H, ddt, *J* 16.5, 10.0, 6.5, H-16), 5.46 (1 H, dd, *J* 9.0, 6.0, H-6), 5.32 (1 H, dd, *J* 15.0, 1.5, H-14a), 5.21 (1 H, dd, *J* 9.5, 1.5, H-14b), 5.08 (1 H, dd, *J* 16.5, 1.5, H-17a), 4.97 (1 H, dd, *J* 10.0, 1.5, H-17b), 4.89 (1 H, d, *J* 14.5, H-22a), 4.80-4.71 (2 H, m, H-12), 4.37 (1 H, d, *J* 17.5, H-9a), 4.36 (1 H, d, *J* 14.5, H-22b), 4.11 (1 H, d, *J* 17.5, H-9b), 3.81 (3 H, s, H-27), 3.22 (2 H, d, *J* 6.5, H-15), 1.88-1.78 (1 H, m, H-19), 1.68-1.55 (2 H, m, H-18), 1.08 (3 H, d, *J* 6.5, H-20/21), 0.97 (3 H, d, *J* 6.5, H-20/21); δ_C (100 MHz, $CDCl_3$) 166.2 (C-4/7), 163.8 (C-4/7), 161.3 (C-2), 159.5 (C-26), 150.4 (C-10), 134.6 (C-16), 132.8 (C-13), 129.5 (C-24), 127.2 (C-23), 117.3 (C-14), 115.1 (C-17), 114.3 (C-25), 102.1 (C-3), 67.2 (C-12), 55.2 (C-27), 54.2 (C-6), 48.8 (C-22), 48.7 (C-9), 40.6 (C-18), 27.1 (C-15), 24.8 (C-19), 23.1 (C-20/21), 21.6 (C-20/21); *m/z* (ESI) 438 $[MH]^+$. Calcd. for $C_{25}H_{32}N_3O_4$: 438.2387. Found: $[MH]^+$, 438.2386 (1.2 ppm error).

Lab. Book: RD05/045/C1

(8*R,11*R**)-11-(1-Hydroxy-2-methylpropyl)-8-*iso*-butyl-10-(4-methoxybenzyl)-2,5,10,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione 286**

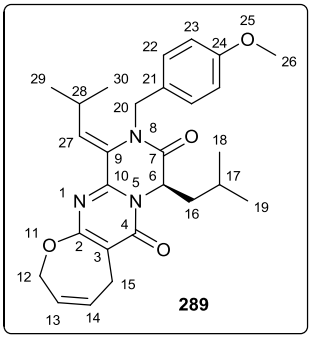


A solution of LiHMDS was prepared by the addition of *n*-BuLi (0.900 mL, 1.6 M solution in *n*-hexane, 1.44 mmol, 2.05 eq.) to a solution of HMDS (0.310 mL, 1.47 mmol, 2.1 eq.) in THF (1 mL) at 0 °C (ice). Following stirring at 0 °C for 20 min the solution was diluted with THF (4 mL) and cooled to –78 °C (CO_2/acetone). A solution of dihydro-oxepine **x** (0.288 g, 0.700 mmol, 1.0 eq.) in THF (4 mL) was then added dropwise over 5 min. The reaction mixture was stirred at –78 °C for 45 min before the addition of *iso*-butyraldehyde **221** (0.128 mL, 1.40 mmol, 2.0 eq.) and TMSCl (0.177 mL, 1.40 mmol, 2.0 eq.). Following stirring at –78 °C for 1 h the reaction mixture was quenched by the addition of TFA (0.5 mL) and water (2 mL) and allowed to warm to room temperature over 2 h. The reaction mixture was partitioned between EtOAc (15 mL) and water (10 mL) and the organic phase washed with water (3 × 10 mL), sat. $NaHCO_3$ (aq.) (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (3:2 *n*-hexane/EtOAc) to furnish the *title compound* **286** (0.136 g, 44%) as a pale yellow crystalline solid: mp 141-143 °C; R_f 0.26 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3422 (broad, O-H stretch), 2959 (C-H stretch), 1647 (C=O stretch), 1549 (C=C stretch), 1513 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.11 (2 H, d, *J* 8.5, H-22), 6.80 (2 H, d, *J* 8.5, H-23), 6.24 (1 H, dt, *J* 10.0, 6.0, H-14), 6.02 (1 H, dt, *J* 10.0, 6.5, H-13), 5.47 (1 H, d, *J* 15.0, H-20a), 5.16 (1 H, dd, *J* 10.0, 4.0, H-6), 4.74 (2 H, d, *J* 6.5, H-12), 4.35 (1 H, d, *J* 2.5, H-9), 3.77 (1 H, d, *J* 15.0, H-20b), 3.76 (3 H, s, H-26), 3.56 (1 H, ddd, *J* 8.5, 5.5, 2.5, H-27), 3.46 (2 H, d, *J* 6.0, H-15), 2.20-1.99 (3 H, m, H-16a, 17, 28), 1.69 (1 H, ddd, *J* 13.5, 9.5, 4.0, H-16b), 1.14 (3 H, d, *J* 6.5, H-18/19), 1.02 (3 H, d, *J* 6.5, H-18/19), 0.98 (3 H, d, *J* 6.5, H-29/30), 0.95 (3 H, d, *J* 6.5, H-29/30); δ_C (100 MHz, $CDCl_3$) 166.8 (C-4/7), 165.7 (C-4/7), 162.4 (C-2), 159.5 (C-24), 150.3 (C-10), 135.6 (C-14), 129.7 (C-22), 127.2 (C-21), 126.7 (C-13), 114.4 (C-23), 102.4 (C-3), 78.4 (C-27), 65.3 (C-12), 60.8 (C-9), 55.2 (C-26), 54.7 (C-6), 46.5 (C-20), 43.1 (C-16), 30.7 (C-17), 25.6 (C-28), 23.5 (C-18/19), 22.3 (C-15), 21.2 (C-18/19), 19.8

(C-29/30), 18.3 (C-29/30); *m/z* (ESI) 482 $[MH]^+$. Calcd. for $C_{27}H_{36}N_3O_5$: 482.2649. Found: $[MH]^+$, 482.2651 (0.4 ppm error).

Lab. Book: RD06/007/C1

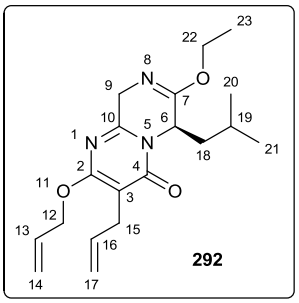
(8*R,11*Z*)-8-*iso*-Butyl-10-(4-methoxybenzyl)-11-(2-methylpropylidene)-2,5,10,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione 289**



To a solution of alcohol **286** (0.0600 g, 0.120 mmol, 1.0 eq.) in DCM (2.5 mL) was added NEt_3 (0.0430 mL, 0.310 mmol, 2.5 eq.), MsCl (0.0240 mL, 0.310 mmol, 2.5 eq.) and DMAP (0.001 g, cat.). The reaction mixture was stirred at room temperature for 5 h before the addition of sat. NH_4Cl (aq.) (10 mL). The organic phase was separated and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was taken in THF (2.5 mL) and to this was added *t*-BuOK (0.033 g, 0.31 mmol, 2.5 eq.). The reaction mixture was stirred at room temperature for 1 h before the addition of sat. NH_4Cl (aq.) (10 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (7:3 *n*-hexane/EtOAc) to furnish the *title compound* **289** (0.0120 g, 22%) as yellow film: R_f 0.45 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2969 (C-H stretch), 1691 (C=O stretch), 1650 (C=O stretch), 1588 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.08 (2 H, d, *J* 8.5, H-22), 6.78 (2 H, d, *J* 8.5, H-23), 6.23 (1 H, dt, *J* 10.0, 6.0, H-14), 6.17 (1 H, d, *J* 11.0, H-27), 6.03 (1 H, dt, *J* 10.0, 6.0, H-13), 5.42 (1 H, dd, *J* 9.0, 6.5, H-6), 5.17 (1 H, d, *J* 15.0, H-20a), 4.79 (2 H, d, *J* 6.0, H-12), 4.49 (1 H, d, *J* 15.0, H-20b), 3.76 (3 H, s, H-26), 3.47 (2 H, ddd, *J* 6.0, 4.0, 1.0, H-15), 2.77 (1 H, dsept., *J* 11.0, 6.5, H-28), 1.75-1.51 (3 H, m, H-16, 17), 1.14 (3 H, d, *J* 6.5, H-29/30), 1.04 (3 H, d, *J* 6.5, H-29/30), 1.03 (3 H, d, *J* 6.5, H-18/19), 0.96 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 166.7 (C-4/7), 166.6 (C-4/7), 161.9 (C-2), 159.1 (C-24), 150.2 (C-10), 135.2 (C-27), 134.9 (C-13), 128.6 (C-22), 128.5 (C-9), 128.2 (C-21), 126.6 (C-14), 114.1 (C-23), 102.7 (C-3), 65.6 (C-12), 55.2 (C-26), 54.9 (C-6), 50.1 (C-20), 40.6 (C-16), 27.6 (C-28), 25.0 (C-17), 23.0 (C-18/19), 22.5 (C-15), 22.3 (C-18/19), 21.7 (C-29/30), 21.6 (C-29/30); *m/z* (ESI) 464 $[MH]^+$. Calcd. for $C_{27}H_{34}N_3O_4$: 464.2544. Found: $[MH]^+$, 464.2534 (2.5 ppm error).

Lab. Book: RD06/025/C1

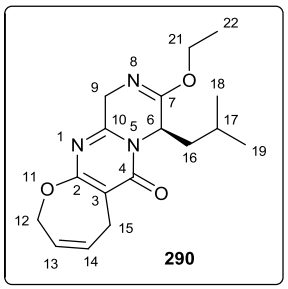
(6*R)-3-Allyl-2-(allyloxy)-7-ethoxy-6-*iso*-butyl-6,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidin-4-one 292**



To a solution of diallyl pyrimidinone **50** (1.00 g, 3.14 mmol, 1.0 eq.) and K_2CO_3 (1.73 g, 12.6 mmol, 4.0 eq.) in anhydrous DCM (30 mL) containing activated, powdered 4 Å molecular sieves (1.50 g, 0.500 g/mmol), was added triethyloxonium tetrafluoroborate (1.19 g, 6.28 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 2 h before filtration through Celite®. The filtrate was washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (9:1 PE/EtOAc) to furnish the *title compound* **292** (0.939 g, 87%) as a colourless oil: R_f 0.70 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2958 (C-H stretch), 1668 (C=O stretch), 1600 (C=C stretch), 1536 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 5.99 (1 H, ddt, *J* 17.0, 10.5, 5.0, H-13), 5.87 (1 H, ddt, *J* 17.0, 10.0, 6.5, H-16), 5.34 (1 H, dd, *J* 17.0, 1.5, H-14a), 5.28 (1 H, t, *J* 7.5, H-6), 5.21 (1 H, dd, *J* 10.5, 1.5, H-14b), 5.01 (1 H, dd, *J* 17.0, 1.5, H-17a), 4.96 (1 H, dd, *J* 10.0, 1.5, H-17b), 4.84-4.80 (2 H, m, H-12), 4.58 (1 H, d, *J* 20.0, H-9a), 4.51 (1 H, d, *J* 20.0, H-9b), 4.16 (2 H, q, *J* 7.0, H-22), 3.23 (2 H, d, *J* 6.5, H-15), 1.76-1.65 (1 H, m, H-19), 1.61 (2 H, dd, *J* 7.5, 6.5, H-18), 1.30 (3 H, t, *J* 7.0, H-23), 1.05 (3 H, d, *J* 6.5, H-20/21), 0.92 (3 H, d, *J* 6.5, H-20/21); δ_C (100 MHz, $CDCl_3$) 164.7 (C-4/7), 164.2 (C-4/7), 161.8 (C-2), 153.9 (C-10), 135.0 (C-16), 133.1 (C-13), 117.2 (C-14), 114.9 (C-17), 101.3 (C-3), 67.1 (C-12), 62.1 (C-22), 50.7 (C-9), 50.3 (C-6), 40.3 (C-18), 27.1 (C-15), 25.1 (C-19), 23.3 (C-20/21), 21.5 (C-20/21), 14.1 (C-23); *m/z* (ESI) 346 $[MH]^+$. Calcd. for $C_{19}H_{28}N_3O_3$: 346.2125. Found: $[MH]^+$, 346.2129 (1.1 ppm error).

Lab. Book: RD06/037/C1

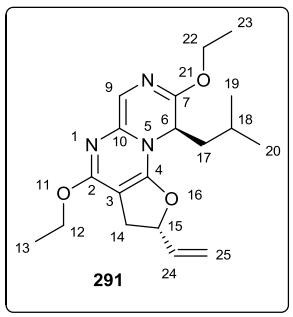
(8*R)-9-Ethoxy-8-*iso*-butyl-8,11-dihydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 290**



To a refluxing solution of diallyl pyrimidinone **292** (0.345 g, 1.00 mmol, 1.0 eq.) in degassed anhydrous DCM (400 mL) under an inert atmosphere was added a solution of Grubbs second generation catalyst **148** (0.085 g, 0.1 mmol, 0.1 eq.) in degassed anhydrous DCM (20 mL) in two 10 mL batches separated by 1 h, dropwise over 15 min. The reaction mixture was heated at reflux for a further 3 h before cooling to room temperature, direct loading onto a column of silica gel and purification by flash column chromatography (1:1 DCM/Et_2O). The *title compound* **290** (0.258 g, 81%) was isolated as a red/brown oil: R_f 0.28 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2958 (C-H stretch), 1655 (C=O stretch), 1598 (C=C stretch), 1548 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.23 (1 H, dt, *J* 10.0, 6.0, H-14), 6.03 (1 H, app. dt (ddd), *J* 10.0, 6.0, H-13), 5.19 (1 H, dd, *J* 8.5, 6.5, H-6), 4.78 (2 H, 2 × dd (overlapping), *J* 15.5, 6.0, H-12), 4.59 (1 H, d, *J* 20.0, H-9a), 4.51 (1 H, d, *J* 20.0, H-9b), 4.16 (2 H, q, *J* 7.0, H-21), 3.48 (2 H, d, *J* 6.0, H-15), 1.76-1.66 (1 H, m, H-17), 1.63-1.58 (2 H, m, H-16), 1.30 (3 H, t, *J* 7.0, H-22), 1.06 (3 H, d, *J* 6.5, H-18/19), 0.94 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 166.7 (C-4/7), 164.3 (C-4/7), 162.4 (C-2), 153.5 (C-10), 134.7 (C-14), 126.7 (C-13), 102.3 (C-3), 65.6 (C-12), 62.1 (C-21), 50.5 (C-6), 50.3 (C-9), 40.3 (C-16), 25.0 (C-17), 23.2 (C-18/19), 22.3 (C-15), 21.6 (C-18/19), 14.1 (C-22); *m/z* (ESI) 318 $[MH]^+$. Calcd. for $C_{17}H_{24}N_3O_3$: 318.1812. Found: $[MH]^+$, 318.1820 (1.9 ppm error).

Lab. Book: RD06/024/C1

(2*S,9*R**)-4,8-Diethoxy-9-*iso*-butyl-2-vinyl-2,3,6,9-tetrahydro-5a*H*-furo[3,2-*e*]pyrazino[1,2-*a*]pyrimidine 291**

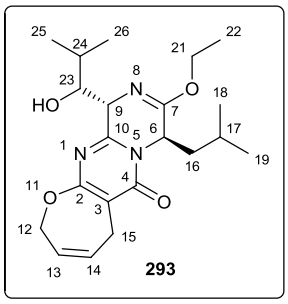


To a solution of dihydro-oxepine **215** (1.00 g, 3.14 mmol, 1.0 eq.) and K_2CO_3 (1.73 g, 12.6 mmol, 4.0 eq.) in anhydrous DCM (30 mL) containing activated, powdered 4 Å molecular sieves (1.50 g, 0.500 g/mmol), was added triethyloxonium tetrafluoroborate (1.19 g, 6.28 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 2 h before filtration through Celite®. The filtrate was washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified

by flash column chromatography on silica gel (7:3 PE/EtOAc) to furnish dihydro-oxepine **290** (0.0230 g, 36%) and the *title compound* **291** (0.0230 g, 33%) as brown oil (single diastereomer): R_f 0.32 (4:1 *n*-hexane/EtOAc); υ_{max}/cm^{-1} (neat) 2958 (C-H stretch), 1690 (lactim C-O stretch), 1667 (C=C stretch), 1640 (C=C stretch), δ_H (400 MHz, $CDCl_3$) 5.87 (1 H, s, H-9), 5.72 (1 H, ddd, *J* 17.0, 10.5, 9.0, H-24), 5.28 (1 H, dd, *J* 17.0, 1.5, H-25a), 5.18 (1 H, t, *J* 7.5, H-6), 5.13 (1 H, dd, *J* 10.5, 1.5, H-25b), 4.19 (2 H, q, *J* 7.0, H-12), 3.87 (1 H, dq, *J* 14.0, 7.0, H-22a), 3.75 (1 H, dq, *J* 14.0, 7.0, H-22b), 2.47 (1 H, dt, *J* 9.0, 8.5, H-15), 2.12 (1 H, dd, *J* 8.5, 4.0, H-14a), 2.07 (1 H, dd, *J* 8.5, 4.0, H-14b), 1.55-1.44 (3 H, m, H-17, 18), 1.32 (3 H, t, *J* 7.0, H-13), 1.21 (3 H, t, *J* 7.0, H-23), 0.94 (6 H, app. d (2 × d), *J* 6.0, H-19, 20); δ_C (100 MHz, $CDCl_3$) 166.5 (C-2/4/7), 162.4 (C-2/4/7), 159.4 (C-2/4/7), 132.7 (C-24), 123.3 (C-10), 119.3 (C-25), 103.2 (C-9), 62.4 (C-12), 48.5 (C-6), 39.7 (C-15), 38.8 (C-17), 36.2 (C-3), 35.2 (C-3), 24.1 (C-18), 22.6 (C-19/20), 22.5 (C-19/20), 21.7 (C-14), 14.2 (C-13), 12.4 (C-23); *m/z* (ESI) 346 $[MH]^+$. Calcd. for $C_{19}H_{28}N_3O_3$: 346.2125. Found: $[MH]^+$, 346.2134 (2.8 ppm error).

Lab. Book: RD06/024/C1

(8*R,11*R**)-9-Ethoxy-11-(1-hydroxy-2-methylpropyl)-8-*iso*-butyl-2,5,8,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 293**



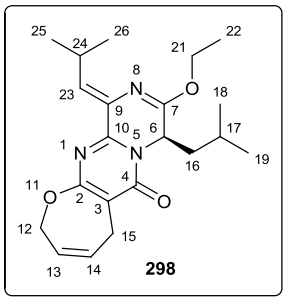
293

A solution of LiHMDS was prepared by the addition of *n*-BuLi (1.34 mL, 2.5 M solution in *n*-hexane, 3.34 mmol, 2.10 eq.) to a solution of HMDS (0.727 mL, 3.42 mmol, 2.15 eq.) in THF (5 mL) at 0 °C (ice). Following stirring at 0 °C for 20 min the solution was diluted with THF (10 mL) and cooled to –78 °C (CO_2/acetone) before a solution of imidate **290** (0.504 g, 1.59 mmol, 1.0 eq.) in THF (5 mL) was added. The reaction mixture was stirred at –78 °C for 10 min before the addition of *iso*-butyraldehyde **221** (0.440 mL, 4.77 mmol, 3.00 eq.) and then held for a further 10 min before the reaction mixture was quenched by the addition of AcOH (1 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between EtOAc (20 mL) and water (25 mL), the organic phase separated, washed with sat. $NaHCO_3$ (aq.) (2 × 25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (4:1 *n*-hexane/EtOAc) to furnish the *title compound* **293** (0.425 g, 70%) as a yellow oil: R_f 0.59 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3433 (br, O-H stretch), 2960 (C-H stretch), 1647 (C=O stretch), 1593 (C=C stretch),

1544 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.23 (1 H, dt, *J* 10.0, 6.0, H-14), 6.02 (1 H, dt, *J* 10.0, 6.5, H-13), 5.00 (1 H, dd, *J* 9.5, 4.5 H-6), 4.81 (1 H, dd, *J* 13.5, 6.5, H-12a), 4.72 (1 H, dd, *J* 13.5, 6.5, H-12b), 4.42 (1 H, d, *J* 8.5, H-9), 4.17 (2 H, m, H-21), 3.46 (2 H, d, *J* 6.0, H-15), 3.43 (1 H, ddd, *J* 8.5, 3.0, 2.5, H-23), 2.10 (1 H, sept.d, *J* 7.0, 3.0, H-24), 1.91-1.82 (1 H, m, H-17), 1.73 (1 H, ddd, *J* 13.5, 9.5, 4.5, H-16a), 1.52 (1 H, ddd, *J* 13.5, 9.5, 4.5, H-16b), 1.29 (3 H, t, *J* 7.0, H-22), 1.06 (3 H, d, *J* 6.5, H-18/19), 1.05 (3 H, d, *J* 7.0, H-25/26), 1.01 (3 H, d, *J* 7.0, H-25/26), 0.90 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 165.9 (C-4/7), 162.4 (C-4/7), 162.0 (C-2), 155.1 (C-10), 134.9 (C-13), 126.6 (C-14), 102.1 (C-3), 78.8 (C-23), 65.5 (C-12), 62.3 (C-9), 61.8 (C-21), 50.1 (C-6), 44.8 (C-16), 29.7 (C-24), 25.4 (C-17), 23.5 (C-18/19), 22.3 (C-15), 21.4 (C-18/19), 19.8 (C-25/26), 14.7 (C-25/26), 14.1 (C-22); *m/z* (ESI) 390 $[MH]^+$. Calcd. for $C_{21}H_{32}N_3O_4$: 390.2387. Found: $[MH]^+$, 390.2399 (1.1 ppm error).

Lab. Book: RD06/054/C1

(8*R,11*Z*)-9-Ethoxy-8-*iso*-butyl-11-(2-methylpropylidene)-2,5,8,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 298**

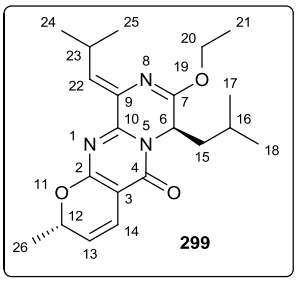


To a solution of aldol adduct **294** (0.0970 g, 0.250 mmol, 1.0 eq.) in pyridine (4 mL) at room temperature was added MsCl (0.0390 mL, 0.500 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 18 h before the addition of DBU (0.0740 mL, 0.500 mmol, 2.0 eq.). The reaction mixture was heated at 50 °C for 1 h, cooled to room temperature and then diluted with EtOAc (10 mL), washed with 1 M HCl (aq.) (3 × 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (9:1 *n*-hexane/EtOAc) to furnish the *title compound* **298** (0.0590 g, 64%) as a yellow oil: R_f 0.69 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2959 (C-H stretch), 1653 (C=O stretch), 1579 (C=C stretch), 1534 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.49 (1 H, d, *J* 9.5, H-23), 6.24 (1 H, dt, *J* 10.0, 6.0, H-14), 6.03 (1 H, dt, *J* 10.0, 6.0, H-13), 5.24 (1 H, app. t (dd), *J* 6.5, H-6), 4.85 (1 H, dd, *J* 13.5, 6.0, H-12a), 4.76 (1 H, dd, *J* 13.5, 6.0, H-12b), 4.31 (2 H, m, H-21), 3.49 (2 H, d, *J* 6.0, H-15), 3.18 (1 H, dsept., *J* 9.5, 6.5, H-24), 1.71-1.63 (1 H, m, H-17), 1.61-1.59 (2 H, m, H-16), 1.34 (3 H, t, *J* 7.0, H-22), 1.09 (3 H, d, *J* 6.5, H-25/26), 1.03 (3 H, d, *J* 6.5, H-18/19), 1.01 (3 H, d, *J* 6.5, H-25/26), 0.87 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 166.8 (C-4/7), 162.6 (C-4/7), 161.8 (C-2), 148.9 (C-10), 137.8 (C-

23), 134.8 (C-14), 131.2 (C-9), 126.7 (C-13), 101.9 (C-3), 65.4 (C-12), 62.4 (C-21), 50.5 (C-6), 42.2 (C-16), 26.4 (C-24), 24.8 (C-17), 23.4 (C-18/19), 22.5 (C-15), 22.3 (C-25/26), 21.9 (C-18/19), 21.7 (C-25/26), 14.1 (C-22); *m/z* (ESI) 372 $[MH]^+$. Calcd. for $C_{21}H_{30}N_3O_3$: 372.2282. Found: $[MH]^+$, 372.2290 (2.2 ppm error).

Lab. Book: RD06/047/C1

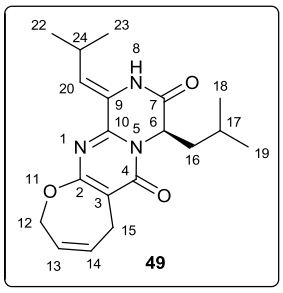
(2*S,5*R**)-6-Ethoxy-5-*iso*-butyl-2-methyl-8-[2-methyl-prop-(*Z*)-ylidene]-5,8,8a,9-tetrahydro-2*H*-1-oxa-7,9,10a-triaza-anthracen-10-one 299**



To a solution of aldol adduct **294** (0.368 g, 0.950 mmol, 1.0 eq.) in pyridine (5.0 mL) at room temperature was added MsCl (0.146 mL, 1.89 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 2 h and then at 50 °C for 30 min before the addition of DBU (0.710 mL, 4.75 mmol, 5.0 eq.) and further stirring at 50 °C for 30 min. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with 1 M HCl (aq.) (3 × 20 mL), sat. $NaHCO_3$ (aq.) (3 × 20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (12:1 *n*-hexane/EtOAc) to furnish the *title compound* **299** (0.228 g, 70%) as a yellow oil: R_f 0.72 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2959 (C-H stretch), 2870 (C-H stretch), 1663 (C=O stretch), 1517 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.56 (1 H, d, *J* 9.5, H-22), 6.55 (1 H, d, *J* 10.0, H-14), 5.41 (1 H, dd, *J* 10.0, 3.0, H-13), 5.29-5.23 (2 H, m, H-6, 12), 4.30 (2 H, m, H-20), 3.19 (1 H, dsept., *J* 9.0, 7.0, H-23), 1.68-1.57 (3 H, m, H-15, 16), 1.50 (3 H, d, *J* 6.5, H-26), 1.33 (3 H, t, *J* 7.0, H-21), 1.09 (3 H, d, *J* 7.0, H-24/25), 1.03 (3 H, d, *J* 7.0, H-24/25), 0.98 (3 H, d, *J* 6.5, H-18/19), 0.86 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 164.1 (C-4/7), 161.7 (C-4/7), 158.6 (C-2), 151.1 (C-10), 138.9 (C-22), 131.5 (C-9), 121.4 (C-13), 117.9 (C-14), 97.7 (C-3), 74.9 (C-12), 62.4 (C-20), 50.1 (C-6), 42.3 (C-15), 26.4 (C-23), 24.7 (C-16), 23.2 (C-18/19), 22.2 (C-24/25), 21.8 (C-26), 21.8 (C-24/25), 21.7 (C-18/19), 14.0 (C-21); *m/z* (ESI) 372 $[MH]^+$. Calcd. for $C_{21}H_{30}N_3O_3$: 372.2282. Found: $[MH]^+$, 372.2287 (1.1 ppm error).

Lab. Book: RD06/092/C1

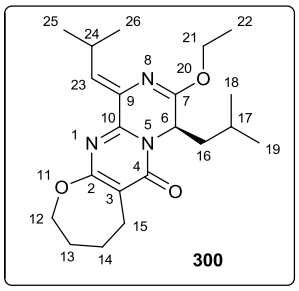
(8*R,11*Z*)-8-*iso*-Butyl-11-(2-methylpropylidene)-2,5,10,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione – 'Dihydro-janoxepin' 49**



A solution of imidate **298** (0.102 g, 0.270 mmol, 1.0 eq.) in AcOH (4 mL) and water (1 mL) was heated at 50 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* before purification by flash column chromatography on silica gel (1:1 *n*-hexane/EtOAc) to furnish the *title compound* **49** (0.0680 g, 73%) as a yellow solid: mp 164-166 °C; R_f 0.39 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3191 (N-H stretch), 2961 (C-H stretch), 1689 (C=O stretch), 1649 (C=O stretch), 1536 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.98 (1 H, br s, H-8), 6.31 (1 H, d, *J* 10.5, H-20), 6.25 (1 H, dt, *J* 10.0, 6.0, H-14), 6.05 (1 H, dt, *J* 10.0, 6.5, H-13), 5.34 (1 H, ddd, *J* 9.0, 5.5, 1.0, H-6), 4.86 (1 H, dd, *J* 13.5, 6.5, H-12a), 4.77 (1 H, dd, *J* 13.5, 6.5, H-12b), 3.50 (2 H, dd, *J* 6.0, 4.5, H-15), 2.73 (1 H, dsept., *J* 10.5, 6.5, H-21), 1.86-1.74 (1 H, m, H-17), 1.71-1.58 (2 H, m, H-16), 1.11 (3 H, d, *J* 6.5, H-22/23), 1.10 (3 H, d, *J* 6.5, H-22/23), 1.07 (3 H, d, *J* 6.5, H-18/19), 0.92 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 166.8 (C-4/7), 166.4 (C-4/7), 162.2 (C-2), 146.7 (C-10), 135.0 (C-13), 127.9 (C-20), 126.7 (C-14), 123.8 (C-9), 102.7 (C-3), 65.5 (C-12), 54.1 (C-6), 42.5 (C-16), 26.1 (C-21), 24.8 (C-17), 23.2 (C-18/19), 22.5 (C-15), 22.2 (C-22/23), 22.0 (C-22/23), 21.2 (C-18/19); *m/z* (ESI) 344 $[MH]^+$. Calcd. for $C_{19}H_{26}N_3O_3$: 344.1969. Found: $[MH]^+$, 344.1968 (0.1 ppm error).

Lab. Book: RD06/083/C1

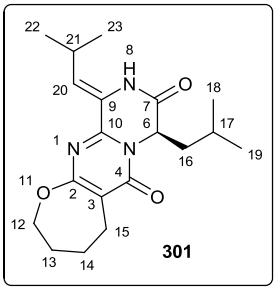
(8*R,11*Z*)-9-Ethoxy-8-*iso*-butyl-11-(2-methylpropylidene)-2,3,4,5,8,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 300**



To a solution of dihydro-oxepine **298** (0.0540 g, 0.140 mmol, 1.0 eq.) in EtOAc (4 mL) was added 3% Pd/C (0.012 g, 0.004 mmol, 2.5 mol%) and the reaction mixture was placed under an atmosphere of H_2. After stirring at room temperature for 1 h the reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (17:3 PE/EtOAc) to furnish the *title compound* **300** (0.0430 g, 82%) as a yellow oil: R_f 0.32 (4:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2958 (C-H stretch), 1651 (C=O stretch), 1579 (C=C stretch), 1531 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.50 (1 H, d, *J* 9.5, H-23), 5.25 (1 H, app. t (dd), *J* 6.5, H-6), 4.35-4.24 (4 H, m, H-21, 12), 3.19 (1 H, dsept., *J* 9.5, 6.5, H-24), 2.75-2.72 (2 H, m, H-15), 2.06-1.89 (2 H, m, H-14), 1.87-1.81 (2 H, m H-13), 1.70-1.57 (3 H, m, H-16, H-17), 1.33 (3 H, t, *J* 7.0, H-22), 1.08 (3 H, d, *J* 6.5, H-25/26), 1.02 (3 H, d, *J* 6.5, H-18/19), 0.99 (3 H, d, *J* 6.5, H-25/26), 0.85 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 168.7 (C-4/7), 163.2 (C-4/7), 161.8 (C-2), 148.6 (C-10), 137.6 (C-23), 131.4 (C-9), 105.9 (C-3), 71.2 (C-21), 62.4 (C-12), 50.4 (C-6), 42.2 (C-16), 29.0 (C-14), 26.4 (C-24), 24.8 (C-17), 23.8 (C-13), 23.4 (C-18/19), 22.3 (C-15), 22.2 (C-25/26), 21.9 (C-18/19), 21.7 (C-25/26), 14.1 (C-22); *m/z* (ESI) 374 $[MH]^+$. Calcd. for $C_{21}H_{32}N_3O_3$: 374.2438. Found: $[MH]^+$, 374.2422 (4.5 ppm error).

Lab Book: RD09/057/C1

(8*R,11*Z*)-8-*iso*-Butyl-11-(2-methylpropylidene)-2,3,4,5,10,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione – 'Tetrahydro-janoxepin' 301**



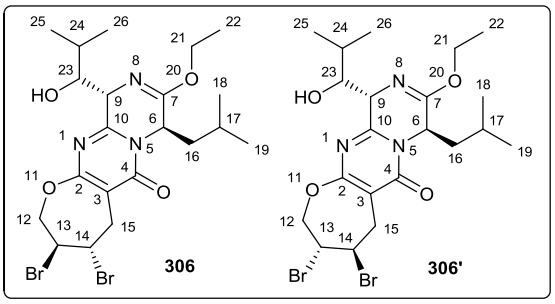
A solution of tetrahydro-oxepine **300** (0.0260 g, 0.0690 mmol, 1.0 eq.) in AcOH (0.8 mL) and water (0.2 mL) was heated at 50 °C for 1 h before being concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 PE/EtOAc) to furnish the *title compound* **301** (0.0200 g, 84%) as a pale yellow crystalline solid: mp 169-170 °C; R_f 0.12 (4:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3189 (broad, N-H stretch), 2960 (C-H stretch), 1689

(C=O stretch), 1655 (C=O stretch), 1581 (N-H bend), 1533 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 9.19 (1 H, br. s, H-8), 6.33 (1 H, d, *J* 10.5, H-20), 5.36 (1 H, dd, *J* 9.0, 5.5, H-6), 4.41-4.31 (2 H, m, H-12), 2.80-2.71 (3 H, m, H-21, 15), 2.08-2.00 (1 H, m, H-13a), 1.98-1.92 (1 H, m, H-13b), 1.90-1.84 (2 H, m, H-14), 1.82-1.77 (1 H, m, H-17), 1.71-1.59 (2 H, m, H-16), 1.11 (3 H, d, *J* 6.5, H-22/23), 1.10 (3 H, d, *J* 6.5, H-22/23), 1.08 (3 H, d, *J* 6.5, H-18/19), 0.92 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 168.3 (C-4/7), 166.7 (C-4/7), 162.8 (C-2), 146.3 (C-10), 127.7 (C-20), 124.0 (C-9), 106.9 (C-3), 71.4 (C-12), 54.0 (C-6), 42.6 (C-16), 28.9 (C-13), 26.1 (C-21), 24.8 (C-17), 23.7 (C-14), 23.2 (C-18/19), 22.4 (C-15), 22.2 (C-22/23), 22.0 (C-22/23), 21.2 (C18/19); *m/z* (ESI) 346 $[MH]^+$. Calcd. for $C_{19}H_{28}N_3O_3$: 346.2125. Found: $[MH]^+$, 346.2113 (3.5 ppm error).

Lab Book: RD09/066/C1

6.3 Chapter 4 – Dihydro-Oxepine Elaboration: The Synthesis of (±)-Janoxepin (**1**)

(3*S**,4*S**,8*R**,11*R**)-3,4-Dibromo-9-ethoxy-11-[(1*S*)-1-hydroxy-2-methylpropyl]-8-*iso*-butyl-2,3,4,5,8,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one **306**

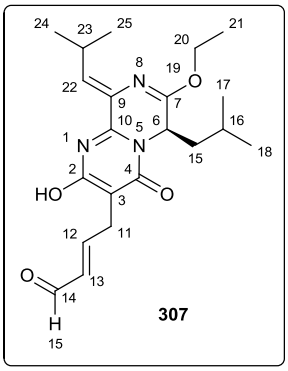


To a solution of dihydro-oxepine **294** (0.0470 g, 0.120 mmol, 1.0 eq.) in DCM (2.0 mL) was added pyridine hydrotribromide (0.0420 g, 0.132 mmol, 1.1 eq.). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (10 mL), washed with sat. $NaHCO_3$ (aq.) (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (4:1 PE/EtOAc) to furnish the *title compound* **306** (0.0450 g, 68%) as a pale yellow crystalline solid (1:1 mixture of diastereomers): mp 75-77 °C; R_f 0.57 (4:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 3454 (O-H stretch), 2961 (C-H stretch), 1663 (C=O stretch), 1596 (C=C stretch), 1545 (C=N stretch); δ_H (400 MHz, $CDCl_3$) 5.07-4.97 (2 H, m, H-6, 6a), 4.70-4.55 (6 H, m, H-9, 9', 12a, 12'a, 13, 13'), 4.49 (2 H, m, H-14, 14'), 4.43-4.38 (2 H, m, H-12a, 12'a), 4.23-4.19 (4 H, m, H-21, 21'), 3.55-3.39 (6 H, m, H-15, 15', 23, 23'), 2.13 (1 H, sept.d, *J* 7.0, 3.5, H-24), 2.12 (1 H, sept.d, *J* 7.0, 3.5, H-24'), 1.93-1.78 (2 H, m, H-17, 17'), 1.76-1.66 (2 H, m, H-16,

16'), 1.62-1.51 (2 H, m, H-16a, 16'a), 1.30 (6 H, app. t, *J* 7.0, H-22, 22'), 1.08-1.01 (18 H, m, H-18, 18', 25, 25', 26, 26'), 0.91 (3 H, d, *J* 6.5, H-19), 0.90 (3 H, d, *J* 6.5, H-19'); δ_C (100 MHz, $CDCl_3$) 167.4 (C-4/7), 167.3 (C-4'/7'), 162.6 (C-4/7), 162.5 (C-4'/7'), 161.9 (C-2), 161.8 (C-2'), 156.8 (C-10), 156.7 (C-10'), 104.3 (C-3), 104.2 (C-3'), 79.0 (C-23), 78.7 (C-23'), 70.8 (C-12), 70.5 (C-12'), 62.8 (C-13/14), 62.6 (C-13'/14'), 62.5 (C-21), 62.0 (C-21'), 53.7 (C-13/14), 53.0 (C-13'/14'), 50.5 (C-6), 50.2 (C-6'), 50.2 (C-9), 50.0 (C-9'), 45.0 (C-16), 44.8 (C-16'), 29.9 (C-24), 29.7 (C-24'), 27.9 (C-15), 27.2 (C-15'), 25.4 (C-17), 25.3 (C-17'), 23.5 (C-18/19), 23.4 (C-18'/19'), 21.7 (C-18/19), 21.7 (C-18'/19'), 21.4 (C-25/26), 21.3 (C-25'/26'), 19.9 (d, C-25/26), 19.8 (d, C-25'/26'), 14.1 (d, C-22, 22'); *m/z* (ESI) 548 $[MH]^+$. Calcd. for $C_{21}H_{32}{}^{79}Br_2N_3O_4$: 548.0754. Found: $[MH]^+$, 548.0764 (1.8 ppm error).

Lab. Book: RD07/005/C1

(2*E*)-4-[(6*R,9*Z*)-7-Ethoxy-2-hydroxy-6-*iso*-butyl-9-(2-methylpropylidene)-4-oxo-6,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidin-3-yl]but-2-enal 307**

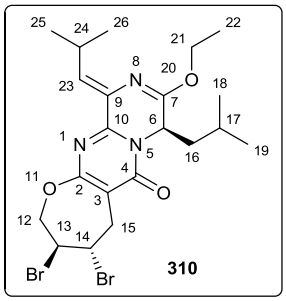


To a solution of dibromide **306** (0.0280 g, 0.0500 mmol, 1.0 eq.) in DMSO (1 mL) was added TBAF (1 M solution in THF, 0.210 mL, 0.210 mmol, 4.1 eq.). The reaction mixture was stirred at room temperature for 30 min and quenched by the addition of 1 M HCl (aq.) (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with 1 M HCl (aq.) (3 × 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (3:2 PE/EtOAc) to furnish the *title compound* **307** (0.0090 g, 47%) as an orange film: R_f 0.57 (1:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2960 (C-H stretch), 1691 (C=O stretch), 1656 (C=O stretch), 1523 (C=C stretch), 1446 (C=N stretch); δ_H (400 MHz, $CDCl_3$) 9.49 (1 H, d, *J* 8.0, H-14), 6.93 (1 H, dt, *J* 15.5, 6.0, H-12), 6.34 (1 H, dd, *J* 9.5, 2.5, H-22), 6.11 (1 H, ddt, *J* 15.5, 8.0, 1.5, H-13), 5.33 (1 H, dd, *J* 8.5, 5.5, H-6), 4.35-4.31 (2 H, m, H-20), 3.49 (2 H, ddd, *J* 6.0, 3.5, 1.5, H-11), 3.23 (1 H, dsept., *J* 9.5, 6.5, H-23), 1.70-1.63 (1 H, m, H-16), 1.61-1.54 (2 H, m, H-15), 1.36 (3 H, t, *J* 7.0, H-21), 1.14 (3 H, d, *J* 6.5, H-24/25), 1.04 (3 H, d, *J* 6.5, H-24/25), 1.03 (3 H, d, *J* 6.5, H-17/18), 0.90 (3 H, d, *J* 6.5, H-17/18); δ_C (100 MHz, $CDCl_3$) 194.1 (C-14), 163.7 (C-4/7), 162.9 (C-4/7), 160.8 (C-2), 155.3 (C-12), 150.9 (C-10), 139.6 (C-22), 132.8 (C-

13), 130.0 (C-9), 96.5 (C-3), 63.0 (C-20), 50.6 (C-6), 41.9 (C-15), 26.6 (C-11), 26.5 (C-23), 25.0 (C-16), 23.3 (C-17/18), 22.1 (C-24/25), 21.8 (C-24/25), 21.5 (C-17/18), 14.1 (C-21); *m/z* (ESI) 388 $[MH]^+$. Calcd. for $C_{21}H_{30}N_3O_4$: 388.2231. Found: $[MH]^+$, 388.2239 (1.6 ppm error).

Lab. Book: RD07/010/C1

(3*S,4*S**,8*R**,11*Z*)-3,4-Dibromo-9-ethoxy-8-*iso*-butyl-11-(2-methylpropylidene)-2,3,4,5,8,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 310**

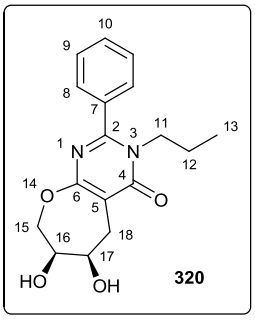


310

To a solution of dibromide **306** (0.0600 g, 0.110 mmol, 1.0 eq.) in DCM (2.0 mL) was added DBU (0.0670 mL, 0.450 mmol, 4.1 eq.). The reaction mixture was stirred at room temperature for 30 min before being quenched by the addition of 10% HCl (aq.) (10 mL). The organic phase was separated and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic phase was washed with 10% HCl (aq.) (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (19:1 PE/EtOAc) to furnish the *title compound* **310** (0.0220 g, 38%) as an orange film (single diastereomer): R_f 0.32 (19:1 PE/EtOAc); υ_{max}/cm^{-1} (neat) 2959 (C-H stretch), 1657 (C=O stretch), 1587 (C=C stretch), 1537 (C=N stretch); δ_H (400 MHz, $CDCl_3$) 6.60 (1 H, d, *J* 9.5, H-23), 5.23 (1 H, dd, *J* 7.5, 6.0, H-6), 4.65 (1 H, ddd, *J* 5.0, 4.0, 2.5, H-13), 4.52 (1 H, dd, *J* 12.5, 2.5, H-12a), 4.39 (1 H, dd, *J* 12.5, 5.0, H-12b), 4.36-4.26 (2 H, m, H-21), 4.00 (1 H, dd, *J* 11.5, 3.0, H-15a), 3.82 (1 H, dd, *J* 11.5, 8.0, H-15b), 3.52 (1 H, ddd, *J* 8.0, 4.0, 3.0, H-14), 3.20 (1 H, dsept., *J* 9.5, 6.5, H-24), 1.73-1.63 (1 H, m, H-17), 1.60-1.57 (2 H, m, H-16), 1.35 (3 H, t, *J* 7.0, H-22), 1.09 (3 H, d, *J* 6.5, H-25/26), 1.04 (3 H, d, *J* 6.5, H-18/19), 1.01 (3 H, d, *J* 6.5, H-25/26), 0.87 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 164.0 (C-4/7), 161.7 (C-4/7), 161.1 (C-2), 151.3 (C-10), 139.4 (C-23), 131.4 (C-9), 95.2 (C-3), 68.1 (C-12), 62.6 (C-21), 50.2 (C-6), 44.0 (C-15), 42.5 (C-16), 42.4 (C-14), 41.4 (C-13), 26.5 (C-24), 24.9 (C-17), 23.3 (C-18/19), 22.3 (C-25/26), 21.8 (C-25/26), 21.6 (C-18/19), 14.1 (C-22); *m/z* (ESI) 530 $[MH]^+$. Calcd. for $C_{21}H_{30}{}^{79}Br_2N_3O_3$: 530.0648. Found: $[MH]^+$, 530.0668 (3.6 ppm error).

Lab. Book: RD07/014/C2

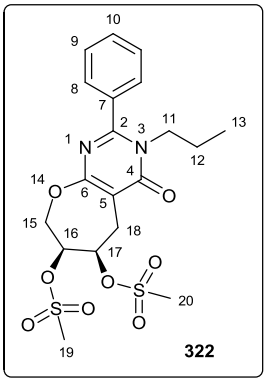
(6*R,7*S**)-6,7-Dihydroxy-2-phenyl-3-propyl-5,6,7,8-tetrahydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 320**



To a solution of dihydro-oxepine **197** (0.195 g, 0.690 mmol, 1.0 eq.) in acetone (3.8 mL) and water (1.2 mL) was added NMO (0.105 g, 0.900 mmol, 1.3 eq.) and OsO_4 (0.105 mL, 4% w/w solution in water, 0.0170 mmol, 0.025 eq.). The reaction mixture was stirred at room temperature for 20 min before being filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (19:1 EtOAc/MeOH) to furnish the *title compound* **320** (0.185 g, 85%) as a pale yellow crystalline solid: mp 142-144 ^{o}C; R_f 0.10 (19:1 EtOAc/MeOH); υ_{max}/cm^{-1} (neat) 3397 (broad, O-H stretch), 2967 (C-H stretch), 1641 (C=O stretch), 1592 (aromatic C=C stretch), 1539 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.51-7.43 (5 H, m, H-8, 9, 10), 4.31 (1 H, dd, *J* 11.0, 2.5, H-15a), 4.20-4.11 (3 H, m, H-15b, 16, 17), 3.86 (2 H, dd, *J* 9.5, 6.0, H-11), 3.24 (1 H, dd, *J* 16.0, 9.0, H-18a), 2.85 (1 H, dd, *J* 16.0, 2.0, H-18b), 1.65-1.59 (2 H, m, H-12), 0.75 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 167.5 (C-4), 165.0 (C-6), 158.2 (C-2), 134.2 (C-7), 130.2 (C-10), 128.6 (C-9), 127.7 (C-8), 103.9 (C-5), 71.1 (C-15), 70.6 (C-16), 68.5 (C-17), 48.2 (C-11), 26.3 (C-18), 21.9 (C-12), 11.1 (C-13); *m/z* (ESI) 317 $[MH]^+$. Calcd. for $C_{17}H_{21}N_2O_4$: 317.1496. Found: $[MH]^+$, 317.1483 (4.0 ppm error).

Lab. Book: RD04/048/C1

(6*R,7*S**)-4-Oxo-2-phenyl-3-propyl-3,4,5,6,7,8-hexahydrooxepino[2,3-*d*]pyrimidine-6,7-diyl dimethanesulfonate 322**

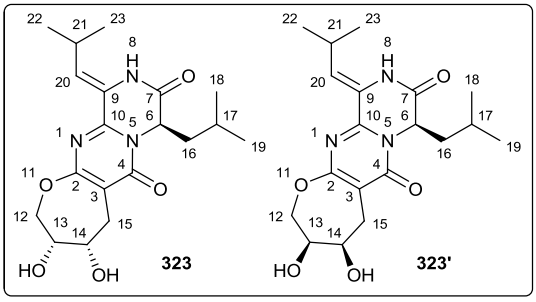


To a solution of diol **320** (0.178 g, 0.560 mmol, 1.0 eq.) in DCM (8 mL) was added NEt_3 (0.315 mL, 2.26 mmol, 4.0 eq.), MsCl (0.175 mL, 2.26 mmol, 4.0 eq.) and DMAP (0.007 g, 0.06 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 1 h before being quenched by the addition of sat. $NaHCO_3$ (aq.) (10 mL). The organic phase was separated and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic phase was washed with water (15 mL), sat. NH_4Cl (aq.) (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (7:3 EtOAc/*n*-

hexane) to furnish the *title compound* **322** (0.251 g, 95%) as a colourless crystalline solid: mp 65-68 °C; R_f 0.65 (9:1 EtOAc/MeOH); υ_{max}/cm^{-1} (neat) 2968 (C-H stretch), 1656 (C=O stretch), 1597 (aromatic C=C stretch), 1541 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.55-7.45 (5 H, m, H-8, 9, 10), 5.22 (1 H, ddd, *J* 9.0, 2.5, 1.5, H-17), 5.17 (1 H, ddd, *J* 8.0, 4.0, 2.5, H-16), 4.38 (1 H, d, *J* 13.0, 4.0, H-15a), 4.26 (1 H, dd, *J* 13.0, 8.0, H-15b), 3.88 (2 H, ddd, *J* 9.0, 6.5, 3.0, H-11), 3.56 (1 H, dd, *J* 16.0, 9.0, H-18a), 3.19 (3 H, s, H-19/20), 3.16 (3 H, s, H-19/20), 2.93 (1 H, dd, *J* 16.0, 1.5, H-18b), 1.68-1.57 (2 H, m, H-12), 0.77 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 167.2 (C-4), 164.1 (C-6), 159.2 (C-2), 133.9 (C-7), 130.3 (C-10), 128.7 (C-9), 127.5 (C-8), 103.4 (C-5), 76.4 (C-16), 75.5 (C-17), 67.9 (C-15), 48.3 (C-11), 39.1 (C-19/20), 38.7 (C-19/20), 24.3 (C-18), 21.8 (C-12), 10.9 (C-13); *m/z* (ESI) 517 $[MHCOO]^-$. Calcd. for $C_{20}H_{25}N_2O_{10}S_2$: 517.0596. Found: $[MHCOO]^-$, 517.0963 (1.8 ppm error).

Lab. Book: RD04/061/C1

(3*R,4*S**,8*R**,11*Z*)-3,4-Dihydroxy-8-*iso*-butyl-11-(2-methylpropylidene)-2,3,4,5,10,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione 323**

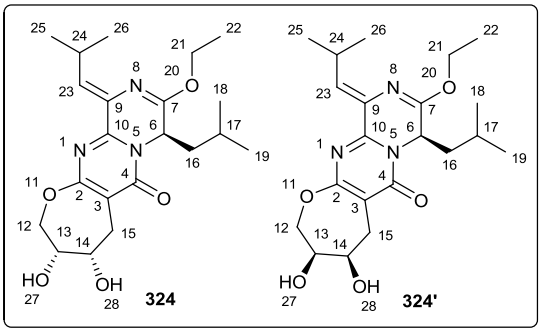


To a solution of 'dihydro-janoxepin' **49** (0.0680 g, 0.200 mmol, 1.0 eq.) in *tert*-butanol (2.2 mL), THF (0.6 mL) and water (0.2 mL) at room temperature was added NMO (0.0240 g, 0.210 mmol, 1.05 eq.) followed by OsO_4 (0.0120 mL, 4% w/w solution in water, 0.01 eq.). The reaction mixture was stirred at room temperature for 1 h before the addition of sat. $NaHSO_3$ (aq.) (10 mL). After 30 min the reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic phase washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (98:2 EtOAc/MeOH) to furnish the *title compound* **323** (0.0440 g, 58%) as a colourless solid (1:1 mixture of diastereomers): mp 105-107 °C; *Rf* 0.16 (EtOAc); υ_{max}/cm^{-1} (neat) 3396 (broad, O-H/N-H stretch), 2961 (C-H stretch), 1689 (C=O stretch), 1646 (C=O stretch), 1584 (C=C stretch), 1533 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.48 (1 H, s, H-8), 8.47 (1 H, s, H-8'), 6.24 (1 H, d, *J* 10.5, H-20), 6.20 (1 H, d, *J* 10.5, H-20'), 5.35 (2 H, app. dt, *J* 9.0, 5.0, H-6, 6'), 4.22-3.96 (8 H, m, H-12, 12', 13, 13', 14, 14'), 3.21 (1 H, dd, *J*

16.0, 8.5, H-15a), 3.19 (1 H, dd, *J* 16.0, 8.5, H-15'a), 2.91-2.65 (4 H, m, H-21, 21', 15b, 15'b), 1.77-1.56 (6 H, m, H-16, 16', 17, 17'), 1.10 (12 H, app. d, *J* 6.5, H-22/23, 22'/23'), 1.03 (6 H, app. d, *J* 6.5, H-18/19), 0.92 (6 H, app. d, *J* 6.5, H-18'/19'); δ_C (100 MHz, $CDCl_3$) 168.2 (C-4/7), 168.1 (C-4'/7'), 166.7 (d, C-4/7, 4'/7'), 163.2 (C-2), 163.1 (C-2'), 149.3 (C-10), 149.1 (C-10'), 130.1 (C-20), 130.0 (C-20'), 125.9 (C-9), 125.8 (C-9'), 103.5 (C-3), 103.3 (C-3'), 71.5 (C-12), 71.0 (C-12'), 70.8 (C-13/14), 70.2 (C-13'/14'), 68.4 (C-13/14), 68.3 (C-13'/14'), 54.4 (C-6), 54.2 (C-6'), 42.5 (C-16), 42.4 (C-16'), 26.1 (d, C-15, 15'), 24.8 (d, C-21, 21'), 23.2 (d, C-17, 17'), 22.1 (d, C-18, 19), 22.0 (d, C-22, 23), 21.3 (d, C-22', 23'), 22.2 (d, C-18', 19'); *m/z* (ESI) 378 $[MH]^+$. Calcd. for $C_{19}H_{28}N_3O_5$: 378.2023. Found: $[MH]^+$, 378.2031 (1.9 ppm error).

Lab. Book: RD06/084/C1

(3*R,4*S**,8*R**,11*Z*)-9-Ethoxy-3,4-dihydroxy-8-*iso*-butyl-11-(2-methylpropylidene)-2,3,4,5,8,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 324**

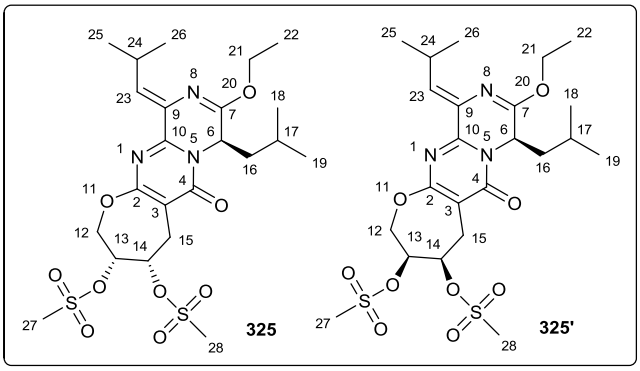


To a solution of dihydro-oxepine **298** (0.0670 g, 0.180 mmol, 1.0 eq.) in *tert*-butanol (2.2 mL), THF (0.6 mL) and water (0.2 mL) was added NMO (0.0220 g, 0.190 mmol, 1.05 eq.) and OsO_4 (0.011 mL, 4% w/w solution in water, 0.002 mmol, 0.01 eq.). The reaction mixture was stirred at room temperature for 1 h before the addition of sat. $NaHSO_3$ (aq.) (10 mL). After 30 min the reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic phase washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 EtOAc/*n*-hexane) to furnish the *title compound* **324** (0.0450 g, 62%) as a pale yellow waxy solid (1:1 mixture of diastereomers): R_f 0.33 (EtOAc); υ_{max}/cm^{-1} (neat) 3414 (broad, O-H stretch), 2959 (C-H stretch), 1654 (C=O stretch), 1581 (C=C stretch), 1530 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.53 (1 H, d, *J* 9.5, H-23), 6.51 (1 H, d, *J* 9.5, H-23'), 4.39-4.26 (6 H, m, H-12a, 12'a, 21, 21'), 4.20-4.06 (6 H, m, H-12b, 12'b, H-13, 13', H-14, 14'), 3.24-3.13 (4 H, m, H-24, 24', H-15a, 15'a), 2.83-2.76 (4 H, m, H-15'b, 15'b, 27, 27'), 2.56 (1 H, d, *J* 4.0, H-28), 5.52 (1 H, d, *J* 4.0, H-28'), 1.70-1.64 (2 H, m, H-17, 17'), 1.61-1.57 (4 H, m, H-16, 16'), 1.35 (6 H, app. t, *J* 7.0, H-22, 22'), 1.11 (3 H, d, *J* 7.0, H-25/26), 1.10 (3 H, d, *J* 7.0, H-25'/26'), 1.04 (3 H, d, *J* 7.0, H-

25/26), 1.03 (3 H, d, *J* 7.0, H-25'/26'), 1.01 (3 H, d, *J* 6.5, H-18/19), 1.00 (3 H, d, *J* 6.5, H-18'/19'), 0.87 (6 H, app. d, *J* 6.5, H-18/19, 18'/19'); δ_C (100 MHz, $CDCl_3$) 168.6 (C-4/7), 168.5 (C-4'/7'), 163.4 (d, C-4/7, 4'/7'), 161.7 (d, C-2, 2'), 149.7 (C-10), 149.5 (C-10'), 138.5 (C-9), 138.4 (C-9'), 131.3 (C-23), 131.2 (C-23'), 102.4 (C-3), 102.1 (C-3'), 71.3 (C-12), 70.9 (C-12'), 70.8 (C-13/14), 70.3 (C-13'/14'), 68.5 (C-13/14), 68.4 (C-13'/14'), 62.5 (d, C-21, 21'), 50.8 (C-6), 50.7 (C-6'), 42.2 (C-16), 42.1 (C-16'), 26.4 (d, C-24, 24'), 26.3 (C-15), 26.2 (C-15'), 24.8 (d, C-17, 17'), 23.3 (d, C-18/19, 18'/19'), 22.3 (d, C-25/26, 25'/26'), 21.8 (d, C-18/19, 18'/19'), 21.6 (d, C-25/26, 25'/26'), 14.1 (d, C-22, 22'); *m/z* (ESI) 406 $[MH]^+$. Calcd. for $C_{21}H_{32}N_3O_5$: 406.2336. Found: $[MH]^+$, 406.2348 (1.8 ppm error).

Lab. Book: RD06/069/C2

(3*R,4*S**,8*R**,11*Z*)-9-Ethoxy-8-*iso*-butyl-11-(2-methylpropylidene)-6-oxo-2,3,4,5,8,11-hexahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-3,4-diyl dimethanesulfonate 325**

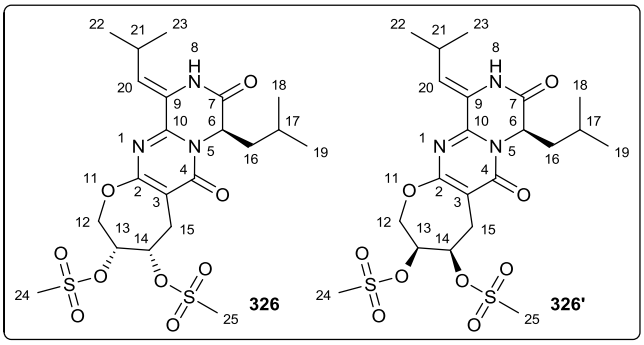


To a solution of diol **324** (0.0380 g, 0.0940 mmol, 1.0 eq.) in pyridine (1.5 mL) was added MsCl (0.0360 mL, 0.470 mmol, 5.0 eq.). The reaction mixture was stirred at room temperature for 4 h before being diluted with EtOAc (10 mL), washed with 1 M HCl (aq.) (3 × 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (3:2 PE/EtOAc) to furnish the *title compound* **325** (0.0400 g, 76%) as a pale yellow film (1:1 mixture of diastereomers): R_f 0.66 (EtOAc); υ_{max}/cm^{-1} (neat) 2960 (C-H stretch), 1656 (C=O stretch), 1586 (C=C stretch), 1531 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.57 (1 H, d, *J* 9.5, H-23), 6.54 (1 H, d, *J* 9.5, H-23'), 5.25 (1 H, dd, *J* 8.0, 5.5, H-6), 5.24 (1 H, dd, *J* 8.0, 5.5, H-6'), 5.19-5.12 (4 H, m, H-13, 13', 14, 14'), 4.39-4.21 (8 H, m, H-12, 12', 21, 21'), 3.47 (2 H, dd, *J* 16.0, 9.0, 1.0, H-15a, 15'a), 3.24-3.15 (2 H, m, H-24, 24'), 3.18 (3 H, s, H-27/28), 3.17 (3 H, s, H-27'/28'), 3.11 (3 H, s, H-27/28), 3.10 (3 H, s, H-27'/28'), 2.88 (1 H, dd, *J* 16.0, 2.0, H-15b), 2.87 (1 H, dd, *J* 16.0, 2.0, H-15'b), 1.65-1.53 (6 H, m, H-16, 16', 17, 17'), 1.35 (3 H, t, *J* 7.0, H-22), 1.34 (3 H, t, *J* 7.0, H-22'), 1.11 (3 H, d *J* 6.5, H-25/26), 1.10 (3 H, d *J*

6.5, H-25'/26'), 1.05 (3 H, d, *J* 7.0, H-18/19), 1.04 (3 H, d, *J* 7.0, H-18'/19'), 1.01 (3 H, t, *J* 7.0, H-18/19), 0.99 (3 H, d, *J* 7.0, H-18'/19'), 0.88 (3 H, d *J* 6.5, H-25/26), 0.87 (3 H, d *J* 6.5, H-25'/26'); δ_C (100 MHz, $CDCl_3$) 168.4 (C-4/7), 168.3 (C-4'/7'), 162.8 (C-4/7), 162.7 (C-4'/7'), 161.7 (d, C-2, 2'), 150.9 (C-10), 150.7 (C-10'), 139.6 (C-23), 139.4 (C-23'), 131.4 (C-9), 131.3 (C-9'), 102.0 (C-3), 101.7 (C-3'), 76.6 (C-13/14), 76.4 (C-13'/14'), 75.7 (C-13/14), 75.5 (C-13'/14'), 68.2 (C-12), 68.1 (C-12'), 62.8 (d, C-21, 21'), 51.0 (C-6), 50.9 (C-6'), 42.4 (C-16), 42.2 (C-16'), 39.3 (C-27/28), 39.1 (C-27'/28'), 38.9 (d, C-27/28, 27'/28'), 26.6 (d, C-24, 24'), 25.0 (C-17), 24.9 (C-17'), 24.4 (C-15), 24.3 (C-15'), 23.5 (C-18/19), 23.3 (C-18'/19'), 22.3 (d, C-25/26, 25'/26'), 22.0 (C-18/19), 21.9 (C-18'/19'), 21.7 (d, C-25/26, 25'/26'), 14.2 (d, C-22, 22'); *m/z* (ESI) 562 $[MH]^+$. Calcd. for $C_{23}H_{36}N_3O_9S_2$: 562.1887. Found: $[MH]^+$, 562.1886 (0.2 ppm error).

Lab. Book: RD06/071/C1

(3*R,4*S**,8*R**,11*Z*)-8-*iso*-Butyl-11-(2-methylpropylidene)-6,9-dioxo-2,3,4,5,8,9,10,11-octahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-3,4-diyl dimethanesulfonate 326**

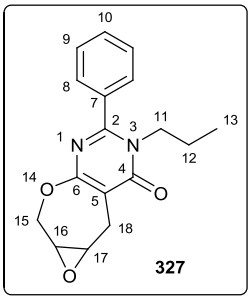


To a solution of diol **323** (0.0400 g, 0.100 mmol, 1.0 eq.) in pyridine (1.5 mL) was added MsCl (0.0380 mL, 0.500 mmol, 5.0 eq.). The reaction mixture was stirred at room temperature for 2 h before being diluted with EtOAc (10 mL), washed with 1 M HCl (aq.) (3 × 10 mL), sat. $NaHCO_3$ (aq.) (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish the title compound **326** (0.0530 g, 98%) as a colourless waxy solid (1:1 mixture of diastereomers) which was used without further purification: R_f 0.50 (EtOAc); υ_{max}/cm^{-1} (neat) 3402 (N-H stretch), 2961 (C-H stretch), 1689 (broad, C=O stretch), 1586 (C=C stretch), 1534 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.45 (1 H, s, H-8), 8.38 (1 H, s, H-8'), 6.39 (1 H, d, *J* 10.0, H-20), 6.37 (1 H, d, *J* 10.0, H-20'), 5.36 (1 H, dd, *J* 9.0, 5.5, H-6), 5.35 (1 H, d, *J* 9.0, 5.5, H-6'), 5.20-5.14 (4H, m, H-13, 13', 14, 14'), 4.39 (1 H, dd, *J* 12.5, 3.5, H-12a), 4.36 (1 H, dd, *J* 12.5, 3.5, H-12'a), 4.27 (1 H, dd, *J* 13.5, 6.0, H-12b), 4.25 (1 H, dd, *J* 13.5, 6.0, H-12'b), 3.49 (1 H, 2 dd, *J* 16.0, 9.0, H-15a), 3.47 (1 H, dd, *J* 16.0, 9.0, H-15'a), 3.19 (6 H, br s, H-24/25, 24'/25'), 3.12 (3 H, s, H-24/25), 3.11

(3 H, s, H-24'/25'), 2.90 (2 H, app. dd, *J* 16.0, 3.5, H-15b, 15'b), 2.74-2.64 (2 H, m, H-21, 21'), 1.82-1.61 (6 H, m, H-16, 16', 17, 17'), 1.14 (6 H, app. d, *J* 6.5, H-22/23), 1.13 (6 H, app. d, *J* 6.5, H-22'/23'), 1.07 (3 H, d, *J* 6.5, H-18/19), 1.05 (3 H, d, *J* 6.5, H-18'/19'), 0.93 (3 H, d, *J* 6.5, H-18/19), 0.92 (3 H, d, *J* 6.5, H-18'/19'); δ_C (100 MHz, $CDCl_3$) 168.0 (C-4/7), 167.9 (C-4'/7'), 165.9 (d, C-4/7, 4'/7'), 162.7 (C-2), 162.4 (C-2'), 147.5 (C-10), 147.4 (C-10'), 128.7 (d, C-20, 20'), 123.8 (d, C-9, 9'), 102.6 (C-3), 102.3 (C-3'), 78.7 (C-13/14), 77.2 (d, C-13'/14'), 70.2 (C-13/14), 69.9 (C-13'/14'), 67.6 (d, C-12, 12'), 54.4 (C-6), 54.3 (C-6'), 42.8 (C-16), 42.6 (C-16'), 39.0 (C-24/25), 38.9 (C-24'/25'), 38.8 (C-24/25), 38.7 (C-24'/25'), 26.3 (d, C-21, 21'), 24.8 (d, C-15, 15'), 23.2 (C-17), 23.1 (C-17'), 22.1 (d, C-22/23, 22'/23'), 21.9 (d, C-22/23, 22'/23'), 21.5 (d, C-18/19, 18'/19'), 21.3 (d, C-18/19, 18'/19'); *m/z* (ESI) 534 $[MH]^+$. Calcd. for $C_{21}H_{32}N_3O_9S_2$: 534.1574. Found: $[MH]^+$, 534.1579 (1.3 ppm error).

Lab. Book: RD06/085/B1

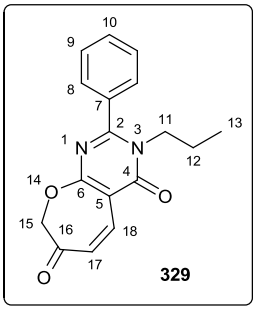
5-Phenyl-6-propyl-1a,6,8,8a-tetrahydrooxireno[5,6]oxepino[2,3-*d*]pyrimidin-7(2*H*)-one 327



To a solution of dihydro-oxepine **197** (0.0500 g, 0.180 mmol, 1.0 eq.) in acetone (0.25 mL) at –78 °C (CO_2/acetone) was added DMDO (5.90 mL, 0.0610 M solution in acetone, 0.360 mmol, 2.0 eq.). The reaction mixture was stirred at –78 °C for 2.5 h before being concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (3:2 EtOAc/PE) to furnish the *title compound* **327** (0.0070 g, 13%) as a yellow oil: R_f 0.13 (1:1 EtOAc/PE); υ_{max}/cm^{-1} (neat) 2925 (C-H stretch), 1644 (C=O stretch), 1586 (aromatic C=C stretch), 1547 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.48-7.41 (5 H, m, H-8, 9, 10), 4.61 (1 H, dd, *J* 13.0, 4.5, H-15a), 4.44 (1 H, dd, *J* 13.0, 8.0, H-15b), 3.85 (1 H, dd, *J* 13.5, 7.5, H-11), 3.83 (1 H, dd, *J* 13.5, 7.5, H-11a), 3.54 (1 H, dd, *J* 17.0, 6.0, H-18a), 3.52 (1 H, app. dt (ddd), *J* 6.0, 4.5, H-17), 3.39 (1 H, app. dt (ddd), *J* 8.0, 4.5, H-16), 2.97 (1 H, dd, *J* 17.0, 6.0, H-18b), 1.64-1.55 (2 H, m, H-12), 0.74 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 165.0 (C-4), 164.2 (C-6), 158.3 (C-2), 134.3 (C-7), 130.1 (C-10), 128.6 (C-9), 127.7 (C-8), 100.2 (C-5), 68.3 (C-15), 52.6 (C-17), 50.2 (C-16), 48.0 (C-11), 23.5 (C-18), 22.0 (C-12), 11.1 (C-13); *m/z* (ESI) 299 $[MH]^+$. Calcd. for $C_{17}H_{19}N_2O_3$: 299.1390. Found: $[MH]^+$, 299.1383. (2.8 ppm error).

Lab. Book: RD06/001/C1

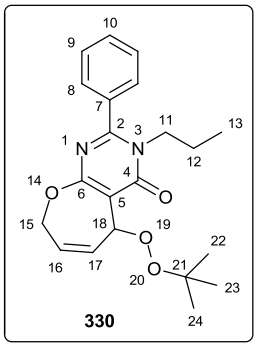
2-Phenyl-3-propyloxepino[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione 329



To a solution of dihydro-oxepine **197** (0.103 g, 0.360 mmol, 1.0 eq.) in xylenes (6.0 mL) at room temperature was added SeO_2 (0.0610 g, 0.550 mmol, 1.5 eq.). The reaction mixture was heated at 125 °C for 18 h, cooled to room temperature, filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 PE/EtOAc) to furnish the *title compound* **329** (0.0400 g, 38%) as a yellow oil: R_f 0.54 (1:1 *n*-hexane/EtOAc); υ_{max}/cm^{-1} 2967 (C-H stretch), 1660 (C=O stretch), 1604 (aromatic C=C stretch), 1528 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.72 (1 H, d, *J* 12.0, H-18), 7.55-7.48 (5 H, m, H-8, 9, 10), 6.45 (1 H, d, *J* 12.0, H-17), 4.70 (2 H, s, H-15), 3.97-3.93 (2 H, m, H-11), 1.65 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.78 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 191.9 (C-16), 168.5 (C-4), 163.1 (C-6), 161.4 (C-2), 136.3 (C-7), 133.7 (C-17), 130.9 (C-10), 128.9 (C-9), 128.8 (C-18), 127.6 (C-8), 105.3 (C-5), 76.0 (C-15), 48.5 (C-11), 21.9 (C-12), 11.0 (C-13); *m/z* (ESI) 297 $[MH]^+$. Calcd. for $C_{17}H_{17}N_2O_3$: 297.1234. Found: $[MH]^+$, 297.1930 (1.3 ppm error).

Lab. Book: RD08/002/C1

5-(*tert*-Butylperoxy)-2-phenyl-3-propyl-5,8-dihydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 330

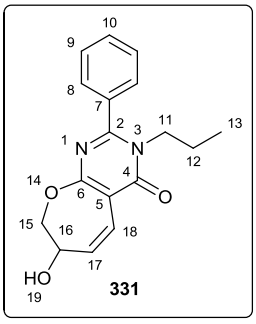


To a stirred solution of dihydro-oxepine **197** (0.0520 g, 0.180 mmol, 1.0 eq.) in benzene (2.3 mL) at room temperature was added Celite® (0.300 g), pyridinium dichromate (0.280 g, 0.740 mmol, 4.0 eq.) and *tert*-butyl hydrogen peroxide (5.5 M solution in decane, 0.130 mL, 0.740 mmol, 4.0 eq.). The reaction mixture was stirred at room temperature for 4 d before being filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 - 2:3 *n*-hexane/EtOAc) to furnish enone **329** (0.0180 g, 33%) and the *title compound* **330** (0.0080 g, 12%) as a colourless oil: R_f 0.61 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 2973 (C-H stretch), 1651 (C=O stretch), 1570 (aromatic C=C stretch), 1549 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.49-7.42 (5 H, m, H-8, 9, 10), 6.46 (1 H, ddt, *J* 10.0, 7.0, 1.5, H-17), 6.17 (1 H, app. dtd (dddd), *J* 10.0, 7.0, 1.5, H-16), 5.82 (1 H, dd, *J* 7.0, 1.5, H-18), 5.50 (1 H, ddd, *J* 12.5, 7.0, 1.5, H-15a), 4.49 (1 H, ddd,

J 12.5, 7.0, 1.5, H-15b), 3.92-3.78 (2 H, m, H-11), 1.67-1.56 (2 H, m, H-12), 1.32 (9 H, s, H-22, 23, 24), 0.74 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 167.0 (C-4), 164.0 (C-6), 160.2 (C-2), 135.8 (C-17), 134.4 (C-7), 130.1 (C-10), 128.6 (C-9), 127.9 (C-16), 127.6 (C-8), 99.9 (C-5), 81.0 (C-21), 72.0 (C-18), 64.5 (C-15), 48.0 (C-11), 26.5 (C-22, 23, 24), 22.0 (C-12), 11.0 (C-13); *m/z* (ESI) 371 $[MH]^+$. Calcd. for $C_{21}H_{27}N_2O_4$: 371.1965. Found: $[MH]^+$, 371.1967 (0.4 ppm error).

Lab. Book: RD07/096/C1

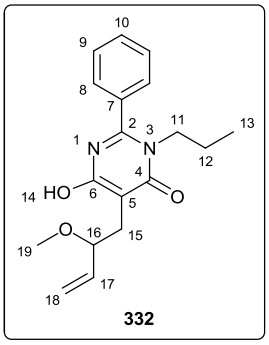
7-Hydroxy-2-phenyl-3-propyl-7,8-dihydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 331



To a solution of dihydro-oxepine **197** (0.101 g, 0.360 mmol, 1.0 eq.) in 1,4-dioxane (6 mL) at room temperature was added SeO_2 (0.0440 g, 0.390 mmol, 1.1 eq.). The reaction mixture was heated at 75 °C for 1 h, cooled to room temperature, filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 EtOAc/PE) to furnish enone **xx** (0.0110 g, 10%) and the *title compound* **331** (0.0560 g, 52%) as an off-white foam: R_f 0.23 (1:1 *n*-hexane/EtOAc); υ_{max}/cm^{-1} 3391 (O-H) stretch, 2968 (C-H stretch), 1649 C=O stretch), 1569 (aromatic C=C stretch), 1538 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.52-7.44 (5 H, m, H-8, 9, 10), 6.89 (1 H, dd, *J* 12.0, 1.0, H-18), 6.17 (1 H, dd, *J* 12.0, 5.0, H-17), 4.50 (1 H, app. tdd (dddd), *J* 5.0, 2.0, 1.0, H-16), 4.37 (1 H, ddd, *J* 11.5, 5.0, 1.0, H-15a), 4.31 (1 H, dd, *J* 11.5, 2.0, H-15b), 3.92-3.88 (2 H, m, H-11), 1.89 (1 H, br. s, H-19), 1.63 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.75 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 166.1 (C-4), 163.8 (C-6), 158.2 (C-2), 134.0 (C-7), 132.5 (C-17), 130.3 (C-10), 128.6 (C-9), 127.7 (C-8), 120.3 (C-18), 103.3 (C-5), 73.5 (C-15), 68.3 (C-16), 48.1 (C-11), 21.9 (C-12), 11.0 (C-13); *m/z* (ESI) 299 $[MH]^+$. Calcd. for $C_{17}H_{19}N_2O_3$: 299.1390. Found: $[MH]^+$, 299.1397 (1.9 ppm error).

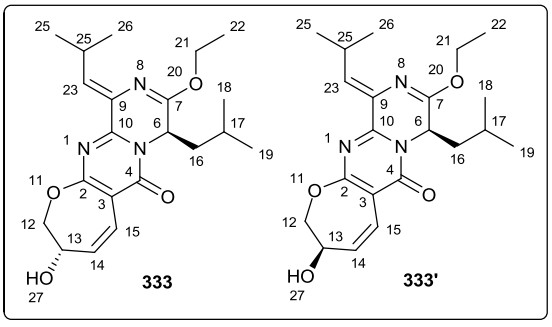
Lab. Book: RD07/028/C1

6-Hydroxy-5-(2-methoxybut-3-en-1-yl)-2-phenyl-3-propylpyrimidin-4(3*H*)-one 332



A solution of dihydro-oxepine **197** (0.0500 g, 0.180 mmol, 1.0 eq.) in MeOH (3.0 mL) was heated at reflux for 5 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1:1 *n*-hexane/EtOAc) to furnish the *title compound* **332** (0.0310 g, 55%) as a colourless waxy solid: R_f 0.20 (1:1 *n*-hexane/EtOAc); υ_{max}/cm^{-1} 3040 (O-H stretch), 2967 (C-H stretch), 1627 (C=O stretch), 1533 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 10.29 (1 H, br. s, H-14), 7.51-7.43 (5 H, m, H-8, 9, 10), 5.73 (1 H, ddd, *J* 17.5, 10.5, 8.0, H-17), 5.25 (1 H, ddd, *J* 10.5, 1.5, 0.5, H-18a), 5.27 (1 H, ddd, *J* 17.5, 1.5, 1.0, H-18b), 3.91 (1 H, app. td (ddd), *J* 8.0, 3.5, H-16), 3.85 (1 H, app. t (dd), *J* 7.5, H-11), 3.83 (1 H, app. t (dd), *J* 7.5, H-11a), 3.36 (3 H, s, H-19), 2.97 (1 H, dd, *J* 15.0, 3.5, H-15a), 2.75 (1 H, dd, *J* 15.0, 8.0, H-15b), 1.59 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.73 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 165.0 (C-4), 163.8 (C-6), 158.7 (C-2), 136.9 (C-17), 133.9 (C-7), 130.1 (C-10), 128.5 (C-9), 127.6 (C-8), 117.8 (C-18), 99.2 (C-5), 83.0 (C-16), 56.2 (C-19), 47.7 (C-11), 29.3 (C-15), 22.1 (C-12), 11.0 (C-13); *m/z* (ESI) 315 $[MH]^+$. Calcd. for $C_{18}H_{23}N_2O_3$: 315.1703. Found: $[MH]^+$, 315.1698 (2.2 ppm error).
Lab. Book: RD07/053/C1

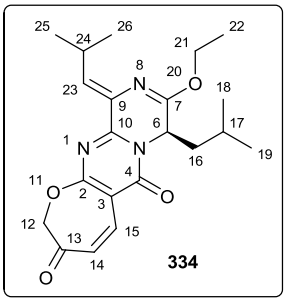
(3*S,8*R**,11*Z*)-9-Ethoxy-3-hydroxy-8-*iso*-butyl-11-(2-methylpropylidene)-2,3,8,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 333**



To a solution of dihydro-oxepine **298** (0.188 g, 0.510 mmol, 1.0 eq.) in 1,4-dioxane (8 mL) was added SeO_2 (0.0620 g, 0.560 mmol, 1.1 eq.). The reaction mixture was heated to 90 °C for 30 min before being cooled to room temperature, filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 DCM/acetone) to afford enone **334** (0.250 g, 13%) and the *title compound* **333** (0.116 g, 58%) as a yellow oil (1:1 mixture of diastereomers): R_f 0.26 (3:2 n-hexane/EtOAc); υ_{max}/cm^{-1} 3400 (O-H stretch), 2959

(C-H stretch), 1658 (C=O stretch), 1524 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.80 (1 H, d, *J* 12.0, H-15), 6.79 (1 H, d, *J* 12.0, H-15'), 6.57 (1 H, d, *J* 9.5, H-23), 6.55 (1 H, d, *J* 9.5, H-23'), 6.08 (1 H, dd, *J* 12.0, 4.0, H-14), 6.04 (1 H, dd, *J* 12.0, 4.0, H-14'), 5.25 (1 H, dd, *J* 10.0, 6.0, H-6), 5.23 (1 H, dd, *J* 10.0, 6.0, H-6'), 4.51-4.44 (2 H, m, H-13, 13'), 4.38-4.21 (8 H, m, H-12, 12', 21, 21'), 3.26-3.16 (2 H, m, H-24, 24'), 1.83 (1 H, d, *J* 9.0, H-27), 1.80 (1 H, d, *J* 9.0, H-27'), 1.68-1.59 (6 H, m, H-16, 16', 17, 17'), 1.35 (6 H, app. t, *J* 7.0, H-22, 22'), 1.08 (3 H, d, *J* 6.5, H-25/26), 1.07 (3 H, d, *J* 6.5, H-25'/26'), 1.02 (3 H, d, *J* 6.5, H-25/26), 1.01 (3 H, d, *J* 6.5, H-25'/26'), 0.96 (6 H, app. d, *J* 6.0, H-018/19, 18'/19'), 0.84 (3 H, d, *J* 6.0, H-18/19), 0.83 (3 H, d, *J* 6.0, H-18'/19'); δ_C (100 MHz, $CDCl_3$) 167.7 (C-4/7), 167.2 (C-4'/7'), 162.4 (d, C-4/7, 4'/7'), 161.8 (d, C-2, 2'), 149.6 (C-10), 149.5 (C-10'), 139.6 (C-23), 139.4 (C-23'), 131.5 (C-14), 131.4 (C-14'), 131.3 (C-9), 131.0 (C-9'), 121.1 (C-15), 120.4 (C-15'), 102.4 (d, C-3, 3'), 73.8 (C-12), 73.6 (C-12'), 68.9 (C-13), 68.6 (C-13'), 62.7 (d, C-21, 21'), 50.8 (C-6), 50.7 (C-6'), 42.4 (C-16), 42.3 (C-16'), 26.6 (d, C-24, 24'), 24.9 (d, C-17, 17'), 23.5 (C-18/19), 23.4 (C-18'/19'), 22.3 (d, C-25/26, 25'/26'), 21.9 (d, C-25/26, 25'/26'), 21.7 (d, C-18/19, 18'/19'), 14.1 (d, C-22, 22'); *m/z* (ESI) 388 $[MH]^+$. Calcd. for $C_{21}H_{30}N_3O_4$: 388.2231. Found: $[MH]^+$, 388.2228 (1.4 ppm error).

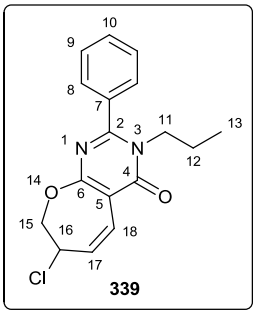
Lab Book: RD08/015/C1; RD07/068/C1



Also isolated was (8*R**,11*Z*)-9-ethoxy-8-*iso*-butyl-11-(2-methylpropylidene)-8,11-dihydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-3,6(2*H*)-dione **334** (0.0250 g, 13%) as a yellow oil: R_f 0.20 (4:1 n-hexane/EtOAc); υ_{max}/cm^{-1} 2960 (C-H stretch), 1659 (C=O stretch), 1514 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.65 (1 H, d, *J* 12.0, H-15), 6.73 (1 H, d, *J* 9.5, H-23), 6.38 (1 H, d, *J* 12.0, H-14), 5.31 (1 H, dd, *J* 7.5, 5.5, H-6), 4.68 (2 H, s, H-12), 4.40-4.26 (2 H, m, H-21), 3.23 (1 H, dsept., *J* 9.5, 6.5, H-24), 1.67-1.60 (3 H, m, H-16, 17), 1.37 (3 H, t, *J* 7.0, H-22), 1.12 (3 H, d, *J* 6.5, H-25/26), 1.07 (3 H, d, *J* 6.5, H-18/19), 1.01 (3 H, d, *J* 6.5, H-25/26), 0.90 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 192.0 (C-13), 169.4 (C-4/7), 161.6 (C-4/7), 161.5 (C-2), 152.3 (C-10), 142.0 (C-23), 136.1 (C-15), 131.3 (C-9), 127.9 (C-14), 104.3 (C-3), 76.0 (C-12), 62.9 (C-21), 50.8 (C-6), 42.4 (C-16), 26.8 (C-24), 24.9 (C-17), 23.2 (C-18/19), 22.1 (C-25/26), 21.8 (C-18/19), 21.7 (C-25/26), 14.1 (C-22); *m/z* (ESI) 386 $[MH]^+$. Calcd. for $C_{21}H_{28}N_3O_4$: 386.2074. Found: $[MH]^+$, 386.2075 (0.4 ppm error).

Lab Book: RD08/008/A1, RD08/015/C1

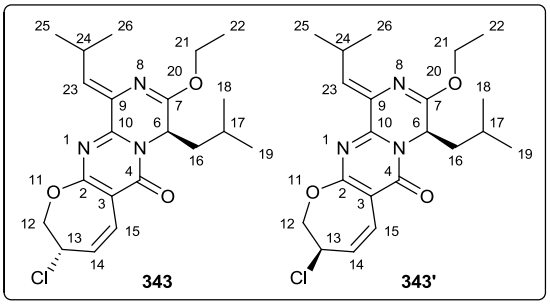
7-Chloro-2-phenyl-3-propyl-7,8-dihydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 339



To a stirred solution of allylic alcohol **331** (0.0300 g, 0.100 mmol, 1.0 eq.) in DCM (2 mL) was added NEt_3 (0.0280 mL, 0.200 mmol, 2.0 eq.), MsCl (0.0160 mL, 0.200 mmol, 2.0 eq.) and DMAP (0.001 g, 0.010 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 4 h before being quenched by the addition of sat. NH_4Cl (aq.) (10 mL) and extracted with DCM (2 × 10 mL). The combined organic phase was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The *title compound* **339** was isolated as a yellow film (0.031 g, 98%) and was used without further purification: R_f 0.57 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 2967 (C-H stretch), 1658 (C=O stretch), 1567 (aromatic C=C stretch), 1538 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.51-7.44 (5 H, m, H-8, 9, 10), 6.89 (1 H, dd, *J* 12.0, 1.5, H-18), 6.11 (1 H, ddd, *J* 12.0, 4.0, 1.0, H-17), 4.86 (1 H, dddd, *J* 7.0, 4.0, 3.0, 1.5, H-16); 4.64 (1 H, ddd, *J* 12.0, 3.0, 1.0, H-15a), 4.35 (1 H, dd, *J* 12.0, 7.0, H-15b), 3.96-3.83 (2 H, m, H-11), 1.62 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.75 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 166.2 (C-4), 163.6 (C-6), 158.6 (C-2), 134.1 (C-7), 130.4 (C-10), 129.9 (C-17), 128.7 (C-9), 127.7 (C-8), 120.9 (C-18), 102.8 (C-5), 72.3 (C-15), 54.9 (C-16), 48.2 (C-11), 21.9 (C-12), 11.0 (C-13); *m/z* (ESI) 317 $[MH]^+$. Calcd. for $C_{17}H_{18}ClN_2O_2$: 317.1051. Found: $[MH]^+$, 317.1051 (0.1 ppm error).

Lab. Book: RD07/032/C1

(3*S,8*R**,11*Z*)-3-Chloro-9-ethoxy-8-*iso*-butyl-11-(2-methylpropylidene)-2,3,8,11-tetrahydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 343**

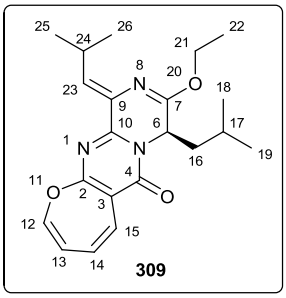


To a solution of allylic alcohol **333** (0.236 g, 0.610 mmol, 1.0 eq.) in DCM (9 mL) was added NEt_3 (0.130 mL, 0.910 mmol, 1.5 eq.), MsCl (0.0700 mL, 0.910 mmol, 1.5 eq.) and DMAP (0.0070 g, 0.0610 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 1.5 h and then quenched by the addition of sat. NH_4Cl (aq.) (10 mL) and extracted with DCM (3 × 10 mL). The combined organic phase was washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish the *title compound* **343** (0.230 g, 93%) as a yellow oil

(1:1 mixture of diastereomers) which was used without further purification: R_f 0.61 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 2959 (C-H stretch), 1658 (C=O stretch), 1524 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.83 (1 H, dd, *J* 12.0, 1.0, H-15), 6.81 (1 H, dd, *J* 12.0, 1.0, H-15'), 6.60 (2 H, app. d, *J* 9.5, H-23, 23'), 6.06-6.00 (2 H, m, H-14, 14'), 5.29-5.25 (2 H, m, H-6, 6'), 4.87-4.82 (2 H, m, H-13, 13'), 4.64 (1 H, ddd, *J* 12.0, 3.0, 1.0, H-12a), 4.58 (1 H, ddd, *J* 12.0, 2.5, 1.0, H-12'a), 4.41 (1 H, dd, *J* 12.0, 6.0, H-12b), 4.40 (1 H, dd, *J* 12.0, 6.0, H-12'b), 4.34-4.26 (4 H, m, H-21, 21'), 3.25-3.16 (2 H, m, H-24, 24'), 1.62-1.56 (6 H, m, H-16, 16', 17, 17'), 1.35 (3 H, t, *J* 7.0, H-22), 1.34 (3 H, t, *J* 7.0, H-22'), 1.10 (6 H, app. d, *J* 7.0, H-25/26, 25'/26'), 1.04 (6 H, app. d, *J* 7.0, H-25/26, 25'/26'), 1.00 (3 H, d, *J* 6.5, H-18/19), 0.99 (3 H, d, *J* 6.5, H-18'/19'), 0.88 (3 H, d, *J* 6.5, H-18/19), 0.87 (3 H, d, *J* 6.5, H-18'/19'); δ_C (100 MHz, $CDCl_3$) 167.2 (C-4/7), 167.0 (C-4'/7'), 162.1 (d, C-4/7, 4'/7'), 161.7 (d, C-2, 2'), 149.7 (d, C-10, 10'), 139.7 (d, C-23, 23'), 131.2 (d, C-9), 129.1 (C-14'), 128.7 (C-14'), 121.2 (C-15), 120.5 (C-15'), 101.7 (C-3), 101.6 (C-3'), 72.4 (C-12), 72.3 (C-12'), 62.6 (d, C-21, 21'), 55.5 (C-13), 54.7 (C-13'), 50.6 (C-6), 50.5 (C-6'), 42.2 (d, C-16, 16'), 26.6 (d, C-24, 24'), 24.8 (d, C-17, 17'), 23.3 (C-18/19), 23.2 (C-18'/19'), 22.2 (d, C-25/26, 25'/26'), 21.8 (d, C-25/26, 25'/26'), 21.7 (C-18/19), 21.6 (C-18'/19'), 14.1 (d, C-22, 22'); *m/z* (APCI, sample injected in MeCN) 406 $[MH]^+$. Calcd. for $C_{21}H_{29}{}^{35}ClN_3O_3$: 406.1892. Found: $[MH]^+$, 406.1882 (2.4 ppm error).

Lab. Book: RD08/007/C1, RD09/097/B1

(8*R**,11*Z*)-9-Ethoxy-8-*iso*-butyl-11-(2-methylpropylidene)-8,11-dihydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidin-6-one 309



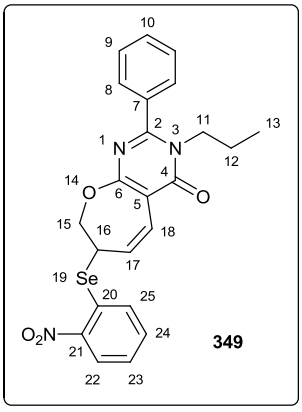
309

To a solution of allylic chloride **343** (0.225 g, 0.550 mmol, 1.0 eq.) in DMSO (9 mL) at room temperature was added TBAF (1 M solution in THF, 1.17 mL, 1.17 mmol, 2.1 eq.). The reaction mixture was stirred at room temperature for 10 min, quenched by the addition of sat. NH_4Cl (aq.) (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (19:1 PE/EtOAc) to furnish the *title compound* **309** (0.0200 g, 10%) as an orange oil: R_f 0.47 (9:1 PE/EtOAc); υ_{max}/cm^{-1} 2959 (C-H stretch), 1660 (C=O stretch), 1515 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 6.74 (1 H, d, *J* 11.0, H-15), 6.56 (1 H, d, *J* 9.0, H-23),

6.09 (1 H, dd, *J* 11.0, 5.5, H-14), 6.09 (1 H, d, *J* 5.5, H-12), 5.59 (1 H, app. t (dd), *J* 5.5, H-13), 5.30-5.27 (1 H, m, H-6), 4.41-4.27 (2 H, m, H-21), 3.21 (1 H, dsept., *J* 9.0, 6.5, H-24), 1.72-1.58 (3 H, m, H-16, 17), 1.35 (3 H, t, *J* 7.0, H-22), 1.12 (3 H, d, *J* 6.5, H-25/26), 1.05 (3 H, d, *J* 7.0, H-18/19), 1.01 (3 H, d, *J* 6.5, H-25/26), 0.88 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 163.5 (C-4/7), 161.7 (C-4/7), 160.9 (C-2), 151.8 (C-10), 142.9 (C-12), 139.5 (C-23), 131.4 (C-9), 127.0 (C-14), 125.8 (C-15), 117.1 (C-13), 109.4 (C-3), 62.7 (C-21), 50.6 (C-6), 42.2 (C-16), 26.6 (C-24), 24.9 (17), 23.3 (C-18/19), 22.3 (C-25/26), 21.8 (C-18/19), 21.7 (C-25/26), 14.1 (C-22); *m/z* (ESI) 370 $[MH]^+$. Calcd. for $C_{21}H_{28}N_3O_3$: 370.2125. Found: $[MH]^+$, 370.2126 (0.5 ppm error).

Lab. Book: RD09/098/C1

7-[(2-Nitrophenyl)seleno]-2-phenyl-3-propyl-7,8-dihydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 349

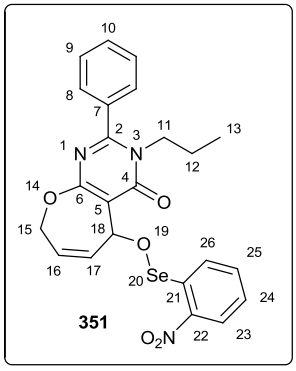


349

To a solution of allylic alcohol **331** (0.0250 g, 0.0840 mmol, 1.0 eq.) and 2-nitrophenyl selanocyanate (0.0380 g, 0.170 mmol, 2.0 eq.) in degassed THF (1.0 mL) at room temperature was added tributyl phosphine (0.105 mL, 0.420 mmol, 5.0 eq.). The reaction mixture was stirred at room temperature for 1 h before being concentrated *in vacuo* and purified by flash column chromatography on silica gel (1:1 *n*-hexane/EtOAc) to furnish the *title compound* **349** (0.025 g, 62%) as a yellow film: R_f 0.18 (1:1 *n*-hexane/EtOAc); υ_{max}/cm^{-1} 2966 (C-H stretch), 1655 (C=O stretch), 1566 (aromatic C=C stretch), 1535 (C=C stretch), 1513 (N-O asymmetric stretch); δ_H (400 MHz, $CDCl_3$) 8.28 (1 H, dd, *J* 8.5, 1.5, H-22), 7.67 (1 H, dd, *J* 8.0, 1.5, H-25), 7.57 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-24), 7.52-7.47 (5 H, m, H-8, 9, 10), 7.38 (1 H, ddd, *J* 8.5, 7.0, 1.5, H-23), 6.97 (1 H, dd, *J* 12.0, 1.5, H-18), 6.26 (1 H, dd, *J* 12.0, 5.0, H-17), 4.67 (1 H, dd, *J* 12.0, 2.0, H-15a), 4.60 (1 H, dd, *J* 12.0, 6.0, H-15b), 4.55-4.52 (1 H, m, H-16), 3.94-3.90 (2 H, m, H-11), 1.65 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.77 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 166.0 (C-4), 163.7 (C-6), 158.0 (C-2), 147.4 (C-20), 134.2 (C-7), 133.8 (C-24), 131.4 (C-21), 130.3 (C-10), 129.7 (C-25), 128.7 (C-17), 128.6 (C-9), 127.8 (C-8), 126.6 (C-22), 126.3 (C-23), 122.3 (C-18), 103.0 (C-5), 71.4 (C-15), 48.2 (C-11), 42.6 (C-16), 21.9 (C-12), 11.1 (C-13); *m/z* (ESI) 484 $[MH]^+$. Calcd. for $C_{23}H_{22}N_3O_4Se$: 484.0771. Found: $[MH]^+$, 484.0770 (1.4 ppm error).

Lab. Book: RD08/042/C1

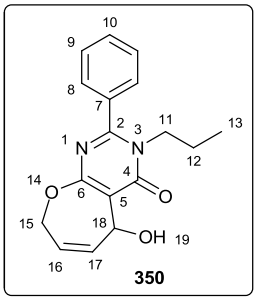
4-Oxo-2-phenyl-3-propyl-3,4,5,8-tetrahydrooxepino[2,3-*d*]pyrimidin-5-yl 2-nitrobenzeneselenenate 351



To a solution of selenide **349** (0.0430 g, 0.0900 mmol, 1.0 eq.) in DCM (3.5 mL) at –78 °C (CO_2/acetone) was added *m*-CPBA (0.0170 g, 0.0990 mmol, 1.1 eq.). The reaction mixture was stirred at –78 °C for 2 h before being quenched by the addition of sat. $NaHCO_3$ (aq.) (5 mL) and extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified by flash column chromatography on silica gel (3:2 *n*-hexane/EtOAc) to furnish allylic alcohol **350** (0.0040 g, 15%) and the *title compound* **351** (0.015 g, 33%) as an orange waxy solid: R_f 0.43 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 2965 (C-H stretch), 1644 (C=O stretch), 1569 (aromatic C=C stretch), 1547 (aromatic C=C stretch), 1501 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.42 (1 H, dd, *J* 8.5, 1.0, H-23), 8.34 (1 H, dd, *J* 8.5, 1.0, H-26), 7.79 (1 H, ddd, *J* 8.5, 7.0, 1.5, H-25), 7.50-7.43 (5 H, m, H-8, 9, 10), 7.39 (1 H, ddd, *J* 8.5, 7.0, 1.5, H-24), 6.59 (1 H, ddt, *J* 10.0, 7.0, 1.5, H-17), 6.27 (1 H, dtd, *J* 10.0, 7.0, 1.0, H-16), 5.61 (1 H, ddd, *J* 12.5, 7.0, 1.5, H-15a), 5.60 (1 H, dd, *J* 7.0, 1.0, H-18), 4.59 (1 H, ddd, *J* 12.5, 7.0, 1.5, H-15b), 3.90-3.86 (2 H, m, H-11), 1.63 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.77 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 166.2 (C-4), 164.2 (C-6), 160.2 (C-2), 144.2 (C-22), 141.3 (C-21), 137.6 (C-17), 134.8 (C-25), 134.3 (C-7), 130.3 (C-10), 128.6 (C-9), 128.5 (C-16), 127.6 (C-8), 126.9 (C-23), 126.1 (C-24), 125.2 (C-26), 103.7 (C-5), 72.5 (C-18), 64.6 (C-15), 48.1 (C-11), 22.0 (C-12), 11.1 (C-13); *m/z* (ESI) 500 $[MH]^+$. Calcd. for $C_{23}H_{22}N_3O_5Se$: 500.0270. Found: $[MH]^+$, 500.0271 (1.5 ppm error).

Lab. Book: RD08/051/C1

5-Hydroxy-2-phenyl-3-propyl-5,8-dihydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 350

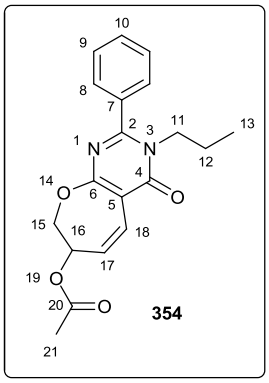


To a stirred solution of selenide **350** (0.0310 g, 0.0630 mmol, 1.0 eq.) in THF (1.25 mL) at 0 °C (ice) was added pyridine (0.0360 mL, 0.0690 mmol, 1.1 eq.) followed by hydrogen peroxide (30% w/v solution in water, 0.0720 mL, 0.640 mmol, 10.0 eq.). The reaction mixture was stirred at 0 °C for 3 h, diluted with EtOAc

(10 mL), washed with sat. $NaHCO_3$ (aq.) (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 EtOAc/n-hexane) to furnish the *title compound* **350** (0.0140 g, 70%) as a colourless solid: mp 122-124 °C; R_f 0.17 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 3410 (O-H stretch), 2965 (C-H stretch), 1635 (C=O stretch), 1572 (aromatic C=C stretch), 1546 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.51-7.44 (5 H, m, H-8, 9, 10); 6.33 (1 H, ddd, *J* 10.5, 6.0, 0.5, H-17), 6.17 (1 H, app. dt (ddd), *J* 10.5, 6.5, H-16), 5.63 (1 H, d, *J* 6.0, H-18), 5.01 (1 H, ddd, *J* 13.0, 6.5, 0.5, H-15a), 4.60 (1 H, dd, *J* 13.0, 6.5, H-15b), 4.20 (1 H, br. s, H-19), 3.88-3.84 (2 H, m, H-11), 1.63 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.76 (3 H, *t*, J 7.5); δ_C (100 MHz, $CDCl_3$) 165.7 (C-4), 165.4 (C-6), 158.8 (C-2), 137.1 (C-17), 134.0 (C-7), 130.3 (C-10), 128.6 (C-9), 127.7 (C-8), 127.0 (C-16), 105.0 (C-5), 65.4 (C-15), 63.5 (C-18), 47.8 (C-11), 22.0 (C-12), 11.1 (C-13); *m/z* (ESI) 299 $[MH]^+$. Calcd. for $C_{17}H_{19}N_2O_3$: 299.1390. Found: $[MH]^+$, 299.1387 (1.4 ppm error).

Lab. Book: RD09/010/C1

4-Oxo-2-phenyl-3-propyl-3,4,4a,7,8,9a-hexahydrooxepino[2,3-*d*]pyrimidin-7-yl acetate 354



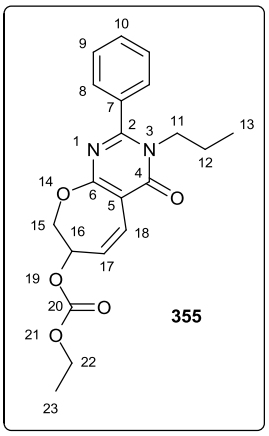
354

To a solution of allylic alcohol **331** (0.0430 g, 0.140 mmol, 1.0 eq.) in DCM (2.0 mL) at room temperature was added NEt_3 (0.039 mL, 0.280 mmol, 2.0 eq.), AcCl (0.0120 mL, 0.170 mmol, 1.2 eq.) and DMAP (cat.). The reaction mixture was stirred at room temperature for 30 min before being quenched by the addition of sat. NH_4Cl (aq.) (5 mL) and extracted with DCM (2 × 10 mL). The combined organic phase was washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 *n*-hexane/EtOAc) to furnish the *title compound* **354** (0.0260 g, 54%) as a colourless film: R_f 0.35 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 2967 (C-H stretch), 1738 (C=O stretch), 1659 (C=O stretch), 1568 (C=C stretch), 1538 (aromatic C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.51-7.44 (5 H, m, H-8, 9, 10), 7.01 (1 H, dd, *J* 12.0, 1.0, H-18), 6.04 (1 H, dd, *J* 12.0, 4.5, H-17), 5.59 (1 H, app. tdd (dddd), *J* 4.5, 2.5, 1.0, H-16), 4.41 (1 H, *J* 12.0, 4.5, H-15a), 4.37 (1 H, dd, *J* 12.0, 2.5, H-15b), 3.92-3.88 (2 H, m, H-11), 2.11 (3 H, s, H-21), 1.62 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.75 (3 H, t,

J 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 170.1 (C-20), 166.2 (C-4), 163.7 (C-6), 158.5 (C-2), 134.2 (C-7), 130.3 (C-10), 128.6 (C-9), 127.7 (C-8), 127.7 (C-17), 122.7 (C-18), 102.8 (C-5), 70.3 (C-15), 69.9 (C-16), 48.1 (C-11), 21.9 (C-12), 20.9 (C-21), 11.0 (C-13); *m/z* (ESI) 341 $[MH]^+$. Calcd. for $C_{19}H_{21}N_2O_4$: 341.1496. Found: $[MH]^+$, 341.1494 (0.4 ppm error).

Lab. Book: RD08/089/C1

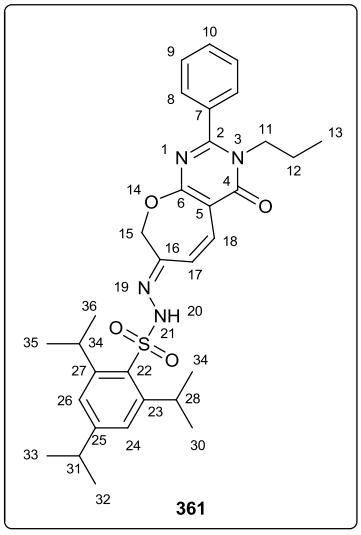
Ethyl 4-oxo-2-phenyl-3-propyl-3,4,7,8-tetrahydrooxepino[2,3-*d*]pyrimidin-7-yl carbonate 355



To a solution of allylic alcohol **331** (0.0500 g, 0.170 mmol, 1.0 eq.) in DCM (2.0 mL) at 0 °C (ice) was added NEt_3 (0.0280 mL, 0.200 mmol, 1.2 eq.), ethyl chloroformate (0.0240 mL, 0.250 mmol, 1.5 eq.) and DMAP (cat.). The reaction mixture was stirred at 0 °C for 1 h before being quenched by the addition of sat. NH_4Cl (aq.) (5 mL) and extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated *in vacuo* and the resulting crude product purified by flash column chromatography on silica gel (65:35 *n*-hexane/EtOAc) to furnish the *title compound* **355** (0.0340 g, 54%) as a colourless film: R_f 0.46 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 2969 (C-H stretch), 1743 (C=O stretch), 1660 (C=O stretch), 1568 (C=C stretch), 1539 (C=C stretch), 1253 (C-O stretch); δ_H (400 MHz, $CDCl_3$) 7.51-7.43 (5 H, m, H-8, 9, 10), 7.02 (1 H, dd, *J* 12.0, 1.5, H-18), 6.09 (1 H, dd, *J* 12.0, 4.0, H-17), 5.44 (1 H, dddd, *J* 5.5, 4.0, 2.5, 1.5, H-16), 4.46 (1 H, dd, *J* 12.0, 2.5, H-15a), 4.41 (1 H, dd, *J* 12.0, 5.5, H-15b), 4.23 (2 H, q, *J* 7.0, H-22), 3.91-3.87 (2 H, m, H-11), 1.62 (2 H, app. sext. (tq), *J* 7.5, H-12), 1.32 (3 H, t, *J* 7.0, H-23), 0.75 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 166.1 (C-4), 163.6 (C-6), 158.6 (C-2), 154.3 (C-20), 134.2 (C-7), 130.3 (C-10), 128.6 (C-9), 127.7 (C-8), 127.2 (C-17), 122.7 (C-18), 102.7 (C-5), 72.8 (C-16), 69.9 (C-15), 64.5 (C-22), 48.1 (C-11), 21.9 (C-12), 14.2 (C-13), 11.0 (C-23); *m/z* (ESI) 371 $[MH]^+$. Calcd. for $C_{20}H_{23}N_2O_5$: 371.1601. Found: $[MH]^+$, 371.1590 (3.4 ppm error).

Lab. Book: RD08/090/C1, RD09/003/C1

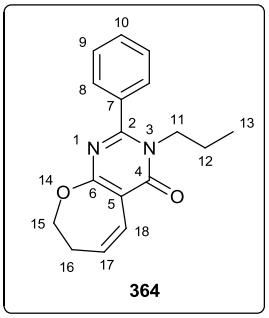
2,4,6-Tri-*iso*-propyl-*N*'-[(7*E*)-4-oxo-2-phenyl-3-propyl-3,4-dihydrooxepino[2,3-*d*]pyrimidin-7(8*H*)-ylidene]benzenesulfonohydrazide 361



To a solution of enone **329** (0.0330 g, 0.110 mmol, 1.0 eq.) in THF (0.25 mL) at room temperature was added 2,4,6-tri-*iso*-propylbenzenesulfonohydrazide (0.0410 g, 0.140 mmol, 1.5 eq.). After 2 h the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (1:1 *n*-hexane/EtOAc) to furnish the *title compound* **361** (0.0580 g, 91%) as a yellow oil: R_f 0.30 (3:2 PE/EtOAc); υ_{max}/cm^{-1} 3198 (N-H stretch), 2962 (C-H stretch), 1647 (C=O stretch), 1601 (aromatic C=C stretch), 1560 (aromatic C=C stretch), 1530 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.96 (1 H, s, H-20), 7.53-7.43 (5 H, m, H-8, 9, 10), 7.37 (1 H, d, *J* 12.0, H-18), 7.17 (2 H, s, H-24, 26), 6.45 (1 H, d, *J* 12.0, H-17), 4.75 (2 H, s, H-15), 4.26-4.19 (1 H, m, H-26/34), 4.18-4.12 (1 H, m, H-26/34), 3.93-3.90 (2 H, m, H-11), 2.95-2.86 (1 H, m, H-31), 1.63 (2 H, app. sext. (tq), *J* 7.0, H-12), 1.27 (6 H, d, *J* 7.0, H-29/30), 1.26 (6 H, d, *J* 7.0, H-32/33), 1.25 (6 H, d, *J* 7.0, H-35/36), 0.76 (3 H, t, *J* 7.0, H-13); δ_C (100 MHz, $CDCl_3$) 167.6 (C-4), 163.5 (C-6), 159.7 (C-2), 153.7 (d, C-16), 151.7 (C-23/27), 151.3 (C-23/27), 145.9 (C-22), 133.8 (C-7), 131.1 (C-25), 130.6 (C-18), 129.0 (C-10), 128.7 (C-9), 127.7 (C-8), 123.9 (C-24/26), 123.8 (C-24/26), 116.2 (C-17), 103.9 (C-5), 73.0 (C-15), 48.3 (C-11), 34.1 (C-31), 29.9 (C-28/34), 29.7 (C-28/34), 24.9 (C-29/30), 24.7 (C-32/33), 23.5 (C-35/36), 21.9 (C-12), 11.0 (C-13); *m/z* (ESI) 577 $[MH]^+$. Calcd. for $C_{32}H_{41}N_4O_4S$: 577.2843. Found: $[MH]^+$, 577.2837 (1.4 ppm error).

Lab. Book: RD08/044/C1

2-Phenyl-3-propyl-7,8-dihydrooxepino[2,3-*d*]pyrimidin-4(3*H*)-one 364

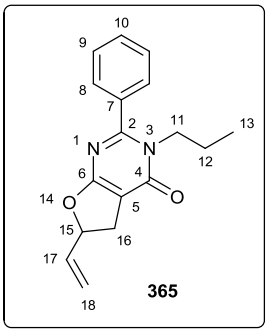


A solution of dihydro-oxepine **197** (0.0510 g, 0.180 mmol, 1.0 eq.) and $RuCl_2(PPh_3)_3$ (0.0040 g, 0.0040 mmol, 0.02 eq.) in THF (1.0 mL) was heated in a sealed microwave tube at 60 °C for 4 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by

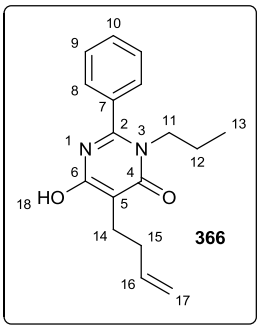
flash column chromatography on silica gel (3:2 PE/EtOAc) to furnish dihydro-oxepine **197** (0.0100 g, 20%) and the *title compound* **364** (0.0180 g, 35%) as a colourless crystalline solid: mp 107-109 °C; R_f 0.46 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 2966 (C-H stretch), 1652 (C=O stretch), 1566 (C=C stretch), 1538 (aromatic C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.50-7.45 (5 H, m, H-8, 9, 10), 6.84 (1 H, dd, *J* 12.0, 1.5, H-18), 6.08 (1 H, dt, *J* 12.0, 5.0, H-17), 4.42 (2 H, t, *J* 4.5, H-15), 3.91-3.87 (2 H, m, H-11), 2.69 (2 H, dtd, *J* 5.0, 4.5, 1.5, H-16), 1.63 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.76 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 165.9 (C-4), 164.1 (C-6), 157.0 (C-2), 134.5 (C-7), 130.5 (C-17), 130.1 (C-10), 128.5 (C-9), 127.8 (C-8), 120.3 (C-16), 103.3 (C-5), 69.5 (C-15), 48.0 (C-11), 33.1 (C-16), 22.0 (C-12), 11.1 (C-13); *m/z* (ESI) 283 $[MH]^+$. Calcd. for $C_{17}H_{19}N_2O_2$: 283.1441. Found: $[MH]^+$, 283.1444 (0.9 ppm error).

Lab. Book: RD09/085/C1

2-Phenyl-3-propyl-6-vinyl-5,6-dihydrofuro[2,3-*d*]pyrimidin-4(3*H*)-one 365



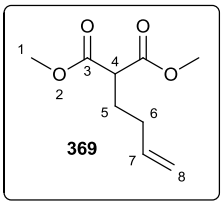
To a solution of dihydro-oxepine **197** (0.0540 g, 0.190 mmol, 1.0 eq.) in dry, degassed EtOH (5.0 mL) was added $Rh(PPh_3)_3Cl$ (0.0180 g, 0.0190 mmol, 0.1 eq.) and DBU (0.0090 mL, 0.0570 mmol, 0.3 eq.). The reaction mixture was heated at 78 °C for 1 h before being cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 PE/EtOAc) to furnish the *title compound* **365** (0.0240 g, 44%) as a colourless film: R_f 0.26 (3:2 PE/EtOAc); υ_{max}/cm^{-1} 2965 (C-H stretch), 1679 (C=O stretch), 1606 (C=C stretch), 1516 (aromatic C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.50-7.42 (5 H, m, H-8, 9, 10), 6.01 (1 H, ddd, *J* 17.0, 10.5, 6.0, H-17), 5.42 (1 H, dt, *J* 17.0, 1.0, H-18a), 5.34 (1 H, dddt, *J* 10.0, 7.0, 6.0, 1.0, H-15), 5.26 (1 H, dt, *J* 10.5, 1.0, H-18b), 3.94-3.82 (2 H, m, H-11), 3.36 (1 H, dd, *J* 15.5, 10.0, H-16a), 2.95 (1 H, dd, *J* 15.5, 7.0, H-16b), 1.60 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.74 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 170.7 (C-4), 162.4 (C-6), 160.6 (C-2), 136.1 (C-17), 135.0 (C-7), 130.1 (C-10), 128.6 (C-9), 127.6 (C-8), 117.1 (C-18), 97.6 (C-5), 83.2 (C-15), 47.5 (C-11), 31.7 (C-16), 22.3 (C-12), 11.0 (C-13); *m/z* (ESI) 283 $[MH]^+$. Calcd. for $C_{17}H_{19}N_2O_2$: 283.1441. Found: $[MH]^+$, 283.1441 (0.0 ppm error).



Also isolated was 5-(but-3-en-1-yl)-6-hydroxy-2-phenyl-3-propylpyrimidin-4(3*H*)-one **366** (0.0040 g, 7%) as a colourless film: R_f 0.13 (4:1 PE/EtOAc); υ_{max}/cm^{-1} 3067 (O-H stretch), 2966 (C-H stretch), 1656 (C=O) stretch, 1532 (aromatic C=C stretch), 1444 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.56-7.39 (5 H, m, H-8, 9, 10), 5.78 (1 H, ddt, *J* 17.0, 10.0, 6.5, H-16), 4.97 (1 H, ddt, *J* 17.0, 2.0, 1.5, H-17a), 4.90 (1 H, ddt, *J* 10.0, 2.0, 1.0, H-17b), 3.82-3.78 (2 H, m, H-11), 2.43-2.39 (2 H, m, H-14), 2.18-2.13 (2 H, m, H-15), 1.57 (2 H, app. sext. (tq), *J* 7.5, H-12), 0.73 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 163.3 (C-4), 163.1 (C-2), 158.1 (C-2), 138.7 (C-16), 132.9 (C-7), 130.4 (C-10), 128.6 (C-9), 127.6 (C-8), 114.3 (C-17), 102.3 (C-5), 47.5 (C-11), 31.6 (C-15), 22.7 (C-14), 22.2 (C-12), 11.0 (C-3); *m/z* (ESI) 285 $[MH]^+$. Calcd. for $C_{17}H_{21}N_2O_2$: 285.1598. Found: $[MH]^+$, 285.1586 (3.3 ppm error).

Lab. Book: RD09/091/C1 and C2; RD09/078/C1

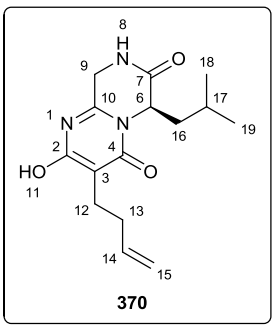
Dimethyl but-3-en-1-ylmalonate 369



To a solution of NaH (60% dispersion in mineral oil, 1.89 g, 47.0 mmol, 1.1 eq.) in DMF (100 mL) at 0 °C (ice) was added dropwise dimethyl malonate (5.00 mL, 43.0 mmol, 1.0 eq.). The reaction mixture was allowed to warm to room temperature before the addition of 4-bromo-1-butene (4.03 mL, 43.0 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for a further 18 h before being quenched by the addition of sat. NH_4Cl (aq.) (100 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phase washed with water (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 PE/ Et_2O) to furnish the *title compound* **369** (4.50 g, 56%) as a yellow oil: R_f 0.35 (9:1 PE/Et_2O); υ_{max}/cm^{-1} 2955 (C-H stretch), 1736 (C=O stretch), 1437 (C-O stretch); δ_H (400 MHz, $CDCl_3$) 5.76 (1 H, ddt, *J* 17.0, 10.0, 6.5, H-7), 5.06-4.99 (2 H, m, H-8), 3.73 (6 H, s, H-1), 3.40 (1 H, t, *J* 7.5, H-4), 2.12-2.06 (2 H, m, H-5), 2.04-1.98 (2 H, m, H-6). Data in agreement with those in the literature.[134]

Lab. Book: RD10/001/C1

(6*R)-3-(But-3-en-1-yl)-2-hydroxy-6-*iso*-butyl-8,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidine-4,7(6*H*)-dione 370**

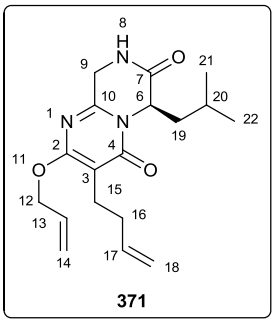


370

A solution of NaOMe was prepared by the portionwise addition of Na (0.408 g, 17.0 mmol, 6.0 eq.), to rigorously dried MeOH (8.0 mL) containing activated, powdered 3Å molecular sieves (2.00 g, 0.500 g/mmol). An exotherm occurred. Once the Na had completely reacted the solution was cooled to room temperature and dimethyl but-3-en-1-ylmalonate **369** (0.825 g, 4.43 mmol, 1.5 eq.) in MeOH (2.0 mL) followed by amidine **52** (0.500 g, 2.96 mmol, 1.0 eq.) in MeOH (2.0 mL) were added. The reaction mixture was heated at 65 °C for 2 h. After cooling to room temperature the reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (70:28:2 DCM/MeOH/aq. NH_3) before recrystallization from MeOH furnished the *title compound* **370** (0.564 g, 65%) as a colourless crystalline solid: mp 222-224 °C; R_f 0.30 (70:28:2 DCM/MeOH/aqueous NH_3); Found: C, 61.52; H, 7.18; N, 14.29; $C_{15}H_{21}N_3O_3$ requires: C, 61.84; H, 7.27; N, 14.42%; υ_{max}/cm^{-1} 3065 (N-H/O-H stretch), 2925 (C-H stretch), 1684 (C=O stretch), 1651 (C=O stretch), 1540 (C=C stretch); δ_H (400 MHz, DMSO *d*-6) 11.41 (1 H, br s, H-11), 8.52 (1 H, d, *J* 5.0, H-8), 5.79 (1 H, ddt, *J* 17.0, 10.0, 6.5, H-14), 5.00-4.95 (2 H, m, H-6, 15a), 4.90 (1 H, ddt, *J* 10.0, 2.0, 1.0, H-15b), 4.69 (1 H, d, *J* 17.5, H-9a), 3.99 (1 H, d, *J* 17.5, 5.0, H-9b), 2.38 (2 H, t, *J* 7.5, H-12), 2.17-2.11 (2 H, m, H-13), 1.74-1.59 (2 H, m, H-16a, 17), 1.45 (1 H, ddd, *J* 12.5, 7.5, 6.5, H-16b), 0.95 (3 H, d, *J* 6.5, H-18/19), 0.91 (3 H, d, *J* 6.5, H-19); δ_C (100 MHz, DMSO *d*-6) 167.7 (C-4/7), 164.2 (C-4/7), 161.3 (C-2), 151.6 (C-10), 138.4 (C-14), 114.6 (C-15), 99.1 (C-3), 53.2 (C-6), 43.4 (C-9), 39.5 (C-16), 31.5 (C-13). 24.3 (C-17), 22.7 (C-18/19), 22.1 (C-12), 21.6 (C-18/19); *m/z* (ESI) 292 $[MH]^+$. Calcd. for $C_{15}H_{22}N_3O_3$: 292.1656. Found: $[MH]^+$, 292.1647 (2.9 ppm error).

Lab. Book: RD10/013/D1

(6*R)-2-(Allyloxy)-3-(but-3-en-1-yl)-6-*iso*-butyl-8,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidine-4,7(6*H*)-dione 371**

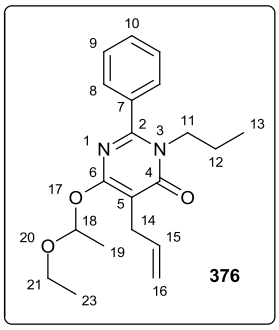


371

To a solution of pyrimidinone **370** (0.250 g, 0.860 mmol, 1.0 eq.) and allyl alcohol (0.150 mL, 2.23 mmol, 2.6 eq.) in THF (10.0 mL) at 0 °C (ice) was added PPh_3 (0.496 g, 1.89 mmol, 2.2 eq.) followed by DIAD (0.370 mL, 1.89 mmol, 2.2 eq.). The reaction mixture was allowed to warm to room temperature and then stirred for a further 2 h. The reaction mixture was quenched by the addition of 5% HCl (aq.) (20 mL) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phase washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel (1:1 PE/EtOAc) to furnish the *title compound* **371** (0.180 g, 63%) as a colourless crystalline solid: mp 144-146 °C; R_f 0.23 (1:1 PE/EtOAc); υ_{max}/cm^{-1} 3238 (N-H stretch), 2958 (C-H stretch), 1665 (C=O stretch), 1602 (C=O stretch), 1542 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.42 (1 H, d, *J* 5.0, H-8), 5.99 (1 H, ddt, *J* 17.0, 10.5, 5.5, H-13), 5.85 (1 H, ddt, *J* 17.0, 10.0, 6.5, H-17), 5.38-5.32 (2 H, m, H-6, 14a), 5.24 (1 H, app. dq (ddd), *J* 10.0, 1.5, H-14b), 4.99 (1 H, ddd, *J* 17.0, 3.5, 1.0, H-18a), 4.91 (1 H, ddd, *J* 10.0, 3.5, 1.5, H-18b), 4.86-4.75 (2 H, m, H-12), 4.54 (1 H, d, *J* 17.0, H-9a), 4.31 (1 H, dd, *J* 17.0, 5.0, H-9b), 2.59 (2 H, t, *J* 7.5, H-15), 2.32-2.22 (2 H, m, H-16), 1.85-1.69 (2 H, m, H-19a, 20), 1.64-1.59 (1 H, m, H-19b), 1.08 (3 H, d, *J* 6.5, H-21/22), 0.98 (3 H, d, *J* 6.5, H-21/22); δ_C (100 MHz, $CDCl_3$) 170.1 (C-4/7), 163.9 (C-4/7), 161.9 (C-2), 150.1 (C-10), 138.3 (C-17), 133.0 (C-13), 117.3 (C-14), 114.6 (C-18), 103.7 (C-3), 67.2 (C-12), 53.9 (C-6), 44.7 (C-9), 40.4 (C-19), 31.9 (C-16), 24.8 (C-20), 23.0 (C-21/22), 22.4 (C-15), 21.6 (C-21/22); *m/z* (ESI) 332 $[MH]^+$. Calcd. for $C_{18}H_{26}N_3O_3$: 332.1969. Found: $[MH]^+$, 332.1963 (2.2 ppm error).

Lab. Book: RD10/028/C1

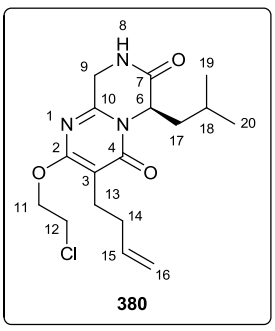
5-Allyl-6-(1-ethoxyethoxy)-2-phenyl-3-propylpyrimidin-4(3*H*)-one 376



To a solution of pyrimidinone **199** (0.0530 g, 0.190 mmol, 1.0 eq.) in ethyl vinyl ether **378** (2.0 mL, solvent) was added NEt_3 (0.0160 mL, 0.110 mmol, 0.6 eq.) and $Hg(O_2CF_3)_2$ (0.0420 g, 0.0980 mmol, 0.5 eq.). The reaction mixture was heated in a sealed microwave tube at 40 °C for 18 h before being cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 PE/EtOAc) to furnish pyrimidinone **199** (0.0230 g, 43%) and the *title compound* **376** (0.0240 g, 47%) as a colourless oil: R_f 0.50 (7:3 PE/EtOAc); υ_{max}/cm^{-1} 2925 (C-H stretch), 1662 (C=O stretch), 1595 (C=C aromatic stretch), 1531 (C=C stretch), 1443 (C-O stretch); δ_H (400 MHz, $CDCl_3$) 7.52-7.41 (5 H, m, H-8, 9, 10), 6.18 (1 H, q, *J* 5.0, H-18), 5.95 (1 H, ddt, *J* 16.5, 10.0, 6.5, H-15), 5.16 (1 H, ddt, *J* 17.0, 2.0, 1.5, H-16a), 5.00 (1 H, ddt, *J* 10.0, 2.0, 1.5, H-16b), 3.87-3.83 (2 H, m, H-11), 3.76 (1 H, dq, *J* 9.5, 7.0, H-21a), 3.53 (1 H, dq, *J* 9.5, 7.0, H-21b), 3.29 (2 H, dt, *J* 6.5, 1.5, H-14), 1.67-1.57 (2 H, m, H-12), 1.46 (3 H, d, *J* 5.0, H-19), 1.18 (3 H, t, *J* 7.0, H-23), 0.75 (3 H, t, *J* 7.5, H-13); δ_C (100 MHz, $CDCl_3$) 163.6 (C-4), 162.9 (C-6), 157.4 (C-2), 135.2 (C-15), 135.1 (C-7), 129.9 (C-10), 128.5 (C-9), 127.7 (C-8), 115.1 (C-16), 102.6 (C-5), 97.8 (C-18), 63.8 (C-21), 47.7 (C-11), 27.4 (C-14), 22.2 (C-12), 21.2 (C-19), 15.1 (C-22), 11.1 (C-13); *m/z* (ESI) 343 $[MH]^+$. Calcd. for $C_{20}H_{27}N_2O_3$: 343.2016. Found: $[MH]^+$, 343.2021 (0.3 ppm error).

Lab. Book: RD10/007/C1

(6*R)-3-(But-3-en-1-yl)-2-(2-chloroethoxy)-6-*iso*-butyl-8,9-dihydro-4*H*-pyrazino[1,2-*a*]pyrimidine-4,7(6*H*)-dione 380**

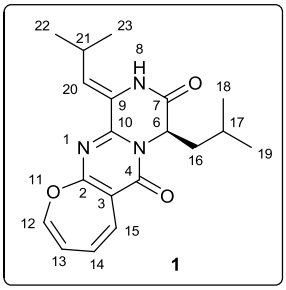


To a solution of pyrimidinone **370** (0.0500 g, 0.170 mmol, 1.0 eq.) and chloroethanol (0.0290 mL, 0.440 mmol, 2.6 eq.) in THF (2.0 mL) at 0 °C (ice) was added PPh_3 (0.0990 g, 0.380 mmol, 2.2 eq.) followed by DIAD (0.0740 mL, 0.380 mmol, 2.2 eq.). The reaction mixture was allowed to warm to room temperature and then stirred for a further 2 h. The reaction mixture was quenched by the addition of 5% HCl (aq.) (20 mL) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 10

mL) and the combined organic phase washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel (8:2 EtOAc/PE) to furnish the *title compound* **380** (0.0470 g, 78%) as a colourless crystalline solid: mp 131-132 °C; R_f 0.35 (9:1 EtOAc/PE); υ_{max}/cm^{-1} 3229 (N-H stretch), 2959 (C-H stretch), 1664 (C=O stretch), 1604 (C=O stretch), 1544 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 7.27 (1 H, d, *J* 5.0, H-8), 5.85 (1 H, ddt, *J* 17.0, 10.0, 6.5, H-15), 5.36 (1 H, ddd, *J* 9.0, 6.0, 1.0, H-6), 4.99 (1 H, ddd, *J* 17.0, 3.5, 1.5, H-16a), 4.92 (1 H, ddd, *J* 10.0, 3.5, 1.5, H-16b), 4.58-4.48 (3 H, m, H-9a, 11), 4.31 (1 H, dd, *J* 17.0, 5.0, H-9b), 3.76 (2 H, t, *J* 6.0, H-12), 2.58 (2 H, t, *J* 7.5, H-13), 2.31-2.21 (2 H, m, H-14), 1.87-1.78 (1 H, m, H-18), 1.76-1.69 (1 H, m, H-17a), 1.66-1.59 (1 H, m, H-17b), 1.08 (3 H, d, *J* 6.5, H-19/20), 0.98 (3 H, d, *J* 6.5, H-19/20); δ_C (100 MHz, $CDCl_3$) 169.9 (C-4/7), 163.5 (C-4/7), 161.8 (C-2), 150.3 (C-10), 138.3 (C-15), 114.7 (C-16), 104.1 (C-3), 66.2 (C-11), 53.9 (C-6), 44.6 (C-9), 41.9 (C-12), 40.3 (C-17), 31.9 (C-14), 24.8 (C-18), 23.0 (C-19/20), 22.3 (C-13), 21.6 (C-19/20); *m/z* (ESI) 354 $[MH]^+$. Calcd. for $C_{17}H_{25}{}^{35}ClN_3O_3$: 354.1579. Found: $[MH]^+$, 354.1572 (1.1 ppm error).

Lab. Book: RD10/017/C1

(8*R,11*Z*)-8-*iso*-Butyl-11-(2-methylpropylidene)-10,11-dihydro-6*H*-oxepino[2,3-*d*]pyrazino[1,2-*a*]pyrimidine-6,9(8*H*)-dione – (±)–Janoxepin (1)**



1

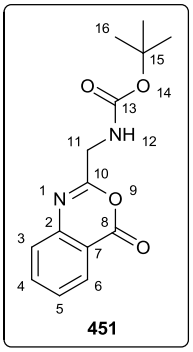
A solution of imidate **309** (0.0190 g, 0.0510 mmol, 1.0 eq.) in AcOH (1.6 mL) and water (0.4 mL) was heated at 50 °C for 1.5 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the crude product purified by flash column chromatography on silica gel (3:1 PE/EtOAc) to furnish the *title compound* **1** (0.0170 g, 98%, *er* 53:47) as an orange crystalline powder: mp 179-180 °C (Lit.[1] 88-89 °C); R_f 0.17 (7:3 PE/EtOAc); υ_{max}/cm^{-1} 3193 (N-H stretch), 2961 (C-H stretch), 1689 (C=O stretch), 1567 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.38 (1 H, s, H-8), 6.74 (1 H, d, *J* 11.0, H-15), 6.38 (1 H, d, *J* 10.0, H-20), 6.14 (1 H, dd, *J* 11.0, 5.5, H-14), 6.08 (1 H, d, *J* 5.5, H-12), 5.63 (1 H, app. t (dd), *J* 5.5, H-13), 5.39 (1 H, ddd, *J* 9.0, 5.0, 1.0, H-6), 2.67 (1 H, dsept., *J* 10.0, 6.5, H-21), 1.86-1.76 (1 H, m, H-17), 1.74-1.61 (2 H, m, H-16), 1.14 (3 H, d, *J* 6.5, H-22/23), 1.14 (3 H, d, *J* 6.5, H-22/23), 1.08 (3 H, d, *J* 6.5, H-18/19), 0.93 (3 H, d, *J* 6.5, H-18/19); δ_C (100 MHz, $CDCl_3$) 165.9 (C-7), 162.8 (C-2), 160.5 (C-4), 149.1 (C-10),

143.0 (C-12), 129.1 (C-20), 127.8 (C-14), 125.6 (C-15), 124.0 (C-9), 117.2 (C-13), 110.4 (C-3), 54.2 (C-6), 42.7 (C-16), 26.3 (C-21), 24.9 (C-17), 23.2 (C-18/19), 22.1 (C-18/19), 22.0 (C-22/23), 21.3 (C-22/23); *m/z* (ESI) 342 $[MH]^+$. Calcd. for $C_{19}H_{24}N_3O_3$: 342.1812. Found: $[MH]^+$, 342.1810 (0.9 ppm error); HPLC: Chiralpak AD-H (95:5 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 14.15 min (47.28%), 15.10 (52.72%). X-Ray crystallography: CCDC 848130 contains the supplementary crystallographic data for this compound, see Appendix **V**. Crystals were grown by slow evaporation of MeOH.

Lab. Book: RD10/022/C1, RD10/003/C1

6.4 Chapter 5 – Biomimetic Oxepine Construction: Synthesis of a Janoxepin Biosynthetic Precursor

tert-Butyl [(4-oxo-4*H*-3,1-benzoxazin-2-yl)methyl]carbamate 451

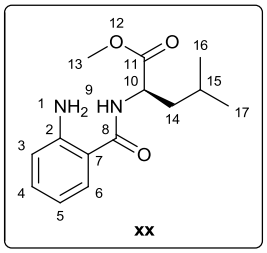


451

A suspension of anthranilic acid **42** (0.0550 g, 0.400 mmol, 1.0 eq.), *N*-Boc-glycine **450** (0.0700 g, 0.400 mmol, 1.0 eq.) and $P(OPh)_3$ (0.130 mL, 0.480 mmol, 1.2 eq.) in dry pyridine (2.0 mL) in a sealed microwave tube was heated at 70 °C for 18 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the crude product was purified by flash column chromatography on silica gel (4:1 PE/EtOAc) to furnish the *title compound* **451** (0.0610 g, 55%) as a colourless crystalline solid: 129-131 °C; R_f 0.20 (4:1 PE/EtOAc); υ_{max}/cm^{-1} 3349 (N-H stretch), 2979 (C-H stretch), 1764 (C=O stretch, 1697 (C=O stretch), 1525 (aromatic C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.19 (1 H, dd, *J* 8.0, 1.5, H-6), 7.81 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-4), 7.59 (1 H, d, *J* 8.0, H-3), 7.53 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-5), 5.32 (1 H, br s, H-12), 4.31 (2 H, d, *J* 5.5, H-11), 1.48 (9 H, s, H-16); δ_C (100 MHz, $CDCl_3$) 159.1 (C-8), 158.8 (C-10), 155.6 (C-13), 145.7 (C-2), 136.6 (C-4), 128.6 (C-6), 128.6 (C-5), 126.7 (C-3), 116.9 (C-7), 80.3 (C-15), 42.3 (C-11), 28.3 (C-16); m/z (ESI) 299 $[MH]^+$. Calcd. for $C_{14}H_{16}N_2NaO_4$: 299.1002. Found: $[MH]^+$, 299.0995 (2.1 ppm error). Compound previously reported as an intermediate, but not isolated.[155]

Lab. Book: RD10/062/C1

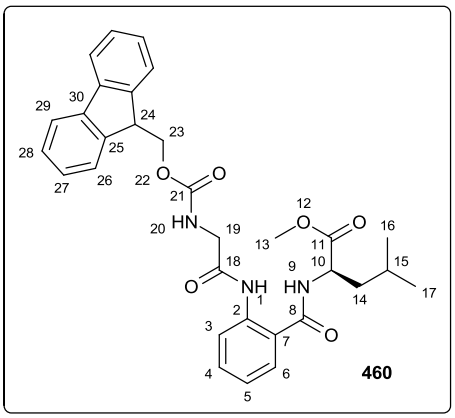
Methyl *N*-(2-aminobenzoyl)-D-leucinate 458



A suspension of isatoic anhydride **457** (5.00 g, 0.0310 mol, 1.0 eq.), methyl D-leucinate **452** (4.62 g, 0.0310 mol, 1.0 eq.) and NEt_3 (8.60 mL, 0.0620 mol, 2.0 eq.) in EtOAc (200 mL) was heated at 77 °C for 18 h. The reaction mixture was cooled to room temperature, filtered through Celite® and washed with water (200 mL) and brine (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish the *title compound* **458** (7.13 g, 87%) as a yellow-brown solid which was used without further purification: mp 64-66 °C (Lit.[183] 42-46 °C); R_f 0.26 (4:1 PE/EtOAc); $[\alpha]_D^{16}$ +7 (*c* = 2.00, DCM); δ_H (400 MHz, $CDCl_3$) 7.39 (1 H, dd, *J* 8.5, 1.5, H-6), 7.21 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-4), 6.67 (1 H, d, *J* 8.0, H-3), 6.68-6.64 (1 H, m, H-5), 6.41 (1 H, d, *J* 8.0, H-9), 5.47 (2 H, br s, H-1), 4.80 (1 H, app. td (ddd), *J* 8.0, 5.0, H-10), 3.76 (3 H, s, H-13), 1.77-1.62 (3 H, m, H-14, 15), 0.98 (3 H, d, *J* 6.0, H-16/17), 0.97 (3 H, d, *J* 6.0, H-16/17); m/z (ESI) 265 $[MH]^+$. Calcd. for $C_{14}H_{21}N_2O_3$: 265.1547. Found: $[MH]^+$, 265.1545 (0.7 ppm error). Data are consistent with those in the literature.[183]

Lab. Book: RD10/077/C1 and RD10/093/C1

Methyl *N*-[2-({*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]glycyl}amino)benzoyl]-D-leucinate 460

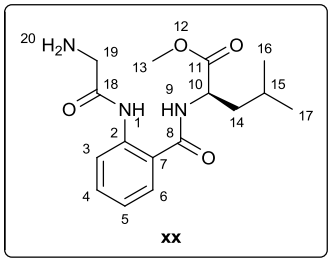


To a solution of methyl *N*-(2-aminobenzoyl)-D-leucinate **458** (3.79 g, 0.0140 mol, 1.0 eq.) in DCM (230 mL) at room temperature was added Fmoc-Gly-Cl **459** (4.89 g, 0.0160 mol, 1.1 eq.). The reaction mixture was stirred for 30 min before the addition of 1 M Na_2CO_3 (aq.) and stirring for a further 1 h. The organic phase was then separated over 18 h and the aqueous phase extracted with DCM (3 × 100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish the *title compound* **460** (6.05 g, 79%) as an off-white crystalline solid which was used without further purification: mp 61-63 °C; R_f 0.07 (4:1 PE/EtOAc); υ_{max}/cm^{-1} 3332 (N-H stretch), 3020 (aromatic C-H

stretch), 2957 (C-H stretch), 1729 (C=O stretch), 1646 (C=O stretch), 1589 (C=O stretch), 1521 (aromatic C=C stretch), 1449 (C-O stretch), 1251 (aromatic C-H bend); $[\alpha]_D^{19}$ –9 (*c* = 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 11.42 (1 H, br s, H-1), 8.60 (1 H, d, *J* 8.0, H-6), 7.77 (2 H, d, *J* 7.5, H-29), 7.66 (2 H, d, *J* 7.5, H-26), 7.55 (1 H, dd, *J* 8.0, 1.5, H-3), 7.51 (1 H, app. t (dd), *J* 8.0, H-4), 7.40 (2 H, app. t (dd), *J* 7.5, H-28), 7.32 (2 H, app. t (dd), *J* 7.5, H-27), 7.13 (1 H, app. t (dd), *J* 8.0, H-5), 6.62 (1 H, d, *J* 8.0, H-9), 5.57 (1 H, t, *J* 5.5, H-20), 4.77-4.71 (1 H, m, H-10), 4.44 (1 H, dd, *J* 14.0, 7.5, H-23a), 4.41 (1 H, dd, *J* 14.0, 7.5, H-23b), 4.28 (1 H, app. t (dd), *J* 7.5, H-24), 4.09 (1 H, dd, *J* 5.5, 2.0, H-19), 3.72 (3 H, s, H-13), 1.73-1.60 (3 H, m, H-14, 15), 0.94 (6 H, app. d, *J* 6.0, H-16, 17); δ_C (100 MHz, $CDCl_3$) 173.3 (C-11), 168.4 (C-8), 167.7 (C-18), 156.4 (C-21), 143.9 (C-25), 143.8 (C-30), 141.2 (C-2), 139.0 (C-7), 132.9 (C-4), 127.6 (C-28), 127.0 (C-27), 126.7 (C-3), 125.2 (C-26), 123.2 (C-5), 121.4 (C-6), 119.9 (C-29), 67.3 (C-23), 52.5 (C-13), 51.0 (C-10), 47.1 (C-24), 45.3 (C-19), 41.3 (C-14), 24.9 (C-15), 22.7 (C-16/17), 21.9 (C-16/17); m/z (ESI) 566 $[MH]^+$. Calcd. for $C_{31}H_{33}N_3NaO_6$: 566.2262. Found: $[MH]^+$, 566.2261 (0.2 ppm error).

Lab. Book: RD10/083/C1 and RD11/014/C1

Methyl *N*-[2-(glycylamino)benzoyl]-D-leucinate 456



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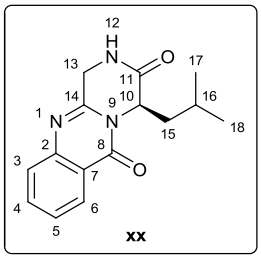
To a solution of Fmoc-amide **460** (6.05 g, 0.0110 mol, 1.0 eq.) in DCM (80 mL) was added piperidine (20 mL). The reaction mixture was stirred at room temperature for 30 min and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel (95:5 DCM/MeOH) to furnish the *title compound* **456** (2.40 g, 68%, *er* 95:5) as colourless crystalline solid: mp 130-132 °C; R_f 0.32 (9:1 DCM/MeOH); υ_{max}/cm^{-1} 3261 (N-H stretch), 2957 (C-H stretch), 1743 (C=O stretch), 1645 (C=O stretch), 1583 (C=O stretch), 1518 (aromatic C=C stretch), 1449 (C-O stretch), 1286 (aromatic C-H bend); $[\alpha]_D^{19}$ –13 (*c* = 1.02, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 11.57 (1 H, br s, H-19), 8.63 (1 H, dd, *J* 8.5, 1.0, H-6), 7.54 (1 H, dd, *J* 7.5, 1.5, H-3), 7.49 (1 H, ddd, *J* 8.5, 7.5, 1.5, H-5), 7.11 (1 H, app. td (ddd), *J* 7.5, 1.0, H-4), 6.55 (1 H, d, *J* 8.0, H-9), 4.86 (1 H, dt, *J* 8.0, 5.0, H-10), 3.77 (3 H, s, H-13), 3.51 (2 H, br s, H-20), 1.80-1.64 (3 H, m, H-14, 15), 0.99 (3 H, d, *J* 7.0, H-16/17), 0.97 (3 H, d, *J* 7.0, H16/17); δ_C (100 MHz, $CDCl_3$) 173.2 (C-11), 168.3 (C-18), 138.6 (C-2), 132.5 (C-5), 126.9 (C-3), 122.9 (C-4), 121.4 (C-6), 121.1 (C-7), 52.3 (C-13), 51.0 (C-10), 46.0 (C-19), 41.3 (C-14), 24.9 (C-15), 22.7 (C-

16/17), 21.9 C-16/17); m/z (ESI) 322 $[MH]^+$. Calcd. for $C_{16}H_{24}N_3O_4$: 322.1761. Found: $[MH]^+$, 377.1749 (3.9 ppm error); HPLC: Chiralpak AD-H (80:20 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 7.25 min (94.91%), 9.09 min (5.09%).

Lab. Book: RD10/091/C1 and RD11/053/C1

(4*R)-4-*iso*-Butyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione 431



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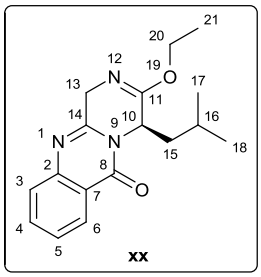
A solution of amine **456** (0.200 g, 0.620 mmol, 1.0 eq.) and $Sc(OTf)_3$ (0.306 g, 0.620 mmol, 1.0 eq.) in DMF (2.0 mL) in a sealed vial was irradiated in the microwave (50 W, 140 °C) for 10 min. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (97:1.9:0.1 DCM/MeOH/aqueous NH_3) to furnish the *title compound* **431** (0.105 g, 62%, *er* 51:49) as a yellow/brown solid: mp 220-221 °C (MeOH); R_f 0.33 (96:3.8:0.2 DCM/MeOH/aqueous NH_3); υ_{max}/cm^{-1} 3243 (N-H stretch), 2959 (C-H stretch), 1686 (C=O stretch), 1609 (C=O stretch), 1471 (C=C stretch); $[\alpha]_D^{24}$ –0.5 (*c* = 1.02, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.28 (1 H, dd, *J* 8.0, 1.5, H-6), 7.77 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-4), 7.64 (1 H, dd, *J* 8.0, 1.0, H-3), 7.51 (1 H, ddd, *J* 8.0, 7.0, 1.0, H-5), 7.34 (1 H, br s, H-12), 5.51 (1 H, ddd, *J* 8.5, 6.5, 1.5, H-10), 4.69 (1 H, d, *J* 17.0, H-13a), 4.48 (1 H, dd, *J* 17.0, 5.5, H-13b), 1.87-1.79 (2 H, m, H-15a, 16), 1.69 (1 H, ddd, *J* 15.0, 8.5, 6.5, H-15b), 1.10 (3 H, d, *J* 6.5, H-17/18), 1.02 (3 H, d, *J* 6.5, H-17/18); δ_C (100 MHz, $CDCl_3$) 170.1 (C-11), 160.3 (C-8), 148.2 (C-2), 147.0 (C-14), 134.8 (C-4), 127.2 (C-5), 127.0 (C-3), 126.9 (C-6), 120.3 (C-7), 54.1 (C-10), 45.0 (C-13), 40.5 (C-15), 24.9 (C-16), 22.9 (C-17/18), 21.8 (C-17/18); m/z (ESI) 272 $[MH]^+$. Calcd. for $C_{15}H_{18}N_3O_2$: 272.1394. Found: $[MH]^+$, 272.1391 (1.3 ppm error); HPLC: Chiralcel OD (80:20 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 9.71 min (50.59%), 18.83 min (49.41%). Data consistent with those in the literature.[177]

Lab. Book: RD11/006/C1 and RD11/047/C1

(4*R)-3-Ethoxy-4-*iso*-butyl-1,2,3,4-tetrahydro-6*H*-pyrazino[2,1-*b*]quinazolin-6-one 461**



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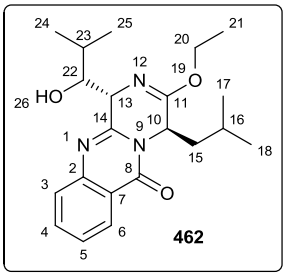
To a solution of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** (0.572 g, 2.11 mmol, 1.0 eq.) in DCM (50 mL) was added K_2CO_3 (1.16 g, 8.44 mmol, 4.0 eq.) and BF_4OEt_3 (0.802 g, 4.22 mmol, 2.0 eq.). The reaction mixture was heated at 45 °C for 1 h. After cooling to room temperature, the reaction mixture was quenched by the addition of sat. NH_4Cl (aq.) (50 mL) and the organic phase separated. The aqueous phase was extracted with DCM (2 × 30 mL) and the combined organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 PE/EtOAc) to furnish the *title compound* **461** (0.423 g, 67%) as a pale yellow oil: R_f 0.22 (3:2 PE/EtOAc); υ_{max}/cm^{-1} 2959 (C-H stretch), 1677 (C=O stretch), 1603 (aromatic C=C stretch), 1471 (C-O stretch); δ_H (400 MHz, $CDCl_3$) 8.26 (1 H, dd, *J* 8.0, 1.5, H-6), 7.74 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-4), 7.64 (1 H, dd, *J* 8.0, 1.0, H-3), 7.45 (1 H, ddd, *J* 8.0, 7.0, 1.0, H-5), 5.40 (1 H, ddd, *J* 8.5, 6.0, 1.0, H-10), 4.78 (1 H, d, *J* 19.5, H-13a), 4.67 (1 H, dd, *J* 19.5, 1.0, H-13b), 4.22-4.18 (2 H, m, H-20), 1.77-1.64 (3 H, m, H-15, 16), 1.33 (3 H, t, *J* 7.0, H-21), 1.07 (3 H, d, *J* 6.5, H-17/18), 0.97 (3 H, d, *J* 6.5, H-17/18); δ_C (100 MHz, $CDCl_3$) 164.6 (C-8), 160.4 (C-11), 151.3 (C-14), 147.4 (C-2), 134.5 (C-4), 126.8 (C-3), 126.6 (C-6), 126.5 (C-5), 120.2 (C-7), 62.1 (C-20), 50.9 (C-13), 50.3 (C-10), 40.3 (C-15), 25.1 (C16), 23.1 (C-17/18), 21.7 (C-17/18), 14.1 (C-21); m/z (ESI) 300 $[MH]^+$. Calcd. for $C_{17}H_{22}N_3O_2$: 300.1707. Found: $[MH]^+$, 300.1698 (3.1 ppm error).

Lab. Book: RD11/020/C1

(1*R,4*R**)-3-Ethoxy-1-(1-hydroxy-2-methylpropyl)-4-*iso*-butyl-1,4-dihydro-6*H*-pyrazino[2,1-*b*]quinazolin-6-one 462**

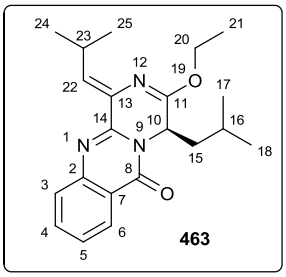


A solution of LiHMDS was prepared by the addition of *n*-BuLi (0.350 mL, 2.0 M solution in *n*-hexane, 0.700 mmol, 2.05 eq.) to a solution of HMDS (0.150 mL, 0.720 mmol, 2.10 eq.) in THF (1.0 mL) at 0 °C (ice). Following stirring at 0 °C for 20 min the solution was diluted with THF (1.0 mL) and cooled to –78 °C (CO_2/acetone). To this was added a solution of imidate **461** (0.102 g, 0.340 mmol, 1.0 eq.) in THF (2.0 mL) pre-cooled to –78 °C. The reaction

mixture was stirred at –78 °C for 10 min before the addition of *iso*-butyraldehyde **221** (0.0930 mL, 1.02 mmol, 3.0 eq.). Following stirring for a further 10 min the reaction mixture was quenched by the addition of AcOH (0.5 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between EtOAc and water (30 mL) and the organic phase separated. This was washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (85:15 PE/EtOAc) to furnish the *title compound* **462** (0.0830 g, 66%) as a pale yellow waxy solid (single diastereomer): mp 73-75 °C (*n*-hexane); R_f 0.32 (4:1 PE/EtOAc); υ_{max}/cm^{-1} 3385 (O-H stretch), 2914 (C-H stretch), 1657 (C=O stretch), 1568 (aromatic C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.25 (1 H, dd, *J* 8.0, 1.5, H-6), 7.75 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-4), 7.64 (1 H, dd, *J* 8.0, 1.0, H-3), 7.46 (1 H, ddd, *J* 8.0, 7.0, 1.0, H-5), 5.22 (1 H, ddd, *J* 9.0, 4.5, 1.0, H-10), 4.61 (1 H, d, *J* 9.0, H-13), 4.42 (1 H, br s, H-26), 4.25-4.21 (2 H, m, H-20), 3.56 (1 H, dd, *J* 9.0, 2.5, H-22), 2.17 (1 H, sept.d, *J* 7.0, 2.5, H-23), 1.94-1.84 (1 H, m, H-16), 1.76 (1 H, ddd, *J* 13.5, 9.0, 4.5, H-15a), 1.58 (1 H, ddd, *J* 13.5, 9.0, 5.0, H-15b), 1.33 (3 H, t, *J* 7.0, H-21), 1.11-1.09 (9 H, m, H-17/18, 24, 25), 0.93 (3 H, d, *J* 6.5, H-17/18); δ_C (100 MHz, $CDCl_3$) 161.7 (C-8), 160.3 (C-11), 153.4 (C-14), 146.4 (C-2), 134.7 (C-4), 126.7 (C-5), 126.7 (C-3), 126.6 (C-6), 120.0 (C-7), 78.4 (C-22), 62.5 (C-13), 61.7 (C-20), 49.6 (C-10), 45.2 (C-15), 29.5 (C-23), 25.3 (C-16), 23.4 (C-17/18), 21.5, 19.2, 14.4 (C-17/18/24/25), 14.2 (C-21); m/z (ESI) 372 $[MH]^+$. Calcd. for $C_{21}H_{30}N_3O_3$: 372.2282. Found: $[MH]^+$, 372.2278 (1.0 ppm error).

Lab. Book: RD11/043/D1

(1*Z*,4*R**)-3-Ethoxy-4-*iso*-butyl-1-(2-methylpropylidene)-1,4-dihydro-6*H*-pyrazino[2,1-*b*]quinazolin-6-one 463

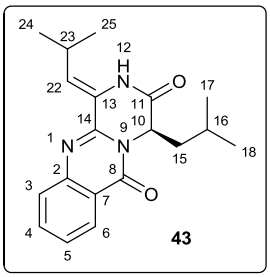


To a solution of aldol adduct **462** (0.0670 g, 0.180 mmol, 1.0 eq.) in pyridine (2.0 mL) was added MsCl (0.0420 mL, 0.540 mmol, 3.0 eq.). The reaction mixture was heated at 50 °C for 2 h, cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (95:5 PE/EtOAc) to furnish the *title compound* **463** (0.0490 g, 77%) as a pale yellow oil: R_f 0.30 (9:1 PE/EtOAc); υ_{max}/cm^{-1} 2958 (C-H stretch), 1662 (C=O stretch), 1579 (aromatic C=C stretch), 1560 (C=C stretch), 1469 (C-O stretch); δ_H (400 MHz, $CDCl_3$) 8.24 (1 H, dd, *J* 8.0, 1.5, H-6), 7.73 (1 H, ddd, *J*

8.5, 6.5, 1.5, H-4), 7.70 (1 H, dd, *J* 8.5, 1.5, H-3), 7.42 (1 H, ddd, *J* 8.0, 6.5, 1.5, H-5), 6.57 (1 H, d, *J* 9.5, H-22), 5.45 (1 H, dd, *J* 8.0, 5.5, H-10), 4.37-4.33 (2 H, m, H-20), 3.24 (1 H, dsept., *J* 9.5, 6.5, H-23), 1.70-1.59 (3 H, m, H-15, 16), 1.37 (3 H, t, *J* 7.0, H-21), 1.19 (3 H, d, *J* 6.5, H-24/25), 1.08 (3 H, d, *J* 6.5, H-24/25), 1.02 (3 H, d, *J* 6.0, H-17/18), 0.89 (3 H, d, *J* 6.0, H-17/18); δ_C (100 MHz, $CDCl_3$) 161.9 (C-8), 160.7 (C-11), 147.8 (C-14), 147.1 (C-2), 136.5 (C-22), 134.3 (C-4), 132.5 (C-13), 127.4 (C-3), 126.6 (C-6), 126.1 (C-5), 119.9 (C-7), 62.4 (C-20), 50.1 (C-10), 42.1 (C-15), 26.4 (C-23), 24.9 (C-16), 23.2 (C-17/18), 22.5 (C-24/25), 22.1 (C-24/25), 21.8 (C-17/18), 14.1 (C-21); m/z (ESI) 354 $[MH]^+$. Calcd. for $C_{21}H_{28}N_3O_2$: 354.2176. Found: $[MH]^+$, 354.2183 (2.0 ppm error).

Lab. Book: RD11/023/C1

(1*Z*,4*R)-4-*iso*-Butyl-1-(2-methylpropylidene)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione 43**

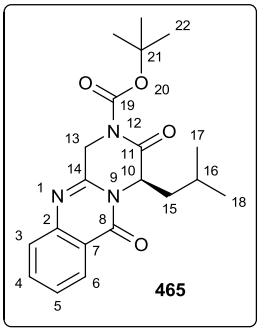


A solution of imidate **463** (0.107 g, 0.300 mmol, 1.0 eq.) in AcOH (8.0 mL) and water (2.0 mL) was heated at 50 °C for 1.5 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (7:3 PE/EtOAc) to furnish the *title compound* **43** (0.0820 g, 84%, *er* 50:50) as a colourless crystalline solid: mp 229-231 °C (MeOH/*n*-hexane); R_f 0.55 (1:1 PE/EtOAc); Found: C, 69.89; H, 7.09; N, 12.81; $C_{19}H_{23}N_3O_2$ requires: C, 70.13; H, 7.12; N, 12.91%; υ_{max}/cm^{-1} 3187 (N-H stretch), 3078 (aromatic C-H stretch), 2960 (C-H stretch), 1686 (C=O stretch), 1582 (aromatic C=C stretch), 1562 (C=C stretch); δ_H (400 MHz, $CDCl_3$) 8.59 (1 H, br s, H-12), 8.27 (1 H, dd, *J* 8.0, 1.5, H-6), 7.76 (1 H, ddd, *J* 8.5, 7.0, 1.5, H-4), 7.69 (1 H, d, *J* 8.5, 1.5, H-3), 7.47 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-5), 6.45 (1 H, d, *J* 10.0, H-22), 5.58 (1 H, ddd, *J* 8.5, 5.5, 1.0, H-10), 2.75 (1 H, dsept., *J* 10.0, 6.5, H-23), 1.83-1.71 (2 H, m, H-15a, 16), 1.65 (1 H, ddd, *J* 13.5, 8.5, 5.5, H-16), 1.21 (3 H, d, *J* 6.5, H-24/25), 1.18 (3 H, d, *J* 6.5, H-24/25), 1.08 (3 H, d, *J* 6.5, H-17/18), 0.94 (3 H, d, *J* 6.5, H-17/18); δ_C (100 MHz, $CDCl_3$) 167.4 (C-11), 160.4 (C-8), 147.4 (C-14), 145.1 (C2), 134.6 (C-4), 127.8 (C-22), 127.4 (C-3), 126.8 (C-5), 126.8 (C-6), 124.9 (C-13), 120.0 (C-7), 53.7 (C-10), 42.6 (C-15), 26.1 (C-23), 24.9 (C-16), 23.1 (C-17/18), 22.4 (C-24/25), 22.3 (C-24/25), 21.5 (C-17/18); m/z (ESI) 326 $[MH]^+$. Calcd. for $C_{19}H_{24}N_3O_2$: 326.1863. Found: $[MH]^+$, 326.1859 (0.9 ppm error). HPLC:

Chiralcel OD (95:5 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 9.74 min (50.10%), 20.02 min (49.90%). X-Ray crystallography: CCDC 862145 contains the supplementary crystallographic data for this compound, see Appendix **V**. Crystals were grown by slow diffusion (Et_2O/DCM).

Lab. Book: RD11/025/C1 and RD11/049/D1

***tert*-Butyl (4*R**)-4-*iso*-butyl-3,6-dioxo-1,3,4,6-tetrahydro-2*H*-pyrazino[2,1-*b*]quinazoline-2-carboxylate 465**



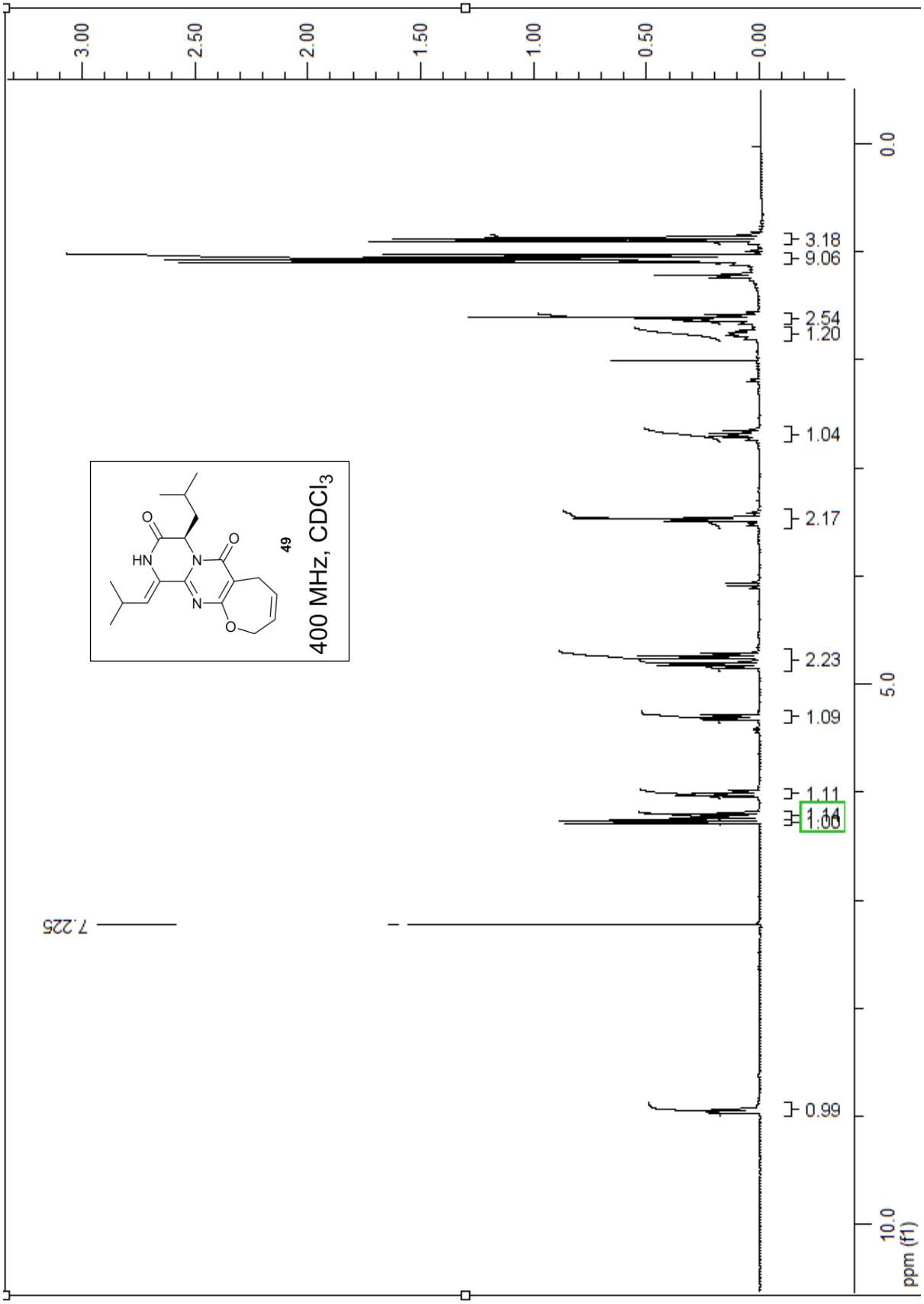
465

To a solution of pyrazino[2,1-*b*]quinazoline-3,6-dione **431** (0.105 g, 0.390 mmol, 1.0 eq.) in THF (6.0 mL) at room temperature was added NEt_3 (0.0540 mL, 0.390 mmol, 1.0 eq.) and Boc_2O (0.170 g, 0.780 mmol, 2.0 eq.) followed by DMAP (0.0050 g, 0.0390 mmol, 0.1 eq.). The reaction mixture was stirred at room temperature for 2 h before being quenched by the addition of sat. NH_4Cl (aq) (10 mL) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 15 mL) and the combined organic phase washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel (4:1 PE/EtOAc) to furnish the *title compound* **465** (0.107 g, 74%) as a colourless crystalline solid: mp 158-159 °C; R_f 0.25 (4:1 PE/EtOAc); υ_{max}/cm^{-1} 2962 (C-H stretch), 1780 (C=O stretch), 1732 (C=O stretch), 1687 (C=O stretch), 1611 (aromatic C=C stretch), 1300 (aromatic C-H bend); δ_H (400 MHz, $CDCl_3$) 8.27 (1 H, dd, *J* 8.0, 1.5, H-6), 7.78 (1 H, ddd, *J* 8.0, 7.0, 1.5, H-4), 7.66 (1 H, dd, *J* 8.0, 1.0, H-3), 7.51 (1 H, ddd, *J* 8.0, 7.0, 1.0, H-5), 5.64 (1 H, dd, *J* 8.5, 7.0, H-10), 5.27 (1 H, d, *J* 17.0, H-13a), 4.69 (1 H, d, *J* 17.0, H-13b), 1.90-1.78 (2 H, m, H-15a, 16), 1.68 (1 H, app. td (ddd), *J* 13.0, 7.0, H-15b), 1.57 (9 H, s, H-22), 1.08 (3 H, d, *J* 6.5, H-17/18), 1.04 (3 H, d, *J* 6.5, H-17/18); δ_C (100 MHz, $CDCl_3$) 165.9 (C-11), 159.8 (C-8), 150.3 (C-19), 147.9 (C-14), 147.1 (C-2), 134.8 (C-4), 127.4 (C-5), 127.1 (C-3), 126.9 (C-6), 120.4 (C-7), 85.1 (C-21), 55.6 (C-10), 47.4 (C-13), 40.7 (C-15), 27.9 (C-22), 24.9 (C-16), 22.7 (C-17/18), 21.8 (C-17/18); m/z (ESI) 372 $[MH]^+$. Calcd. for $C_{20}H_{26}N_3O_4$: 372.1918. Found: $[MH]^+$, 372.1908 (2.4 ppm error).

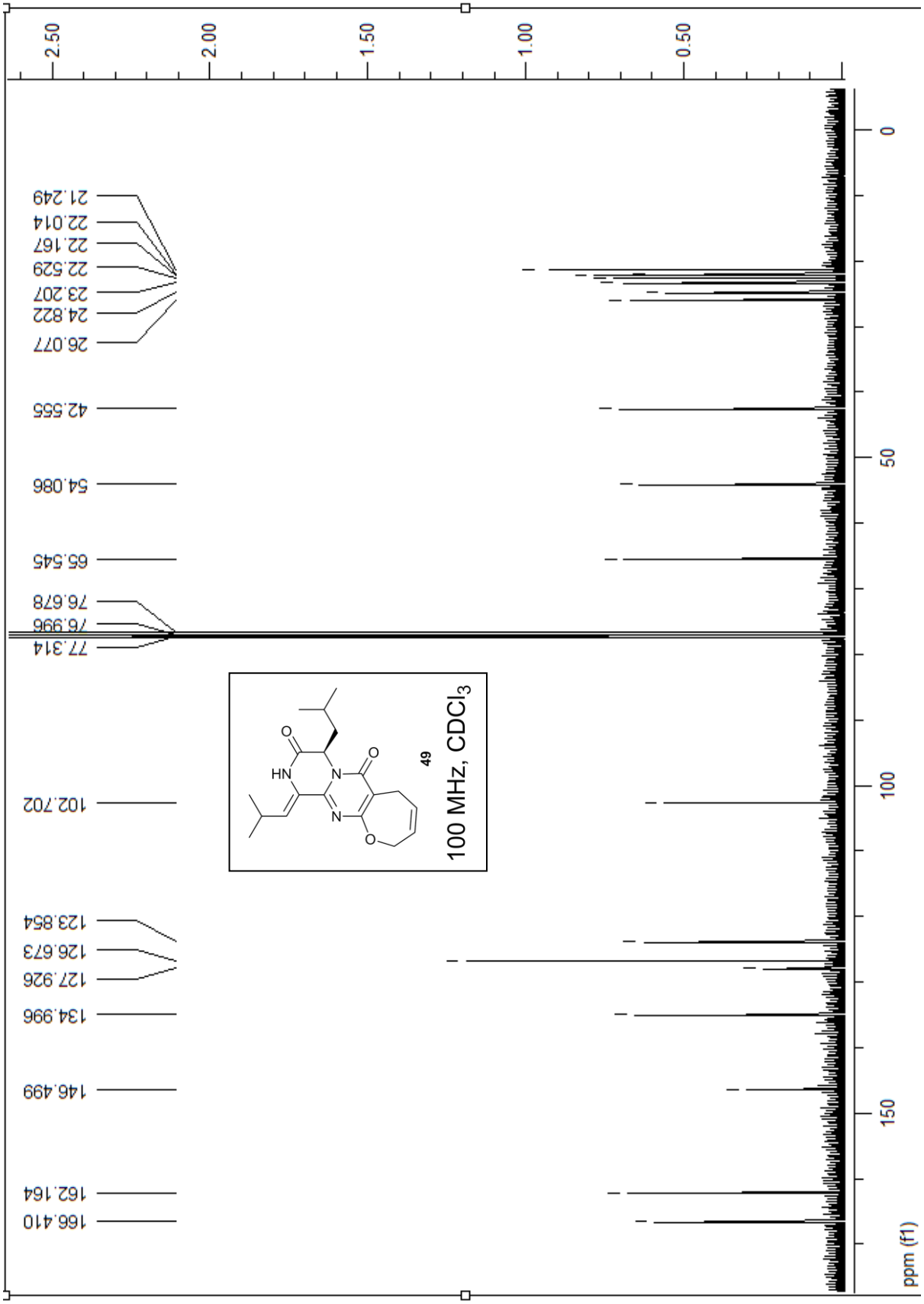
Lab. Book: RD11/011/C1

Appendix I. ^{1}H- and ^{13}C-NMR Spectra for Dihydro-Janoxepin 49

^{1}H-NMR Spectrum of Dihydro-Janoxepin **49**

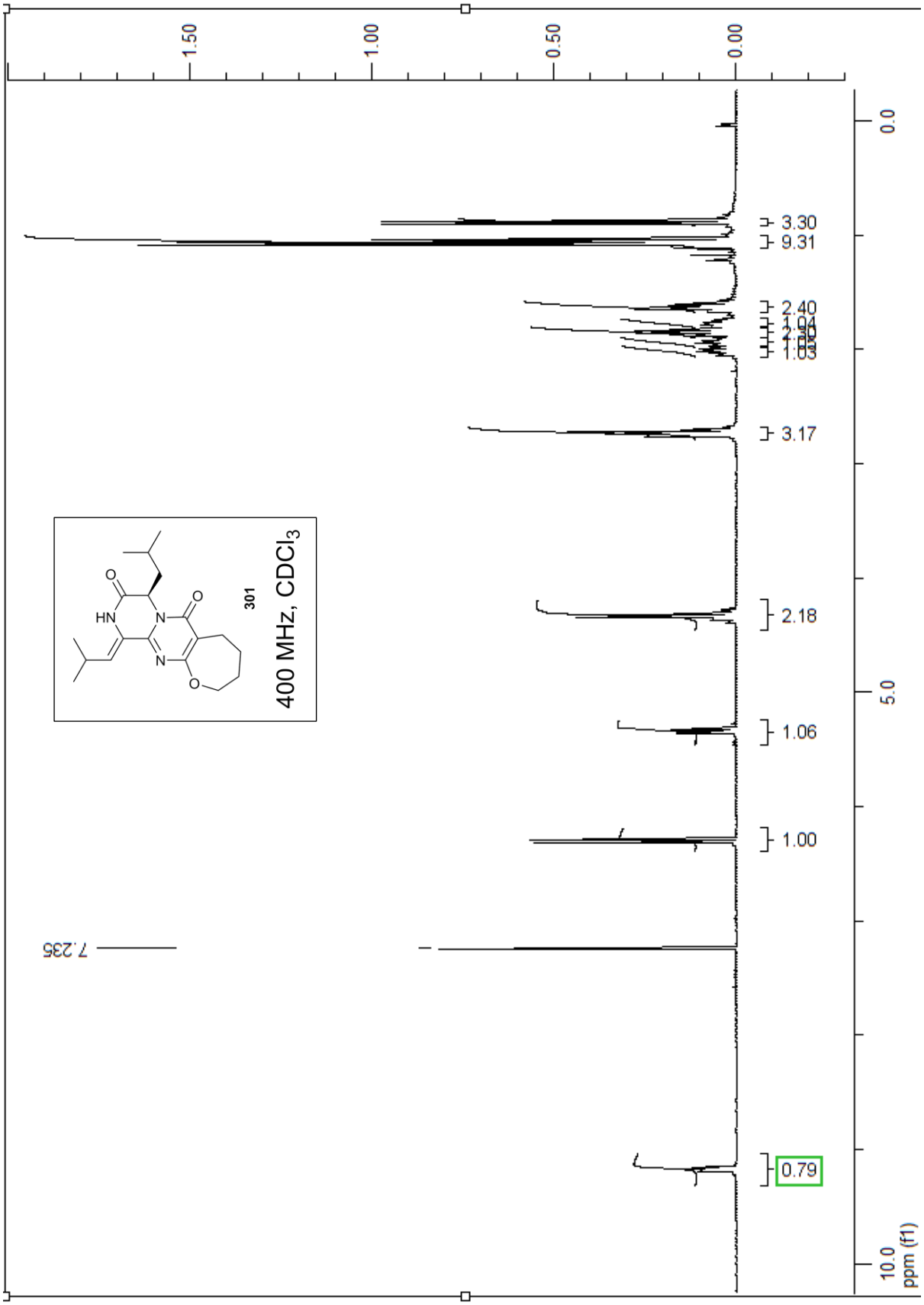


^{13}C-NMR Spectrum of Dihydro-Janoxepin **49**

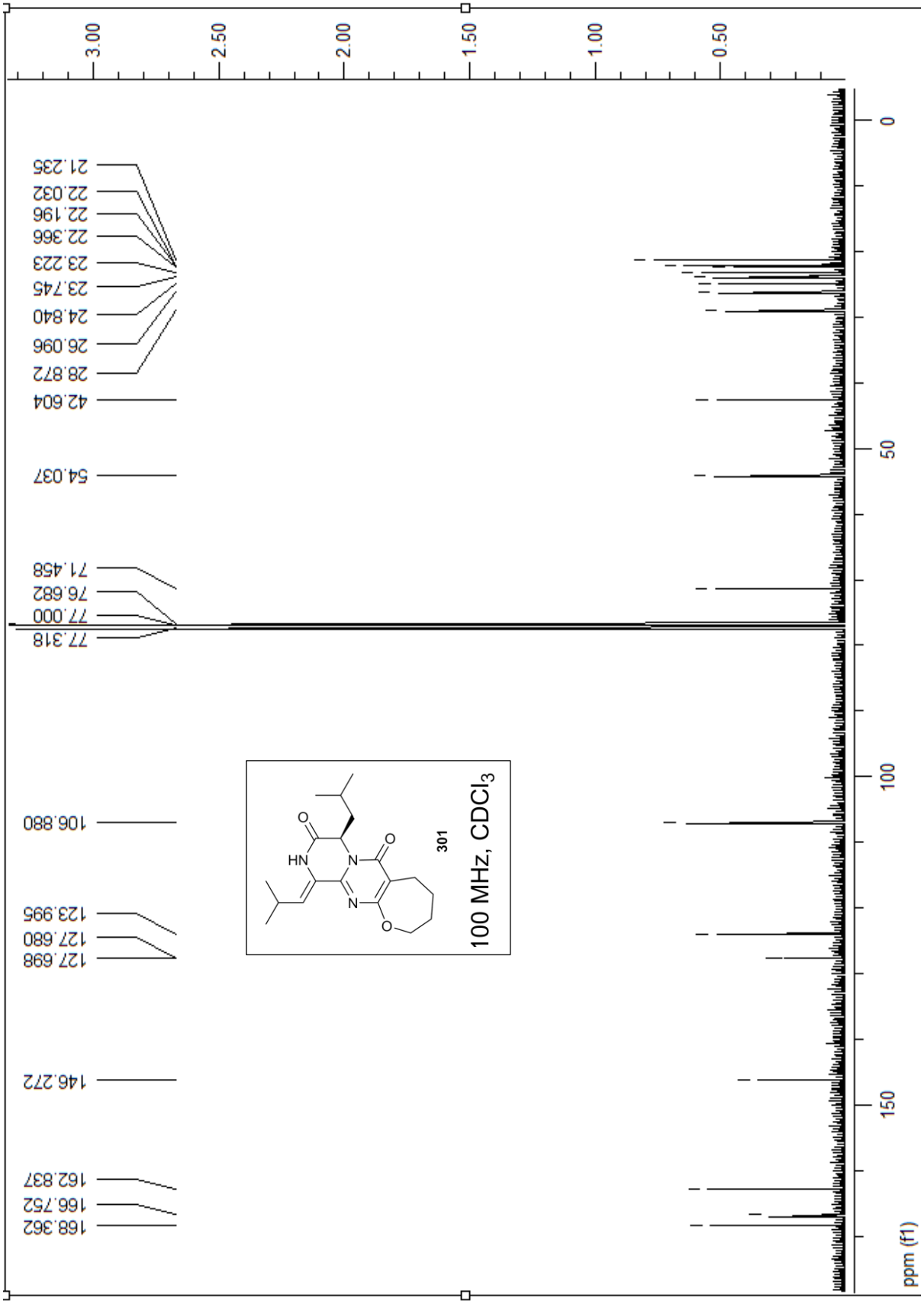


Appendix II. ^{1}H- and ^{13}C-NMR Spectra for Tetrahydro-Janoxepin 301

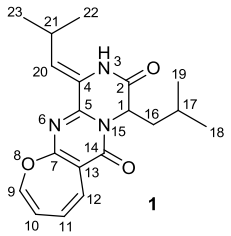
^{1}H-NMR Spectrum of Tetrahydro-Janoxepin **301**



^{13}C-NMR Spectrum of Tetrahydro-Janoxepin **301**



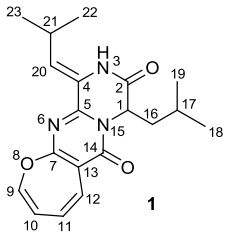
Appendix III. ^{1}H- and ^{13}C-NMR Data for (±)-Janoxepin (1)



1

Table I. Comparison of ^{1}H-NMR Spectral Data. 400 MHz, $CDCl_3$

Atom	δ (ppm) Reported	δ (ppm) Synthetic
1	5.31 (ddd, 9.1, 5.5, 0.9)	5.38 (ddd, 9.0, 5.5, 1.0)
2	-	-
3	8.68 (s, br)	8.26 (s)
4	-	-
5	-	-
7	-	-
9	6.01 (d, 5.3)	6.08 (d, 5.5)
10	5.55 (t, 5.3)	5.62 (t, 5.5)
11	6.06 (dd, 10.7, 5.3)	6.13 (dd, 11.0, 5.5)
12	6.67 (d, 10.7)	6.73 (d, 11.0)
13	-	-
14	-	-
16	1.61 (m)	1.72-1.61 (m)
17	1.75 (m)	1.86-1.76 (m)
18	0.87 (d, 6.5)	0.92 (d, 6.5)
19	1.02 (d, 6.4)	1.07 (d, 6.5)
20	6.31 (d, 10.2)	6.37 (d, 10.0)
21	2.66 (dsept, 10.2, 6.5)	2.65 (dsept, 10.0, 6.5)
22	1.08 (d, 6.7)	1.13 (d, 6.5)
23	1.07 (d, 6.5)	1.13 (d, 6.5)

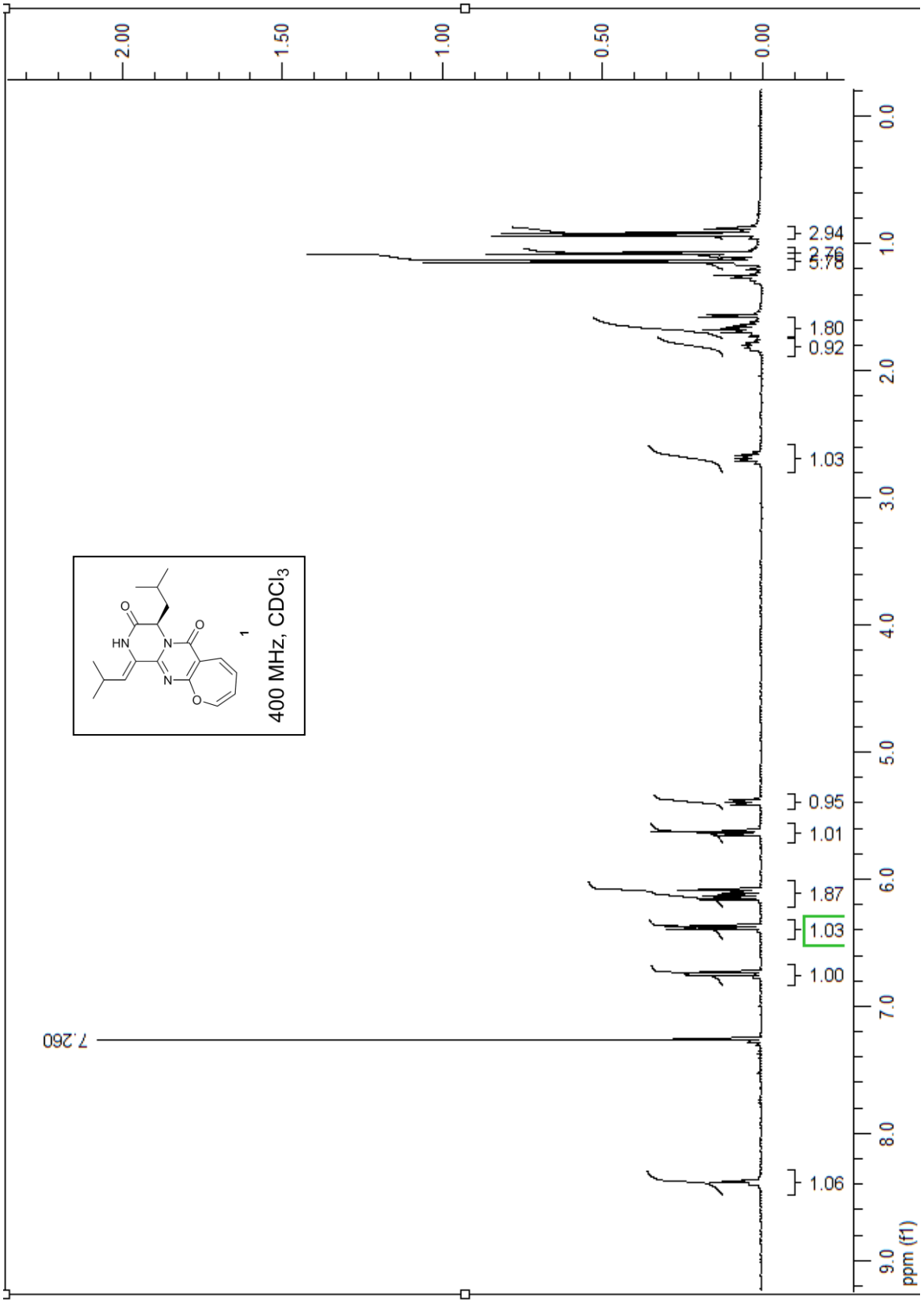


1

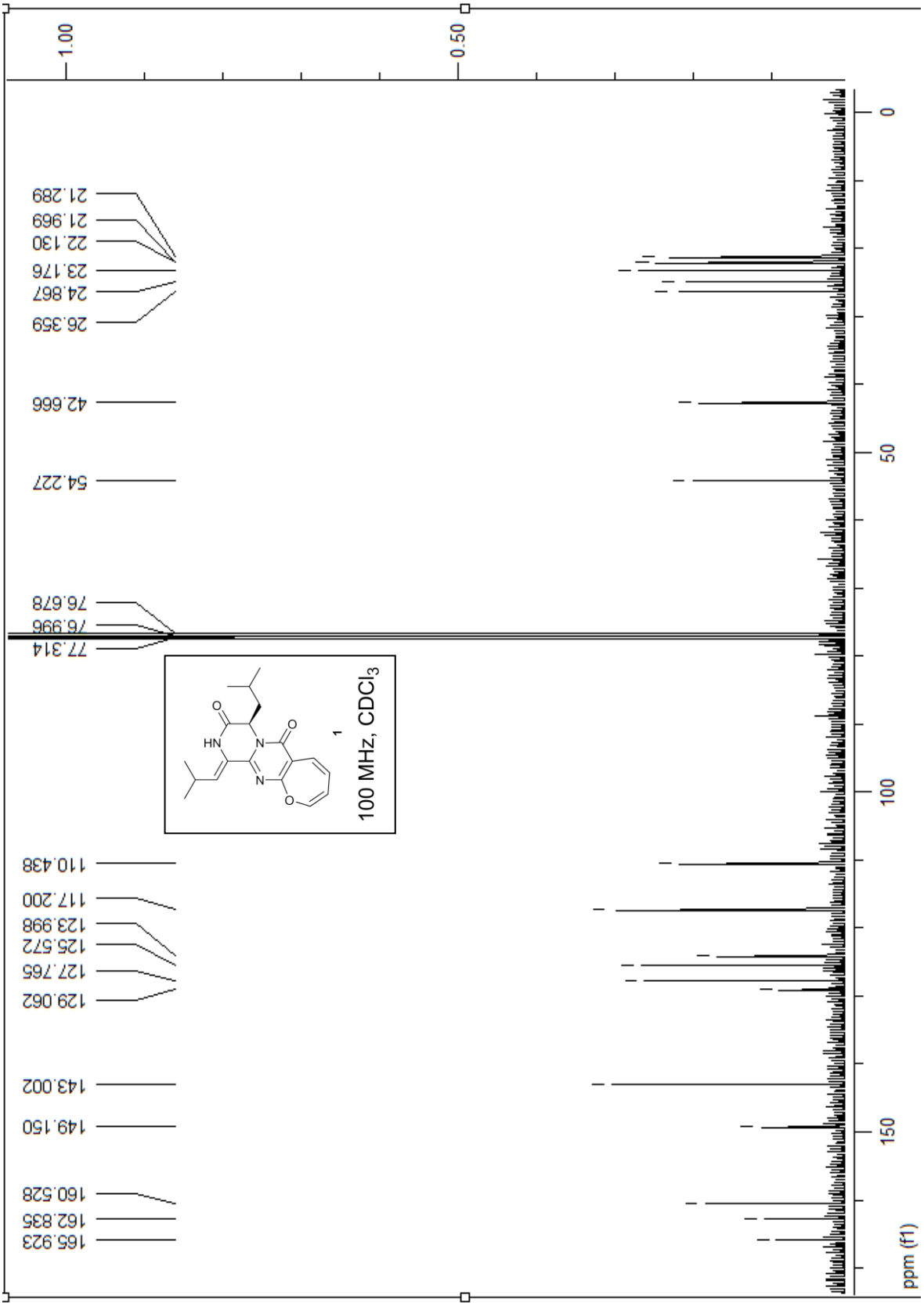
Table II. Comparison of ^{13}C-NMR spectral data. 100 MHz, $CDCl_3$

Atom	δ (ppm) Reported	δ (ppm) Synthetic
1	54.1	54.3
2	165.9	165.2
4	123.9	124.0
5	149.0	149.0
7	162.7	162.8
9	142.9	143.0
10	117.1	117.2
11	127.6	127.8
12	125.5	125.6
13	110.3	110.5
14	160.4	160.4
16	42.6	42.8
17	24.8	24.8
18	22.1	22.1
19	23.1	23.1
20	129.0	128.4
21	26.3	26.3
22	21.1	21.4
23	21.9	21.9

[1]H-NMR Spectrum of (±)-Janoxepin (**1**)

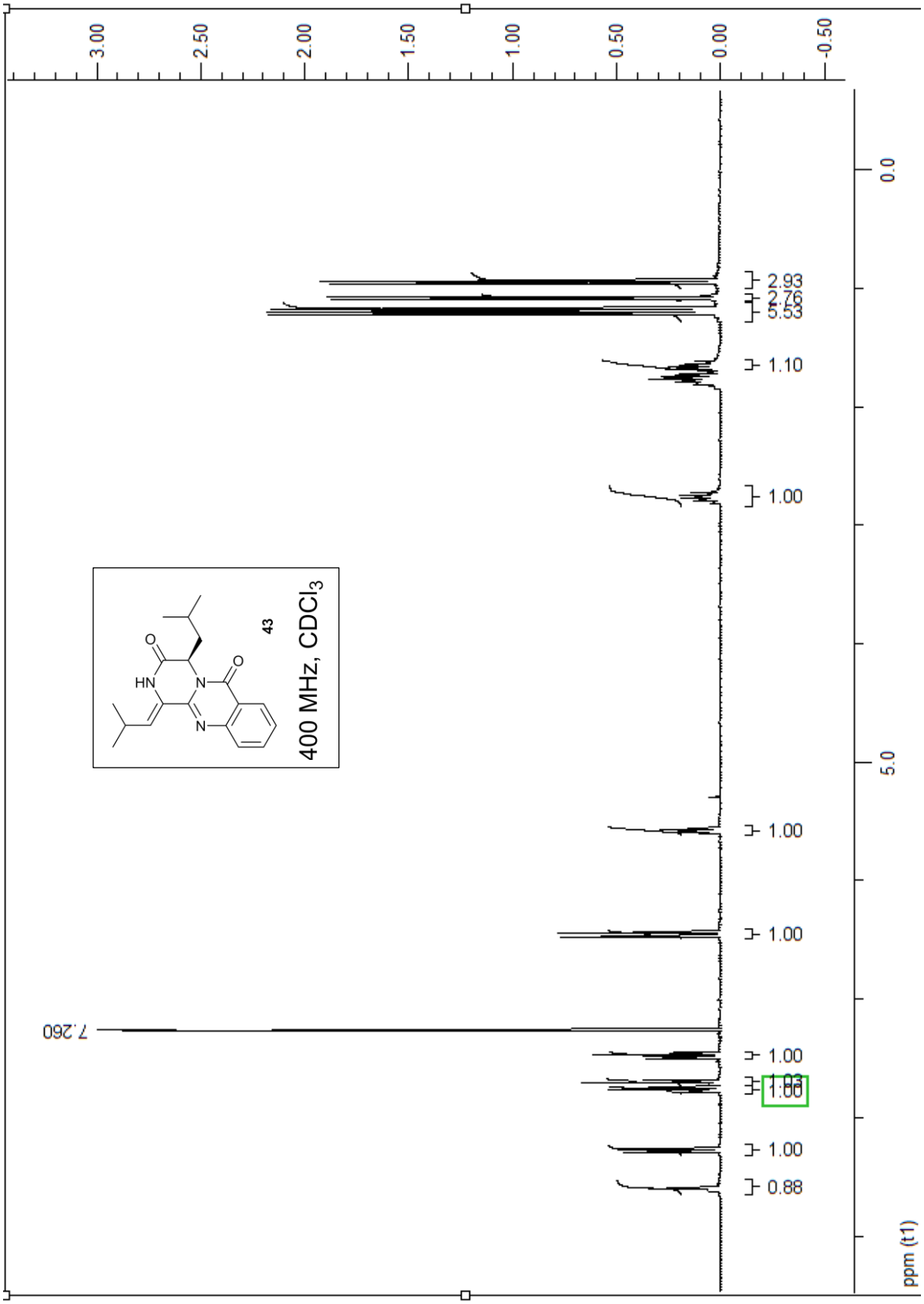


^{13}C-NMR Spectrum of (±)-Janoxepin (**1**)

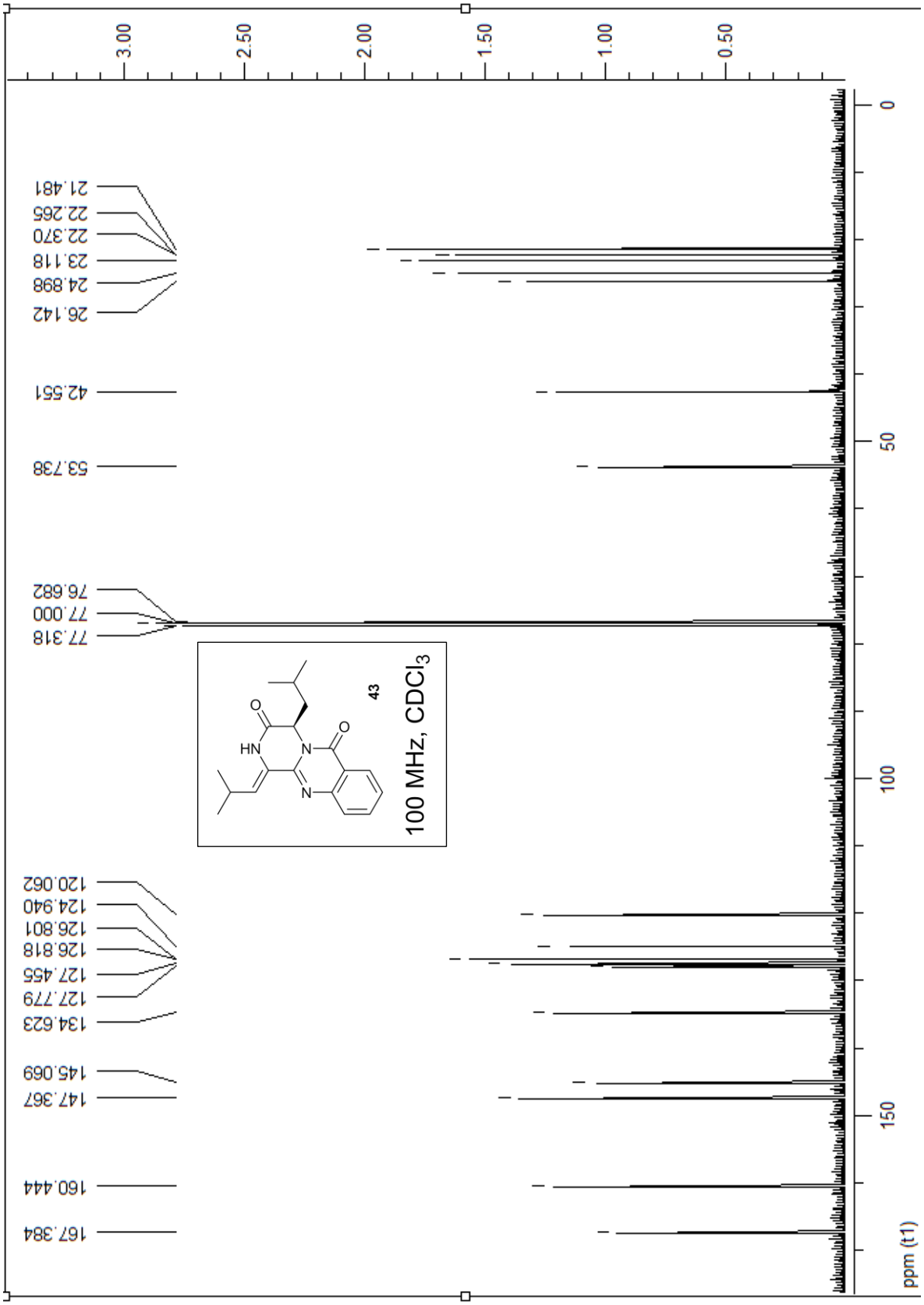


Appendix IV. ^{1}H- and ^{13}C-NMR Spectra for the Putative Janoxepin Biosynthetic Intermediate 43

^{1}H-NMR Spectrum of the Putative Janoxepin Biosynthetic Intermediate **43**

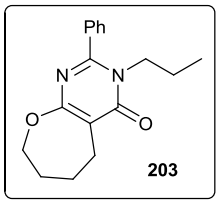


^{13}C-NMR Spectrum of the Putative Janoxepin Biosynthetic Intermediate **43**



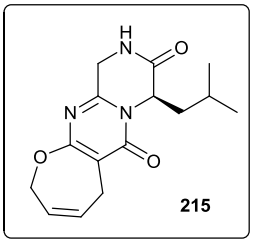
Appendix V. X-Ray Crystallography Data

Tetrahydro-Oxepine **203** (CCDC 862141)



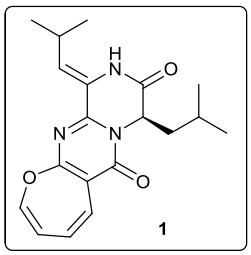
Identification code	rjt1012
Empirical formula	$C_{17}H_{20}N_2O_2$
Formula weight	284.35
Temperature / K	110.0
Crystal system	monoclinic
Space group	$P2_1/n$
a / Å, b / Å, c / Å	5.8281(3), 8.4825(14), 29.5706(13)
α/°, β/°, γ/°	90.00, 92.203(4), 90.00
Volume / Å^3	1460.8(3)
Z	4
ρ_{calc} / mg mm^{-3}	1.293
μ / mm^{-1}	0.085
F(000)	608
Crystal size / mm^3	0.1669 × 0.1279 × 0.0382
2Θ range for data collection	7.08 to 57.44°
Index ranges	$-6 \leq h \leq 7$, $-7 \leq k \leq 10$, $-39 \leq l \leq 22$
Reflections collected	5248
Independent reflections	3173[R(int) = 0.0175]
Data/restraints/parameters	3173/0/191
Goodness-of-fit on F^2	1.076
Final R indexes [I>2σ (I)]	$R_1 = 0.0473$, $wR_2 = 0.0950$
Final R indexes [all data]	$R_1 = 0.0594$, $wR_2 = 0.1029$
Largest diff. peak/hole / e Å^{-3}	0.248/-0.246

Dihydro-Oxepine **215** (CCDC 848129)



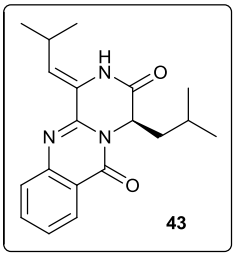
Identification code	rjt0908m	
Empirical formula	C15 H19 N3 O3	
Formula weight	289.33	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.9526(16) Å	a= 99.921(3)°.
	b = 11.3040(17) Å	b= 98.521(3)°.
	c = 12.2597(19) Å	g = 97.849(3)°.
Volume	1458.0(4) $Å^3$	
Z	4	
Density (calculated)	1.318 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	616	
Crystal size	0.22 x 0.05 x 0.02 mm^3	
Theta range for data collection	1.71 to 25.02°.	
Index ranges	-13<=h<=13, -13<=k<=13, -14<=l<=14	
Reflections collected	14953	
Independent reflections	5123 [R(int) = 0.0533]	
Completeness to theta = 25.02°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.998 and 0.872	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5123 / 0 / 391	
Goodness-of-fit on F^2	0.983	
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.0945	
R indices (all data)	R1 = 0.0874, wR2 = 0.1111	
Largest diff. peak and hole	0.181 and -0.197 $e.Å^{-3}$	

(±)-Janoxepin (**1**) (CCDC 848130)



Identification code	rjkt1101
Empirical formula	$C_{19}H_{23.00158}N_3O_3$
Formula weight	341.41
Temperature/K	110.0
Crystal system	triclinic
Space group	P-1
a/Å	13.0580(5)
b/Å	13.0653(5)
c/Å	14.0770(6)
α/°	97.904(4)
β/°	105.810(4)
γ/°	112.461(4)
Volume/Å^3	2055.13(18)
Z	4
ρ_{calc}mg/mm^3	1.103
m/mm^{-1}	0.076
F(000)	728
Crystal size/mm^3	0.3654 × 0.1716 × 0.1007
2Θ range for data collection	5.68 to 61.32°
Index ranges	$-18 \leq h \leq 16$, $-17 \leq k \leq 18$, $-17 \leq l \leq 20$
Reflections collected	17882
Independent reflections	11009[R(int) = 0.0225]
Data/restraints/parameters	11009/14/529
Goodness-of-fit on F^2	1.078
Final R indexes [I>=2σ (I)]	R_1 = 0.0686, wR_2 = 0.1927
Final R indexes [all data]	R_1 = 0.0934, wR_2 = 0.2104
Largest diff. peak/hole / e Å^{-3}	0.417/-0.280

Putative Biosynthetic Intermediate **43** (CCDC 862145)



Identification code	rjkt1103
Empirical formula	$C_{19}H_{23}N_3O_2$
Formula weight	325.40
Temperature/K	109.95(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.1662(4)
b/Å	19.8479(7)
c/Å	9.0230(4)
α/°	90.00
β/°	107.643(5)
γ/°	90.00
Volume/Å^3	1735.01(13)
Z	4
ρ_{calc}mg/mm^3	1.246
m/mm^{-1}	0.082
F(000)	696.0
Crystal size/mm^3	0.2144 × 0.0643 × 0.0417
2Θ range for data collection	5.68 to 55.94°
Index ranges	$-13 \leq h \leq 12$, $-25 \leq k \leq 14$, $-11 \leq l \leq 7$
Reflections collected	6967
Independent reflections	3537[R(int) = 0.0445]
Data/restraints/parameters	3537/0/221
Goodness-of-fit on F^2	1.069
Final R indexes [I>=2σ (I)]	$R_1 = 0.0714$, $wR_2 = 0.1780$
Final R indexes [all data]	$R_1 = 0.1084$, $wR_2 = 0.2063$
Largest diff. peak/hole / e Å^{-3}	0.31/-0.29

ORGANIC LETTERS

2012
Vol. 14, No. 4
1122–1125

Total Synthesis of an Oxepine Natural Product, (±)-Janoxepin

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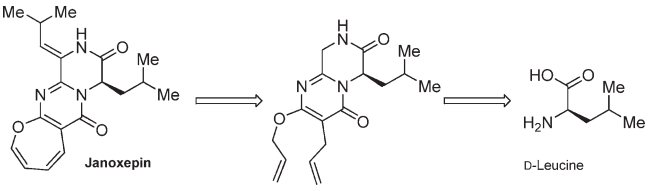
Received January 9, 2012

ABSTRACT



The total synthesis of (±)-janoxepin, a novel antiplasmodial D-leucine derived oxepine-pyrimidinone-ketopiperazine isolated from the fungus *Aspergillus janus*, is described. The cornerstones of the synthetic route are pyrimidinone preparation, ring-closing metathesis, aldol introduction of the enamide, and dihydro-oxepine elaboration. This synthetic route proved very efficient for the formation of a number of janoxepin analogues, including dihydro-janoxepin and tetrahydro-janoxepin.

Janoxepin (**1**) was isolated from the fungus *Aspergillus janus* in 2005 by Sprogøe and co-workers and shown to display antiplasmodial activity against the malaria parasite *Plasmodium falciparum* 3D7 (IC_{50} 28 mg/mL).[1] Structurally, janoxepin is fascinating, being based on an oxepine-pyrimidinone-ketopiperazine tricyclic core derived from D-leucine. The overall structure of janoxepin was determined by a combination of MS and NMR spectroscopy, with the *Z*-configuration of the exocyclic enamide moiety being confirmed by ^{1}H NMR NOE correlations (Figure 1).

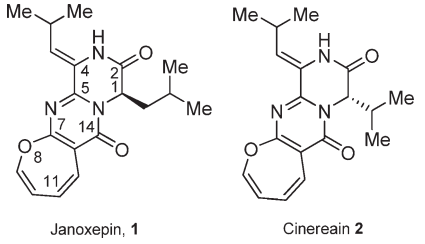


Figure 1. Structure of janoxepin (**1**).

Examples of reduced oxepine-based natural products such as the brevetoxin-like polyether marine metabolites[2] and dihydro-oxepine epidithiodiketopiperazines[3] are well-known and have been the subject of synthetic studies. However, examples containing a higher degree of unsaturation are rare.[4] That said, janoxepin belongs to a small family of pyrimidinone-annelated oxepine natural products including one very close relative in cinereain (**2**)[5] and a number of other related compounds (oxepinamides A–D,[6,7] brevianamides O–P,[8] protuboxepins A–B,[9] circumdatin A (asperloxin A),[10] and circumdatin B).[11]

(1) Sprogøe, K.; Manniche, S.; Larsen, T. O.; Christopherson, C. *Tetrahedron* **2005**, *61*, 8718.

(2) For reviews see: Yamaguchi, S. *Heterocycles* **2009**, *79*, 243. Snyder, N. L.; Haines, H. M.; Peczuh, M. W. *Tetrahedron* **2006**, *62*, 9301. Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301.

(3) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.*, DOI: 10.1021/ja209354e, Publication Date (Web): 24 Oct 2011.

(4) For naturally occurring dibenzo-oxepines and their synthesis, see: Olivera, R.; San Martin, R.; Churruca, F.; Domınguez, E. *Org. Prep. Proced. Int.* **2004**, *36*, 297.

(5) Cutler, H. G.; Springer, J. P.; Arrendale, R. F.; Arison, B. H.; Cole, P. D.; Roberts, R. G. *Agric. Biol. Chem.* **1988**, *52*, 1725.

(6) Belofsky, G. N.; Anguera, M.; Jenson, P. R.; Fenical, W.; Köck, M. *Chem.—Eur. J.* **2000**, *6*, 1355.

(7) Lu, X.-H.; Shi, Q.-W.; Zheng, Z.-H.; Ke, A.-B.; Zhang, H.; Huo, Y.; Ma, C.-H.; Ren, X.; Li, Y.-Y.; Lin, J.; Jiang, Q.; Gu, Y.-C.; Kiyota, H. *Eur. J. Org. Chem.* **2011**, *4*, 802.

(8) Li, G.-Y.; Li, L.-M.; Yang, T.; Chen, X.-Z.; Fang, D.-M.; Zhang, G.-L. *Helv. Chim. Acta* **2010**, *93*, 2075.

(9) Lee, S. U.; Asami, Y.; Lee, D.; Jang, J.-H.; Ahn, J. S.; Oh, H. *J. Nat. Prod* **2011**, *74*, 1284.

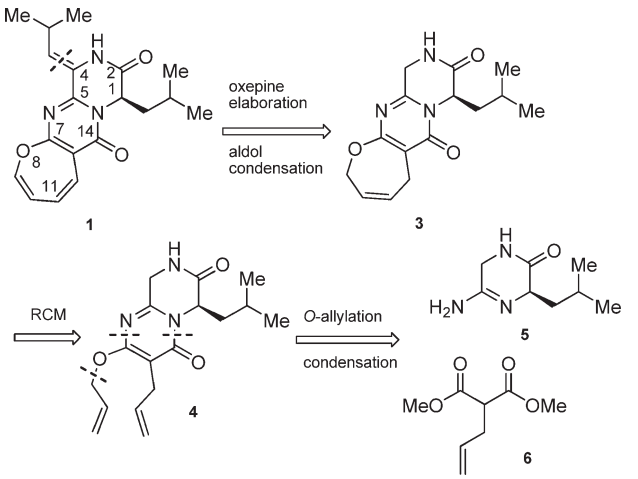
(10) Ookura, R.; Kito, K.; Ooi, T.; Namikoshi, M.; Kusumi, T. *J. Org. Chem.* **2008**, *73*, 4245. See also (erroneous structural assignment): Rahbæck, L.; Breinholt, J.; Frisvad, J. C.; Christopherson, C. *J. Org. Chem.* **1999**, *64*, 1689.

(11) Bode, H. B.; Bethe, B.; Höfs, R.; Zeeck, A. *ChemBioChem* **2002**, *3*, 619.

10.1021/ol300039x
Published on Web 01/30/2012

The oxepine natural products are not only of interest in terms of their biological properties but are also intriguing from a biosynthetic viewpoint: benzene epoxidation/rearrangement has been proposed as a biogenetic route to such oxepine ring systems.[1,7,11] Our interest, however, was to develop a practical synthetic route to the oxepine-based natural products, particularly to janoxepin and synthetic analogues, and the benzene epoxidation route did not seem well-suited to this objective. To the best of our knowledge, there have been no syntheses, or synthetic approaches, reported for janoxepin (**1**). Indeed, as far as we are aware, no syntheses of any oxepine-based natural products lacking benzannelation have yet been reported (which is remarkable as cinereain (**2**) was described as long ago as 1988).

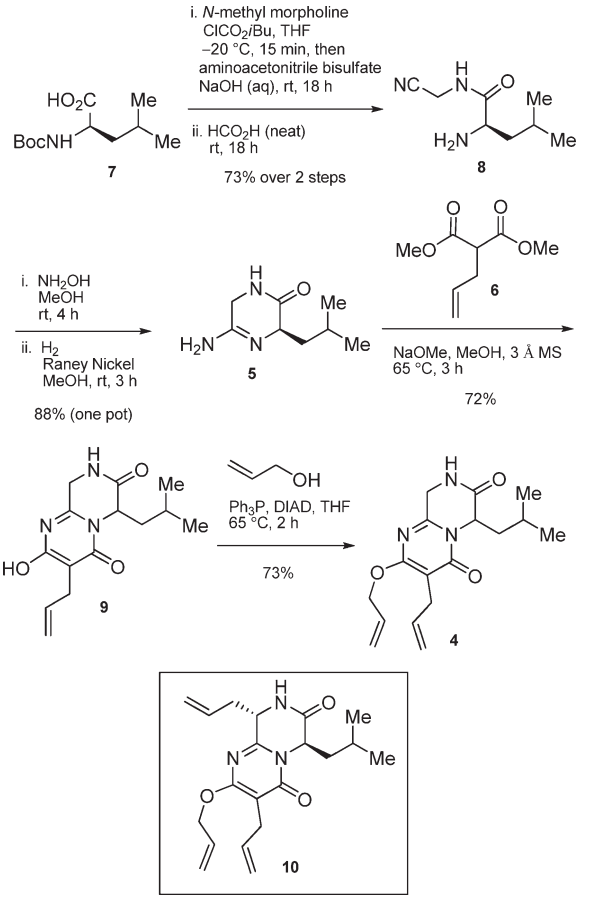
Scheme 1. Retrosynthetic Analysis



The proposed retrosynthetic analysis (Scheme 1) was based upon late-stage dihydro-oxepine elaboration preceded by introduction of the enamide using an aldol condensation between dihydro-oxepine **3** and *iso*-butyraldehyde; dihydro-oxepine **3** would then be prepared from the diallyl pyrimidinone precursor **4** using ring-closing metathesis (RCM) with D-leucine being employed as the ultimate starting material. This approach has the virtue of brevity, and utility for analogue synthesis, but its speculative nature needs emphasis; we could not find a single literature example of oxepine synthesis proceeding by elaboration of the corresponding dihydro-oxepine (see later discussion).

The synthetic study therefore commenced with the preparation of the diallylated pyrimidinone **4** from commercially available *N*-Boc-D-leucine **7** as shown in Scheme 2. Mixed anhydride formation followed by coupling with aminoacetonitrile and Boc deprotection gave the known amine **8** in excellent yield.[12] Amine **8** was next subjected to an efficient, telescoped one-pot oximation–hydrogenation cyclization sequence (based on a published procedure)[13] to

Scheme 2. Synthesis of Diallyl Pyrimidinone **14**



furnish the desired novel amidine **5** {$[\alpha]_D^{22}$ −47 (*c* 1.00, MeOH)} in just 4 steps and 64% overall yield from D-leucine.

Condensation of cyclic amidine **5** with the commercially available allylmalonate **6** using NaOMe as base and strictly anhydrous conditions furnished the required pyrimidinone **9** in excellent yield (72%) on an 8 g scale, although we were disappointed to observe that racemization of the stereogenic center had occurred.[14] The *O*-allylation of compound **9** was investigated next, and the use of allyl alcohol under Mitsunobu conditions (DIAD, PPh_3) was found to be optimal giving the required diallylated pyrimidinone **4** in 73% yield.[14] Interestingly, the use of more conventional alkylating conditions (e.g., allyl bromide, Bu_4NI, K_2CO_3) gave much lower yields of product **4** with substantial quantities of the *bis*-alkylated product **10** being isolated (as a single diastereomer).

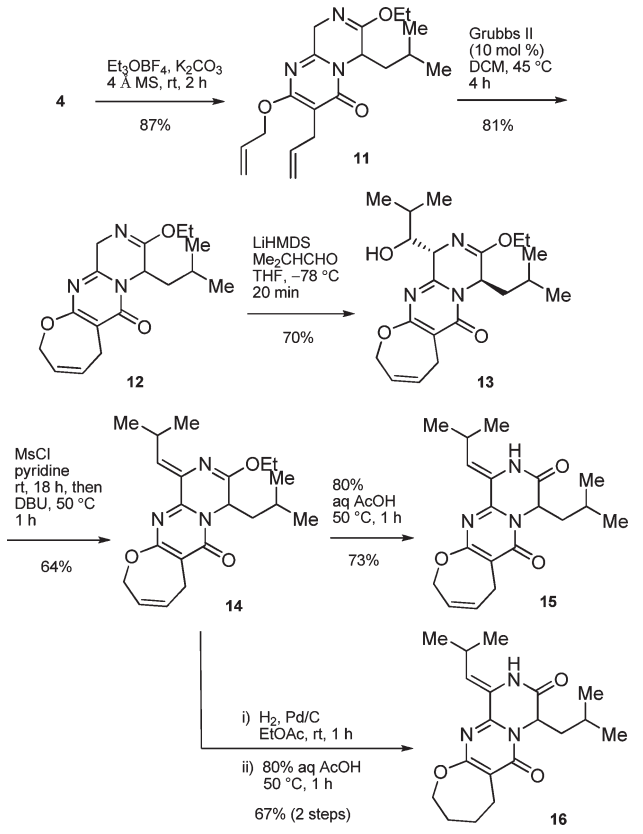
Having previously established that imidate-protected amides were optimal substrates for aldol addition to the ketopiperazine ring, it was found most efficient to protect diallyl pyrimidinone **4** as imidate **11** prior to the key RCM step. (when RCM was carried out first, the basic conditions needed for imidate formation also gave dihydro-oxepine

(12) Frizler, M.; Lohr, F.; Furtmann, N.; Kläs, J.; Gütschow, M. *J. Med. Chem.* **2011**, *54*, 396.

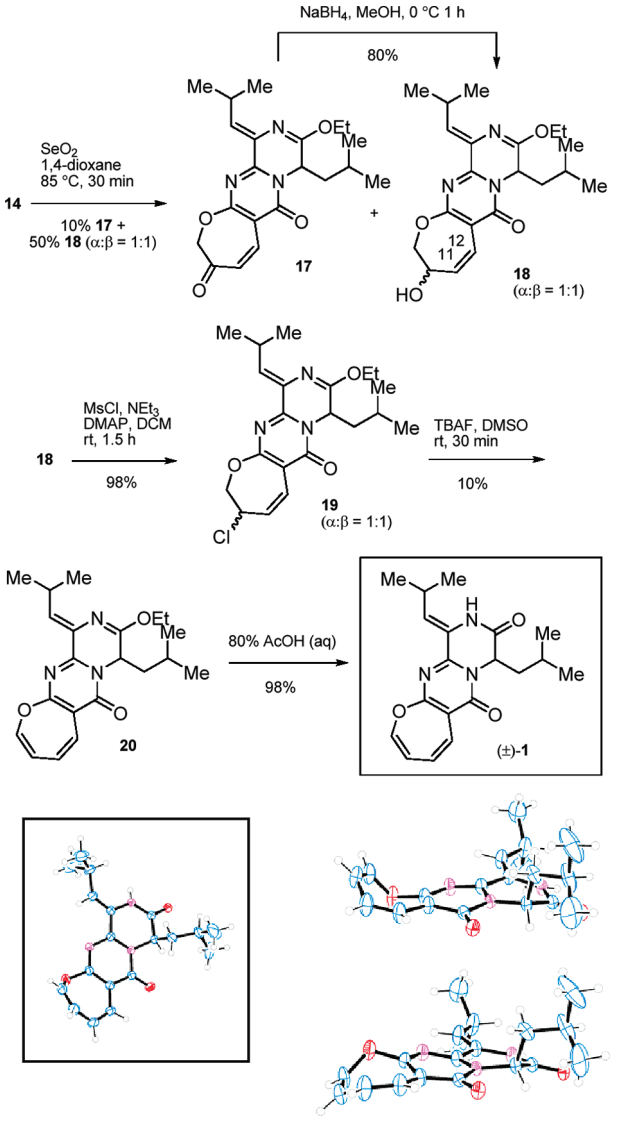
(13) Kuse, M.; Kondo, N.; Ohyabu, Y.; Isobe, M. *Tetrahedron* **2004**, *60*, 835.

(14) {$[\alpha]_D^{22}$ + 0.8 (*c* 1.01, MeOH)}; confirmed by HPLC analysis of compound **14** [Chiralpak AD-H, *n*-hexane/*i*-PrOH (9:1), 1 mL min^{-1}; 14.15 min, 47.3%; 15.10 min, 52.7% (ca. 5% ee)]; see Supporting Information.

Scheme 3. Dihydro-janoxepin **15** and Tetrahydro-janoxepin **16** Preparation



Scheme 4. Synthesis of Janoxepin (**1**)[a]



[a] X-ray structure of janoxepin (**1**) depicted using ORTEP-3 (CCDC 848130).

rearrangement products).[15] Subsequent treatment of compound **11** with the Grubbs second generation catalyst (benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium) then provided dihydro-oxepine **12** in excellent yield as shown in Scheme 3.

We were now in a position to effect the aldol elaboration. This was achieved by deprotonation of imidate **12** with LiHMDS and addition of *iso*-butyraldehyde, which provided aldol adduct **13** as a single diastereomer in excellent yield (70%). A mesylation–elimination sequence was then employed to give enamine **14** as a single isomer. Next, imidate hydrolysis gave dihydro-janoxepin **15** in 73% yield, again as a single enamine isomer, which was confirmed to be in the *Z*-configuration *via* ^{1}H NMR NOE experiments. In pursuit of other novel analogues, hydrogenation of dihydro-oxepine intermediate **14** followed by imidate hydrolysis also provided tetrahydro-janoxepin **16** as the *Z*-alkene.

The key step that remained in order to complete the synthesis of janoxepin (**1**) was to convert one of the dihydro-oxepine intermediates into the corresponding oxepine. This proved to be extremely difficult, however. Initial attempts centered around the formation of 1,2-dibromides, or 1,2-diol-derived sulfonates, and then double elimination to give the required diene. Unfortunately, the elimination sequences all failed, possibly due to the inherent strain of the oxepine (and the base-sensitivity of dihydro-oxepines).[15] After considerable experimentation, an alternative sequence, illustrated in Scheme 4, was devised in which the two alkenes are introduced in a stepwise manner.

Treatment of dihydro-oxepine **14** with selenium dioxide gave allylic oxidation producing a mixture of allylic alcohol **18** (50%, α:β = 1:1) along with a small amount of the corresponding ketone **17** (10%), which could be converted back into alcohol **18** (α:β = 1:1) using sodium borohydride. The 11,12-location of the double bond was established from ^{1}H NMR multiplicities (for a single diastereomer, H-11 and H-12 were observed as a doublet of doublets and doublet, respectively) and was further confirmed by COSY, ^{13}C and HSQC NMR experiments.

(15) Ramachary, D. B.; Ramakumar, K.; Bharanishashank, A.; Narayana, V. V. *J. Comb. Chem.* **2010**, *12*, 855 and references therein.

Following a screen of numerous methods for the dehydration of allylic alcohol **18** to generate oxepine **20** (including sulfurane reagents, acid catalysis, Chugaev elimination, Shapiro/Bamford–Stevens chemistry, selenide oxidation, Tsuji–Trost elimination), it was found necessary to proceed by way of the corresponding chloride **19** (α:β = 1:1) which was formed directly, and in near-quantitative yield, using methanesulfonyl chloride in dichloromethane. Chloride **19** underwent TBAF-mediated dehydrohalogenation[16] to produce oxepine **20** in low (10%), but entirely reproducible, yield which could not be improved upon following an optimization study of base, solvent, and temperature. Although all starting material was consumed in the reaction, no other products could be identified from a complex mixture of polar byproducts. In order to ascertain whether one diastereomer of chloride **19** was undergoing elimination preferentially, the diastereomers of allylic alcohol **18** were separated and the two compounds were subjected separately to the chlorination conditions. However, in both cases an inseparable diastereomeric mixture of chlorides **19** (α:β = 1:1) was obtained preventing further experimentation. The reasons for the disappointing elimination yield leading to oxepine **20** are not yet fully understood, although the base-sensitivity of dihydro-oxepines[15] and the acid and light sensitivity of oxepines[17] are well recognized. However, it must be emphasized that, to our knowledge, this is the first reported preparation of an oxepine from the corresponding dihydro-oxepine (although benzannelated oxepines[18] and dihydro-analogues[3] have been prepared by an eliminative approach). Finally, imidate hydrolysis furnished janoxepin (**1**) in near-quantitative yield. The ^{1}H and ^{13}C NMR data for the synthetic material were in excellent agreement with those published in the isolation paper (*e.g.*, δ_C (reported):[1] C-9 – C-14, 142.9, 117.1, 127.6, 125.5, 110.3, 160.4). δ_C (found): C-9 – C-14, 143.0, 117.2, 127.8, 125.6, 110.5, 160.4). [See Supporting Information for a detailed comparison.]

However, the melting point of synthetic janoxepin (179–180 °C) did not match the reported value (88–89 °C).[1,19] This could be due to polymorphism or to the fact that our material was racemic, but to provide unambiguous structural proof we subjected synthetic janoxepin to X-ray crystallographic analysis. The first X-ray crystal structure of janoxepin (**1**), shown in Scheme 4, confirmed our structural assignment and indicated that it exists in two oxepine conformers in the solid state.[20]

In principle, double deprotonation of racemic janoxepin followed by enantioselective protonation[21] of the resulting enolate should provide a route to the enantioenriched natural product. Unfortunately, using bases such as *sec*-BuLi and a chiral proton source such as (−)-ephedrine resulted in complete decomposition of the substrate, and decomposition was also observed starting from imidate **20** (again demonstrating the base-sensitivity of these oxepines).

In summary, we have completed the first total synthesis of an oxepine-based natural product, and the first of any oxepine-pyrimidinone natural product, the antiplasmodial janoxepin (**1**), confirming the published[1] structural assignment by X-ray crystallography.

The synthesis of janoxepin (**1**) was accomplished in 13 steps from readily available Boc-D-leucine **7** using ring-closing metathesis, aldol introduction of the enamide, and oxepine elaboration as the key steps. The same synthetic approach has been employed to prepare janoxepin analogues including dihydro-janoxepin **15** and tetrahydro-janoxepin **16**. We are currently optimizing the route, in particular the method of oxepine construction, as well as investigating other enantioselective strategies. Ultimately, this methodology will be employed to prepare other members of the oxepine natural product family.

Acknowledgment. We would like to thank the EPSRC (R.G.D.) and the University of York (S.J.) for PhD funding, the Erasmus scheme and the University of Nijmegen for exchange support (R.S.), and Professor C. Christopherson, Department of Chemistry, University of Copenhagen for helpful correspondence. We are also grateful to Dr. A. C. Whitwood for X-ray crystallography studies and to Dr. K. Heaton for invaluable assistance with mass spectrometry.

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all novel compounds. Crystallographic data for janoxepin (**1**) (CCDC 848130). This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Dura, R. D.; Paquette, L. A. *Synthesis* **2006**, 2837.

(17) Boyd, D. R.; O'Kane, G. A. *Tetrahedron Lett.* **1987**, *38*, 6395. Agarwal, R.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2869.

(18) Hoffmann, H.; Djafara, H. *Z. Naturforsch.* **1989**, *44b*, 220.

(19) E-mail correspondence with Prof. Carsten Christophersen, Department of Chemistry, University of Copenhagen (22 June, 2011) established that the original notebooks, samples, and NMR spectra were no longer available.

(20) CCDC 848130 (**1**) contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

(21) Martin, J.; Plaquevent, J. C.; Maddaluno, J.; Rouden, J.; Lasne, M. C. *Eur. J. Org. Chem.* **2009**, 5414 and references therein.

The authors declare no competing financial interest.

Tetrahedron Letters 53 (2012) 2533–2536

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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An expedient synthesis of the proposed biosynthetic precursor of the oxepine natural product, janoxepin

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ARTICLE INFO

Article history:
Received 6 February 2012
Revised 24 February 2012
Accepted 7 March 2012
Available online 13 March 2012

Keywords:
Janoxepin
Oxepine
Biosynthesis
Pyrazino[2,1-*b*]quinazoline-3,6-dione

ABSTRACT

An efficient synthetic route to the putative biosynthetic intermediate of the anti-plasmodial natural product janoxepin is described. This novel enamine-containing pyrazino[2,1-*b*]quinazoline-3,6-dione, and its synthetic precursors, should be of value in studies to elucidate the biosynthetic pathway leading to the oxepine family of natural products. The cornerstones of the synthesis are amide coupling, pyrazino[2,1-*b*]quinazoline-3,6-dione construction and aldol introduction of the enamine.

There is increasing fascination with the growing family of oxepine-containing natural products, particularly in terms of their structural determination, biological activity and biogenesis. We have become interested in this area from a synthetic viewpoint and recently reported the first total synthesis of the anti-plasmodial, oxepine-pyrimidinone-containing natural product janoxepin (**1**) (Fig. 1).[1]

In terms of the biosynthesis of oxepine-containing natural products such as janoxepin (**1**) and related compounds, oxepinamide D (**2**)[2] and brevianamide O (**3**),[3] a common proposal is that the oxepine ring is generated via enzymatic arene-epoxidation of a pyrazino[2,1-*b*]quinazoline-3,6-dione **4** followed by a rearrangement and ring-opening sequence (Scheme 1).[2–4]

The pyrazino[2,1-*b*]quinazoline-3,6-dione skeleton seen in **4** can be found in numerous natural products with considerable biological potential. Many of this family, including acetylardeemin,[5] fiscalin B[6] and serantrypinone[7] (amongst others[8]) have been the subject of elegant syntheses. However, these compounds do not bear the enamine moiety at C-4 present in **4** and the only natural product examples with this structural feature are aurantiomide C (**6**),[9] verrucine F (**7**)[10] and quinadoline A (**8**)[11] (Fig. 2), none of which have succumbed to total synthesis to date. We therefore decided to develop a synthetic route to prepare the putative janoxepin precursor **4**, both to aid biosynthetic studies in the oxepine natural product area, and to provide an entry into the pyrazino[2,1-*b*]quinazoline-3,6-dione natural products shown in Figure 2.

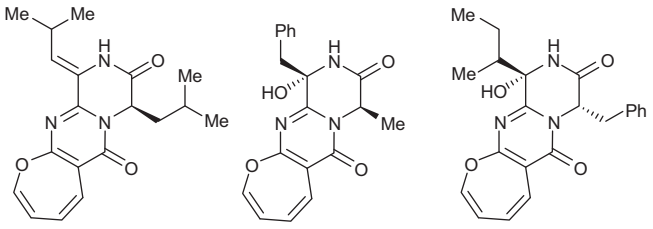

Figure 1. Representative oxepine natural products.

The retrosynthetic analysis of **4** (Scheme 2) relied upon introduction of the aliphatic enamine moiety via an aldol addition to an imidate-protected version of the known[12] pyrazino[2,1-*b*]quinazoline-3,6-dione **9**, followed by a selective elimination to furnish the *Z*-enamine. The tricyclic intermediate **9** would itself be constructed by a double cyclisation of the novel amine **10**, whilst an amide coupling sequence starting from the inexpensive and readily available isatoic anhydride (**11**), Fmoc-Gly-Cl **12** and D-leucine methyl ester (**13**) would ultimately be employed to synthesise this key intermediate.

The study therefore commenced with a modified coupling of the commercially-available isatoic anhydride (**11**) and D-leucine methyl ester (**13**) (Scheme 3) to furnish the known amide **14** in a much improved yield to that previously reported (87% vs 32%[13]). This was followed by a second coupling with the Fmoc-protected glycine chloride **12** to furnish the novel intermediate **15**. The Fmoc protecting group was then removed by treatment of **15** with piperidine to provide the key novel amine intermediate **10** in three

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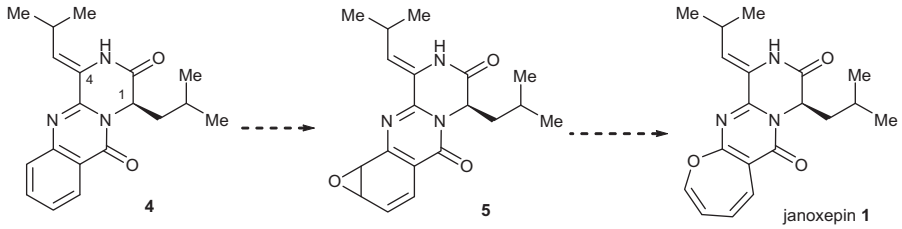
http://dx.doi.org/10.1016/j.tetlet.2012.03.025



Scheme 1. Proposed biosynthesis of janoxepin (**1**).

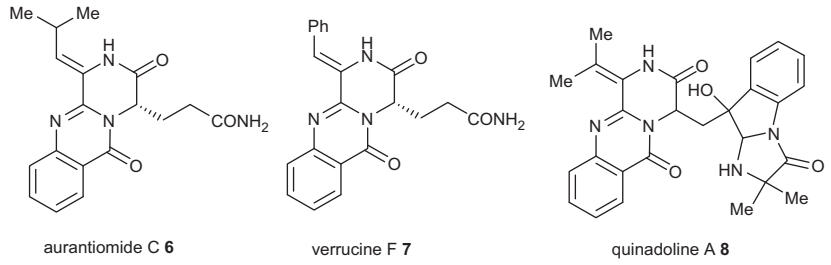
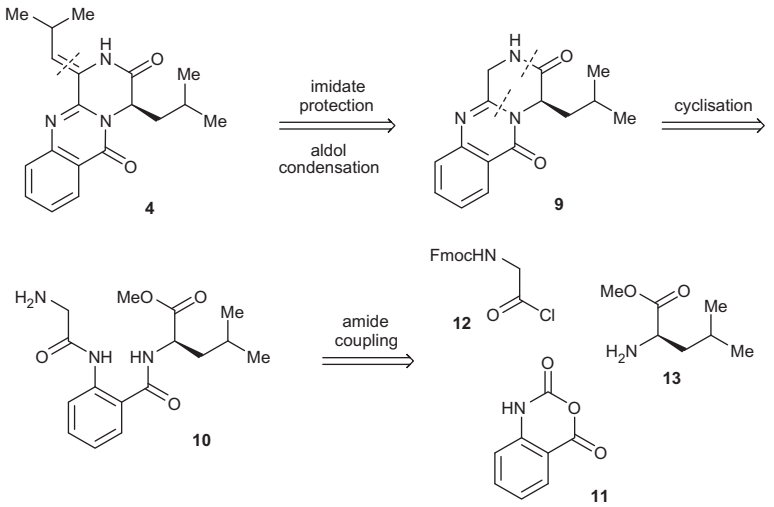
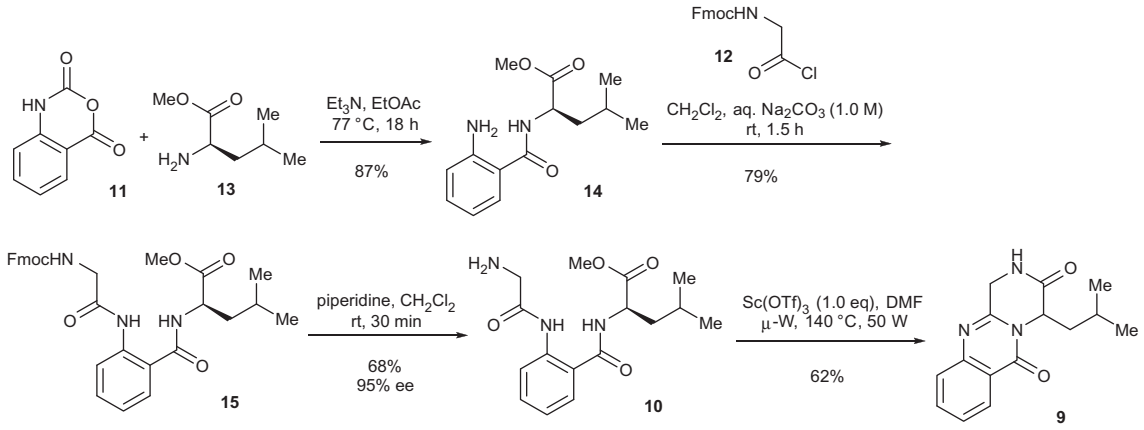


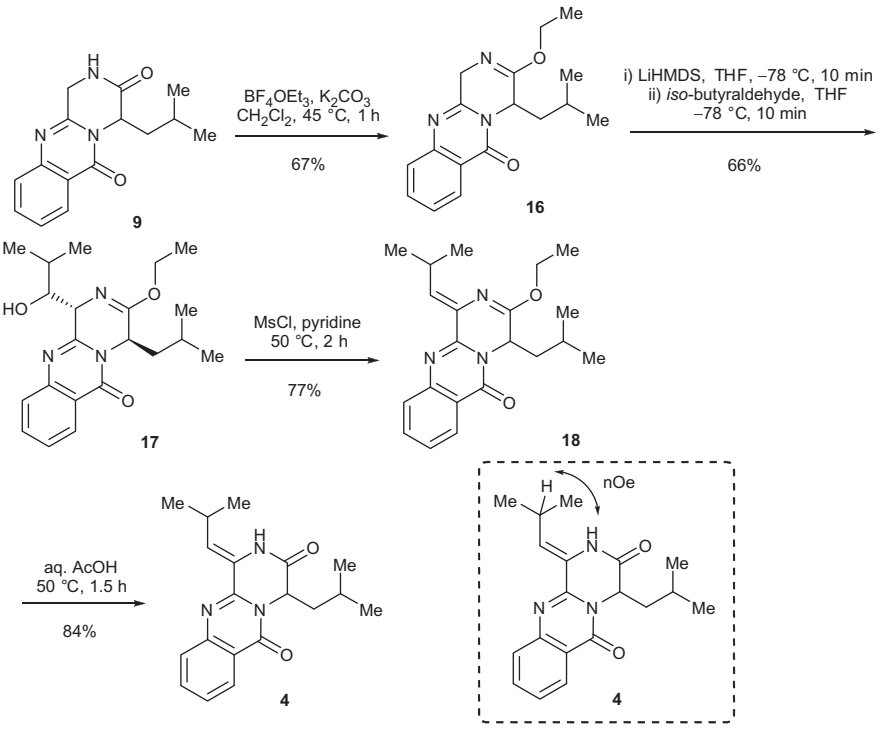
Figure 2. Structures of aurantiomide C (**6**), verrucine F (**7**) and quinadoline A (**8**).



Scheme 2. Retrosynthetic analysis.



Scheme 3. Synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione **9**.



Scheme 4. Synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione **4**.

steps, 47% overall yield and in 95% ee (as shown by chiral HPLC analysis).[14]

In order to effect the double cyclisation to convert amine **10** into pyrazino[2,1-*b*]quinazoline-3,6-dione **9** we utilised the Lewis acid mediated cyclisation procedure reported by Chu and co-workers.[15] Thus, a solution of amine **10** in DMF was treated with 1 equiv of scandium triflate and irradiated in a microwave reactor (CEM Discover) at 140 °C, 50 W for 2 min as reported,[15] but only a trace of the desired tricycle **9** was observed along with unreacted amine **10**. However, microwave irradiation at the same temperature for an extended period (10 min) gave pyrazino[2,1-*b*]quinazoline-3,6-dione **9** in 62% yield (Scheme 3). This result demonstrates that the Chu procedure[15] is compatible with a substituent at C-1 on the ketopiperazine ring. Disappointingly however, due either to the long reaction times, or simply the base-sensitivity of the compounds, complete racemisation was observed (**9**, 51:49 er) under the cyclisation conditions employed here.[16] Future work will investigate the effect of different side chains at the C-1 position and screen alternative Lewis acids in order to demonstrate the broader scope of this procedure. [Compound **9** has previously been prepared by a four-step solid phase 'discrete' synthesis in 53% overall yield from L-leucine-Wang resin, anthranilic acid and Fmoc-Gly-Cl; no isolated mass reported, optical purity unspecified.[12] The long reaction times and large excesses of anthranilic acid, Fmoc-Gly-Cl and iodine needed did not lend this procedure to the gram scale preparation of **9** required in this context].

The key step now remaining was to install the enamine moiety. Amide **9** was first converted into the novel imidate **16** using triethyloxonium tetrafluoroborate. This choice of amide protection has the virtue of facile subsequent removal under mild conditions, whilst being stable to the basic conditions required for ketopiperazine deprotonation and further manipulations. Aldol addition was effected by treatment of compound **16** with LiHMDS in THF at −78 °C followed by the addition of *iso*-butyraldehyde to afford alcohol **17** as a single diastereomer and in good yield. Treatment of **17** with methanesulfonyl chloride in pyridine, with heating to 50 °C, gave enamine **18** directly (as a single isomer) via a one-pot mesylation–elimination sequence. The preparation was completed by imidate hydrolysis using aqueous acetic acid with heating to 50 °C to furnish the target compound **4** in 43% overall yield over the three steps in racemic form (Scheme 4).

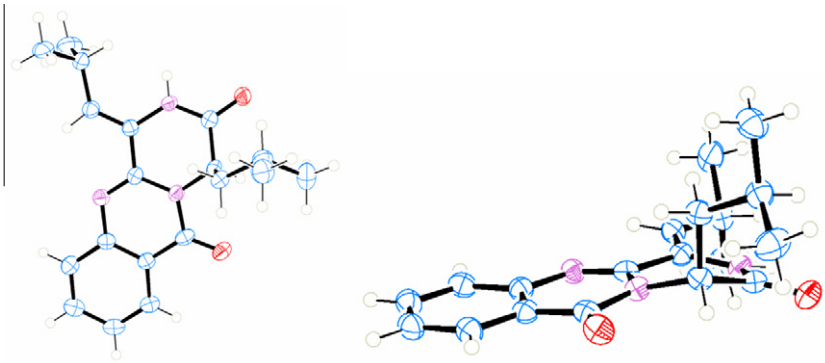
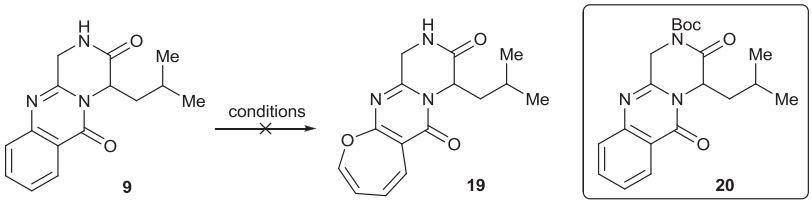


Figure 3. X-ray crystallography of (±)-**4**. ORTEP representations shown with ellipsoids at 50% probability. A single enantiomer (*R*) is shown for clarity. CCDC 862145.[18]

Table 1
Epoxidation conditions screened



Entry	Oxidant	Conditions
1	*m*-CPBA	CH_2Cl_2/aq $NaHCO_3$ (sat.), rt, 18 h
2	NaOCl	*n*-Bu_4NHSO_4, CH_2Cl_2, rt, 18 h
3	DMDO	Acetone, 0 °C–rt, 18 h

The structure of **4** was confirmed by ^1H and ^{13}C NMR spectroscopy in conjunction with COSY and HSQC experiments.[17] NOE correlations (Scheme 4) confirmed that the enamine was in the desired *Z*-configuration, and further proof of this was provided by X-ray crystallographic analysis (Fig. 3).[18]

Preliminary, if speculative, experiments were carried out to investigate whether chemical oxidation could be employed to effect the proposed biomimetic oxepine formation (Table 1). Pyrazino[2,1-*b*]quinazoline-3,6-dione **9** was chosen as the substrate for this study to preclude any problems with competing epoxidisation of an enamine double bond. Unfortunately, there was no sign of the hoped-for oxepine **19** (nor the intermediate epoxide) and only an inseparable mixture of *N*-oxide compounds, starting material and degradation products was observed (oxidation at the ketopiperazine C-4 position cannot be ruled out as this process has been reported previously[19]). In order to remove the possibility of *N*-oxide formation, the corresponding *N*-Boc derivative **20** was subjected to the same reagents with similarly disappointing results. We plan to investigate the chemical oxidation of the putative biosynthetic intermediate **4** and its imidate precursor **18** in due course; however these preliminary results suggest that arene oxidation will be difficult to achieve synthetically.

In summary, the putative biosynthetic precursor to janoxepin (**1**), pyrazino[2,1-*b*]quinazoline-3,6-dione **4**, has been prepared in an efficient eight-step synthesis starting from readily available and inexpensive starting materials. The methodology for installation of the enamine moiety, as well as that for pyrazino[2,1-*b*]quinazoline-3,6-dione construction, not only has application in the preparation of other oxepine biosynthetic precursors, but also in the synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione natural products **6–8** (Fig. 2). Strategies for the asymmetric synthesis of compounds of this type are currently being investigated. With a view to developing a biomimetic strategy for the synthesis of oxepine natural products, a preliminary investigation of chemical arene-epoxidation procedures was unsuccessful. However, an efficient route to these key biosynthetic precursors is now available to underpin future studies using enzymatic epoxidative biotransformations.

Acknowledgments

We would like to thank the EPSRC (R.G.D.) for PhD funding. We are also grateful to Dr. A. C. Whitwood for X-ray crystallography studies and to Dr. K. Heaton for invaluable assistance with mass spectrometry.

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14. HPLC: Chiralpak AD-H (80:20 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 7.25 min (94.91%), 9.09 min (5.09%).
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16. HPLC: Chiralpak OD (80:20 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 9.71 min (50.59%), 18.83 min (49.41%).
17. (±)-**4**: mp 229–231 °C (MeOH/*n*-hexane); R_f 0.55 (1:1 PE/EtOAc); Found: C, 69.89; H, 7.09; N, 12.81; $C_{19}H_{23}N_3O_2$ requires: C, 70.13; H, 7.12; N, 12.91%; υ_{max}/cm^{-1} 3187, 3078, 2960, 1686, 1582, 1562; δ_H (400 MHz, $CDCl_3$) 8.59 (1 H, br s), 8.27 (1 H, dd, *J* 8.0, 1.5), 7.76 (1 H, ddd, *J* 8.5, 7.0, 1.5), 7.69 (1 H, dd, *J* 8.5, 1.5), 7.47 (1 H, ddd, *J* 8.0, 7.0, 1.5), 6.45 (1 H, d, *J* 10.0), 5.58 (1 H, ddd, *J* 8.5, 5.5, 1.0), 2.75 (1 H, d sept, *J* 10.0, 6.5), 1.83–1.71 (2 H, m), 1.65 (1 H, ddd, *J* 13.5, 8.5, 5.5), 1.21 (3 H, d, *J* 6.5), 1.18 (3 H, d, *J* 6.5), 1.08 (3 H, d, *J* 6.5), 0.94 (3 H, d, *J* 6.5); δ_C (100 MHz, $CDCl_3$) 167.4, 160.4, 147.4, 145.1, 134.6, 127.8, 127.4, 126.8, 126.8, 124.9, 120.0, 53.7, 42.6, 26.1, 24.9, 23.1, 22.4, 22.3, 21.5; *m*/*z* (ESI) 326 $[MH]^+$. Calcd for $C_{19}H_{24}N_3O_2$: 326.1863. Found: $[M+H]^+$, 326.1859 (0.9 ppm error); HPLC: Chiralcel OD (95:5 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 9.74 min (50.10%), 20.02 min (49.90%).
18. X-Ray crystallography: CCDC 862145 contains the supplementary crystallographic data for this compound. Crystals were grown by slow diffusion (Et_2O/CH_2Cl_2).
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Abbreviations

Ac	Acetyl
AcOH	Acetic acid
AIBN	Azobis-*iso*-butyronitrile
APCI	Atmospheric-pressure chemical ionisation
app.	Apparent
aq.	Aqueous
Ar	Aryl
BHT	Butylhydroxytoluene
BIRO	Base induced ring opening
Bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
brsm	Based upon recovered starting material
Bu	Butyl
CAN	Cerium (IV) ammonium nitrate
cat.	Catalytic
CCDC	Cambridge Crystallographic Data Centre
COSY	Correlation spectroscopy
m-CPBA	*meta*-Chloroperoxybenzoic acid
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
δ	Chemical shift
Δ	Heat
d	Doublet, day
D	Stereochemically analogous to dextrorotatory enantiomer of glyceraldehyde
DBAD	di-*tert*-butyl azodicarboxylate
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate

DEPT	Distortionless enhancement by polarization transfer
DIAD	Di-*iso*-propyl azodicarboxylate
DIPEA	Di-*iso*-propylethylamine
DKP	Diketopiperazine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMDO	Dimethyldioxirane
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
E	Entgegen, *trans*
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
eq.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
g	Gram
h	Hour(s)
h	Planck's constant
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IC_{50}	Median inhibition concentration
IR	Infra-red
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant in Hz
L	Stereochemically analogous to levorotatory enantiomer of glyceraldehydes
LDA	Lithium di-*iso*-propylamide
m	Multiplet

M	Molar
Me	Methyl
υ_{max}	Wavenumber of peak absorption
mg	Milligram
MHz	Megahertz
mL	Millilitre
mmol	Millimole
min	Minute(s)
mp	Melting point
Ms	Methane sulfonyl (mesyl)
MS	Molecular sieves
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
m/z	Mass to charge ratio
NBS	*N*-Bromosuccinamide
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methylpyrrolidone
nOe	Nuclear Overhauser effect
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PE	Petroleum ether (that fraction which boils at 40 – 60 °C)
Ph	Phenyl
*p*Ka	Acid disassociation constant
PMB	*para*-Methoxybenzyl
ppm	Parts per million
Pr	Propyl
Py	Pyridyl
q	Quartet
quant.	Quantitative
sat.	Saturated
q	Quartet
R	Unspecified group (aliphatic or aromatic)
RCM	Ring closing metathesis
R_f	Retention factor
rsm	Recovered starting material
rt	Room temperature

RTX	Resiniferatoxin
s	Singlet
sept	Septet
sat.	Saturated
t	Triplet
$t_{0.5}$	Half life
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBHP	*tert*-Butyl hydrogen peroxide
Teoc	2-(Trimethylsilyl)ethyl 4-nitrophenyl carbonate
Tf	Trifluoromethanesulfonyl (trifyl)
TFA	Trifluoroacetic acid
TFDO	Methyl(trifluoromethyl)dioxirane
Tf_2O	Trifluoromethanesulfonic anhydride
TfOH	Trifluormethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilane
Tris	2,4,6-Tri-*iso*-propylbenzene
Ts	*para*-Toluenesulfonyl
p-TSA	*para*-Toluenesulfonic acid
υ	Frequency (Hz)
µW	Microwave
Z	Zusammen, *cis*

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