# The Aza-Bohlmann Cyclisation

# and the Synthesis of *Pandanus* Alkaloids

A thesis submitted to the Board of the Faculty of Physical Sciences

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# ASLIB Abstract

## The Aza-Bohlmann Cyclisation and the Synthesis of *Pandanus* Alkaloids

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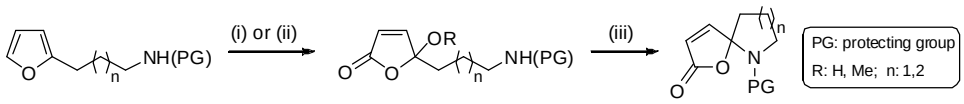
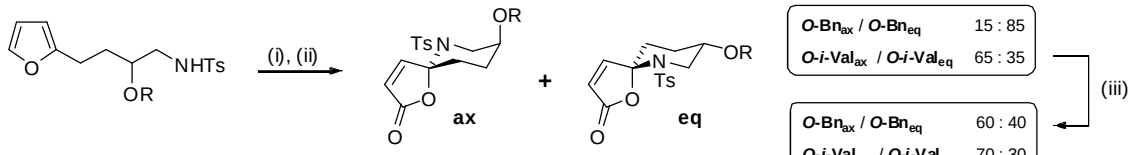
Bohlmann *et al*. reported the oxidative spirocyclisation of 2-(ω-hydroxyalkyl)furans under Clauson-Kaas conditions to furnish 1,6-dioxaspiro[4.5]dec-3-enes, thereafter termed the "Bohlmann cyclisation." This thesis describes the development of an analogous aza-Bohlmann cyclisation. Treatment of 2-(ω-aminoalkyl)furans with *m*-CPBA or singlet oxygen generates hydroxy- or methoxybutenolides, respectively, which undergo spirocyclisation upon treatment with $H_2SO_4$ to generate [4.4]- and [4.5]-spiroaminoacetals.




Conditions: (i) *m*-CPBA, DCM, R = H; or (ii) $O_2$, rose bengal, hν, MeOH, R = Me; (iii) 30% aq. $H_2SO_4$

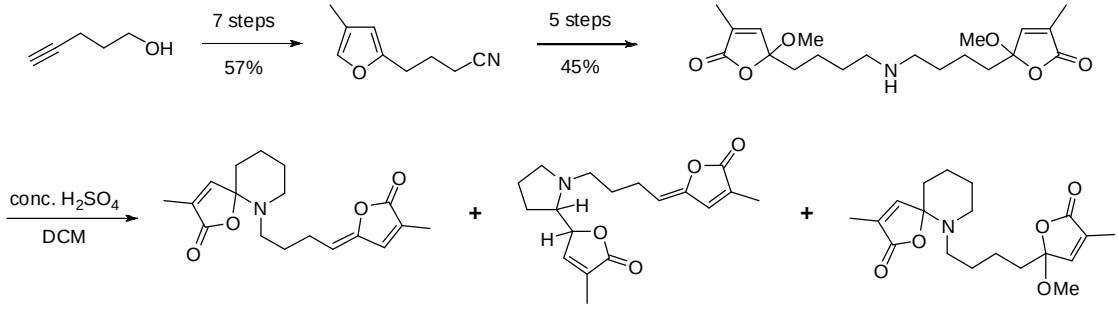
The axial/equatorial preferences of *N*-sulfonylspiroaminoacetals featuring a 3-*O*-isovaleryl or 3-*O*-benzyl substituent are described. Acid-catalysed equilibration revealed that in acetonitrile the axial isomer is thermodynamically favoured for both substrates.




Conditions: (i) $O_2$, rose bengal, hν, MeOH; (ii) 40% $H_2SO_4$; (iii) 1 mol% aq. HI, $CD_3CN$

R = Bn, $C(O)CH_2CH(CH_3)_2$ (*i*-Val)

The first total synthesis of the spiroaminoacetal alkaloid pandamarilactone-1 is discussed, *via* an aza-Bohlmann cyclisation, in 13 steps and 3% overall yield from 4-pentyn-1-ol.




(±)-pandamarilactone-1, 12% (±)-pandamarilactonine-A, B 17% 3%

## Acknowledgements

First and foremost, a huge thanks to Dr. Jeremy Robertson for his help and guidance over the past 4 years. Your boundless knowledge of chemistry never fails to impress and inspire me. Thanks also for your shared appreciation of Dr Who, scary horror films and a good cheese board. Of the JR group – where to start? In order of fumehood proximity…

Thanks to the self-appointed "column king" Feast for being an efficient manager of bar crawls and snuff distribution, having (mostly) excellent film taste, and a shared passion for port, pork pies and pints. Our Californian road trip was definitely one of my highlights of the last four years but I hope we can top it when I come out to visit you in Australia! Just don't try to imitate the local accent, they may not find your accidental Indian/Irish/Jamaican efforts quite so entertaining. Chris "old man" North: I miss our philosophical debates and your contribution towards the lab music library. There's definitely not enough Silverchair and Placebo in lab these days… these young ones don't know what they're missing out on! Kiri – I can't thank you enough for being a constant reassuring female presence in lab. Whether it was providing welcome relief from boring boy chat, instigating lab holidays, or just being my Margarita/champagne/Żubrówka companion, lab would definitely have been a far less exciting place without you around. Tiger: Thanks for being the other grown up in lab, passing on the Achmatowicz/safety rep baton and sharing an enthusiasm for my homeland. Willy: Your superhuman chemistry skills astound me to this day. Thanks for being such a lovely and silly lab/desk companion. I miss your singing, your nose, and your general cheerfulness, though not the wardrobe malfunctions… Anthony: Thanks for your unfaltering optimism in the face of chemical adversity. I still can't quite believe I proved you right with pandamarilactone-1! Thanks also for being an excellent source of restaurant advice and making me appreciate how strange the English language is. Alex: Your constant quest for chemistry knowledge amazes me. Thanks for your constant enthusiasm and curiosity for chemistry inside and outside the lab.

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Thanks to my industrial supervisor Jon "I saved a life" Dallimore, Lab 28, and the CRL support staff.

Finally, thanks to my family for their love, support and resisting the urge to ask when I'm going to get a real job.

# Contents

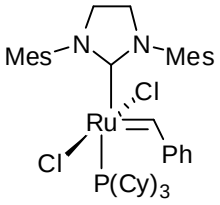
## Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AD | asymmetric dihydroxylation |
| aq. | aqueous |
| Ar | aryl |
| Bn | benzyl |
| Bz | benzoyl |
| Boc | *t*-butyloxycarbonyl |
| Bu | butyl |
| Bus | *t*-butylsulfonyl |
| cat. | catalytic |
| Cbz | benzoyloxycarbonyl |
| CI | chemical ionization |
| conc. | concentrated |
| COSY | correlation spectroscopy |
| CM | cross-metathesis |
| CPBA | chloroperbenzoic acid |
| d | day(s) |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DEPT | distortionless enhancement by polarization transfer |
| DIAD | diisopropyl azodicarboxylate |
| DIBAL-H | diisobutylaluminium hydride |
| DMAP | 4-dimethylaminopyridine |
| DMDO | dimethyldioxirane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| Dpp | diphenylphosphinyl |
| DPPA | diphenylphosphoryl azide |
| *e.e.* | enantiomeric excess |
| eq. | equivalents |
| ESI | electrospray ionization |
| Et | ethyl |
| FI | field ionization |
| GCT | gas chromatography – time of flight mass spectrometry |
| h | hour(s) |
| HMBC | heteronuclear multiple-bond correlation |

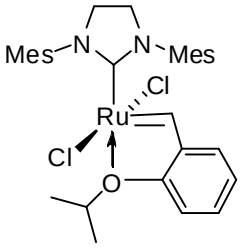
| | |
|---|---|
| HMQC | heteronuclear multiple-quantum correlation |
| *i*- | iso |
| IR | infrared |
| LDA | lithium diisopropylamide |
| lit. | literature value |
| M | molar |
| *m*- | meta |
| Me | methyl |
| min | minute(s) |
| m.p. | melting point |
| Ms | methanesulfonyl |
| MS | molecular sieves |
| *m*/*z* | mass/charge ratio |
| *n*- | normal |
| NBS | *N*-bromosuccinimide |
| NIS | *N*-iodosuccinimide |
| NMO | *N*-Methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| NR | no reaction |
| *o*- | ortho |
| *p*- | para |
| PG | protecting group |
| Ph | phenyl |
| Phth | phthalimide |
| Piv | pivaloyl |
| PMB | *p*-methoxybenzyl |
| p.p.m. | parts per million |
| Pr | propyl |
| PTSA | *p*-toluenesulfonic acid |
| $R_f$ | retention factor |
| RT | room temperature |
| sat. | saturated |
| SES | 2-trimethylsilylethane sulfonyl |
| *t*- | tertiary |
| TBS | *t*-butyldimethylsilyl |
| TBDPS | *t*-butyldiphenylsilyl |
| TCA | trichloroacetic acid |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic acid anhydride |

| | | | |
|---|---|---|---|
| THF | tetrahydrofuran | Ts | *p*-toluenesulfonyl |
| TLC | thin layer chromatography | | |
| TMS | trimethylsilyl | | |
| Troc | 2,2,2-trichlorethoxycarbonyl | | |

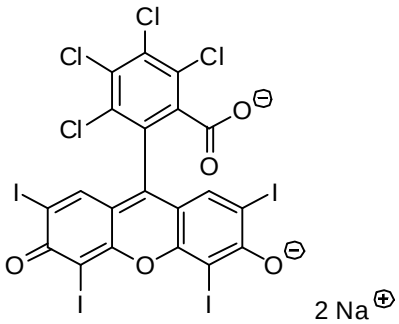
Grubbs' II catalyst



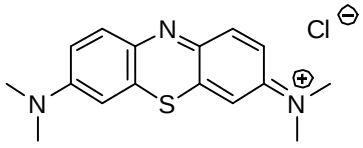

Hoveyda-Grubbs' II catalyst




Rose Bengal




Methylene Blue



# Chapter 1 Introduction

Spiroacetals, also known as spiroketals or 1,7-dioxaspiro[5.5]undecanes, are ubiquitous in nature and have attracted a great deal of interest from the synthetic organic community over the past four decades.[1, 2] By contrast, the spiroaminoacetal moiety occurs in far fewer natural products and, as a consequence, synthetic methods for their creation have been less fully explored.

This thesis is concerned with the synthesis of spiroaminoacetals *via* the oxidative spirocyclisation of 2-(ω-aminoalkyl)furans, henceforth termed the aza-Bohlmann cyclisation. Before the present work is discussed, an overview of current methods for the creation of spiroaminoacetals will be described. The aza-Bohlmann cyclisation has its conceptual roots in the long history of furan oxidation chemistry, in particular Bohlmann's studies on spirocyclic enol ethers and Ciufolini's aza-Achmatowicz rearrangement.[3, 4] Whilst a comprehensive review of furan oxidation chemistry is not possible within the scope of this thesis, a selection of the more relevant and interesting literature examples will be discussed.

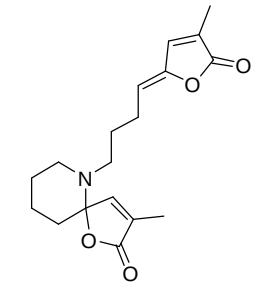
*Pandanus amaryllifolius* Roxb., also known as fragrant screw pine, is a palm-like evergreen shrub grown throughout the tropics. Its leaves are used extensively in traditional medicine as a remedy for rheumatism, epilepsy and leprosy and extracts from the plant have shown hypoglycaemic activity. [5] Several pyrrolidine and piperidine alkaloids have been isolated from this plant; of particular interest to this project is pandamarilactone-1 **1** as it features a spiroaminoacetal core identical to that formed in the aza-Bohlmann cyclisation. To date, no

syntheses of pandamarilactone-1 **1** have been reported yet synthetic efforts towards the spiroaminoacetal core, and syntheses of related *Pandanus* alkaloids will be reviewed.

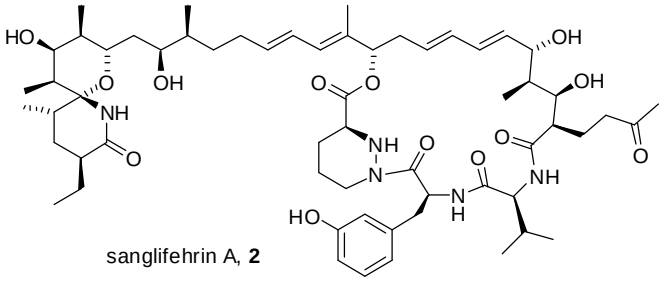
## *1.1 Synthetic approaches to spiroaminoacetals*

Despite their comparative rarity, a number of natural products containing an oxa-aza spirobicyclic framework have been found to exhibit biological activity (Figure 1.1) including the novel immunosuppressant sanglifehrin A[6, 7] **2**, the notorious class of neurotoxins the azaspiracids[8-10] **3** and the steroidal alkaloid tomatidine[11, 12] **4**.

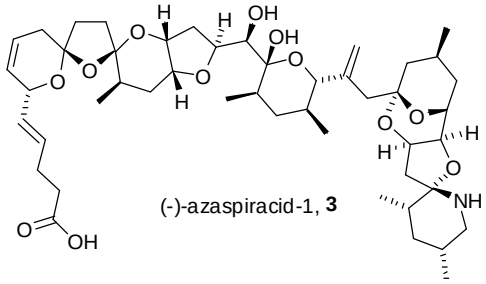
**Figure 1.1**: Spiroaminoacetals in nature



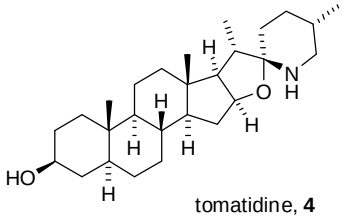
pandamarilactone-1, **1**



sanglifehrin A, **2**



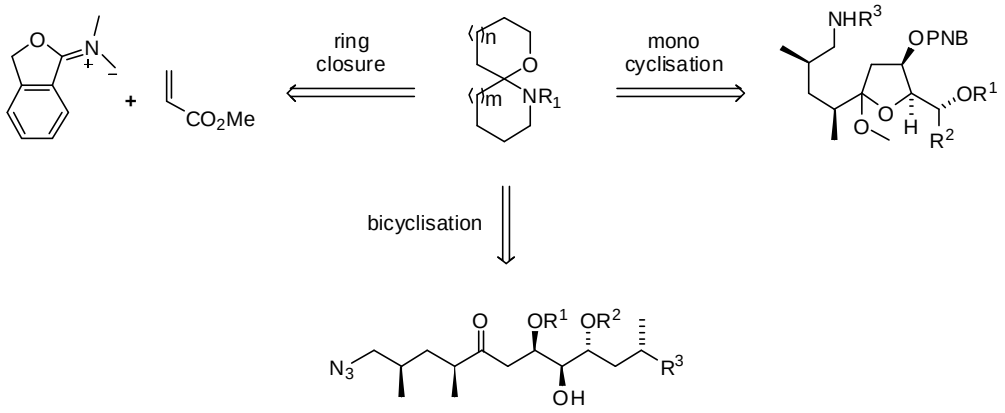
(-)-azaspiracid-1, **3**



tomatidine, **4**

For this reason, a range of strategies for the synthesis of spiroaminoacetals have been reported and can be divided into one of three approaches: (i) ring closure, (ii) monocyclisation, and (iii) bicyclisation (Scheme 1.1).[13]

**Scheme 1.1**: Synthetic approaches to spiroaminoacetals

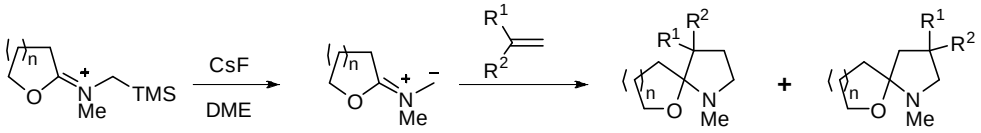



### 1.1.1 Ring closure

Synthetic strategies have been defined as ring closure if the spirocyclisation precursor contains either a pre-formed oxa- or azacycle with both the oxygen and nitrogen atoms attached to the carbon at the spirocentre.

Fishwick *et al*. described the synthesis of [4.4]- and [5.4]-spiroaminoacetals *via* 1,3-dipolar cycloadditions (Scheme 1.2).[14] Imidate methylides **6** were generated by treatment of the imidate salts **5** with CsF and, upon exposure to a range of electron-deficient dipolarophiles, afforded spiroaminoacetals **7** and **8** as a mixture of diastereomers.

**Scheme 1.2**: Azomethine ylide approach to spiroaminoacetals




**5** n = 1 or 2

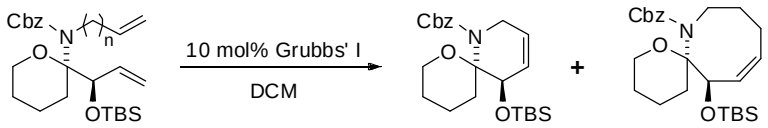
**6**

| | | | |
|---|---|---|---|
| $R^1$ = H | $R^2$ = $CO_2Me$ | - | n = 1, 26% n = 2, 8% |
| $R^1$ = H | $R^2$ = CN | - | n = 1, 26% n = 2, 28% |
| $R^1$ = Me | $R^2$ = $CO_2Me$ | n = 1, 65% | - n = 2, 69% |

**7** **8**

Ring closing metathesis (RCM) is a well established tool for the synthesis of carbocyclic[15, 16] and heterocyclic ring systems[17, 18] yet its application to spirocycles is relatively rare.[19, 20] The Hsung group reported the synthesis of [5.5]- and [5.7]-spiroaminoacetals from hemiaminal precursors **9**, **10** (Scheme 1.3) featuring a pre-formed tetrahydropyran ring.[21]

**Scheme 1.3**: Cross-metathesis approach to spiroaminoacetals




**9** n = 1
**10** n = 3

**11**, 95% from **9**

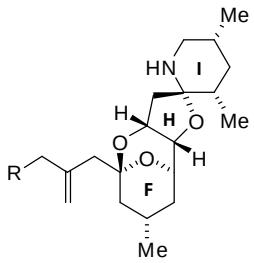
**12**, 94% from **10**

The reaction is stereospecific, with *anti*- and *syn*-hemiaminals forming *anti*-spiroaminoacetals and *syn*-spiroaminoacetals respectively and no spiroepimerisation was observed under the mild reaction conditions. A similar approach, recently reported by Vankar *et al*., furnished sugar-derived spiroaminoacetals.[22]

### 1.1.2 Monocyclisation

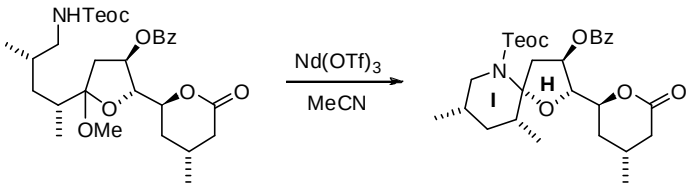
Several groups have reported the formation of spiroaminoacetals through a monocyclisation approach. These differ from the previously discussed ring closure strategies in that only one heteroatom is attached to the spirocentre prior to the spirocyclisation step.

**Figure 1.2**: Azaspiracid HI spiroaminoacetal fragment




This mode of spirocyclisation has proved particularly popular amongst a number of groups reporting syntheses of the HI fragment of the azaspiracids (Figure 1.2).[23-26] While the nature of the catalyst may change, cyclisation occurs through Lewis acid-mediated attack of an internal nitrogen nucleophile onto a ketal such as **13**. (Scheme 1.4). Although this approach may appear straightforward, the intermediate ketals are frequently acid-sensitive and careful screening of catalysts is often required to prevent substrate decomposition in competition with spirocyclisation. In Nicolaou's synthesis of azaspiracid-1 **3**, $Nd(OTf)_3$ was shown to be the most effective Lewis acid for the conversion of ketal **13** to spiroaminoacetal **14**.[26]

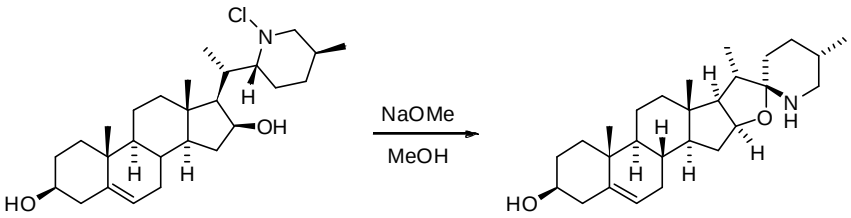
**Scheme 1.4**: Nicolaou synthesis of the HI fragment for the originally proposed structure of azaspiracid-1




**13** **14**, 81%

Groot and co-workers examined the synthesis of spiroaminoacetals as part of their studies towards the synthesis of steroidal hormones from potato glycoalkaloids (Scheme 1.5).[27] Chloroamine **15** underwent dehydrohalogenation upon treatment with sodium methoxide and the incipient imine was trapped by the proximal alcohol group to form tomatidenol **16** in 95% yield.[27]

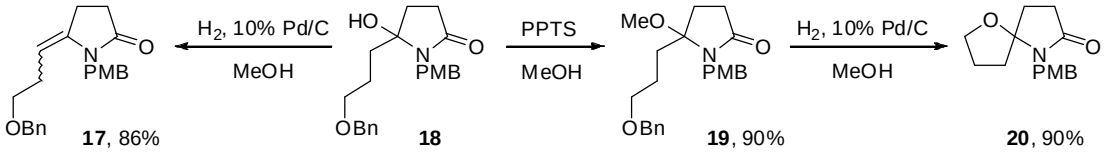
**Scheme 1.5**




**15** tomatidenol, **16**, 95%

The Kende group utilised *N*-acyliminium chemistry in their total synthesis of the *Stemona* alkaloids (±)-stemonamide and (±)-isostemonamide (Scheme 1.6).[28] Hydrogenolysis of methoxy aminal **19** induced spontaneous cyclisation to form spirolactam **20** in high yield. Interestingly, efforts to form **20** directly from hydroxypyrrolidinone **18** failed, leading instead to enamide **17**.

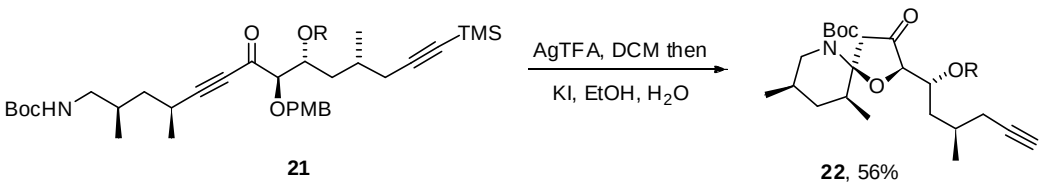
**Scheme 1.6**: Towards the synthesis of (±)-stemonamide




## 1.1.3 Bicyclisation

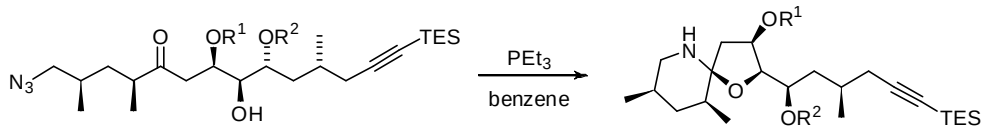
In the bicyclisation approach, neither the oxygen nor nitrogen atom is attached to the spirocarbon centre prior to cyclisation. The spiroaminoacetal is formed through the concomitant double cyclisation of a linear precursor onto a central ketone, two elegant examples of which have been demonstrated by the Forsyth group.[29] In their first approach to azaspiracid-1 **3**, exposure of PMB ether-ynone **21** to AgTFA and KI inititated a cascade of reactions (Scheme 1.7): hetero-Michael addition of the terminal nitrogen onto the ynone, cleavage of the TMS and PMB protecting groups, and stereoselective addition of the liberated hydroxyl group to the intermediate imine to form spirocycle **22** in 56% yield.

**Scheme 1.7**: Double intramolecular hetero-Michael addition approach to azaspiracid HI fragment



In a complementary strategy, a one-pot Staudinger reduction-aza-Wittig sequence afforded spirocycle **24** as a 4:1 mix of diastereomers (Scheme 1.8).

**Scheme 1.8**: Staudinger reduction–aza-Wittig process for the synthesis of azaspiracid HI fragment

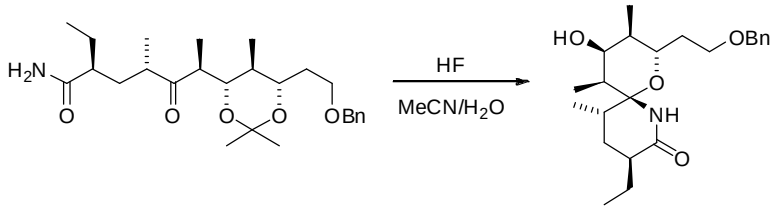



$R^1$ = TES
$R^2$ = TBS

**23** **24**, 75%

In spite of the dominance of azaspiracid-related spiroaminoacetal syntheses in the literature, a few examples originate from synthetic studies of sanglifehrin A **2** (Figure 1.1). The Nicolaou and Paquette groups reported very similar strategies for the synthesis of the spiroaminoacetal fragment of sanglifehrin A **2**. In the first example, Nicolaou utilised HF to unmask the acetonide-protected diol and induce spirocyclisation to afford spirolactam **26** as a single diastereomer (Scheme 1.9).[7]

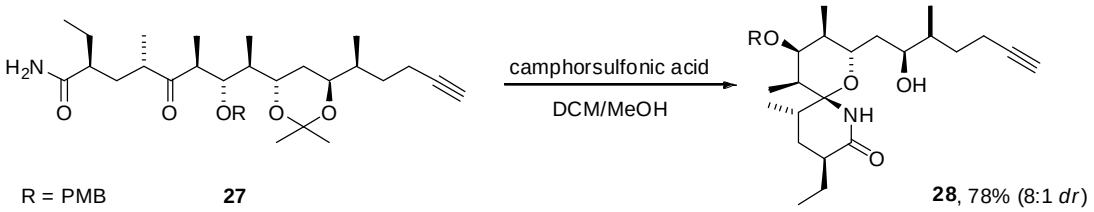
**Scheme 1.9**: Nicolaou synthesis of the spirolactam of sanglifehrin A **2**




**25** **26**, 95%

In Paquette's enantioselective total synthesis of sanglifehrin A, the synthesis of spirolactam **28** was achieved *via* a camphorsulfonic acid-catalysed spirocyclisation (Scheme 1.10).[30]

**Scheme 1.10**: Paquette's CSA-catalysed spirocyclisation

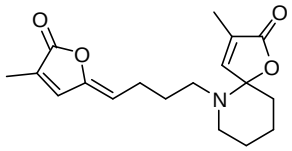



R = PMB **27** **28**, 78% (8:1 *dr*)

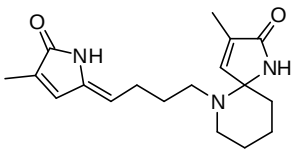
## *1.2 The Pandanus alkaloids*

The first report of alkaloids from *P. amaryllifolius* appeared in a field study of flowering plant species in selected areas of Luzon, Philippines.[31] Significant biogeographic variance appears to occur within the species: piperidine-type alkaloids featuring lactam or lactone rings appear in Filipino samples whereas pyrrolidinone and pyrrolidine-type alkaloids have been isolated from specimens collected in Indonesia and Thailand (Figure 1.3).

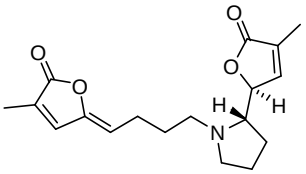
**Figure 1.3**



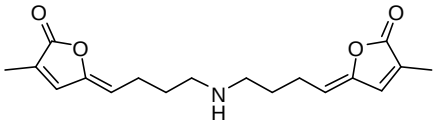
pandamarilactone-1, **1**



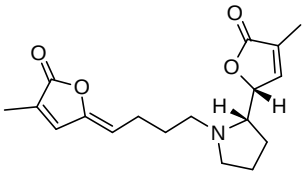
(±)-pandamarine, **29**



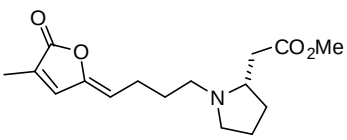
pandamarilactonine-A, **30**



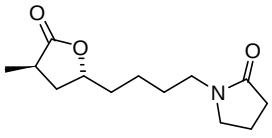
pandanamine, **32**



pandamarilactonine-B, **31**



pandamarilactonine-H, **33**

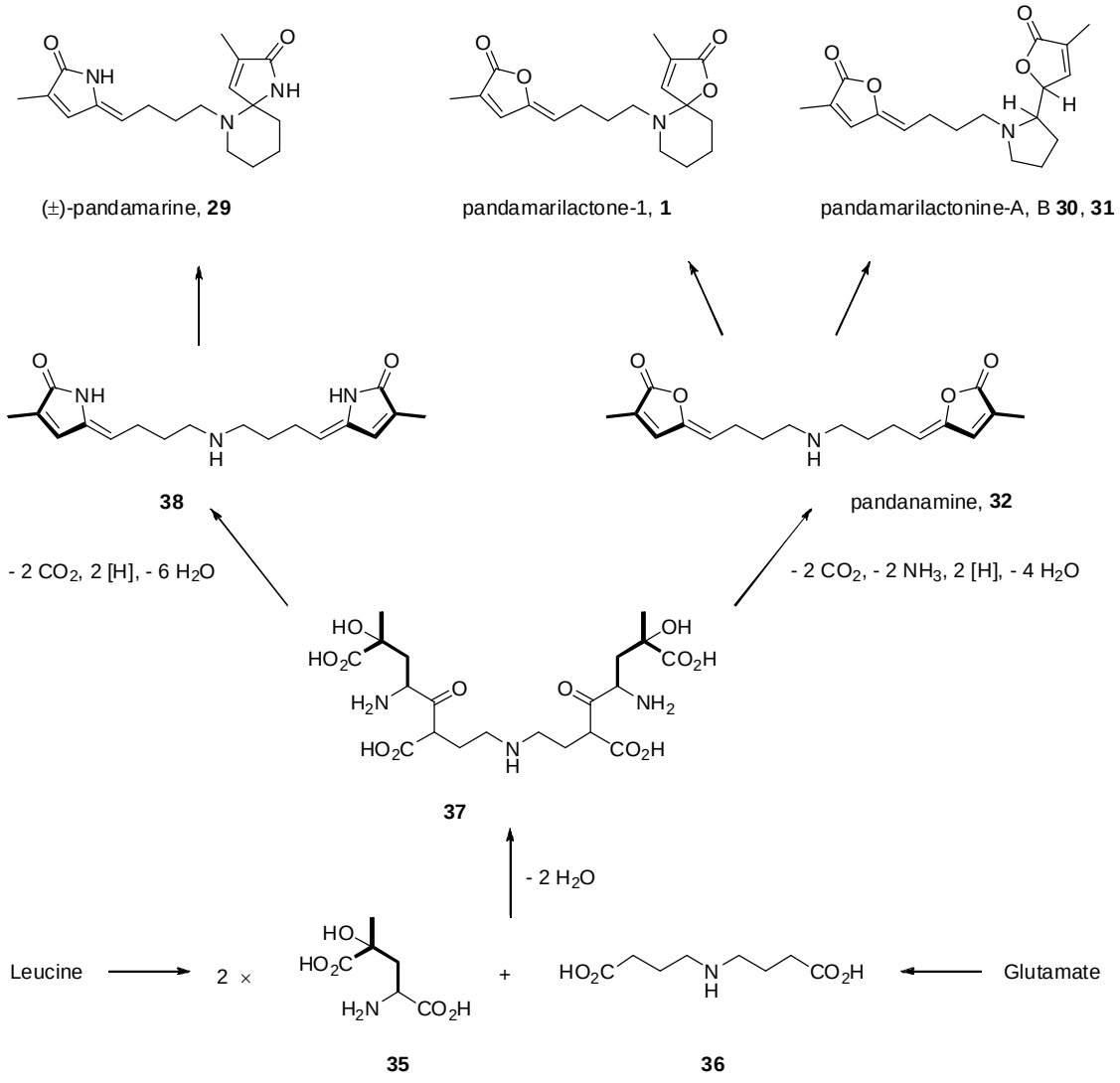


pandamarilactonine-G, **34**

Byrne *et al*.[32] identified the novel alkaloid (±)-pandamarine **29** as the major base isolated from leaves of the plant while Garson *et al*.[0] isolated the lactone analogue pandamarilactone-1 **1** . This is intriguing since **1** differs from **29** only in the replacement of NH by O. While pandamarine **29** was isolated as the racemate, pandamarilactone-1 **1** was found to exhibit optical activity $[\alpha]_D$ –33.0° (c 1.0, MeOH) though the absolute stereochemistry at the spiro centre could not be determined. Although the two studies claim to have examined samples of the same species from the Philippines, the specimens were collected at different times and location and environmentally induced variability in transaminase activity could explain the variance in structures isolated.[0]

Both (±)-pandamarine **29** and pandamarilactone-1 **1** can be envisaged as coming from the biosynthetic route proposed by Garson[1] and Nonato:[33] condensation of 4-hydroxy-4-methylglutamic acid[34] **35** and diacid **36** forms the carbon backbone **37**; a series of decarboxylation, cyclisation, reduction and dehydration steps could then afford the symmetrical lactam **38** and lactone **32** (Scheme 1.11). Intramolecular cyclisation of lactam **38** would then deliver (±)-pandamarine **29**, whereas pandamarilactone-1 **1** and the pandamarilactonines would arise from the cyclisation of pandanamine **32**. This hypothesis was backed up by the subsequent isolation of the proposed biogenetic precursor, pandanamine **32**, by Takayama in 2001.[35]

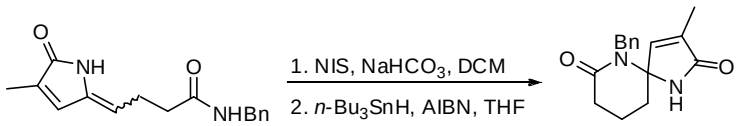
**Scheme 1.11**: Proposed biosynthetic route to the *Pandanus* alkaloids



### 1.2.1 Previous syntheses of *Pandanus* alkaloids

To date, no syntheses of pandamarilactone-1 **1** or (±)-pandamarine **29** have been reported. Bermejo and co-workers have demonstrated an NIS-mediated oxidative cyclisation to form the piperidinone analogue of the spirolactam core of (±)-pandamarine **29** (Scheme 1.12) from alkylidene pyrrolinone **39**.[36]

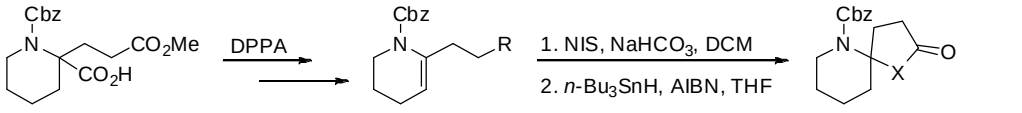
**Scheme 1.12**




**39** (±)–**40**, 51%

In a related approach, the group also developed a protocol for the synthesis of saturated spirolactams and spiroaminoacetals based on a pre-formed piperidine ring (Scheme 1.13). Diphenylphosphoryl azide-promoted thermal fragmentation of pipecolic acid **41** formed tetrahydropyridine **42**. Treatment of **42** with NIS and tributyltin hydride as before afforded saturated [4.5]-spirolactone **43a** and [4.5]-spirolactam **43b** in moderate yield.[37]

**Scheme 1.13**: Bermejo group's NIS-mediated spirocyclisation



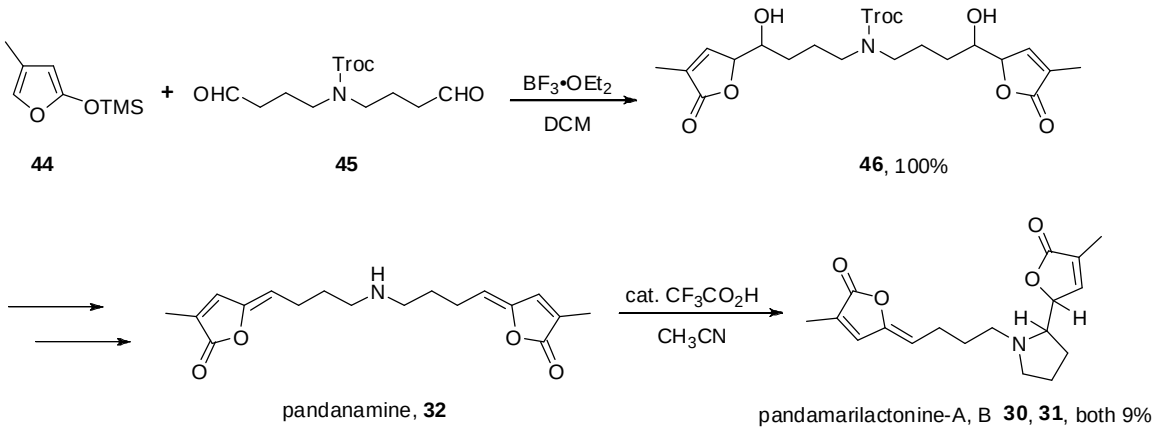

**41**

**42a** : R = COOH
**42b** : R = C(OSiMe$_3$)=NSiMe$_3$

**43a** : X = O, 54%
**43b** : X = NH, 29%

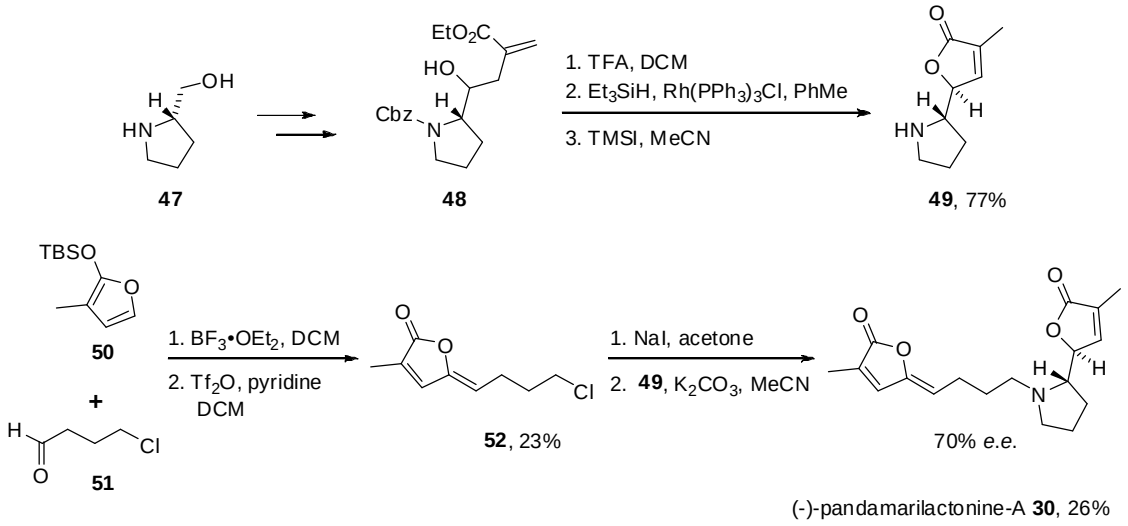
The ready interconversion of *Pandanus* alkaloids has been used to great effect by Takayama[33] and Argade.[38] Takayama reported two syntheses of the pyrrolidine alkaloids pandamarilactonines-A,B **30**, **31**. Using a biomimetic approach (Scheme 1.14), silyl ether **44** was coupled with dialdehyde **45** to afford diol dimer **46**.

**Scheme 1.14**: Takayama's biomimetic synthesis of pandanamine **32** and pandamarilactonines-A, B **30**, **31**



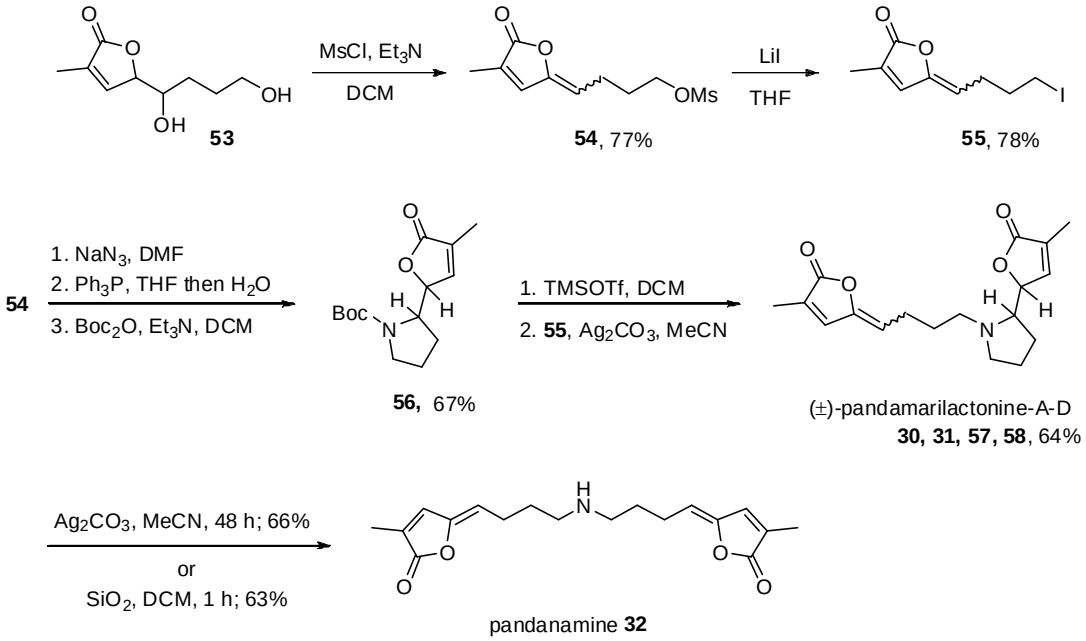

Dehydration and cleavage of the *N*-Troc group furnished pandanamine **32** which, upon treatment with trifluoroacetic acid, delivered (±)-pandamarilactonine-A **30** and (±)-pandamarilactonine-B **31** each in 9% yield. More recently, an asymmetric synthesis starting from L-prolinol **47** afforded (-)-pandamarilactonine-A **30** (Scheme 1.15).[39, 40]

**Scheme 1.15**: Takayama asymmetric synthesis of (-)-pandamarilactonine-A



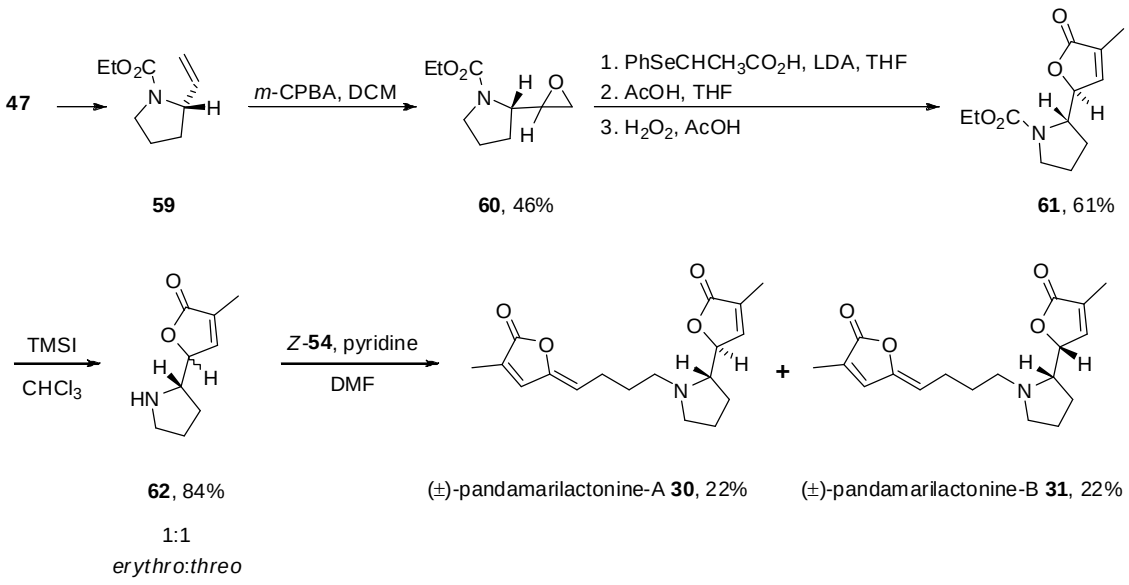

The Argade group chose a divergent strategy for their synthesis of (±)-pandanamine **32** and (±)-pandamarilactonines-A-D. (Scheme 1.16).[38] To form the bicyclic fragment **56**, mesylbutenolide **54** was treated with sodium azide and triphenylphosphine; the resulting iminophosphorane then added in a Michael fashion to the exocyclic olefinic bond to afford pyrrolidine **56**. Meanwhile, mesylbutenolide **54** was also converted to iodobutenolide **55** by treatment with LiI. Following deprotection of the *N*-Boc group, bicycle **56** was coupled with γ-alkylidene butenolide **55** to provide (±)-pandamarilactonines-A-D in good yield. Interestingly, if the coupling reaction was allowed to stir for an extended period of time, or (±)-pandamarilactonines-A-D were stirred with silica in DCM, pandanamine **32** was isolated.

**Scheme 1.16**: Argade's synthesis of pandanamine and (±)-pandamarilactonine-A-D




The Figueredo group described the synthesis of pandamarilactonines-A,B **30**, **31** *via* a similar strategy.[41] Although their synthetic route started from L-prolinol, the group encountered several problems maintaining the stereochemical integrity of the intermediates throughout their synthesis (Scheme 1.17). After epoxidation, the *erythro* and *threo* isomers of **60** were separated and the major *erythro* isomer taken forward. However, upon cleavage of the ethyl carbamate with TMSI, epimerisation occurred and **62** was obtained as a mixture of diastereomers showing low optical activity. Following alkylation with **54**, pandamarilactonines-A,B **30**, **31** were isolated as a racemic mixture each in 22% yield.

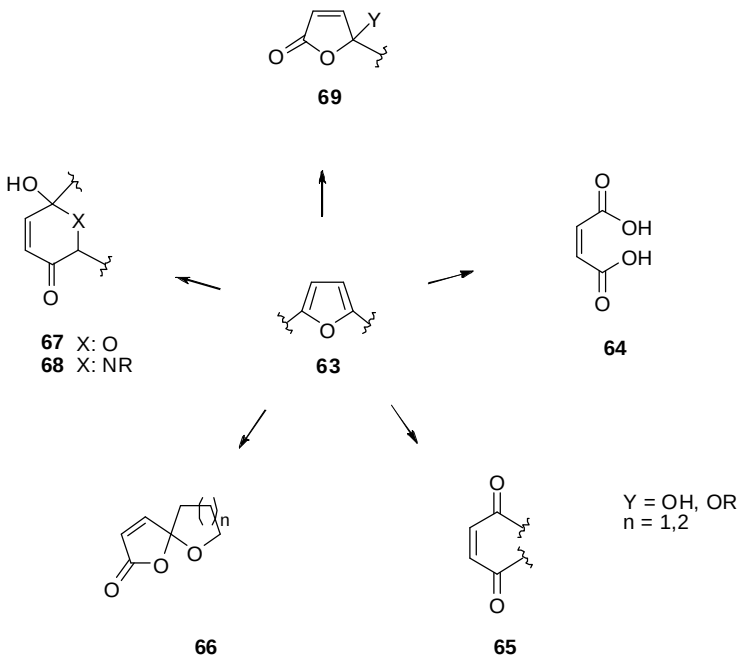
**Scheme 1.17**: Figueredo synthesis of (±)-pandamarilactonine-A, B **30**, **31**



## *1.3 Furan oxidations*

The oxidation of furan can provide access to a variety of structure types depending on the choice of oxidant and substitution pattern around the ring (Scheme 1.18). Reagents used for these oxidation processes include peracids,[42, 43] hydrogen peroxide,[44] NBS,[42, 45] anodic oxidation,[46] dimethyldioxirane,[47] singlet oxygen,[48, 49] pyridinium chlorochromate[50, 51] and Vo(acac)$_2$-*tert*-butylhydroperoxide.[52, 53] If the oxidation takes place in the absence of a nucleophile, enediacid[54] **64** or enedione **65** products may be formed. An internal nucleophile may render spiroacetal **66**, dihydropyranone **67**, or dihydropyridone **68** structures while the presence of an external nucleophile can lead to butenolides **69**.

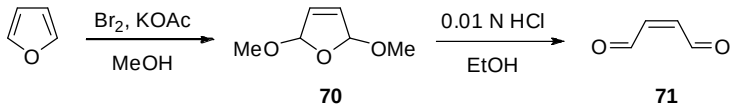
**Scheme 1.18**: Furan oxidation products



### 1.3.1 The Bohlmann cyclisation

Clauson-Kaas published the seminal work in this area in 1948, describing the synthesis of 2,5-dihydro-2,5-dimethoxyfuran **70** by treatment of furan with bromine in methanol (Scheme 1.19).[55] Hydrolysis of **70** affords malealdehyde **71** and this method proved to be a useful route to these unstable 1,4-dicarbonyl compounds.

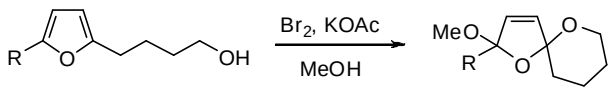
**Scheme 1.19**: Clauson-Kaas oxidative conditions




**70** **71**

Bohlmann and co-workers adapted these oxidative conditions and applied them to δ-hydroxyfuran **72**, generating methoxyspiroacetal **73** *en route* to the synthesis of homo-tonghaosu (Scheme 1.20).[3] Several groups have since utilised the Bohlmann cyclisation and variants with great success in the synthesis of spiroacetal natural products.

**Scheme 1.20**: Bohlmann cyclisation

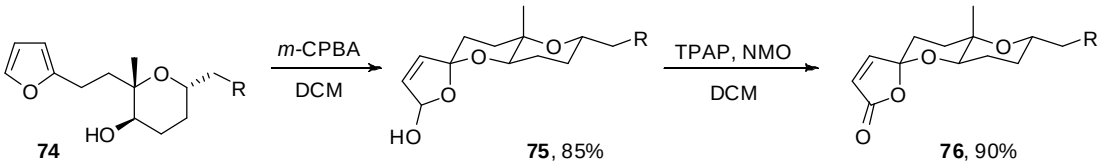



**72** **73**

R = $CH_2(C{\equiv}C)_2CH_3$

Previous work within the Robertson group has been concerned with the synthesis of lituarines A-C.[56] Using a Bohlmann-type cyclisation under Lefebvre conditions,[43] spirolactol **75** was obtained in 85% yield (Scheme 1.21).[57] Although studies on a model system had shown that an excess of *m*-CPBA could drive oxidation up to the lactone, a secondary oxidation step using TPAP proved to be more reliable in this instance and afforded spirolactone **76** in 90% yield. This oxidation protocol was also utilised by Nelson *et al*. in their synthetic studies of hemibrevetoxin B.[58]

**Scheme 1.21**: Robertson group synthesis of lituarine spiroacetal precursor

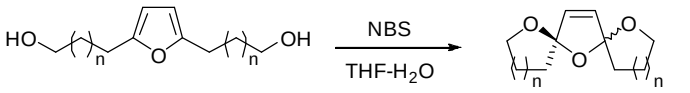



**74** **75**, 85% **76**, 90%

R = $CH_2OTBS$

The trioxadispiroacetal functionality is present in a number of biologically active marine natural products including the aforementioned azaspiracids,[8, 9] the pinnatoxins[59] and pteriatoxins.[60] The Stockman group have demonstrated the synthesis of [4.4.4]- and [5.4.5]-trioxadispiroacetals *via* a double Bohlmann cyclisation process (Scheme 1.22). Exposure of diols **77** and **78** to NBS produced spiroacetals **79** and **80** as 1:1 mixtures of diastereomers in moderate to good yields.[61]

**Scheme 1.22**: Stockman's double Bohlmann cyclisation

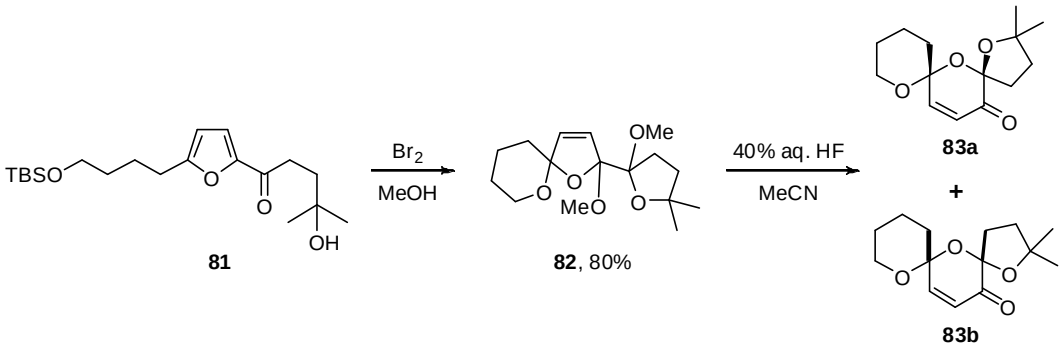



**77**: n = 1
**78**: n = 2

**79**: n = 1; 46%
**80**: n = 2; 65%

As part of their studies towards the synthesis of salinomycin,[62] the Kocienski group used modified Clauson-Kaas conditions to achieve TBS deprotection and spirocyclisation delivering spirobutenolide **82** in good yield (Scheme 1.23).[63] Rearrangement under aqueous HF conditions then provided a 1:1 mixture of dispiroacetals **83a** and **83b**.[64]

**Scheme 1.23**: Kocienski's efforts towards salinomycin




**81**

**82**, 80%

**83a**

+

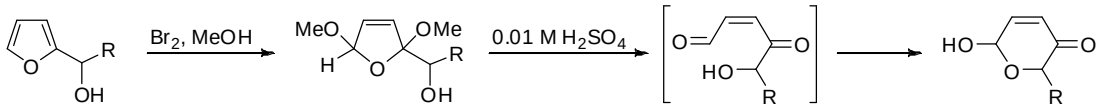
**83b**

1:1, 88%

### 1.3.2 The Achmatowicz rearrangement

In an alternative application of the Clauson-Kaas conditions, Achmatowicz and co-workers demonstrated the formation of dihydropyranones from α-hydroxyfurans.[65] In contrast to the Bohlmann cyclisation, the intermediate enedione **86** is trapped by attack of the chain hydroxyl group at the distal carbonyl forming dihydropyranone **87** products (Scheme 1.24).

**Scheme 1.24**: The Achmatowicz rearrangement

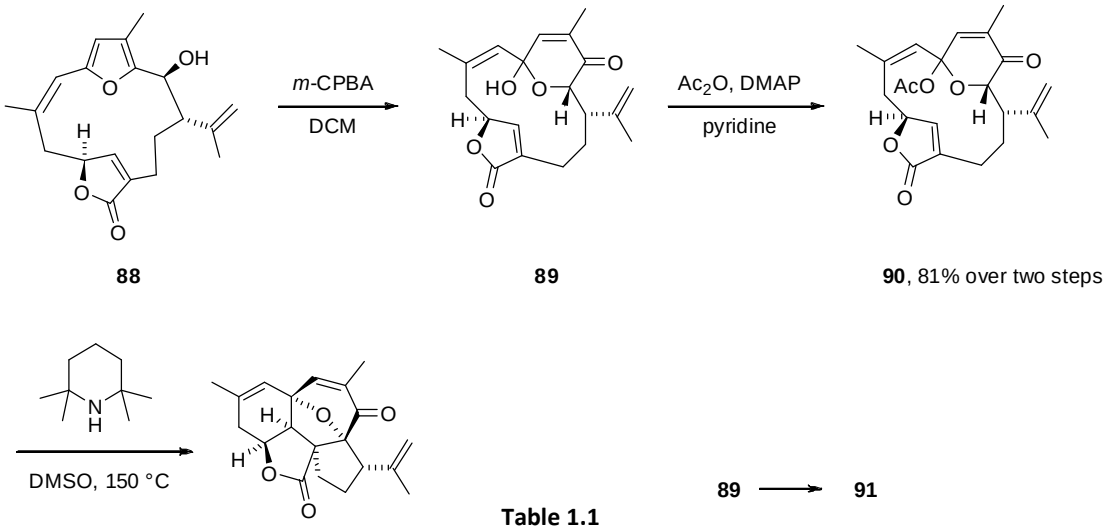



**84** **85** **86** **87**

The Achmatowicz rearrangement has also found widespread utility in the synthesis of natural products. Trauner and co-workers reported an elegant synthesis of (+)-intricarene *via* a transannular 1,3-dipolar cycloaddition (Scheme 1.25).[66] An Achmatowicz rearrangement was used to form key precursor dihydropyranone **89** from (–)-bipinnatin J, *m*-CPBA replacing bromine as the oxidant of choice in this more heavily functionalised molecule. Attempts to form (+)-intricarene **91** directly from **89** under a variety of acidic and dehydration conditions proved largely fruitless, with only trace amounts of the desired cycloadduct **91** recovered (Table 1.1). Instead, conversion to

acetate **90** followed by treatment with 2,2,6,6-tetramethylpiperidine and heating at 150 °C afforded (+)-intricarene **91** in 26% yield.

**Scheme 1.25**: Trauner's synthesis of (+)-intricarene




**88** **89** **90**, 81% over two steps

**91**, 26%
(+)-intricarene

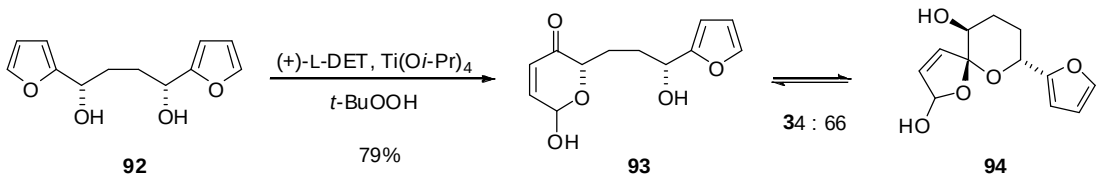
**89** ⟶ **91**

**Table 1.1**

| Solvent | Temp./ °C | Reagent | Result |
|---|---|---|---|
| MeCN | 200 | - | decomp. |
| benzene | 80 | Amberlite 120 | no reaction |
| none | 400 – 500 | - | decomp. |
| none | 120 | on silica | trace |

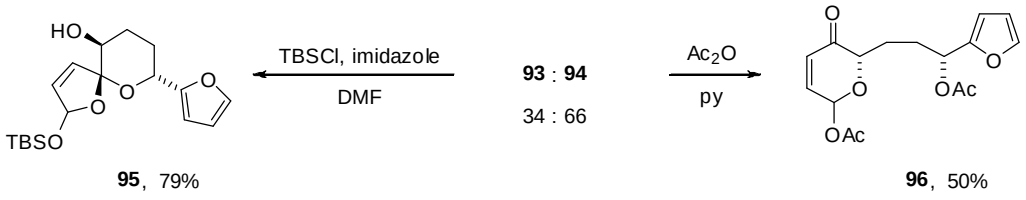
The Nelson group described a procedure for isolating either dihydropyranone **93** or spiroacetal **94** from the oxidation of *meso* diol **92**.[67] Desymmetrisation under Sharpless asymmetric epoxidation conditions[68, 69] afforded an equilibrium mixture of Achmatowicz product **93** and Bohlmann cyclisation spirocycle **94** (Scheme 1.26). Their isolation strategy centred on *O*-protection; selective protection of any hydroxyl group in the mixture would remove the equilibration mechanism between the two ring systems and hence allow for isolation of either *O*-protected **93** or **94**.

**Scheme 1.26**: Nelson's dual Achmatowicz/Bohlmann process



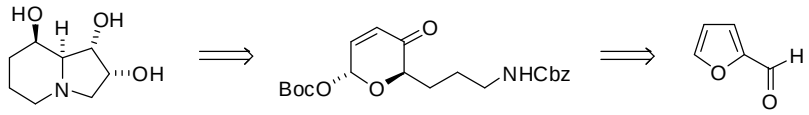

Indeed, treatment of the pyranone-spiroacetal mixture with the bulky TBSCl afforded spiroacetal silyl ether **95** as an 80:20 mixture of diastereomers in good yield (Scheme 1.27). Isolation of Achmatowicz product **93** was achieved by treatment of the pyranone-spiroacetal mixture with acetic anhydride in pyridine, delivering diacetate pyranone **96** as a 73:27 mix of anomers in satisfactory yield.

**Scheme 1.27**




Indolizidines may not appear an obvious candidate for Achmatowicz chemistry but O'Doherty and co-workers have used just such an approach for the asymmetric synthesis of the iminosugar (–)-8a-*epi*-swainsonine **97** (Scheme 1.28).[70]

**Scheme 1.28**: O'Doherty's retrosynthetic analysis of (–)-8a-*epi*-swainsonine **97**

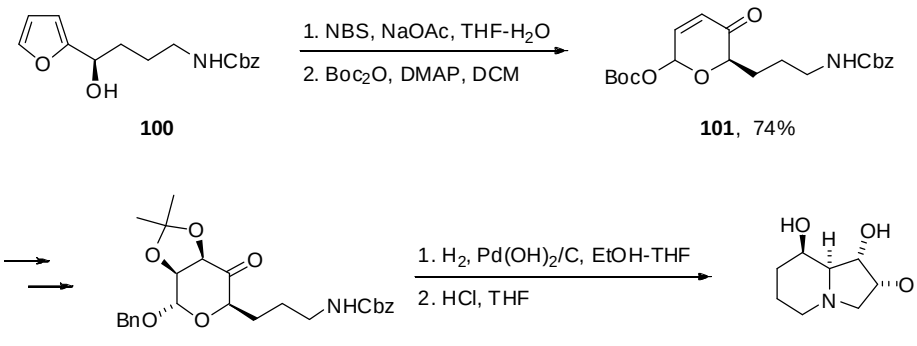



**97** **98** **99**

(–)-8a-*epi*-swainsonine

Furyl alcohol **100** was treated with NBS to afford dihydropyranone **101** as a 7:1 mixture of anomers (Scheme 1.29). Following chromatographic separation, the α anomer was elaborated to acetonide **102** *via* a Pd-catalysed glycosylation,[71] Luche reduction,[72] dihydroxylation, acetonide protection and oxidation sequence. Hydrogenolysis of acetonide **102** resulted in *O*-benzyl deprotection and double reductive cyclisation to form the indolizidine core. Removal of the acetonide protecting group under acidic conditions then furnished (–)-8a-*epi*-swainsonine **97** in 5% overall yield from furfural.

**Scheme 1.29**: Synthesis of (–)-8a-*epi*-swainsonine *via* an Achmatowicz rearrangement




**100** **101**, 74%

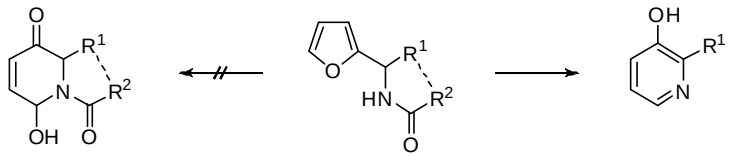
**102** **97**, 70%

(–)-8a-*epi*-swainsonine

### 1.3.3 The Aza-Achmatowicz rearrangement

The aza variant of the Achmatowicz rearrangement was first reported by Ciufolini in 1986, albeit not in its current incarnation.[4] Following the precedent set by Achmatowicz, α-amidofurans **103** were treated with $Br_2$ in methanol (Scheme 1.30) yet instead of the desired dihydropyridones **104**, aromatised pyridinols **105** were recovered.[73]

**Scheme 1.30**

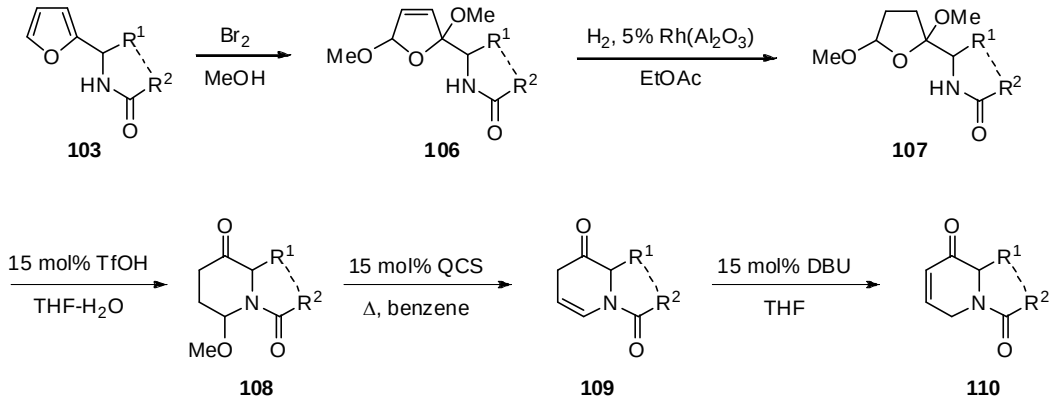



**104** **103** **105**

Conditions: $Br_2$, MeOH then $H_3O^+$ or *m*-CPBA, DCM

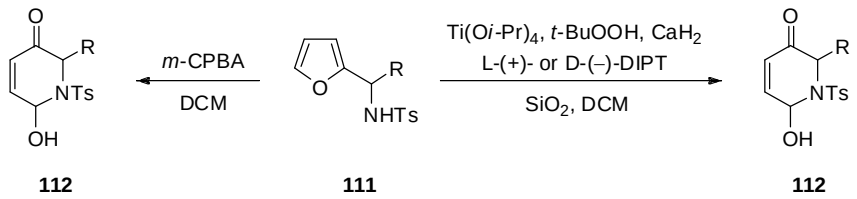
In order to prevent aromatisation of the ring-expanded products, the olefinic bond in dihydrofuran intermediate **106** was removed by hydrogenation (Scheme 1.31). Cyclisation was then achieved on THF derivatives **107** with triflic acid. A series of base-promoted eliminations gave successively enamide **109** and finally the desired dihydropyridone **110**. Clearly this procedure needed some modification as the harsh reduction conditions and the need for two elimination steps hampered its application to more complicated substrates.

**Scheme 1.31**: The aza-Achmatowicz rearrangement



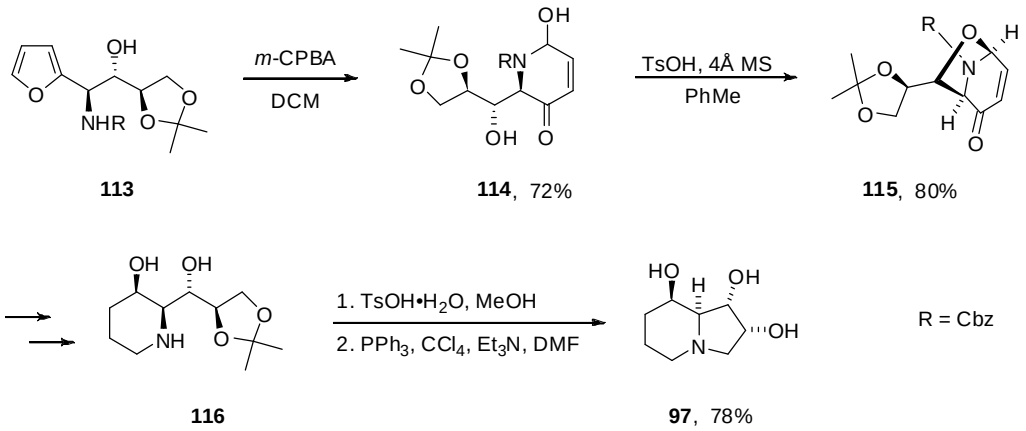

The Zhou group demonstrated that the aza-Achmatowicz reaction could be performed in an analogous fashion to the Achmatowicz rearrangement if the α-aminofuran was protected as a sulfonamide (Scheme 1.32).[74] Under Lefebvre[43] or Sharpless' asymmetric epoxidation conditions[75] hydroxypyridones **112** could be obtained in high yields (typically > 90%).

**Scheme 1.32**: Zhou's modified aza-Achmatowicz conditions



Latterly, *N*-Cbz α-aminofurans have also shown compatibility with the direct aza-Achmatowicz conditions,[76] expanding the versatility of this useful rearrangement. The Aggarwal group exploited the Cbz group's lability towards hydrogenation conditions in their synthesis of (–)-8a-*epi*-swainsonine **97** (Scheme 1.33).

**Scheme 1.33**: Aggarwal approach to (–)-8a-*epi*-swainsonine **97**




**113** **114**, 72% **115**, 80%

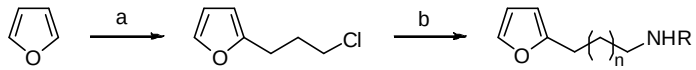
**116** **97**, 78%

Oxidation of aminoalcohol **113** with *m*-CPBA afforded dihydropyridone **114** in good yield. Eschewing further protecting group chemistry, dihydropyridone **114** was protected by the formation of bicycle **115** under refluxing toluene-tosic acid conditions. Subsequent Luche reduction proceeded with high diastereoselectivity, and hydrogenation over Pd/C effected reduction of the olefin, *N*,*O*-acetal and Cbz cleavage to deliver piperidinol **116**. Tosic acid liberated the terminal diol and, under Appel conditions,[77] intramolecular *N*-alkylation afforded (–)-8a-*epi*-swainsonine **97** in 78% yield.

## *1.4 Previous work within the Robertson group*

Prior to the outset of this project, the development of an aza-Bohlmann reaction had been investigated by a Part II student in the group.[78] A variety of *N*-protected amines were subjected to a series of oxidation conditions known to effect Bohlmann cyclisation[3] in the analogous 4-(2-furyl)butan-1-ol substrates.

**Scheme 1.34**




**117**

**118**: n = 2, R = H
**119**: n =1, R = Ts

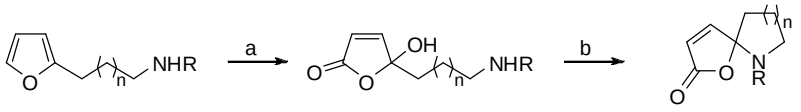
Conditions: (a) *n*-BuLi, 1-bromo-3-chloropropane, $Et_2O$, 92%; (b) **118**: (i) NaCN, DMSO, (ii) $LiAlH_4$, $Et_2O$, 92% over 2 steps; **119**: (i) NaI, butan-2-one, (ii) $TsNH_2$, $K_2CO_3$, DMF, 32% over 2 steps

The synthesis of the furyl amines followed a divergent route based on the cheap starting materials furan and 1,3-bromochloropropane (Scheme 1.34). Addition of lithiofuran to 1-bromo-3-chloropropane afforded chloride **117** in high yield. Cyanide displacement and subsequent $LiAlH_4$ reduction delivered aminoalkylfuran **118** ready for *N*-protection. Elaboration of chloride **117** to the aminopropylfuran substrate was achieved *via* a Finkelstein reaction[79] and subsequent displacement of the intermediate iodide with *p*-toluenesulfonamide to obtain sulfonamide **119** in moderate yield.

*N*-Tosyl, *N*-Tris, *N*-benzoyl and *N*-Boc protected amines were synthesised and subjected to the established *m*-chloroperbenzoic acid conditions utilised in the synthesis of the

lituarines (Scheme 1.35).[57] Unfortunately, hydroxybutenolides **124** – **127** were the only products isolated from the oxidation reaction.

**Scheme 1.35**




**119 :** R = Ts, n = 1 (50)
**120 :** R = Ts, n = 2 (86)
**121 :** R = Tris, n = 2 (63)
**122 :** R = Bz, n = 2 (66)
**123 :** R = Boc, n = 2 (74)

**124 :** R = Ts, n = 1 (23)
**125 :** R = Ts, n = 2 (89)
**126** : R = Tris, n = 2 ( - )†
**127 :** R = Bz, n = 2 (45)

**128 :** R = Ts, n = 1 (22)‡
**129 :** R = Ts, n = 2 (68) (20)‡
**130 :** R = Tris, n = 2 (55) (11)‡
**131 :** R = Boc, n = 2 (6)‡

† Not isolated
‡ Formed directly from **119, 120, 121** or **123** by treatment with AcOOH, DCM
Tris: 2,4,6-triisopropylbenzenesulfonyl

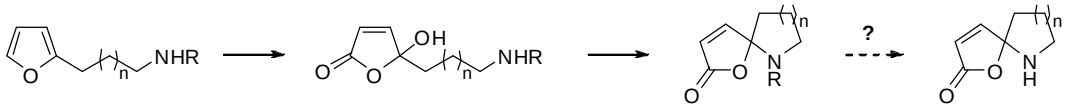
Conditions: (a) *m*-CPBA, DCM; (b) 30% aq. $H_2SO_4$

Subjecting the hydroxybutenolides **124** – **127** to 30% aq. $H_2SO_4$ induced cyclisation in the sulfonamide protected substrates **124** – **126** but led to decomposition with *N*-benzoyl hydroxybutenolide **127**. Best yields were obtained by performing the spirocyclisation in a one-pot process: once consumption of the starting material had occurred as judged by TLC analysis, the solvent was removed *in vacuo* and the crude residue stirred in 30% aq. $H_2SO_4$. Although yields were satisfactory, the fact that only sulfonamide protecting groups were tolerated limited the application of this methodology. Peracetic acid[80] proved the only oxidant capable of performing the aza-Bohlmann directly from the aminoalkylfurans and pleasingly, for the first time *N*-Boc spiroaminoacetal **131** was isolated. However, yields were significantly lower than those obtained by the *m*-CPBA/$H_2SO_4$ process (typically 5 – 20%) with large amounts of polymerised material generated in the reaction.

## *1.5 Project Aims*

The initial focus of the present work was to synthesise a more diverse range of *N*-protected aminoalkylfurans and screen a range of oxidants with a view to developing a higher yielding aza-Bohlmann cyclisation. In particular, early efforts were to be focussed on the synthesis of spiroaminoacetals featuring a labile protecting group that would allow elaboration at nitrogen atom following spirocyclisation (Scheme 1.36). However, free amine spiroaminobutenolides have not been reported in the literature and the viability/stability of such substrates is unknown.

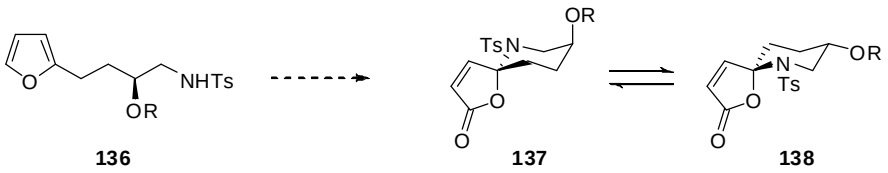
**Scheme 1.36**




**132** **133** **134** **135**

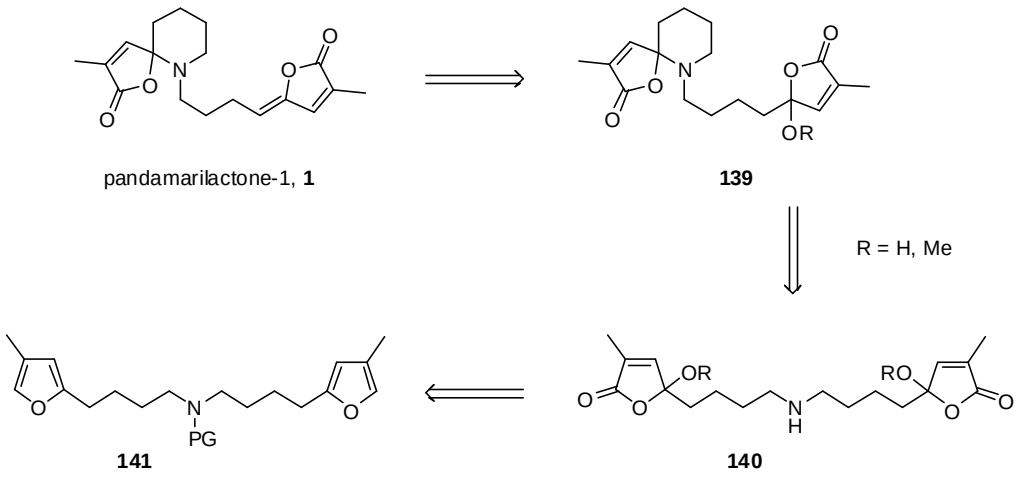
Currently, the spirocyclisation step produces the spiroaminoacetals as a racemic mixture. If the aza-Bohlmann cyclisation were to be applied to more complex systems, it would be useful to have a method for controlling the absolute configuration of the spiro centre. We sought to synthesise a range of *O*-protected δ-amino-γ-hydroxyfurans to investigate whether the axial/equatorial conformational preferences of the *O*-substituent could control the stereochemistry at the spirocentre (Scheme 1.37).

**Scheme 1.37**: Conformational study substrates




Since its isolation by Nonato *et al*. in 1993,[0] there have been no reports of a total synthesis and only scant mention in the literature of synthetic efforts towards pandamarilactone-1 **1**.[5] A key structural feature that appears unique to this alkaloid is the presence of a 1-oxa-6-azaspiro[4.5]dec-3-en-2-one motif, making it an ideal candidate for the application of our aza-Bohlmann methodology. We hoped to complete the first total synthesis of pandamarilactone-1 **1** in a pseudobiomimetic fashion *via* oxidation and spirocyclisation of difuryl amine **141**.

**Scheme 1.38**: Retrosynthetic analysis of pandamarilactone-1



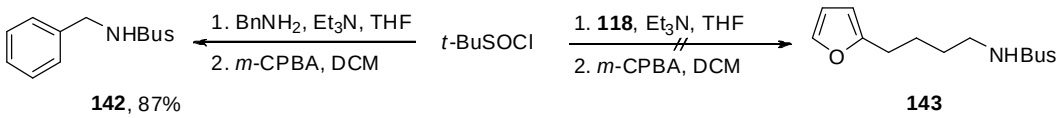
# Chapter 2 The aza-Bohlmann cyclisation

## *2.1 Optimisation of the aza-Bohlmann cyclisation*

### 2.1.1 Alternative *N*-protecting groups

Sulfonamide protecting groups have shown excellent compatibility with the aza-Bohlmann cyclisation (Scheme 1.35) yet the harsh conditions required for their removal could limit the potential applications of our methodology. The *tert*-butylsulfonyl (Bus) group, has been successfully used in aziridine[81] and peptide[82] chemistry and, in contrast to most sulfonamide protecting groups, can be cleaved from primary and secondary amines simply by treatment with TFA.[83]

**Scheme 2.1**




**142**, 87% **143**

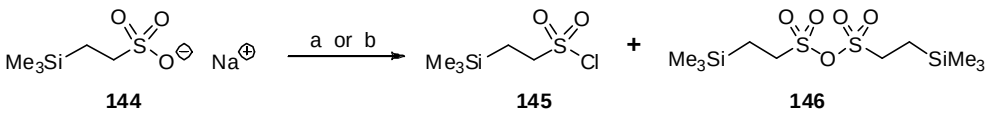
*N*-Protection is carried out in two steps: sulfination with *tert*-butyl sulfinyl chloride then oxidation (usually with *m*-CPBA) of the sulfinamide to the corresponding sulfonamide. In the context of our furan substrate, this may inevitably have led to the isolation of some *N*-sulfonamide hydroxybutenolide since the furan would undergo oxidation in competition with the sulfinamide moiety.[45] Despite successfully carrying out *N*-Bus protection on a model substrate to form sulfonamide **142**, we were unable to isolate the desired *N*-Bus furyl sulfonamide **143** (Scheme 2.1). A large amount of decomposition

occurred in the sulfination step and, following *m*-CPBA oxidation, none of the desired product could be isolated from the crude brown oil following column chromatography.

Prior to their report of the Bus protecting group, Weinreb and co-workers had reported trimethylsilylethanesulfonyl (SES) chloride as an efficient reagent for the protection of amines.[84] The mild deprotection conditions reported for the SES group (TBAF, CsF), combined with its stability under acidic conditions,[85] made it attractive as a *N*-protecting group for the aza-Bohlmann cyclisation. SES chloride is commercially available yet its high cost meant we opted to make it in-house.

Treatment of sodium salt **144** with sulfuryl chloride and triphenylphosphine[86] provided the most reliable route to SES chloride **145** (Scheme 2.2). An alternative procedure using $PCl_5$ in carbon tetrachloride generated a significant amount of SES anhydride **146** as a by-product.[87] Anhydride **146** was easily separated from chloride **145** *via* distillation and could also be used to form *N*-SES amine **147** (Table 2.1, entry 4) yet yields were significantly lower than those obtained with SES chloride **145**.

**Scheme 2.2**

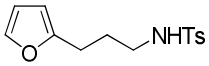
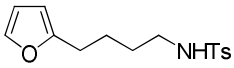
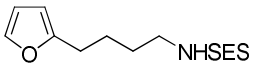
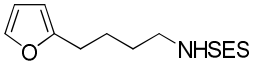
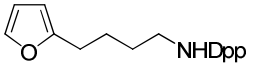
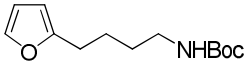
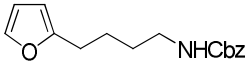
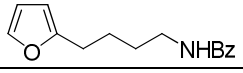



**144** **145** **146**

Conditions: (a) $SO_2Cl_2$, $PPh_3$, DCM (**145**, 68%); (b) $PCl_5$, $CCl_4$ (**145**: 46%, **146**: 24%)

As an alternative to sulfonamides, the use of a phosphinamide protecting group was investigated. The diphenylphosphinyl (Dpp) group exhibits similar acid sensitivity as the *tert*-butyloxycarbonyl (Boc) protecting group but with the advantage that acidic cleavage does not result in the formation of a carbocation that can cause undesired alkylations.[88] Although the stability of the Dpp group towards the two-step aza-Bohlmann procedure was questionable, we had intended, later, to find milder spirocyclisation conditions that would be compatible with the more labile protecting groups. *N*-Boc, *N*-Cbz and *N*-Bz derivatives were also synthesised (Table 2.1).

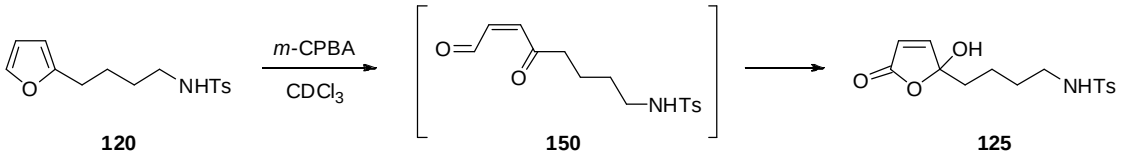
**Table 2.1**: Synthesis of *N*-protected amines

| Entry | | Substrate | Conditions | Yield / % |
|---|---|---|---|---|
| **1** | **119** |  | From **117**: (a) NaI, butan-2-one; (b) *p*-toluenesulfonamide, KOH, DMSO | 77 |
| **2** | **120** |  | *p*-Toluenesulfonyl chloride, $Na_2CO_3$, THF/$H_2O$ | 88 |
| **3** | **147** |  | 2-(Trimethylsilyl)ethanesulfonyl chloride, DMAP, $Et_3N$, DCM | 82 |
| **4** | **147** |  | 2-(Trimethylsilyl)ethanesulfonic anhydride, DMAP, $Et_3N$, DCM | 40 |
| **5** | **148** |  | Diphenylphosphinyl chloride, $Et_3N$, DCM, 0 °C | 72 |
| **6** | **123** |  | Di-*tert*-butyl dicarbonate, $Et_3N$, DCM | 92 |
| **7** | **149** |  | Benzyl chloroformate, $NaHCO_3$, DCM | 95 |
| **8** | **122** |  | Benzoyl chloride, NaOH, DCM | 74 |

### 2.1.2 Improving the oxidation conditions

Before embarking on a hunt for superior oxidants, the established *m*-CPBA/$H_2SO_4$ protocol was scrutinised in a bid to find areas for improvement. Monitoring the *m*-CPBA oxidation of **120** by $^1$H NMR spectroscopy, oxidation was found to be complete within 5 min. Although hydroxybutenolide **125** was visible in the $^1$H NMR spectrum, a significant proportion (*ca*. 50%) of material appeared to correspond to enedione **150** (Scheme 2.3). Complete conversion to the stable hydroxybutenolide **125** occurred within 2 h, resulting in a reduced reaction time compared with the originally reported oxidation time of 16 h.[78]

**Scheme 2.3**

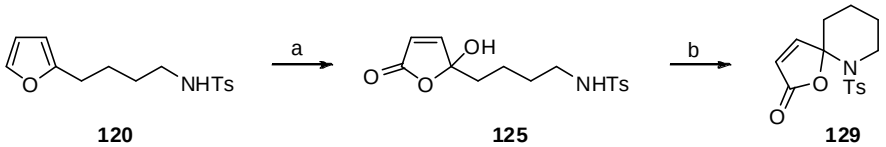



**120** **150** **125**

Given the sensitivity of furans to acid,[89] attempts were made to improve the yield of the oxidation by using purified or buffered *m*-CPBA. Pre-washing a solution of *m*-CPBA with a phosphate buffer (pH 7.5) prior to addition of the aminoalkylfuran made no improvement on the yield, while including a buffer in the reaction system[90, 91] caused a deleterious effect leading to a complex mixture of oxidation products and reduced yields of 20 – 30% ( Table 2.2). The presence of *m*-CBA is apparently critical for formation of the hydroxybutenolide.

During the spirocyclisation step, the hydroxybutenolides do not dissolve in the aqueous acidic solution and, after initially forming a suspension, large deposits formed on the side of the flask. We expected that the use of a suitable co-solvent would improve yields and lead to a decreased reaction time. Dissolving hydroxybutenolide **125** in a minimum volume of acetonitrile prior to the addition of $H_2SO_4$ actually led to slower conversion to the spiroaminoacetal. The use of THF or methanol as co-solvent had no significant effect on yield or reaction time.

**Table 2.2**

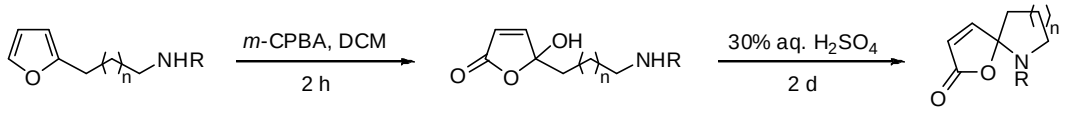


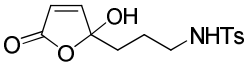
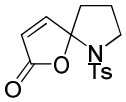
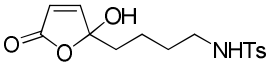
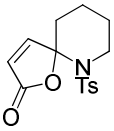
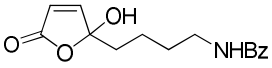
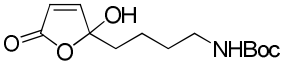
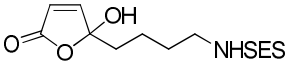
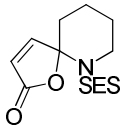
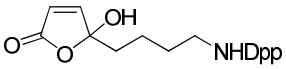
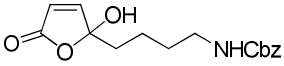

**120** **125** **129**

| Conditions (a) | Yield / % | Conditions (b) | Yield / % |
|---|---|---|---|
| *m*-CPBA pre-washed with phosphate buffer, DCM | 88 | 30% $H_2SO_4$, MeCN, 4 d | 82 |
| *m*-CPBA, $NaHCO_3$, DCM | 24 | 30% $H_2SO_4$, THF, 2 d | 86 |
| *m*-CPBA, $Na_2HPO_4$, DCM | 31 | 30% $H_2SO_4$, MeOH, 2 d | 85 |

Content with our slightly modified conditions, the *N*-protected aminoalkylfurans were treated with *m*-CPBA. Pleasingly, every substrate was smoothly converted to the desired hydroxybutenolides in 2 h in good yield (Table 2.3).

**Table 2.3**: Optimised yields for the *m*-CPBA/$H_2SO_4$ protocol




| Entry | | Substrate | Yield | | Conditions | Yield[†] |
|---|---|---|---|---|---|---|
| **1** | **124** |  | 84 | **128** |  | 78 |
| **2** | **125** |  | 87 | **129** |  | 89 |
| **3** | **126** |  | 71 | | decomposition | 0 |
| **4** | **151** |  | 90 | | decomposition | 0 |
| **5** | **152** |  | -[‡] | **155** |  | 75 |
| **6** | **153** |  | 77 | | decomposition | 0 |
| **7** | **154** |  | 76 | | decomposition | 0 |

[†] Yield based on one-pot reaction

[‡] Not isolated

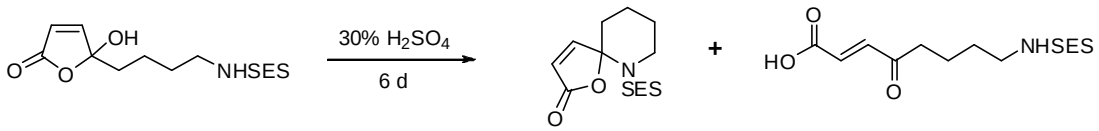
On a small scale (< 30 mg), the hydroxybutenolides were able to be purified simply by removal of the *m*-CPBA and *m*-CBA residues with successive sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ washes. Column chromatography was necessary on a larger scale and optimal

yields were achieved by minimising exposure to water during work-up (only a $Na_2S_2O_3$ wash to quench excess *m*-CPBA).

Of the new protecting groups, only *N*-SES furan **152** survived stirring with 30% $H_2SO_4$ to form the desired novel spiroaminoacetal **155**; the other *N*-protected amines (entries **3, 4 6, 7**) all decomposed to form black tarry solids. The yield of the *N*-tosyl [4.4]-spiroaminoacetal **128** was increased to 78%, compared with 22% yield achieved in previous work using peracetic acid.[78]

Although the sulfonamide hydroxybutenolides and resulting spirocycles are obviously stable under the cyclisation conditions, care must be taken to monitor the progress of the reaction. Extended exposure of *N*-SES hydroxybutenolide **152** to the cyclisation conditions led to the formation of a significant amount of the open chain *E*-keto acid **156** (Scheme 2.4).

**Scheme 2.4**

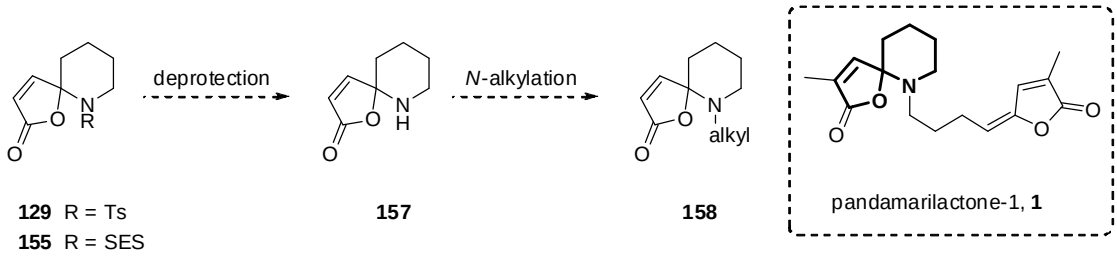



**152** **155**, 56% **156**, 21%

## *2.2 Attempted deprotection of the spiroaminoacetals*

With a view to applying the aza-Bohlmann cyclisation to more complex frameworks and natural product synthesis, deprotection of spiroaminoacetals **129** and **155**, to allow elaboration at the piperidine nitrogen, was investigated (Scheme 2.5).

**Scheme 2.5**




**129** R = Ts
**155** R = SES

**157**

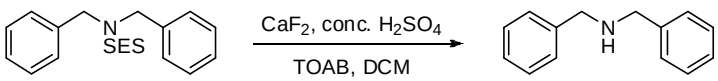
**158**

Treatment of *N*-SES spirocycle **155** with the standard deprotection conditions of TBAF or aqueous HF resulted in the recovery of starting material (Table 2.4). The use of CsF in DMSO was similarly unproductive and no deprotection occurred, generating only small amounts of decomposition products upon extended heating. Although this was disappointing, several groups have also reported difficulties achieving deprotection of *N*-SES secondary amines.[92, 93] To ensure that the failure to achieve *N*-SES deprotection was due to the substrate and not the operator, a variety of deprotection conditions were tested on the model substrate *N*-SES dibenzylamine **159**. While treatment of sulfonamide **159** with CsF at 95 °C afforded benzylamine in good yield, the same

conditions applied to spirocycle **152** only gave starting material and a small amount decomposition.

Declerck *et al*. have reported the use of anhydrous HF for the deprotection of *N*-SES protected pyrrolines.[85] For practicality purposes, the use of anhydrous HF was not ideal but the Sasoon group proposed a convenient alternative.[94] In their procedure, reaction of $CaF_2$ with conc. $H_2SO_4$ in DCM, with tetraoctylammonium bromide (TOAB) as a phase transfer catalyst, proved capable of fluorinating a range of olefins. To our delight, these unusual reaction conditions successfully removed the SES group to liberate dibenzylamine in excellent yield (Scheme 2.6).

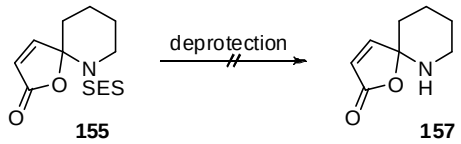
**Scheme 2.6**




**159** 88%

On transferral to our real system, the *in situ* HF conditions appeared to have achieved deprotection yet difficultly separating the product from TOAB hindered identification of the substrate. Control experiments were carried on dibenzylsulfonamide **159** in order to try to reduce the amount of TOAB required for reaction and verify that the *in situ* HF was the active deprotection agent. Surprisingly, deprotection was achieved through the use of $H_2SO_4$ alone and these conditions were applied to spirocycle **155** (Table 2.4).

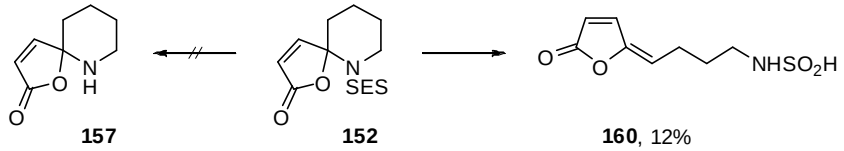
**Table 2.4** Attempted deprotection of *N*-SES spirocycle **155**




| Substrate | Conditions | Result | Yield / % |
|---|---|---|---|
| **152** | TBAF (1 eq.), THF, 50 °C | no reaction | – |
| **152** | 40% aq. HF | no reaction | – |
| **152** | CsF (4 eq.), DMSO, sonication | no reaction | – |
| **152** | CsF (4 eq.), DMSO, 90 °C, 66 h | no reaction | – |
| **152** | CsF (10 eq.), DMF, 95 °C, 96 h | decomposition | – |
| **152** | $CaF_2$, $H_2SO_4$, TOAB, DCM | **160** | 8 |
| **152** | $H_2SO_4$, DCM | **160** | 12 |
| **152** | TBAF/$SiO_2$ (2 eq.), MeCN, 80 °C | no reaction | – |
| **159** | CsF (5 eq.), DMF, 95 °C, 24 h | $Bn_2NH$ | 72 |
| **159** | $CaF_2$, $H_2SO_4$, TOAB (3 mol%), DCM | $Bn_2NH$ | 88 |
| **159** | $CaF_2$, $H_2SO_4$, TOAB (0.5 mol%), DCM | $Bn_2NH$ | 77 |
| **159** | $H_2SO_4$, TOAB, DCM | $Bn_2NH$ | 79 |
| **159** | $CaF_2$, TOAB, DCM | no reaction | – |
| **159** | $H_2SO_4$, DCM | $Bn_2NH$ | 86 |

The same product as that obtained with the *in situ* HF conditions was isolated and the product was identified as *N*-alkyl sulfamic acid **160** (Scheme 2.7).[95]

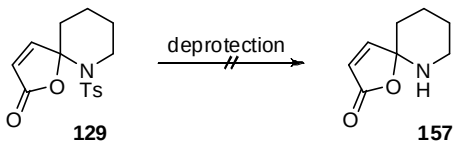
**Scheme 2.7**




Conditions: conc. $H_2SO_4$, DCM

Deprotection efforts then turned towards *N*-tosyl spirocycle **129**. *N*-Tosyl groups are renowned for their robustness[85] and our attempts to achieve deprotection of *N*-tosyl spirocycle **129** certainly lived up to this expectation (Table 2.5). Subjecting **129** to Li/naphthalene[96] led to decomposition, while treatment with Na(Hg)[97] returned only starting material.

**Table 2.5**: Attempts to deprotect *N*-tosyl spirocycle **129**

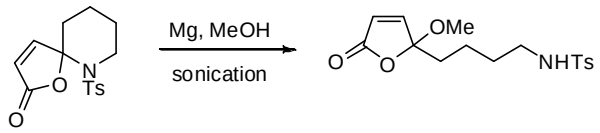



**129** **157**

| Conditions | Result | Yield / % |
|---|---|---|
| Na(Hg), $Na_2HPO_4$, MeOH | no reaction | – |
| Li/naphthalene, THF | decomposition | – |
| Mg, MeOH, sonication | **161** | 38 |
| Mg, MeCN, sonication | no reaction | – |

The only productive reaction came from the use of Ragnarsson's protocol of Mg powder in methanol under ultrasonic conditions.[98] Here, although the *N*-tosyl group remained intact, the spirocycle opened to form methoxybutenolide **161** (Scheme 2.8). Repeating this reaction in acetonitrile, in an attempt to avoid nucleophilic attack of methanol, simply led to the full recovery of starting material.

**Scheme 2.8** Unsuccessful application of Ragnarsson's deprotection conditions




**129** **161**, 38%

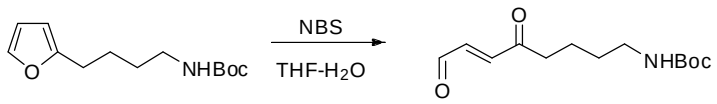
Based on these results, it appears that the formation of free amine spiroaminoacetal **157** is unfavourable and that, even if small amounts of **157** were formed during the reactions, it is not stable enough to survive the harsh deprotection conditions required to remove the sulfonamide protecting groups. With this in mind, we sought to explore alternative oxidation conditions for the aza-Bohlmann cyclisation in a bid to find a reagent capable of tolerating more labile *N*-protecting groups.

## *2.3 Alternative oxidants for the aza-Bohlmann cyclisation*

Inspired by the work of Kocienski and co-workers,[63] NBS was chosen as a potential oxidant for the aza-Bohlmann cyclisation since it had been used to facilitate a double Bohlmann cyclisation in the synthesis of salinomycin (Scheme 1.23). Exposure of *N*-Boc amine **123** to NBS produced *E*-enedial **162** as the major component within a complex mixture of oxidation products (Scheme 2.9). Unsurprisingly, aldehyde **162** proved to be unstable and attempts to purify the crude reaction product led to its complete decomposition. Application of the NBS conditions to aminoalkylfurans **119**, **120**, **122**, **123**, **147** – **149** presumably led to the formation of the analogous unsaturated aldehydes

on the basis of $^1$H NMR signals at ~ 9.5 p.p.m. yet these products decomposed rapidly, even in benzene solution, producing large quantities of insoluble black precipitate that precluded further characterisation.

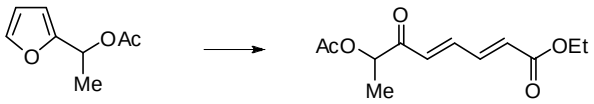
**Scheme 2.9**




**123** **162**, 23%

Marnett *et al.* has successfully used DMDO to prepare enedials from 3-alkyl furans,[99] while McKervey *et al.* oxidised a range of 2-alkyl furans under similar conditions and trapped the unstable unsaturated aldehydes *in situ* with Wittig reagents to prepare a series of dienes (Scheme 2.10).[100]

**Scheme 2.10**: Trapping unsaturated aldehydes *in situ* with Wittig reagents




**163** **164**

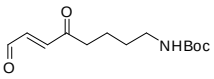
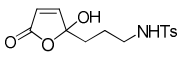
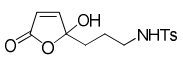
Conditions: DMDO, acetone, 30 min then $Ph_3P{=}CC(O)OEt$, DCM; 85%

Attempts to oxidise amines **119, 120, 123** and **149** with DMDO were unsuccessful, whether using a solution of DMDO in acetone or forming the DMDO *in situ* from Oxone®, $NaHCO_3$ and acetone. As with NBS, oxidation of furan occurred as judged by the

disappearance of the furan signals in $^{1}$H NMR spectra. However, no discernable product could be elucidated from analysis of the NMR spectra of the crude products and the complex mixture of oxidation products decomposed during purification preventing identification of the structures.

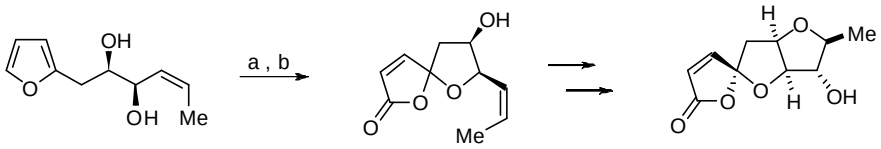
More esoteric oxidants were trialled, including methyltrioxorhenium-UHP[101] and urea·hydrogen peroxide-TFAA[102] – both of which led to complete substrate decomposition. Treatment with $H_2O_2$-TFAA[103] and $NaClO_2$[104] afforded the desired hydroxybutenolide **124** but in yields much lower than those previously obtained with *m*-CPBA (Table 2.6, entries 23 – 24).

**Table 2.6**: Summary of oxidations

| Entry | | n | R | Conditions | Result | | Yield |
|---|---|---|---|---|---|---|---|
| **1** | **119** | 1 | Ts | NBS, THF-$H_2O$ | *decomp* | | – |
| **2** | **120** | 2 | Ts | | *decomp* | | – |
| **3** | **122** | 2 | Bz | | *decomp* | | – |
| **4** | **123** | 2 | Boc | |  | **162** | 23 |
| **5** | **147** | 2 | SES | | *decomp* | | – |
| **6** | **148** | 2 | Dpp | | *decomp* | | – |
| **7** | **149** | 2 | Cbz | | *decomp* | | – |
| **8** | **119** | 1 | Ts | Oxone, $NaHCO_3$, acetone-$H_2O$ | *decomp* | | – |
| **9** | **120** | 2 | Ts | | *decomp* | | – |
| **10** | **122** | 2 | Bz | | *decomp* | | – |
| **11** | **123** | 2 | Boc | | *decomp* | | – |
| **12** | **147** | 2 | SES | | *decomp* | | – |
| **13** | **148** | 2 | Dpp | | *decomp* | | – |
| **15** | **149** | 2 | Cbz | | *decomp* | | – |
| **16** | **119** | 1 | Ts | DMDO, acetone | *decomp* | | – |
| **17** | **120** | 2 | Ts | | *decomp* | | – |
| **18** | **123** | 2 | Boc | | *decomp* | | – |
| **19** | **149** | 2 | Cbz | | *decomp* | | – |
| **20** | **119** | 1 | Ts | MTO, UHP, DCM | *decomp* | | – |
| **21** | **119** | 1 | Ts | UHP, TFAA, $Na_2HPO_4$, DCM | *decomp* | | – |
| **22** | **119** | 1 | Ts | $H_2O_2$, TFAA, $Na_2HPO_4$, DCM | *decomp* | | – |
| **23** | **119** | 1 | Ts | $H_2O_2$, TFAA, DCM |  | **124** | 10 |
| **24** | **119** | 1 | Ts | $NaClO_2$, $Na_2HPO_4$, *t*-BuOH-$H_2O$ |  | **124** | 20 |

With its green chemistry credentials, singlet oxygen is regaining popularity as a cheap, sustainable and mild oxidant in the synthetic organic community. In the context of furan oxidations, the Vassilikogiannakis group have been prolific in their use of singlet oxygen and have reported a number of elegant natural product syntheses *via* Bohlmann-type cyclisations (e.g. Scheme 2.11).[105-111]

**Scheme 2.11** Vassilikogiannakis' singlet oxygen approach to the synthesis of *epi*-pyrenolides D

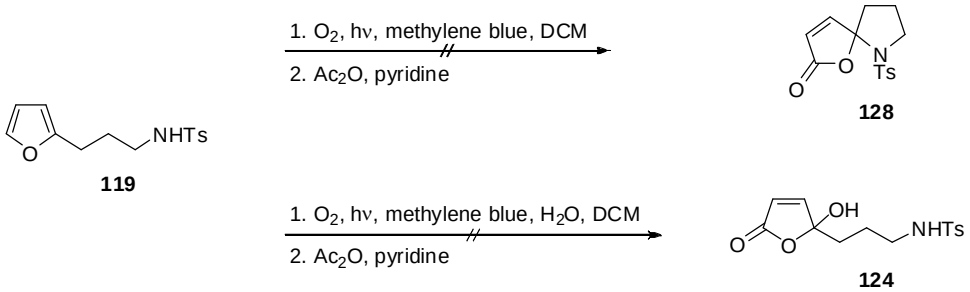



**165** **166** **167**

Conditions: (a) $O_2$, methylene blue, hν, DCM; (b) $Ac_2O$, pyridine, 56% over two steps

Encouraged by this, their favoured methylene blue-sensitised procedure[112] was applied to sulfonamide **119** (Scheme 2.12). A complex mixture of oxidation products was visible in the $^1H$ NMR spectrum of the crude material yet no identifiable components could be recovered following column chromatography.

**Scheme 2.12**

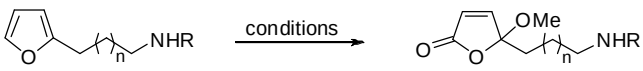


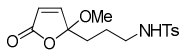
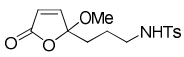
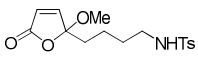
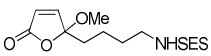

**119** **128** **124**

Postulating that the failure of the methylene blue protocol was due to the inability of nitrogen to trap the unstable intermediate(s), the reaction was repeated in the presence of water in the hope of forming hydroxybutenolide **124**. Neither stoichiometric nor excess quantities of water improved the outcome of the reaction.

Based on a report by Liu,[113] an alternative base-assisted singlet oxygen procedure was applied to furan **119**. Under these conditions, instead of the desired spiroaminoacetal **128**, methoxybutenolide **168** was formed in moderate yield ( Table 2.7, entry 1). A dramatic improvement in yield was achieved by removing Hünig's base from the reaction system and combining the rose bengal-methanol system with a pyridine/acetic anhydride work-up.[114] In this case (entry 2), methoxybutenolide **168** was obtained in 95% yield.

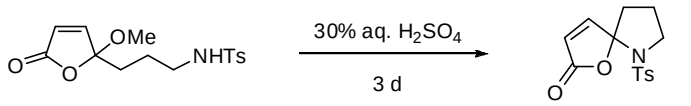
**Table 2.7**




| Entry | | Conditions | Yield | | Product |
|---|---|---|---|---|---|
| 1 | **119** | $O_2$, rose bengal, DIPEA, MeOH | 39 | **168** |  |
| 2 | **119** | (i) $O_2$, rose bengal, MeOH, (ii) $Ac_2O$, pyridine | 95 | **168** |  |
| 3 | **120** | (i) $O_2$, rose bengal, MeOH, (ii) $Ac_2O$, pyridine | 93 | **161** |  |
| 4 | **147** | (i) $O_2$, rose bengal, MeOH, (ii) $Ac_2O$, pyridine | 96 | **169** |  |

Upon exposure of methoxybutenolide **168** to 30% aq. $H_2SO_4$, spiroaminoacetal **128** was obtained in slightly higher yield than that obtained from the hydroxybutenolide **124** though a longer reaction time (3 days vs. 2 days) was required for complete conversion to the spirocycle (Scheme 2.13).

**Scheme 2.13**



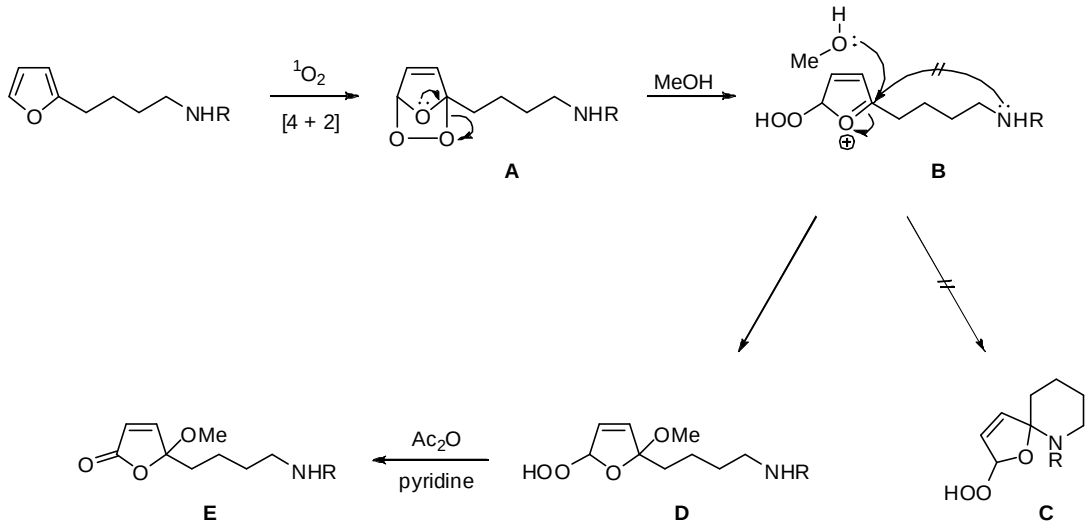

**168** **128**, 89%

However, the formation of a butenolide structure meant the acid-catalysed cyclisation step was required for conversion to desired spiroaminoacetal and, hence, at this stage, the new oxidation protocol was only useful for *N*-sulfonamide protected amines. The singlet oxygen procedure was also applied to sulfonamides **120** and **147** and the corresponding methoxybutenolides **161** and **169** obtained in excellent yield ( Table 2.7, entries 3 and 4). For the *N*-sulfonamide furans, the singlet oxygen oxidation offered an improvement on the *m*-CPBA procedure since no purification was required after oxidation. Oxidation takes place quickly (typically less than 10 min) and yields were significantly higher than those obtained for the corresponding hydroxybutenolides.

However, the fact that butenolides, rather than the desired spiroaminoacetals, were being produced in the oxidation reaction was frustrating. It appears that our

*N*-protected amines are insufficiently nucleophilic to attack the intermediate oxonium ion **B** (Scheme 2.14) in the singlet oxygen oxidation.

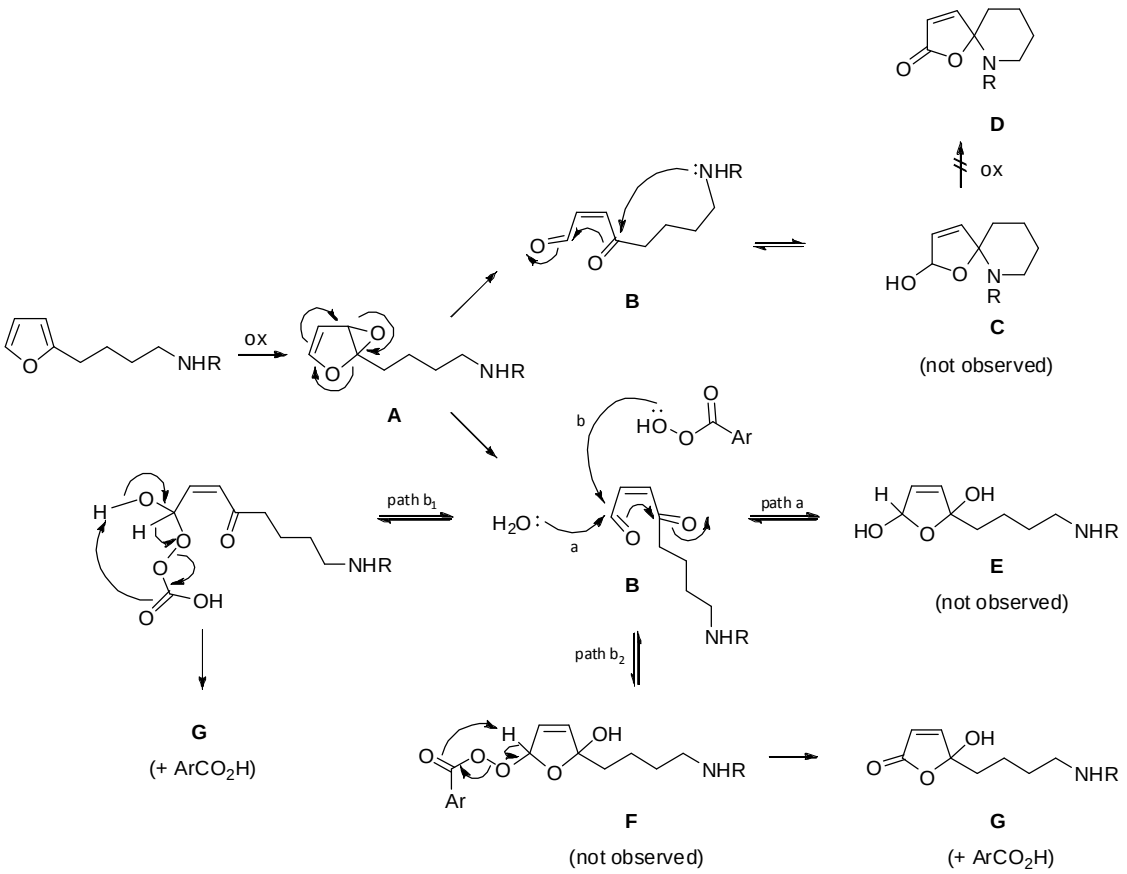
**Scheme 2.14**: Possible intermediates in the $^1O_2$ oxidation of furyl amines




Likewise, in the epoxidation pathway (Scheme 2.15, shown for *m*-CPBA) the nitrogen atom did not attack the internal carbonyl of the enedione **B** or, if it did, the desired intermediate **C** did not persist long enough for oxidation to **D** to occur.

The key difference between the original Bohlmann cyclisation and our aza variant is that the reactivity of the internal nucleophile (OH vs. $NH_2$) has to be tempered with an electron-withdrawing protecting group to prevent the formation of *N*-oxides. Sadly, our chosen protecting groups were hindering the ability of the nitrogen to capture the enedione or oxonium intermediates **B** and, as a result, competing external nucleophiles trapped the reactive intermediates as methoxy- and hydroxybutenolides.

**Scheme 2.15**: Possible intermediates in the oxidation of 2-(ω-aminoalkyl)furans with *m*-CPBA

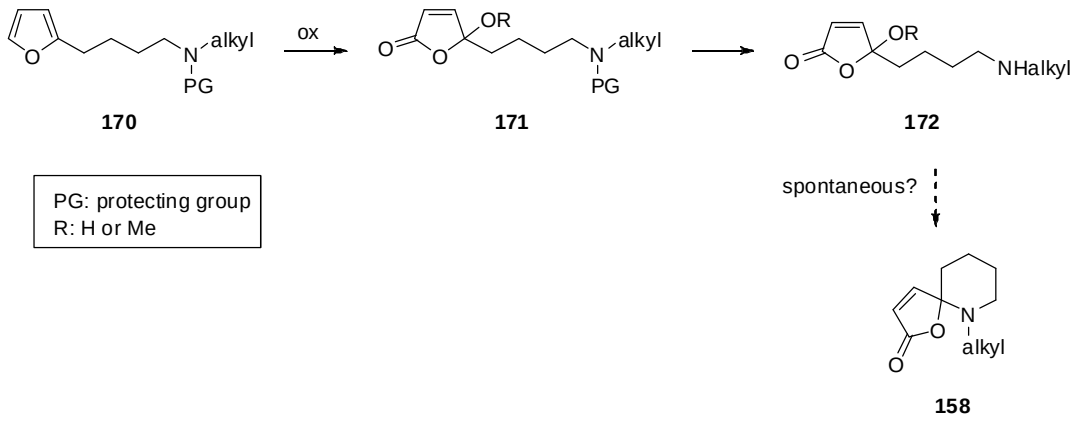



This was disappointing since such *N*-protected amines readily participate in the analogous aza-Achmatowicz reaction. Satisfied that only modifications to the amine moiety, rather than the oxidation conditions, could improve the scope of the aza-Bohlmann cyclisation, investigations into the design of a more nucleophilic aminoalkyl furan system began in earnest.

## *2.4 Increasing the nucleophilicity at the nitrogen centre*

We decided upon the synthesis of a substrate featuring a temporary protecting group and a simple alkyl substituent. The protecting group would remain in place to allow clean oxidation of the furan without *N*-oxide formation. Following conversion to the butenolide, removal of the electron-withdrawing group would release a more nucleophilic dialkyl amine species that we hoped would readily cyclise to form the desired spiroaminoacetal **158** (Scheme 2.16).

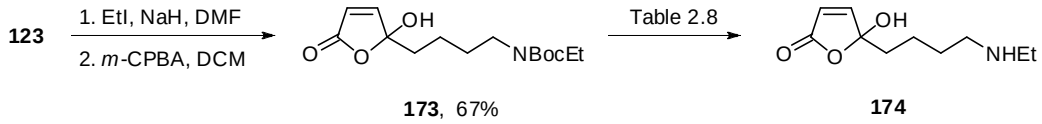
**Scheme 2.16**




The first protecting group examined was the Boc carbamate; ideally, the use of this acid labile protecting group would allow deprotection and cyclisation in one step. An ethyl group was selected as the alkyl substituent since pandamarilactone-1 **1** features an *N*-alkyl chain around the amine moiety (Scheme 2.17). Efforts were concentrated on

hydroxybutenolide **173** rather than the analogous methoxybutenolide since we considered that spontaneous cyclisation would more likely occur due to its equilibrium with the open chain keto acid.[115]

**Scheme 2.17**




**173**, 67% **174**

*N*-Boc furan **123** was alkylated with ethyl iodide and treated under our standard *m*-CPBA conditions to afford hydroxybutenolide **173** in moderate yield. From the $^{1}$H NMR spectrum of the crude product, butenolide **173** appeared to have formed cleanly yet isolated yields of remained stubbornly in the range of 20% – 30% with significant loss of mass during silica gel chromatography. It is surprising that the *N*-ethyl substituent makes such a difference to the acid sensitivity of the hydroxybutenolide yet, thankfully, purification on neutral alumina restored the isolated yield to a more satisfactory 72%. Hydroxybutenolide **173** was then screened against a number of acidic conditions (Table 2.8) in an attempt to obtain *N*-ethyl furan **174**.

**Table 2.8**: Deprotection of *N*-Boc hydroxybutenolide **173**

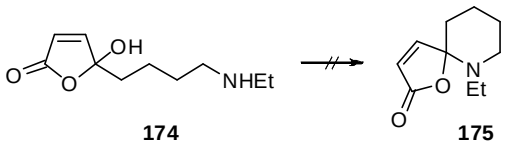
| Conditions | Result | Yield / % |
|---|---|---|
| HF, MeCN | no reaction | – |
| µw, chlorobenzene | no reaction | – |
| NaOEt, EtOH | no reaction | – |
| Formic acid | decomposition | – |
| CAN, MeCN | decomposition | – |
| TFA, DCM | decomposition | – |
| 4 M HCl in dioxane | decomposition | – |
| 30% aq. $H_2SO_4$ | decomposition | – |
| $BF_3{\cdot}OEt_2$, MeCN | decomposition | – |
| $SnCl_2$, DCM | decomposition | – |
| $H_3PO_4$, MeCN | **174** | 23 |
| $H_3PO_4$, MeCN; $NaHCO_3$ quench | **174** | 18 |
| $H_3PO_4$, MeCN; Amberlyst A-21 quench | **174** | 14 |

Given the decomposition that occurred during purification of *N*-Boc hydroxybutenolide **173** on silica, it was not entirely surprising that many of the deprotection conditions screened only led to decomposition. The only reagent capable of removing the Boc group without completely destroying the substrate was $H_3PO_4$ yet mass recovery was poor and samples were contaminated with a number of by-products and large quantities of *t*-butanol. *N*-ethyl hydroxybutenolide **174** did not survive attempts to remove *t*-butanol *in vacuo*, or purification by flash chromatography. Attempts to wash out the alcohol led to loss of material with an unchanged ratio of *t*-butanol : **174**.

Reasoning that the water solubility of butenolide **174** could be contributing to low mass recovery, "dry" work-ups with solid $NaHCO_3$ and Amberlyst A-21 were investigated yet these led to minor decreases in yield. In the end, the best quality and yield of butenolide

**174** was obtained by diluting the reaction with water and extracting the acidic aqueous layer with ethyl acetate. This removed the majority of the *t*-butanol and hydroxybutenolide **174** was recovered following extraction of the basified aqueous layer.

**Scheme 2.18**




**174** **175**

Since spontaneous cyclisation of dialkyl amine **174** had not occurred upon cleavage of the *N*-Boc group, a series of Lewis acid and heating experiments (Table 2.9) were undertaken. Unfortunately, butenolide **174** proved extremely unstable and rapidly decomposed to a viscous brown oil upon exposure to heat or acid, with none of the desired *N*-ethyl spiroaminoacetal **175** isolated.

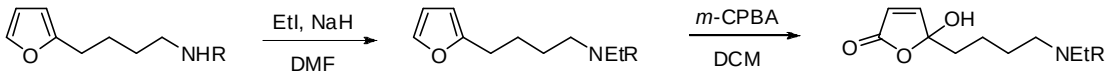
**Table 2.9**

| Conditions | Result |
|---|---|
| $BF_3{\cdot}OEt_2$, DCM | decomposition |
| $Nd(OTf)_3$, MeCN | decomposition |
| $Eu(OTf)_3$, MeCN | no reaction |
| Δ, $CD_3CN$ | decomposition |
| Δ, $CDCl_3$ | decomposition |
| $CDCl_3$ | decomposition |

Access to *N*-dialkyl spiroaminoacetal **175** was also investigated *via* the *N*-Troc and *N*-Cbz amines. We hoped to obtain butenolide **174** in higher yield and greater purity since we

believed that the quality of **174** obtained from the $H_3PO_4$ deprotection was contributing towards its rapid decomposition and hindering cyclisation efforts. *N*-Troc amine **176** and *N*-Cbz amine **149** were alkylated with ethyl iodide and oxidised to furnish hydroxybutenolides **179** and **180** respectively (Scheme 2.19). A range of reductive deprotection conditions were screened for both hydroxybutenolides in an attempt to access *N*-ethyl butenolide **174**.

**Scheme 2.19**



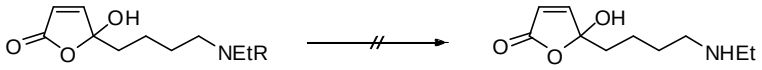

**176**: R = Troc
**149**: R = Cbz

**177**: R = Troc 48%
**178**: R = Cbz 76%

**179**: R = Troc 52%
**180**: R = Cbz 86%

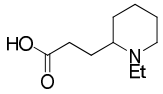
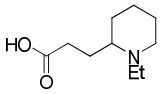
Neither the *N*-Cbz nor the *N*-Troc group could be removed while leaving the hydroxybutenolide intact. Reduction of the butenolide moiety occurred simultaneously and, in the case of Zn-AcOH conditions (Table 2.10, entries 9 and 10), preferentially to the removal of the carbamate protecting group. Exposing hydroxybutenolide **179** or **180** to reductive conditions for an extended length of time led to the isolation of piperidine acid **181**.

**Table 2.10**



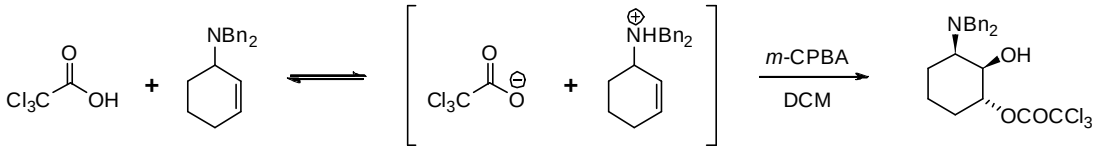

**179**: R = Troc
**180**: R = Cbz

**174**

| Entry | Substrate | Conditions | | Results | Yield / % |
|---|---|---|---|---|---|
| 1 | **179** | Zn, AcOH | | Preferential reduction of butenolide to *N*-Troc cleavage | – |
| 2 | **179** | Zn, AcOH | | Preferential reduction of butenolide to *N*-Troc cleavage | – |
| 3 | **179** | Zn, AcOH, 16 h | **181** |  | 65 |
| 4 | **179** | $(Bu_3Sn)_2$, DMF | | decomposition | – |
| 5 | **179** | MeLi, THF | | decomposition | – |
| 6 | **180** | $H_2$, 10% Pd/C, MeOH/EtOAc, 0.06 M | | Cbz cleavage and reduction of butenolide | – |
| 7 | **180** | $H_2$, 10% Pd/C, MeOH/EtOAc, 0.01 M | | Cbz cleavage and reduction of butenolide | – |
| 8 | **180** | $H_2$, 10% Pd/C, MeOH/EtOAc, 0.06 M , 1 h | **181** |  | 79 |
| 9 | **180** | $H_2$, $Pd(OH)_2$, MeOH/EtOAc | | Cbz cleavage and reduction of butenolide | – |
| 10 | **180** | $NH_4^+ HCO_2^-$ , 10% Pd/C, MeOH | | Cbz cleavage and reduction of butenolide | – |
| 11 | **180** | $Et_3SiH$, $PdCl_2$, $Et_3N$ | | Cbz cleavage and reduction of butenolide | – |
| 12 | **180** | $Ba(OH)_2$, glyme/$H_2O$, 95 °C | | Reduction of butenolide | – |
| 13 | **180** | TMS-Cl, NaI, MeCN | | decomposition | – |

In an alternative approach to traditional protecting group chemistry, the Davies group have reported the use of trichloroacetic acid (TCA) to perform oxidations in the presence of on 1°, 2° and 3° amines.[116] For example, addition of 5 eq. of TCA generated ammonium salt **183** *in situ*, and treatment with *m*-CPBA followed by aq. $NaHCO_3$ afforded diol monotrichloroacetate **184** in excellent yield.

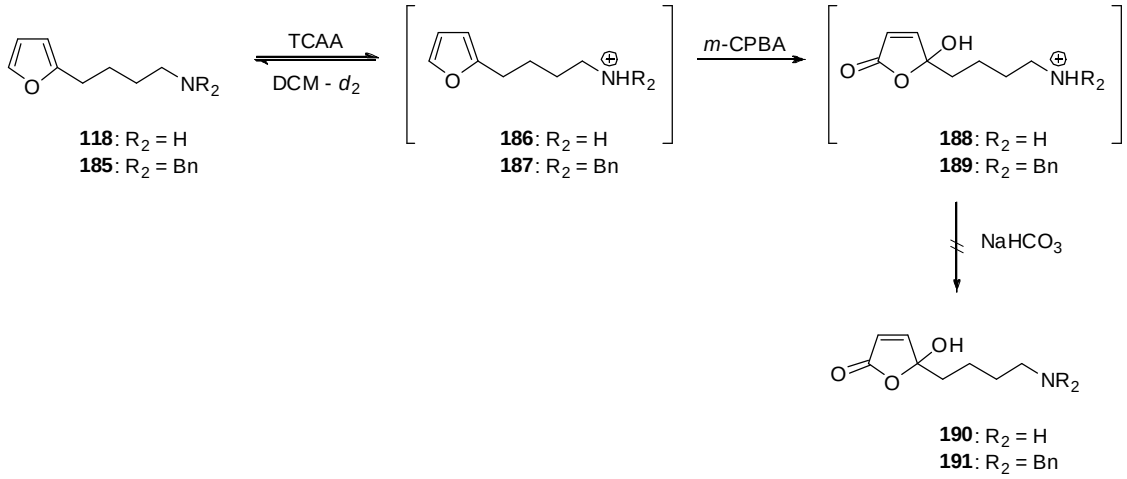
**Scheme 2.20**: Davies' *in situ N*-protection




**182** **183** **184** 99%, 90 *d.e.*

We briefly investigated the application of these conditions to free amine **118** and dialkyl amine **185** (Scheme 2.21). In both cases, complete protonation required 5 eq. of TCA as judged by $^1$H NMR. Addition of *m*-CPBA caused complete decomposition of **186** yet **189** appeared to have formed quite cleanly. However, no identifiable product could be isolated following work-up with either solid or aqueous solutions of $NaHCO_3$. The probable formation of *N*-dibenzyl hydroxybutenolide **189** warrants further investigation to explore conditions that could lead to the successful isolation of hydroxybutenolide **190** or **191**. However, other chemistry took a higher priority at this time and work on temporary ammonium protection was discontinued.

**Scheme 2.21**: Attempts at hydroxybutenolide formation using temporary ammonium protection




**118**: $R_2$ = H
**185**: $R_2$ = Bn

**186**: $R_2$ = H
**187**: $R_2$ = Bn

**188**: $R_2$ = H
**189**: $R_2$ = Bn

**190**: $R_2$ = H
**191**: $R_2$ = Bn

Furthermore, the pursuit of performing an aza-Bohlmann cyclisation on an *N*-dialkyl substrate was also stopped. Clearly, the fact that *N*-ethyl butenolide **174** is so unstable means that it is a reactive species; that it refused to participate in a productive reaction was frustrating.

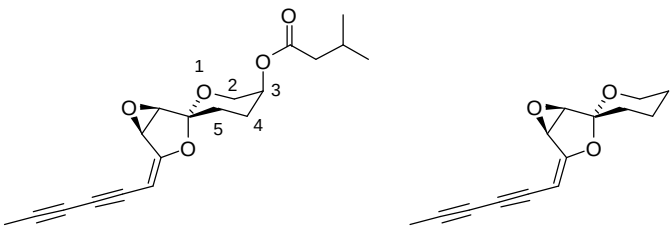
Despite this, work progressed towards the synthesis of pandamarilactone-1 **1** (Chapter 4). Although we intended to access pandamarilactone-1 **1** *via* an aza-Bohlmann cyclisation of di(furylalkyl)amine **141**, other options would be explored if this proved difficult. The fact that *N*-alkyl spiroaminoacetals exist in nature is evidence of their stability and we hoped that our planned precursor would have some inherent thermodynamic stability that would allow us to perform spirocyclisation on the *N*-alkyl amine.

# Chapter 3 Conformational studies of spiroaminoacetals

## *3.1 Introduction*

Previous work within the Robertson group has investigated the synthesis of the spiroacetal natural products AL-1 **192** and AL-2 **193**, isolated from leaves of the edible plant *Artemisia lactiflora* (Figure 3.1).[117, 118] These diacetylenic enol ethers have been found to exhibit an inhibitory effect against TPA-induced tumour promotion and provided an interesting synthetic target for the group as an extension of our established oxidative spirocyclisation methodology.[57, 119, 120]

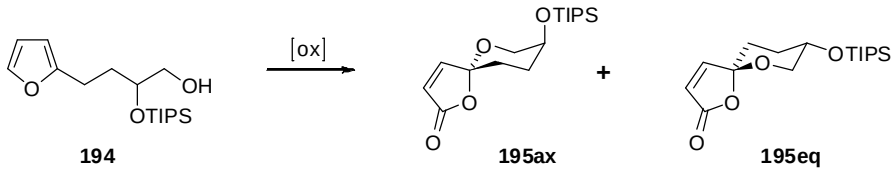
**Figure 3.1**




AL-1, **192** AL-2, **193**

A key step in the synthesis of AL-1 **192** is the installation of an axial *O*-isovalerate substituent at the 3-position of the tetrahydropyran ring. With this in mind, a model study was initiated to examine axial/equatorial preferences of 3-oxy-substituents in these spirobutenolides.

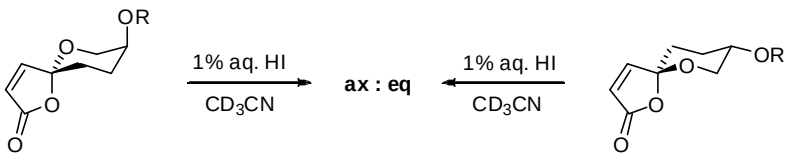
**Scheme 3.1**: Model system in spiroacetal series




**194** **195ax** **195eq**

*O*-Silyl spirobutenolides **195ax** and **195eq** were separated by column chromatography, deprotected and derivatised as the *O*-benzyl, *O*-acetyl, *O*-isovalerate variants. The separated diastereomers were treated with 1 mol% aq. HI and the results monitored by $^1$H NMR spectroscopy (Scheme 3.2).

**Scheme 3.2**: Equilibration studies in the spiroacetal series




**196ax** : R = H
**197ax** : R = Bn
**198ax** : R = Ac
**199ax** : $COCH_2CH(CH_3)_2$

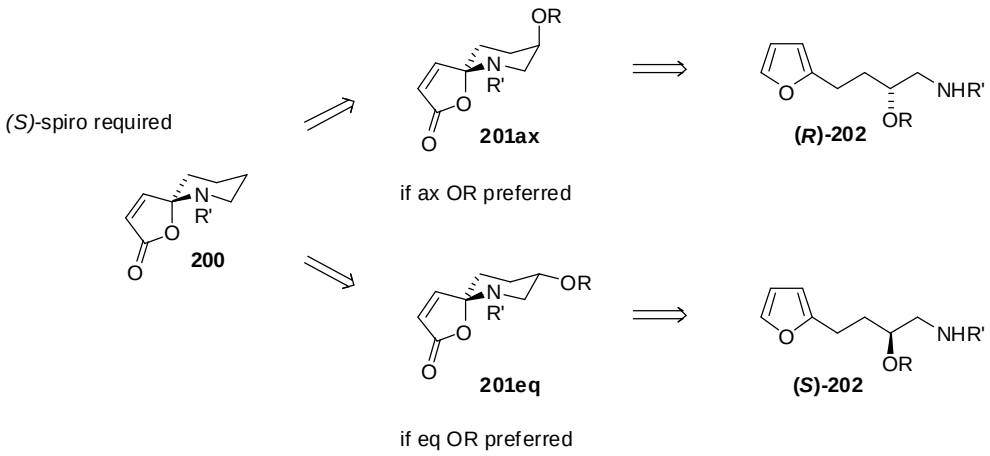
45 : 55
65 : 35
75 : 25
75 : 25

**196eq** : R = H
**197eq** : R = Bn
**198eq** : R = Ac
**199eq** : $COCH_2CH(CH_3)_2$

Interconversion occurred rapidly and both axial and equatorial diastereomers converged to the same equilibrium ratio. In all cases where R ≠ H, the axial diastereomer was preferred. As a comparison, we set out to investigate if the same configurational preferences existed in the corresponding spiroaminoacetal series. If a synthetically useful axial/equatorial bias emerged, the use of the correctly configured 3-oxy centre

could be used as a conformational bias to access spiroaminoacetals with a desired spiroconfiguration.

**Scheme 3.3**: Use of a 3-oxy substituent to provide stereocontrol at the spirocentre in spiroaminoacetals



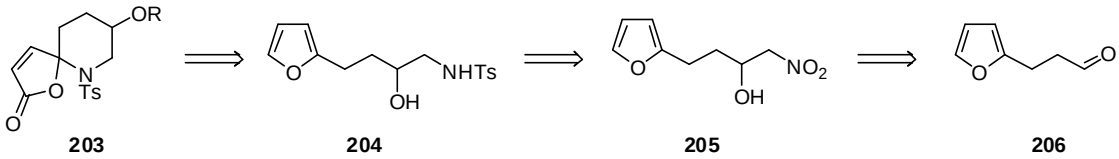

## *3.2 Synthesis of the 3-oxy spiroaminoacetals*

Unlike the spiroacetal series described above, the synthesis of the spiroaminoacetal conformational substrates required the 3-oxy-substituent to be installed before cyclisation as a labile *O*-protecting group would likely not survive the $H_2SO_4$ spirocyclisation conditions. For this reason, synthesis of the *O*-acetoxy spiroaminoacetal was also not pursued.

From the initial retrosynthetic analysis (Scheme 3.4), we envisaged installing the 3-hydroxy moiety *via* a Henry reaction[121] on aldehyde **206**. Reduction of the nitro group,

and alkylation/protection of the alcohol and amine would furnish aza-Bohlmann precursor **204**. *N*-Tosyl protection was selected over *N*-SES protection as we were concerned that the peaks for the *N*-SES group would potentially obscure the signals of the piperidine ring protons in the $^{1}$H NMR spectra.

**Scheme 3.4**: Retrosynthetic analysis of the 3-oxy spiroaminoacetals

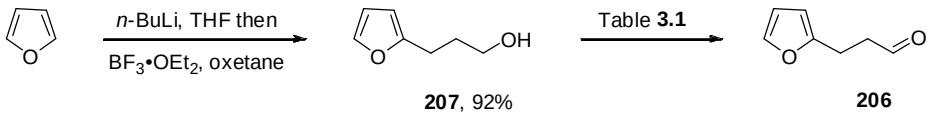



**203** **204** **205** **206**

## 3.2.1 Synthesis of aldehyde 206

Alcohol **207** was easily accessed from addition of lithiofuran to oxetane (Scheme 3.5) yet surprisingly, oxidation to aldehyde **206** proved a stumbling block. Numerous procedures exist in the literature for the oxidation of primary alcohols to aldehydes and, of these, classical Swern conditions[122, 123] and Dess – Martin periodinane[124, 125] have been reported for the synthesis of aldehyde **206**.

**Scheme 3.5**: Synthesis of aldehyde **206** *via* oxidation




**207**, 92% **206**

**Table 3.1**: Oxidation of alcohol **207** to aldehyde **206**

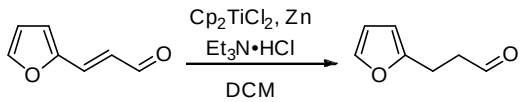
| Entry | Conditions | Scale | Yield / % |
|---|---|---|---|
| 1 | $(COCl)_2$, DMSO, $Et_3N$, DCM, –78 °C | 100 mg | 64 |
| 2 | $(COCl)_2$, DMSO, $Et_3N$, DCM, –78 °C | 400 mg | 59 |
| 3 | $(COCl)_2$, DMSO, $Et_3N$, DCM, –78 °C | 600 mg | 0 |
| 4 | $(COCl)_2$, DMSO, $Et_3N$, DCM, –78 °C | 1.00 g | 20 |
| 5 | $(COCl)_2$, DMSO, $Et_3N$, DCM, –78 °C | 1.00 g | 10 |
| 6 | DMP, DCM | 20 mg | 75 |
| 7 | DMP, DCM | 100 mg | 80 |
| 8 | DMP, DCM | 500 mg | 0 |
| 9 | $SO_3$·pyridine, DMSO, $Et_3N$, DCM | 100 mg | 70 |
| 10 | $SO_3$·pyridine, DMSO, $Et_3N$, DCM | 300 mg | 59 |
| 11 | $SO_3$·pyridine, DMSO, $Et_3N$, DCM | 1.00 g | 10 |
| 12 | TEMPO, $PhI(OAc)_2$, pH 7 buffer, MeCN | 100 mg | 35 |
| 13 | TPAP, NMO, 4Å MS, DCM | 100 mg | 28 |
| 14 | PCC, NaOAc, celite, DCM | 100 mg | 15 |

The Swern oxidation initially appeared promising and an acceptable yield was obtained on a 100 mg scale (Table 3.1, entry 1). However, subsequent attempts to scale the reaction up failed to deliver consistent yields, despite rigorous purification of all the reagents and alcohol **207**. Dess – Martin periodinane proved similarly capricious, giving good conversion on small scale (entries 6 and 7) yet only small amounts of decomposition products were recovered on a 600 mg run. $SO_3$.pyridine proved to be the most reliable oxidant,[126] affording satisfactory yields on 300 mg scale yet plummeting to 10% yield when carried out on a 1.0 g scale (entry 11). TEMPO, TPAP[127] and PCC[128] oxidations produced even poorer yields, with significant quantities of polymeric material produced during the reactions (entries 12 – 14). As a further complication, aldehyde **206**

proved to be unstable to chromatography with significant loss of mass even when the crude material looked clean by $^{1}$H NMR analysis. Alternative purification by petrol trituration of the crude residue or chromatography on neutral alumina did little to improve the quantity of product obtained.

Thankfully, this problematic oxidation could be circumnavigated by accessing aldehyde **206** *via* reduction of the inexpensive, and readily available, food additive 3-(furyl)acrolein (Scheme 3.6). Previous reports on the reduction of 3-(furyl)acrolein by Adkins[129] and Chen[125] found that reduction over Raney nickel and Lindlar's catalyst led to competitive reduction of the C=O bond. Many literature methods exist for the selective reduction of C=C bonds over C=O bonds,[130, 131] yet a recent report by Ashfield[132] proved most attractive. Using Ashfield's protocol, selective reduction of the C=C bond proceeded smoothly, and the use of dichloromethane (over the more usual methanol) meant that the volatile aldehyde **206** was easily isolated from the reaction mixture. As an added bonus, aldehyde **206** was obtained so cleanly that it could be used in subsequent reactions without any purification.

**Scheme 3.6**: Reduction of 3-(furyl)acrolein using Ashfield's protocol

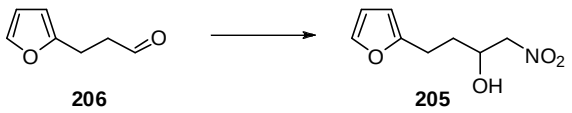



**206**, 96%

### 3.2.2 Elaboration towards β-amino alcohol 204

With a robust synthesis in place, we investigated conversion of aldehyde **206** to the desired aminoalcohol **204** *via* a Henry reaction. This was best achieved with a catalytic quantity of imidazole in water (Table 3.2, entry 1).[133] Alternative bases (DBU, KF/alumina) led to substantial decomposition of the starting material before full conversion to nitroalcohol **205** had occurred.

**Table 3.2**: Conditions for the Henry reaction




**206** **205**

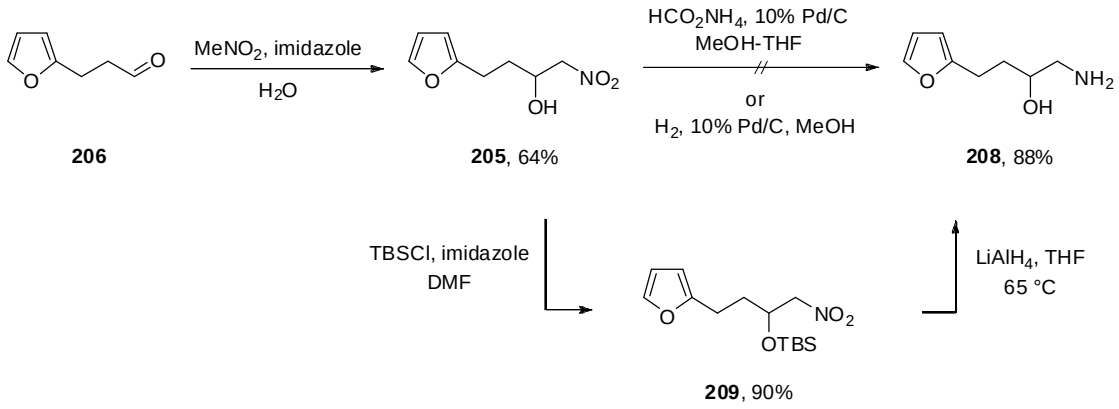
| Conditions | Time | Yield / % |
|---|---|---|
| $MeNO_2$ (3 eq.), 25 mol% imidazole, $H_2O$ | 13 h | 64 |
| $MeNO_2$ (3 eq.), 10 mol% DBU, MeCN | 96 h | 15 |
| $MeNO_2$ (6 eq.), KF/alumina, IPA | 96 h | 43 |

Vicinal nitroalcohols are typically reduced using Raney nickel[134] or electrolytic reduction[135] yet we feared these conditions would lead to reduction of the furan and milder methods for this transformation were sought. Upon submission of nitroalcohol **205** to transfer hydrogenation conditions[136] only starting material was recovered, whilst more standard $H_2$/Pd/C conditions resulted in preferential reduction of the furan ring (Scheme 3.7) with no trace of the desired aminoalcohol **208** was observed. Several groups have reported the use of metal hydrides to effect the reduction of nitro groups,[137-139] yet in vicinal nitroalcohols there is a tendency for retro-Henry reactions to

occur.[140] The Seebach group have reported a work-around to this problem by temporary protection of the alcohol as *O*-TBS ether. $LiAlH_4$ reduction of the nitro group proceeds smoothly and subsequent removal of the *O*-silyl group *in situ* gives direct access to the desired aminoalcohol.[141, 142]

The Seebach protocol was applied to nitroalcohol **205** and, following *O*-TBS protection, treatment with $LiAlH_4$ provided aminoalcohol **208** in 88% yield. The reduction of *O*-silyl ether **209** under Satoh's $NaBH_4/CoCl_2$ protocol[143] was also investigated yet this failed to give any reduction product and only starting material was recovered.

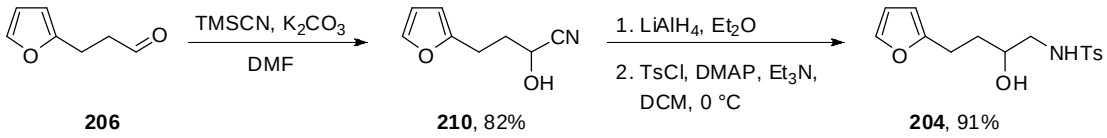
**Scheme 3.7**: Synthesis of aminoalcohol **208**




In order to explore elaboration to the desired *O*-benzyl and *O*-isovaleryl derivatives, the synthesis of aminoalcohol **208** was attempted on a multi-gram scale. Disappointingly, the Henry reaction proved unreliable and nitroalcohol **205** was only isolated in 28% yield when the reaction was carried out on a 1.0 g scale. This, combined with the unwieldy *O*-silyl protection/reduction sequence, meant that we chose to discard the Henry chemistry in favour of cyanohydrin chemistry.

Under the conditions of Olah,[144] treatment of aldehyde **206** with TMSCN and $K_2CO_3$ in DMF afforded cyanohydrin **210** in 82% yield. $LiAlH_4$ reduction proceeded smoothly and *N*-tosylation gave aminoalcohol **204** on a multi-gram scale ready for derivitisation for our conformation studies (Scheme 3.8). It should be noted that *N*-tosylation was carried out under slightly modified conditions to those used previously: using a small excess of tosyl chloride (1.02) and reaction at 0 °C instead of the more normal RT conditions. Higher reaction temperature and/or greater excess of tosyl chloride led to the formation of a mixture of *O*-tosyl, *N*-tosyl and bis-protected products.

**Scheme 3.8**: Large scale synthesis of sulfonamide **204**

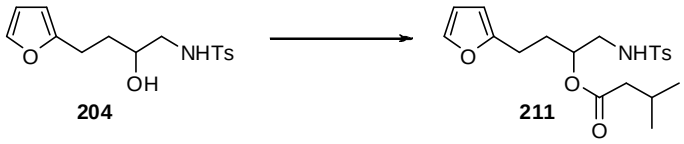



**206** **210**, 82% **204**, 91%

### 3.2.3 Synthesis of the *O*-isovaleryl alkylfuran 211

Elaboration of sulfonamide **204** to isovalerate **211** proved non-trivial. Under Steglich esterification conditions,[145] *N*-acylation occurred preferentially and the desired isovalerate ester was isolated in a low yield (Table 3.3, entry 1). This was somewhat surprising since literature precedent indicated that long reaction times and a stoichiometric amount of DMAP would be required to achieve efficient *N*-acylation of the sulfonamide.[146]

**Table 3.3**: Formation of *O*-isovaleryl furan **211**

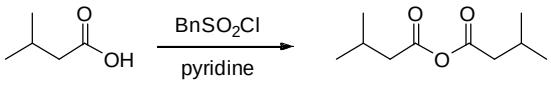



| Entry | Conditions | Yield / % |
|---|---|---|
| 1 | Isovaleric acid, DCC, DMAP, DCM | 12 |
| 2 | Isovaleric acid, TFA | decomposition |
| 3 | Isovaleric acid, $H_2SO_4$ | decomposition |
| 4 | Isovaleric acid, TFA, THF, –20 °C | decomposition |
| 5 | Isovaleric acid, $Sc(OTf)_3$ | 0 |
| 6 | Isovaleric acid, $Sc(OTf)_3$, MeCN | 0 |
| 7 | Isovaleric anhydride, TMSOTf, DCM, –20 °C | 80 |

Acid-catalysed conditions proved no more successful: the use of TFA or $H_2SO_4$ led to extensive substrate decomposition while $Sc(OTf)_3$ produced no reaction with full recovery of sulfonamide **204**.

Esterification of alcohols is often carried out with the acid anhydride and hence isovaleric anhydride **212** was prepared by reaction of isovaleric acid and benzylsulfonyl chloride in pyridine (Scheme 3.9).[147] Exposure of sulfonamide **204** to anhydride **212** and catalytic TMSOTf (entry 7) finally afforded the desired *O*-isovaleryl derivative **211** in 80% yield with no observed decomposition.

**Scheme 3.9**: Preparation of isovalerate anhydride

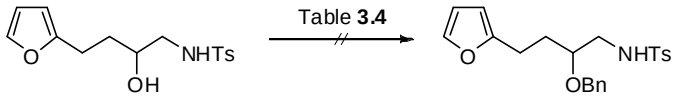



**212**, 100%

### 3.2.4 Synthesis of *O*-benzyl alkylfuran 213

Preparation of the *O*-benzyl derivate from sulfonamide **204** also proved more difficult than first envisaged (Scheme 3.10). Basic conditions (Table 3.4, entries 1 – 3) led, unsurprisingly, to the predominant formation of the *N*-benzyl derivative. The use of $Cs_2CO_3$ afforded some of the desired *O*-benzyl ether **213** but only in a disappointing 5% yield.

**Scheme 3.10**




**204** **213**

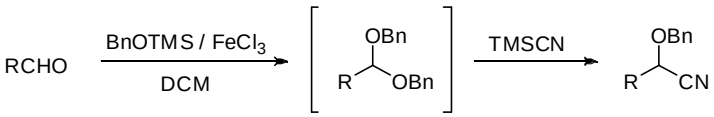
Switching the benzylating agent to benzyltrichloroacetimidate[148] proved no more successful and sulfonamide **204** rapidly decomposed under the acidic conditions. Carrying out the reaction at lower temperatures (entries 5, 7) and adding the acid catalyst slowly in 1 mol% aliquots simply produced a mixture of starting material and decomposition products.

**Table 3.4**: Attempts to *O*-benzylate sulfonamide **204**

| Entry | Conditions | Result |
|---|---|---|
| **1** | BnBr, $Cs_2CO_3$, DMF | **213**, 5% |
| **2** | NaH, BnBr, THF, 60 °C | *N*-benzylation |
| **3** | NaH, BnBr, TBAI, THF | *N*-benzylation |
| **4** | $BnOC(=NH)CCl_3$, 10 mol% TfOH, dioxane | decomposition |
| **5** | $BnOC(=NH)CCl_3$, 1 – 10 mol% TfOH, dioxane, –20 °C | decomposition |
| **6** | $BnOC(=NH)CCl_3$, 5 mol% $BF_3{\cdot}Et_2O$, dioxane | decomposition |
| **7** | $BnOC(=NH)CCl_3$, 1 – 10 mol% TMSOTf, DCM, 0 °C | decomposition |

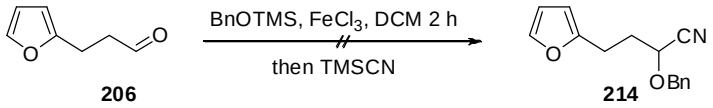
Although alternative benzylation conditions could have been explored, we decided to create the *O*-benzyl functionality before the amino group was installed in the molecule.

**Scheme 3.11**: Oriyama's one-pot synthesis of cyanohydrin benzyl ethers




Oriyama and co-workers described the synthesis of *O*-alkyl protected cyanohydrins from aldehydes *via* a one-pot $FeCl_3$-catalysed procedure (Scheme 3.11).[149] The reaction occurs in two steps: formation of the dialkyl acetal *in situ* then trapping with trimethylsilylcyanide to form the cyanohydrin alkyl ether.[150]

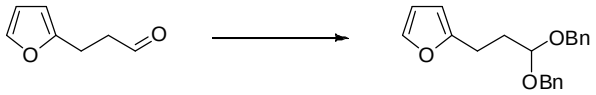
**Scheme 3.12**: Unsuccessful application of Oriyama's one-pot protocol




**206** **214**

Subjecting aldehyde **206** to Oriyama's conditions (Scheme 3.12) led only to the recovery of starting material along with a substantial amount of decomposition. As a result, we opted to investigate the synthesis of *O*-benzyl nitrile **214** under a more standard two step protocol.

**Table 3.5**




**206** **215**

| Entry | Conditions | Yield / % |
|---|---|---|
| **1** | 2 mol% $FeCl_3$, BnOTMS, DCM | no reaction |
| **2** | 1 mol% PTSA, BnOH, PhMe, 120 °C | decomposition |
| **3** | 5 mol% $RuCl_3$, BnOH | no reaction |
| **4** | 5 mol% NCS, 2 mol% thiourea, BnOH | 77% |

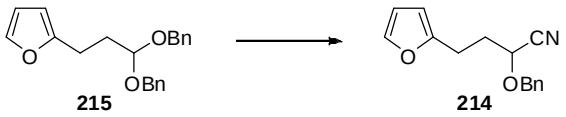
Attempts to utilise Oriyama's BnOTMS/$FeCl_3$-catalysed for the synthesis of acetal **215** failed completely (Table 3.5, entry 1); only starting materials were recovered and no trace of the desired product was visible by $^1$H NMR analysis.

Subjecting aldehyde **206** to classical conditions for acetal formation,[151] in this case BnOH/PTSA (entry 2) resulted in significant decomposition with only low recovery of starting material. More esoteric conditions investigated included the use of $RuCl_3$[152, 153] (entry 3) and a NCS/thiourea-catalysed process.[154] In the first instance only starting material was recovered yet pleasingly, the latter conditions afforded dibenzyl ether **215** in good yield without any sign of decomposition (entry 4).

A number of conditions were then investigated for the conversion of acetal **215** to benzyl cyanohydrin **214** (Table 3.6). No reaction took place under Olah's conditions[144] or Ito's *t*-butyl isocyanide protocol,[155] while Molander's TMSOTf-catalysed procedure[156] led to the complete destruction of acetal **215**.

Masaki's tetracyanoethylene/TMSCN conditions[157] finally afforded cyanohydrin **214** in good yield (entry 5) yet a significant amount of decomposition occurred when the reaction was carried out on greater than 200 mg scales and so a milder procedure was investigated. Fujioka and co-workers have recently reported the formation of *O*,*P*-acetals from *O*,*O*-acetals and their subsequent displacement with various nucleophiles (PhMgBr, PhSLi, $H_2O$).[158] Following this protocol, cyanohydrin **214** was formed in 73% yield (entry 6).

**Table 3.6**: Conversion of dibenzyl acetal **215** to *O*-benzyl cyanohydrin **214**

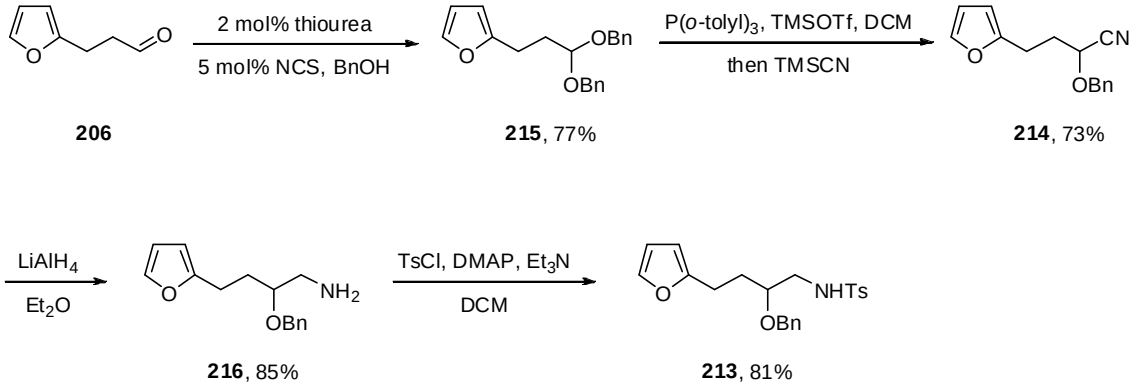



**215** **214**

| Entry | Conditions | Yield / % |
|---|---|---|
| **1** | TMSCN, DMF | no reaction |
| **2** | 5 mol% $K_2CO_3$, TMSCN, DMF | no reaction |
| **3** | *t*-BuNC, $TiCl_4$, DCM, – 78 °C → RT | no reaction |
| **4** | 10 mol% TMSOTf, TMSCN, DCM | decomp. |
| **5** | 20 mol% TCNE, TMSCN, MeCN, 80 °C | 67 |
| **6** | 2 eq. TMSOTf, 2.2 eq. P(*o*-tolyl)$_3$ then TMSCN, DCM | 73 |

$LiAlH_4$ reduction of cyanohydrin **214** and *N*-tosylation under standard protocols (Scheme 3.13) then afforded our second aza-Bohlmann precursor *O*-benzyl **216** and efforts towards the oxidation and cyclisation of our substrates began in earnest.

**Scheme 3.13**: Final route to *O*-benzyl sulfonamide **216**



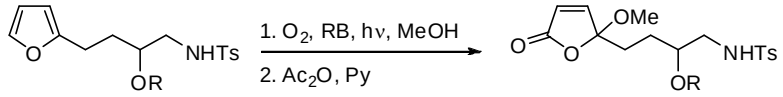

**206** **215**, 77% **214**, 73%

**216**, 85% **213**, 81%

## 3.2.5 Synthesis of 3-oxy spiroaminobutenolides

Given the troubles encountered in the synthesis of sulfonamides **211** and **213**, we were very pleased to discover the end game of the route was realised without complication. Sulfonamides **211** and **213** were converted smoothly to methoxybutenolides **217** and **218** under our standard singlet oxygen oxidation conditions (Scheme 3.14).

**Scheme 3.14**

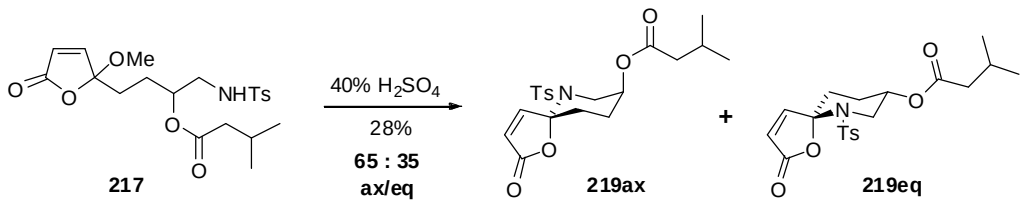



**211**: R = $C(O)CH_2CH(CH_3)_2$
**213**: R = Bn

**217**: R = $C(O)CH_2CH(CH_3)_2$, 100%
**218**: R = Bn, 76%

Spirocyclisation of isovalerate butenolide **217** proved sluggish and, after stirring in 30% $H_2SO_4$ for 4 days, only 20% of material had converted to spiroaminoacetal **219**. Increasing the concentration of the acid to 40% allowed for full conversion after 5 days in a 65:35 mixture of axial/equatorial diastereomers in 28%. The low yield reflects the instability of the isovalerate ester under our acidic conditions and a number of by-products were produced in the reaction.

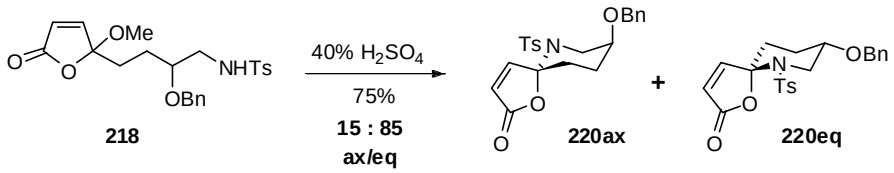
**Scheme 3.15**: Spirocyclisation of isovalerate methoxybutenolide **217**




**217** **219ax** **219eq**

*O*-Benzyl butenolide **218** spirocyclised much more rapidly and cleanly. After stirring in 40% $H_2SO_4$ for 2 days, spiroaminoacetal **220** was obtained as a 15:85 mixture of axial/equatorial diastereomers in 75% yield.

**Scheme 3.16**: Spirocyclisation of benzyl methoxybutenolide **218**

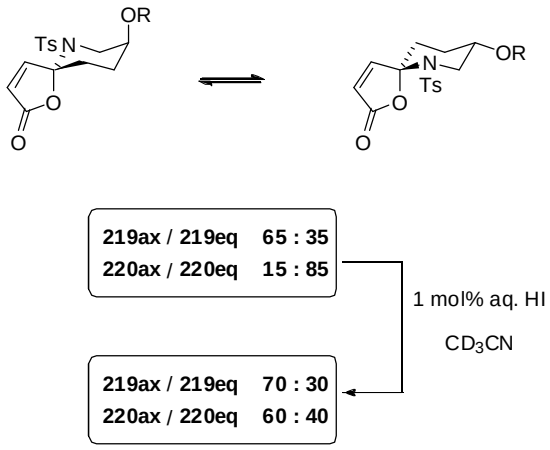



**218** **220ax** **220eq**

### 3.2.6 Equilibrium studies

In contrast to the previous spiroacetal study, the spiroaminoacetals could not be separated by column chromatography into the axial/equatorial diastereomers. Equilibration experiments were therefore carried out on the mixture of diastereomers and the change in ratio calculated by inspection of the $^1$H NMR spectra. **219ax**/**219eq** and **220ax**/**220eq** were treated with 1% mol aq. HI in $CD_3CN$ and $^1$H NMR data collected at various time points. In both cases, equilibration occurred rapidly and no change was observed in the ratio of diastereomers between the $^1$H NMR spectrum taken after 5 min and that collected after 24 h.

**Scheme 3.17**: Equilibriation studies

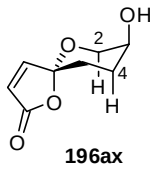



The axial/equatorial ratios observed in the equilibration experiments parallel those obtained in the spiroacetal series: the *O*-isovaleryl derivative **219** showing a higher axial preference than the *O*-benzyl derivative **220**. Whilst the ratios obtained for *O*-isovaleryl spiroaminoacetal **219** were only slightly attenuated after equilibration, the ratio for

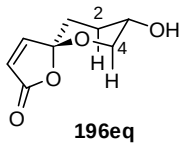
*O*-benzyl spiroaminoacetal **220** varied drastically. By $^{1}$H NMR analysis, the signals corresponding to the axial diastereomer were barely visible following the $H_2SO_4$ cyclisation. Following treatment with HI, the majority of *O*-benzyl spiroaminoacetal **220** exists in the axial configuration. The dramatic difference in ratios is surprising since we expected the strongly acidic conditions to lead to full equilibration.

At present, we are unsure of the origin of the axial/equatorial preferences displayed in both the spiroacetal and spiroaminoacetal series. However the axial preferences could be derived from stabilising interactions associated with an attractive gauche effect, in which two additional (C–H)σ – (C–O)σ* interactions are possible in the axial isomer.

**Figure 3.2**: X-ray crystal data confirmed longer C–H and C–O bond lengths in **196ax** *vs*. **196eq**.




**196ax**




**196eq**

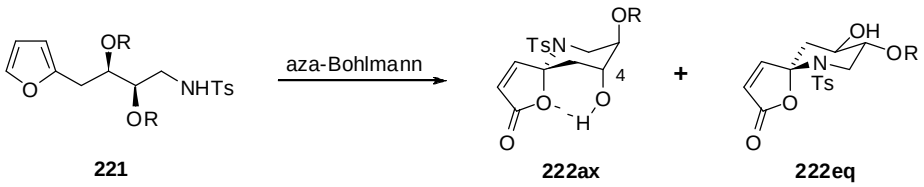
Evidence of these stabilising interactions could come from longer bond lengths in the interacting C–O and C–H bonds. Although crystals have not been obtained for the spiroaminoacetal series, previous data obtained in the group for spiroacetals **196ax** and **196eq** did, indeed, show longer bond lengths for the relevant bonds (C(2)–H, C(4)–H) in **196ax** *vs*. **196eq** ($\Delta_{ave}$ = +0.0455 Å). Longer bond lengths were also found in the relevant C–O bonds, yet the difference was far smaller ($\Delta_{ave}$ = +0.007 Å).

Computational investigation is underway in order to provide greater insight into the configurational preferences in the spiroaminoacetal series.

## *3.3 Progress towards a vicinal diol spiroaminoacetal*

Given the interesting axial/equatorial preferences exhibited in the 3-oxy spiroaminoacetal substrates, we were keen to investigate whether a similar preference existed in, or could be enhanced by, the analogous diol substrates. If the hydroxyl at the C4 position of the piperidine ring was left unprotected, a favourable hydrogen bonding interaction with the endocyclic butenolide oxygen could afford additional stabilisation in the axial isomer of type **222ax** (Scheme 3.18).

**Scheme 3.18**

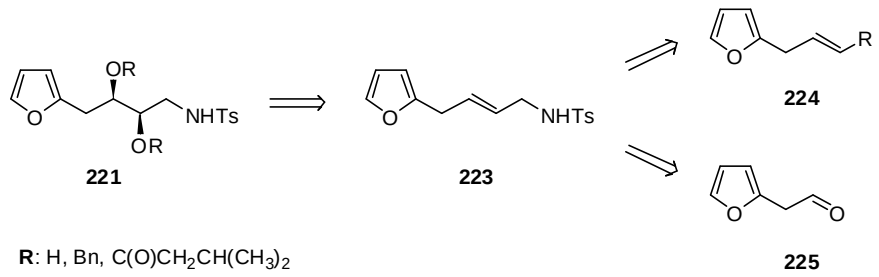



**221** **222ax** **222eq**

**R**: H, Bn, $C(O)CH_2CH(CH_3)_2$

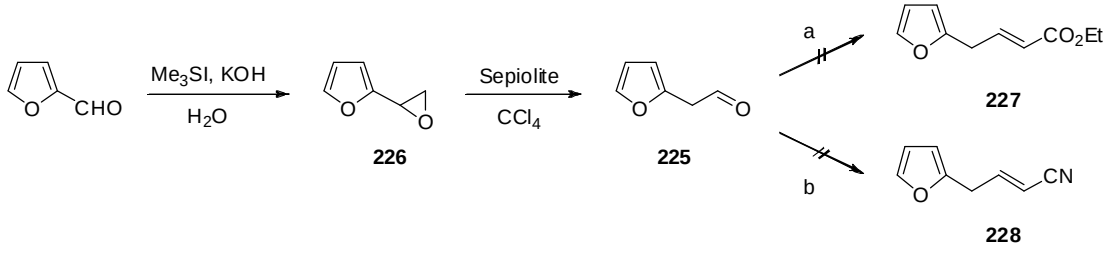
We envisaged installing the diol moiety from dihydroxylation of an olefinic bond and with this in mind, the synthesis of substrate **221** could be explored *via* a cross-metathesis or HWE reaction (Scheme 3.19).

**Scheme 3.19**: Retrosynthetic analysis of diol **221**




However, concurrent work by a postdoctoral worker in the group[159] had investigated the synthesis of aldehyde **225** and subsequent HWE reaction with ethyl ester and cyanophosphonates (Scheme 3.20). Epoxide **226** and aldehyde **225** were difficult compounds, both being were isolated in low yields as complex mixtures that could not be purified. Attempts to perform HWE on contaminated samples of aldehyde **225** failed to give any of the desired product and consequently, efforts to access our vicinal diol **221** *via* aldehyde **225** were not pursued.

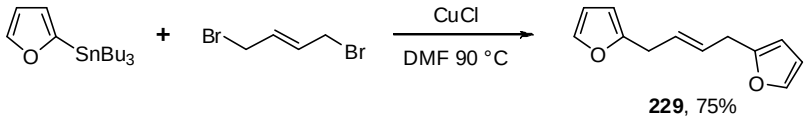
**Scheme 3.20**: Previous group efforts to access olefinic furans *via* HWE chemistry were unsuccessful



### 3.3.1 A cross-metathesis approach to diol 221

In order to install a C=C bond at C(2)–C(3) of the side-chain, the synthesis of an allylic furan CM fragment was investigated. Rather than the more obvious 2-allylfuran, which is volatile, we opted to use the equivalent homodimer **229** as the coupling partner.

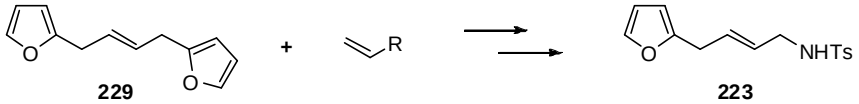
**Scheme 3.21**: Synthesis of cross-metathesis precursor




**229**, 75%

Following the procedure of Nudelman,[160] CuCl-catalysed coupling of 2-(tributylstannyl)furan with 1,4-dibromobutene afforded difuran **229** in good yield. CM with a variety of partners was then investigated (Table 3.7).

**Scheme 3.22**



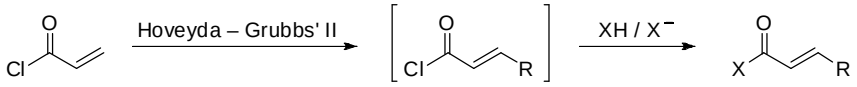

**229** **223**

The ideal CM partner for the synthesis of allyl amine **223**, *N*-tosyl-allylamine, failed to give any of the desired product and only *p*-toluenesulfonamide and starting materials were recovered from the reaction. Presumably, the sulfonamide arises from C=C isomerisation and hydrolysis of the resulting imine; the use of metathesis catalysts for cleaving *N*-allyl protecting groups has been reported by Alcaide.[161]

CM of difuran **229** with allylamine gave no productive reaction yet acrylamide proved more successful (entries 5 – 7). Although acrylamide has been reported to undergo coupling without the use of additives,[162] we found the addition of Ti(O*i*-Pr)$_4$ necessary for reaction to occur.[163] However, productive reaction only occurred with Grubbs' II catalyst and the yield of amide **230** could not be improved above 16% even with extended reaction time and catalyst loading; the use of Hoveyda-Grubbs' II catalyst simply returned starting materials.

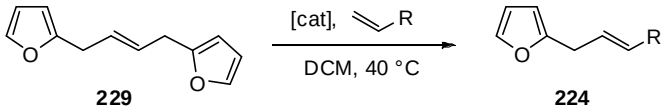
The Cossy group have reported the use of acryloyl chloride as a CM partner *en route* to allylic amides (Scheme 3.23).[164] In their one-pot procedure, a range of terminal olefins were reacted with acryloyl chloride and, upon consumption of the starting material by TLC, the required amine added to the reaction mixture to afford α, β-unsaturated amides. Unfortunately, applying this protocol to difuran **229** only led to the recovery of starting materials and substantial decomposition with either Grubbs' II or Hoveyda-Grubbs' II catalyst.

**Scheme 3.23**: Cossy's synthesis of α,β-unsaturated amines *via* acryloyl chloride

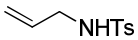
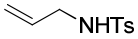
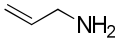
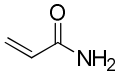
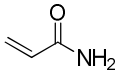
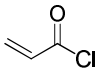
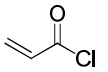
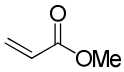
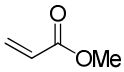
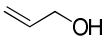
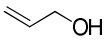



R = alkyl, aryl
XH = $RNH_2$, RNH

**Table 3.7**: Screening of cross-metathesis partners

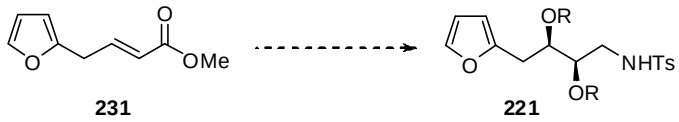



**229** **224**

| Entry | CM partner | Conditions | | Yield / % |
|---|---|---|---|---|
| 1 |  | 5 mol% Grubbs' II, DCM, 40 °C | – | 0 |
| 2 |  | 5 mol% Hoveyda–Grubbs' II, DCM, 40 °C | – | 0 |
| 3 |  | 5 mol% Grubbs' II, DCM, 40 °C | – | 0 |
| 4 |  | 5 mol% Grubbs' II, 1.1 eq. Ti(O*i*-Pr)$_4$, DCM, 40 °C | **230** | 16 |
| 5 |  | 5 mol% Hoveyda–Grubbs' II, 1.1 eq. Ti(O*i*-Pr)$_4$, DCM, 40 °C | – | 0 |
| 6 |  | (i) 5 mol% Hoveyda–Grubbs' II, DCM, 40 °C; (ii) $NH_4OH$ | – | decomposition |
| 6 |  | (i) 5 mol% Grubbs' II, DCM, 40 °C; (ii) $NH_4OH$ | – | decomposition |
| 7 |  | 5 mol% Grubbs' II, DCM, 40 °C | **231** | 65 |
| 8 |  | 5 mol% Hoveyda–Grubbs' II, DCM, 40 °C | **231** | 72 |
| 9 |  | 5 mol% Hoveyda-Grubbs' II, DCM, 40 °C | – | 0 |
| 10 |  | 5 mol% Grubbs' II, DCM, 40 °C | **232** | 8 |

With a view to installing the amine moiety at a later stage, CM reactions with methyl acrylate and allyl alcohol were investigated. Methyl acrylate proved to be the better partner, affording ester **231** in 72% yield with Hoveyda – Grubbs' II catalyst. Reaction of difuran **229** with allyl alcohol delivered only 8% of the hydroxyalkylfuran **232**.

**Scheme 3.24**

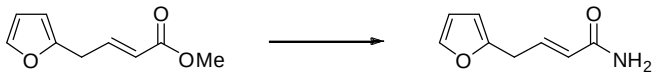



With the carbon backbone in place, efforts turned towards the installation of the amine and dihydroxylation of the C(2)–C(3) olefin (Scheme 3.24).

The conversion of methyl ester to amine was initially attempted on unsaturated ester **231** since we felt amine manipulation would be easier without the presence of the diol group ( Table 3.8). Treatment of ester **231** with aqueous ammonia[165-167] was unproductive and only starting material and unidentified decomposition products were recovered (entries 1 and 2). The Ley group have described the use of $Mg_3N_2$ as a convenient alternative to methanolic ammonia solutions in the preparation of primary amides.[168] Upon treatment with magnesium nitride at 80 °C for 24 h, consumption of ester **231** occurred (TLC), however, the $^1$H NMR spectrum of the crude product indicated a complex mixture of products and none of the desired allylic amide **230** was isolated after purification.

Weinreb has reported the use of alkylchloroaluminium amides for the conversion of esters to amides.[169] Upon addition of amino(methyl)aluminium chloride to ester **231**, the reaction mixture turned a dark brown colour, and analysis of the crude reaction mixture indicated significant decomposition had occurred. However, amide **230** was isolated in 8% yield.

**Table 3.8**

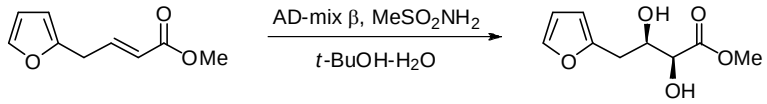


**231** **230**

| Entry | Conditions | Yield / % |
|---|---|---|
| 1 | $NH_3$ (aq.) | decomposition |
| 2 | $NH_4OH$ (aq.), MeOH | decomposition |
| 3 | $MeAl(NH_2)Cl$, PhMe, 0 – 50 °C | 8 |
| 4 | $Mg_3N_2$, MeOH, sealed tube, 80 °C | decomposition |

Due to the significant amount of decomposition products observed in our ammonolysis reactions, ester **231** was elaborated to diol **233** in the hope that removing the double bond would afford increased stability to the ester. This proceeded without event under Sharpless asymmetric dihydroxylation conditions[170] to afford diol **233** in 72% yield (Scheme 3.25).

**Scheme 3.25**




**231** **233**, 72%

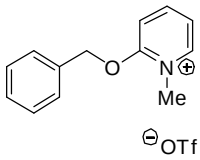
Before resuming ammonolysis reactions, we sought to protect the diol moiety, not only to prevent potential interference with the ester to amide conversion, but also to reduce the polarity of the substrate since a diol amine/amide substrate would be reasonably water soluble and could prove difficult to purify and isolate.

Benzyl ethers were selected to protect the diol moiety as they are resistant to basic and acidic conditions (important for amidation and the acidic cyclisation steps) and the added molecular weight would increase the likelihood of forming crystalline products for single crystal X-ray confirmation of the spiroaminoacetal configuration.

As with the mono-ol substrate **204**, the acidic conditions required for benzylation with benzyl-2,2,2-trichloroacetimidate were incompatible with the furan and rapid decomposition occurred in each instance.

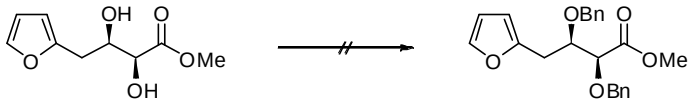
Dudley's reagent (Figure 3.3) is suggested to be a neutral alternative for substrates sensitive to the standard acid-catalysed benzyl-2,2,2-trichloroacetimidate conditions.[171] Indeed, upon treatment of diol **233** with Dudley's reagent no decomposition occurred but no benzylation occurred either and diol **233** was recovered quantitatively.

**Figure 3.3**: Dudley's reagent




Finally, attempted benzylation under basic conditions (NaH, $Ag_2O$, entries 4 – 5) led to complex product mixtures with none of the desired *O*-benzylated diol being isolated after purification. At this point, work on ester **233** was discontinued and a shorter route to diol **221** was pursued.

**Table 3.9**: Benzylation attempts



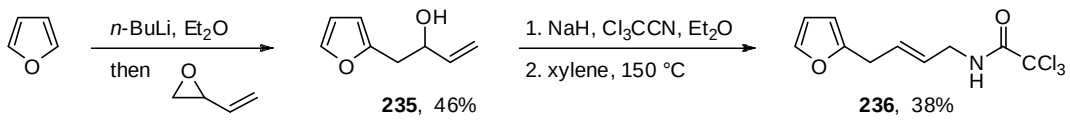

**233** **234**

| Entry | Conditions | Result |
|---|---|---|
| 1 | $BnOC(=NH)CCl_3$, TfOH, dioxane | decomposition |
| 2 | $BnOC(=NH)CCl_3$, TfOH, cyclohexane/DCM, –20 °C | decomposition |
| 3 | Dudley's reagent, MgO, PhMe | no reaction |
| 4 | BnBr, $Ag_2O$, PhMe, 70 °C | decomposition |
| 5 | BnBr, TBAI, NaH, THF, 0 °C → RT | decomposition |

### 3.3.2 Syntheses of allylamine furans

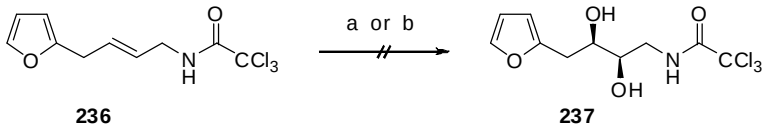
As an alternative to the CM chemistry, we briefly explored the use of an Overman rearrangement[172, 173] to produce an allylic aminofuran. Addition of lithiofuran to 2-vinyloxirane produced allylic alcohol **235** in satisfactory yield. Treatment of **235** with trichloroacetonitrile followed by heating in xylene gave trichloroacetamide **236** in 38% yield.

**Scheme 3.26**: Synthesis of allyl amine *via* an Overman rearrangement



Attempts to dihydroxylate trichloroacetamide **236** under standard AD conditions[170] failed to give any reaction. The Sharpless group reported an acidic dihydroxylation procedure that has found great utility in the dihydroxylation of electron deficient olefins.[174] Despite osmium loadings of up to 10 mol% and extended reaction times, no dihydroxylation took place and only starting material could be recovered.

**Scheme 3.27**: Failed attempts to dihydroxylate trichloroacetamide **236**



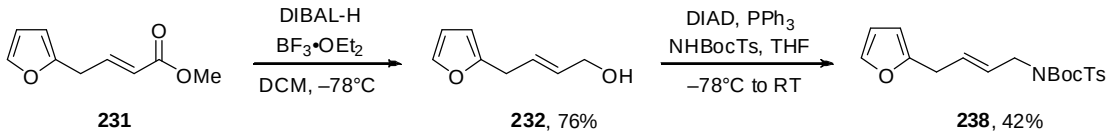

**236** **237**

Conditions: (a) AD-mix β, $MeSO_2NH_2$, *t*-BuOH-$H_2O$, 6 d; or (b) 10 mol% $K_2OsO_2(OH)_4$, NMO, citric acid, *t*-BuOH-$H_2O$, 6 d.

Due to time constraints and more promising results elsewhere, no further attempts were made to dihydroxylate acetamide **236**. However, Donohoe *et al*. have carried out dihydroxylations on similar trichloroacetamide substrates using stoichiometric $OsO_4$ and the use of this procedure warrants further investigation.[175]

Though not as direct as the Overman route, another option for the synthesis of an allylamine furan was investigated from methyl ester **231** (Scheme 3.28). The attraction in this latter route is the installation of the amine moiety with the desired sulfonamide protecting group directly, avoiding the use of later protecting group manipulations.

**Scheme 3.28**: Mitsunobu route towards 2,3-diol sulfonamide **221**



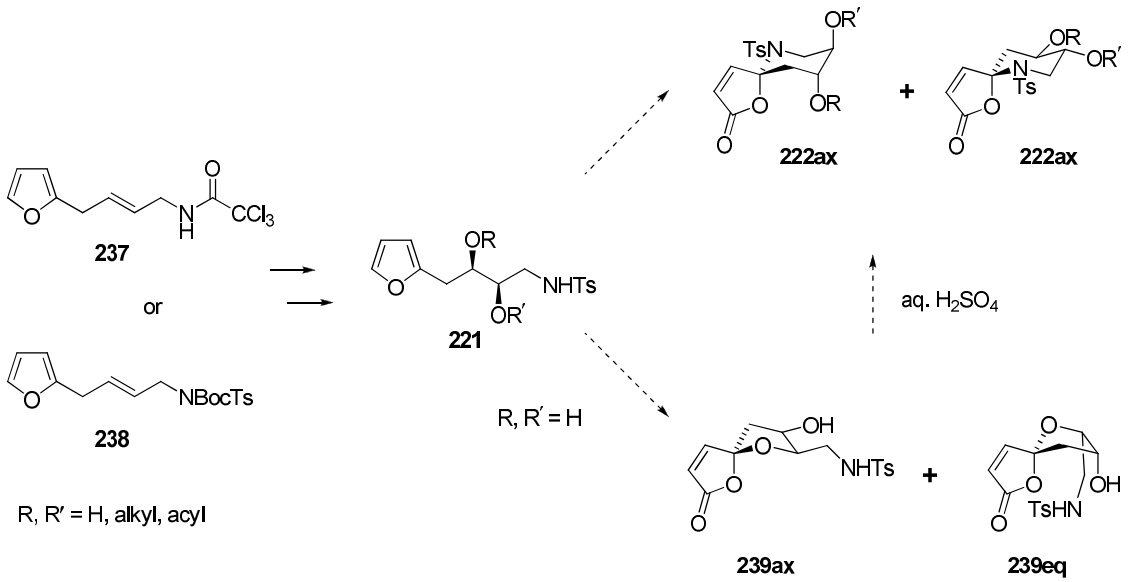

**231** **232**, 76% **238**, 42%

DIBAL-H reduction of methyl ester **231** in the presence of $BF_3{\cdot}OEt_2$[176] proceeded smoothly to afford allyl furan **232** in good yield. Treatment of alcohol **232** with *N*-Boc-*p*-toluenesulfonamide under Mitsunobu conditions[177] afforded di-protected allyl amine **238** in modest yield. Again, due to time constraints, elaboration to the desired 2,3-diol spiroaminoacetal **222** was not investigated.

### 3.3.3 Future work

Both acetamide **236** and sulfonamide **238** should undergo dihydroxylation and could be elaborated to diol **221**. Leaving the diol unprotected would deliver an interesting substrate to test the *O*- versus *N*-selectivity of the Bohlmann cyclisation. Presumably, [4.4]-spiroacetals **239ax** and **239eq** would form after the oxidation step (either *m*-CPBA or $^1O_2$); however, treatment with $H_2SO_4$ may allow for ring opening and subsequent formation of the [4.5]-spiroaminoacetal **222**.

**Scheme 3.29**: Elaboration of allylaminofurans

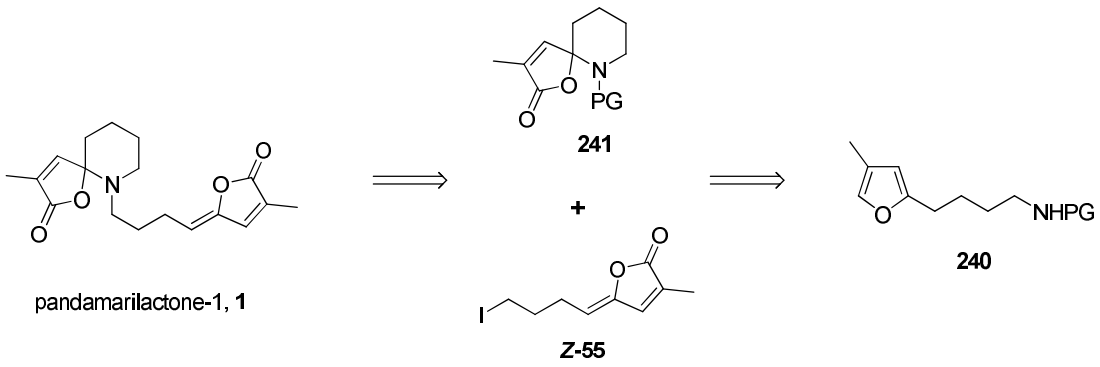


# Chapter 4 Synthesis of *Pandanus* alkaloids

## *4.1 Synthetic strategies for the synthesis of pandamarilactone-1*

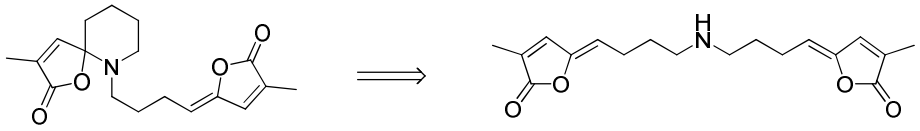
At the beginning of the project, we envisaged the synthesis of pandamarilactone-1 **1** as a simple extension and application of our aza-Bohlmann methodology. Performing the spirocyclisation on 4-methylfuran derivative **240** would provide us with the spiroaminoacetal core **241** that, following deprotection, could be coupled with known fragment **55** to deliver pandamarilactone-1 **1** (Scheme 4.1). However, since we were unable to achieve deprotection of our *N*-protected spiroaminoacetals **129** or **155** (Chapter 2), an alternative strategy had to be devised.

**Scheme 4.1**: Initial retrosynthetic analysis of pandamarilactone-1 **1**




Our new synthetic route was inspired by the proposed biogenic precursor to pandamarilactone-1 **1**: the symmetrical γ-alkylidene butenolide pandanamine **32**.[33, 35]

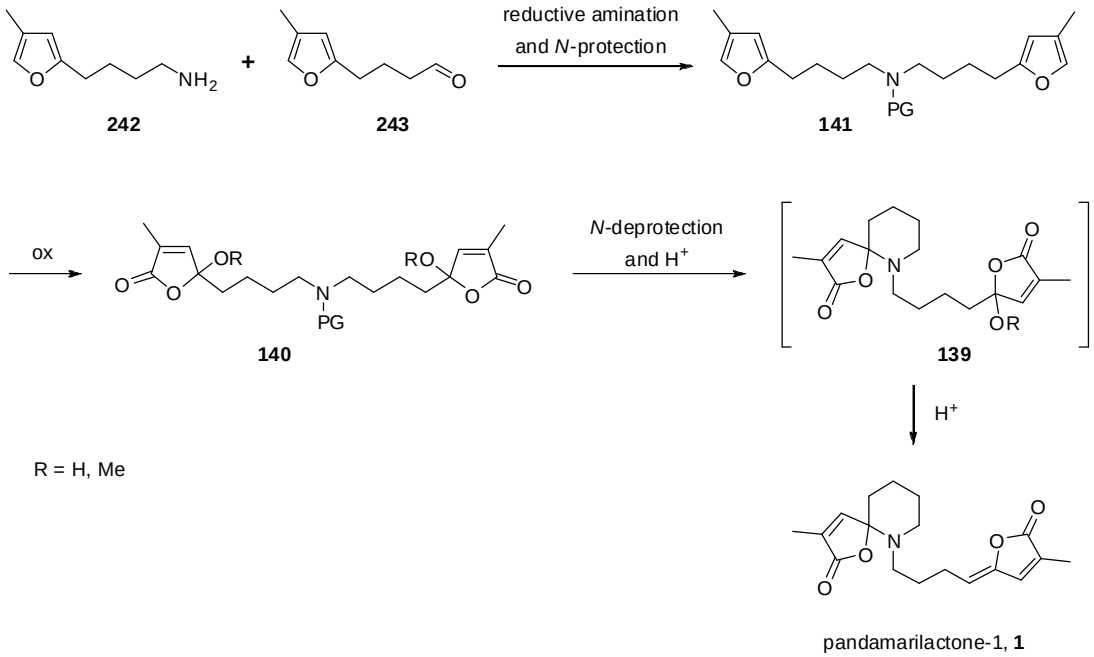
**Scheme 4.2**: Biogenic precursor to pandamarilactone-1 **1** proposed by Nonato



pandamarilactone-1, **1** pandanamine, **32**

Reductive amination of amine **242** and aldehyde **243** followed by *N*-protection would generate aza-Bohlmann precursor **141**. Oxidation of symmetrical amine **141** under Lefebvre[43] or singlet oxygen conditions would then provide access to the hydrated form or methanol adduct of pandanamine **32**. Dibutenolide **140** would then be elaborated to pandamarilactone-1 **1**, possibly *via* spiroaminoacetal **139**, following cleavage of the protecting group and treatment with acid.

**Scheme 4.3**: Synthetic strategy towards pandamarilactone-1 **1**



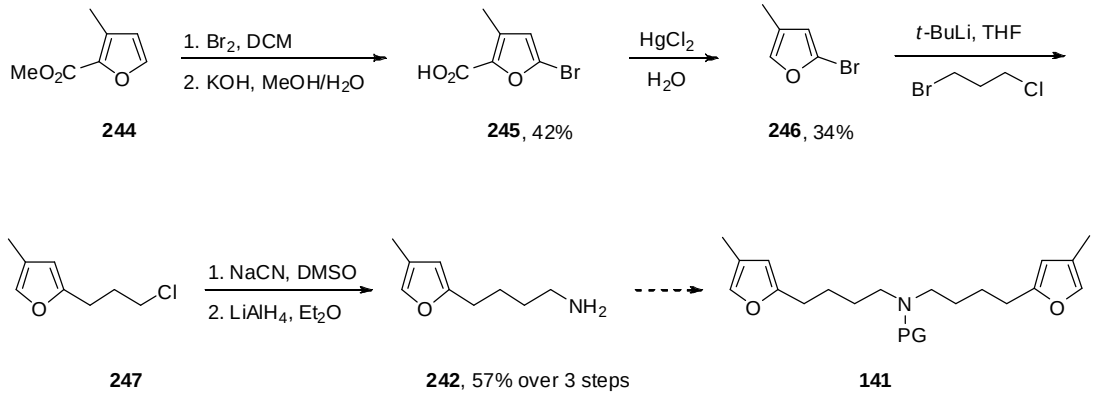

**242** **243** **141** **140** **139** pandamarilactone-1, **1**

## *4.2 Synthesis of 4-methylfurans*

Perhaps surprisingly, the synthesis of the structurally simple 4-methyl furan starting blocks **242** and **243** provided the first challenge of the synthesis. Despite the prevalence of the furan moiety in natural products and the widespread use of furan derivatives as synthons,[178, 179] the occurrence of 2,4-substituted furans featuring a methyl group at C4 are rare; a limited number of methods are available for their synthesis and few useful building blocks are available from commercial suppliers.

The synthesis of 4-methylfuryl amine **242** has previously been investigated in the Robertson group following the procedure of Harwood *et al*.[78, 180] Commercially available methyl 3-methyl-2-furoate was brominated, hydrolysed and decarboxylated to obtain bromofuran **245**. Lithium-halogen exchange, alkylation with 1-bromo-3-chloropropane, cyanide displacement and $LiAlH_4$ reduction provided amine **242** in moderate yield. Low yields in the early stages, combined with the use of toxic reagents, led us to consider an alternative route.

**Scheme 4.4**: Previous Robertson group synthesis of 4-methylfuryl amine **242**




**244** **245**, 42% **246**, 34%

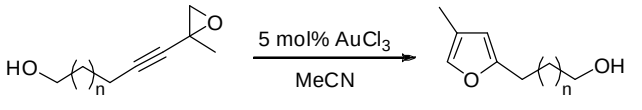
**247** **242**, 57% over 3 steps **141**

### 4.2.1 Preparation of 4-methyl furans *via* metal-catalysed cyclisations

Over the past decade, gold complexes have emerged as useful and mild catalysts capable of performing a range of highly selective chemical transformations.[181] The ability of gold reagents to behave as soft Lewis acids allows them to activate unsaturated functionalities such as alkenes, allenes and alkynes, and therefore facilitate the creation of carbon-carbon and carbon-heteroatom bonds under extremely mild conditions. In particular, the use of gold catalysts to create heterocycles from linear precursors has been an area of great interest to synthetic chemists.[181-183]

Hashmi *et al*. described the gold(III)-catalysed cyclisation of alkynyloxiranes to create 2,4-substituted furans (Scheme 4.5).[184] The synthesis of the 4-methylfuran alcohols appeared straightforward, high-yielding, and avoided the use of toxic chemicals used in the Harwood synthesis of 4-methyl furyl substrates. We sought to utilise this methodology to access alcohol **251**, then perform Mitsunobu chemistry[177] and an oxidation to afford amine **242** and aldehyde **243** respectively.

**Scheme 4.5**: Hashmi synthesis of 4-methylfuryl alcohols



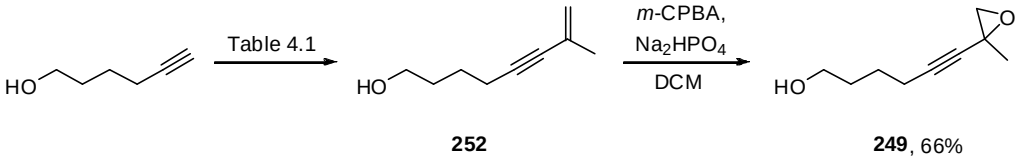

**248**: n = 1
**249**: n = 2

**250**: n = 1, 80%
**251**: n = 2, 84%

### 4.2.2 Preparation of cyclisation precursors

Following the precedent of Hashmi,[184] enyne **252** was prepared *via* a Sonogashira cross-coupling.[185] The use of a Pd(0) catalyst was investigated yet we found it more reliable and cost-effective to use $PdCl_2/PPh_3$ to generate the active catalyst *in situ* (Table 4.1).

**Scheme 4.6**: Synthesis of Hashmi's cyclisation precursor



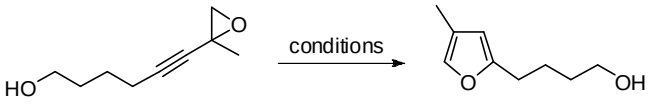

**252** **249**, 66%

**Table 4.1**: Screening of reaction conditions for the Sonogashira coupling

| Entry | Conditions | Yield / % |
|---|---|---|
| 1 | 2-Bromopropene, 5 mol% $Pd(PPh_3)_2Cl_2$, 10 mol% CuI, $Et_3N$, THF | 56 |
| 2 | 2-Bromopropene, 5 mol% $Pd(dppf)_2Cl_2$, 10 mol% CuI, $Et_3N$, THF | 86 |
| 3 | 2-Bromopropene, 2.5 mol% $PdCl_2$, 5 mol% $PPh_3$, 3.5 mol% CuI, $Et_3N$, MeCN | 94 |
| 4 | 2-Bromopropene, 3 mol% 10% Pd/C, 20 mol% $PPh_3$, 5 mol% CuI, $Et_3N$, $H_2O$ | 0 |
| 5 | 2-Bromopropene, 10 mol% $Pd(OAc)_2$, 30 mol% $PPh_3$, 20 mol% CuI, $Et_3N$, DMF | 63 |

Epoxidation of enyne **252** under buffered *m*-CPBA conditions proceeded smoothly yet alkynyl oxirane **249** proved to be quite unstable; rapid purification on neutral alumina and storage in solution at –20 °C were necessary to avoid rapid decomposition into a black tar.

**Table 4.2**: Scoping the Au/Ag-catalysed cyclisation from epoxide **249**



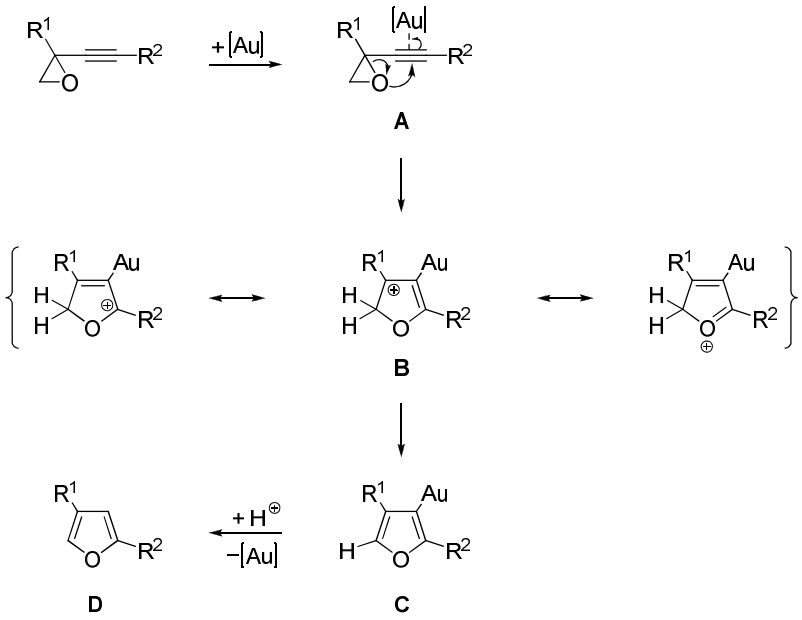

**249** **251**

| Entry | Conditions | Scale | Yield / % |
|---|---|---|---|
| 1 | 5 mol% $AuCl_3$, MeCN | 0.1 mmol | 40 |
| 2 | 5 mol% $AuCl_3$, MeCN | 1 mmol | 0 |
| 3 | 5 mol% $AuCl_3$, DCM/MeOH (9:1) | 1 mmol | 3 |
| 4 | 5 mol% $AuCl_3$, dry DCM | 1 mmol | 0 |
| 5 | 5 mol% AgOTf, 5 mol% *p*-TsOH, DCM/MeOH (9:1) | 0.5 mmol | 24 |
| 6 | 3 mol% $AuCl_3$, 10 mol% AgOTf, THF | 0.5 mmol | 15 |

Given the instability of epoxide **249**, its capricious behaviour in the conversion to furyl alcohol **251** was not unexpected. On a small scale (Table 4.2, entry 1), alcohol **251** was obtained cleanly if the reaction was stopped after 50% conversion. On scaling up to 1 mmol, the starting material was consumed within 5 min yet none of the desired product was visible in the $^1$H NMR spectrum of the crude material. Alternative solvent systems and mixed Au/Ag catalysts were investigated (Table 4.2) but a satisfactory yield could not be obtained above a 0.1 mmol scale. On closer inspection of Hashmi's paper, it was revealed that only two out of seven cyclisation examples were performed on *ca*. 1 mmol scale, the other five being carried out on *ca*. 0.2 mmol scale suggesting that perhaps this methodology is not suitable for larger scale reactions.

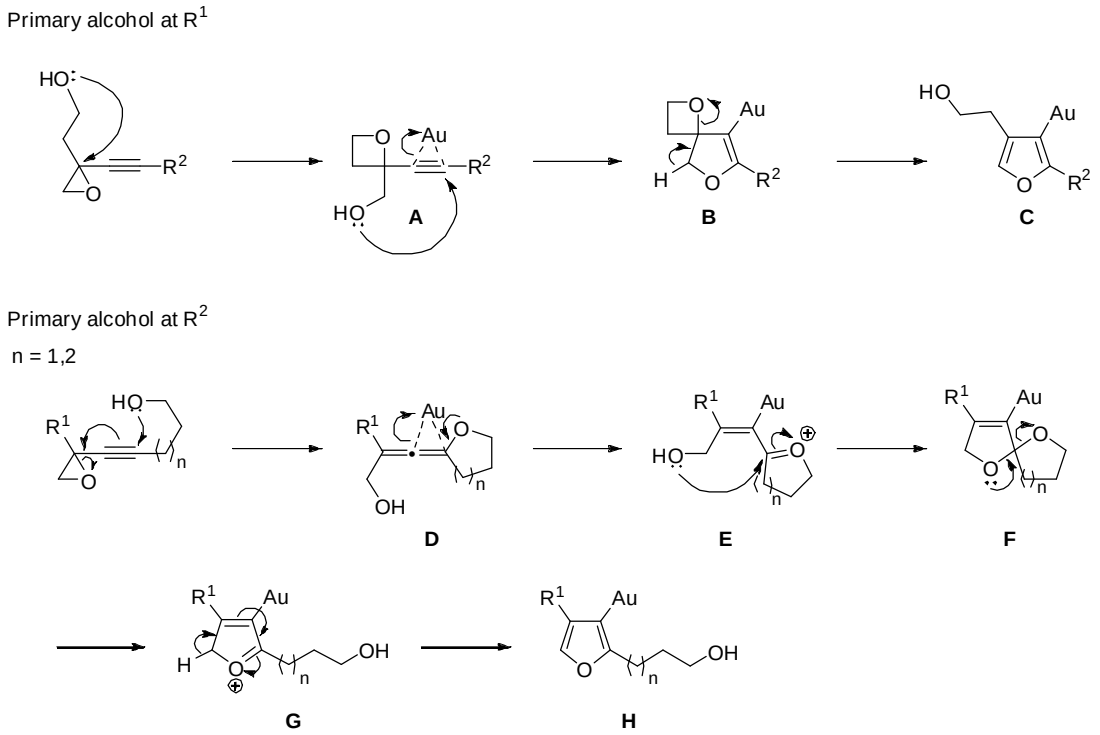
Hashmi's protocol demands anhydrous conditions due to the water sensitivity of $AuCl_3$ and the group's suggested mechanism reflects this (Scheme 4.7). Following activation of the alkyne with gold, it is proposed that the epoxide oxygen attacks the distal position of the triple bond directly to form **B**. The furan is then formed through loss of a proton and proto-deauration.

**Scheme 4.7**: Hashmi's proposed mechanism for the gold-catalysed isomerisation of alkynyl oxiranes to furyl alcohols.



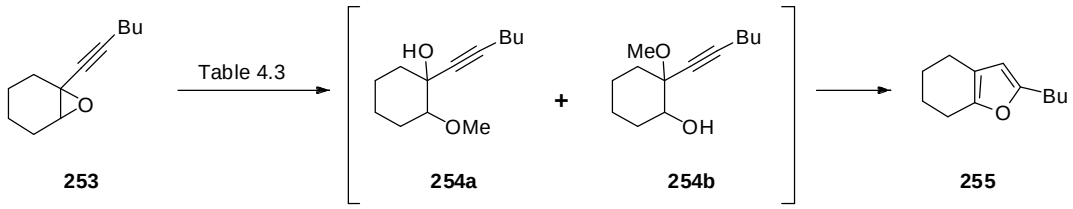

However, what is not explicitly stated in their proposed mechanism is the fact that every one of their reported examples contains a primary alcohol at either $R^1$ or $R^2$. It seems possible that the pendant alcohol activates the substrate towards cyclisation either through the formation of an allenyl intermediate or nucleophilic attack opening the epoxide (Scheme 4.8).[186]

**Scheme 4.8**: Possible mechanisms for alkynyl oxirane isomerisation involving substrate pendant alcohol




The Pale group have studied the Ag and Au-catalysed transformation of alkynyl oxiranes to furans without a free alcohol group.[186] In the Ag-catalysed of **253** under "dry" conditions, adventitious water in the solvent or silver salt catalysed the reaction and varying yields were obtained. The reaction proceeded more smoothly in the presence of methanol and, by following the reactions by $^{1}$H NMR spectroscopy, the group were able to witness the formation of the ring-opened intermediates **254a** and **254b**.

**Scheme 4.9**: Pale and co-workers' mechanistic studies




**253** **254a** **254b** **255**

**Table 4.3**

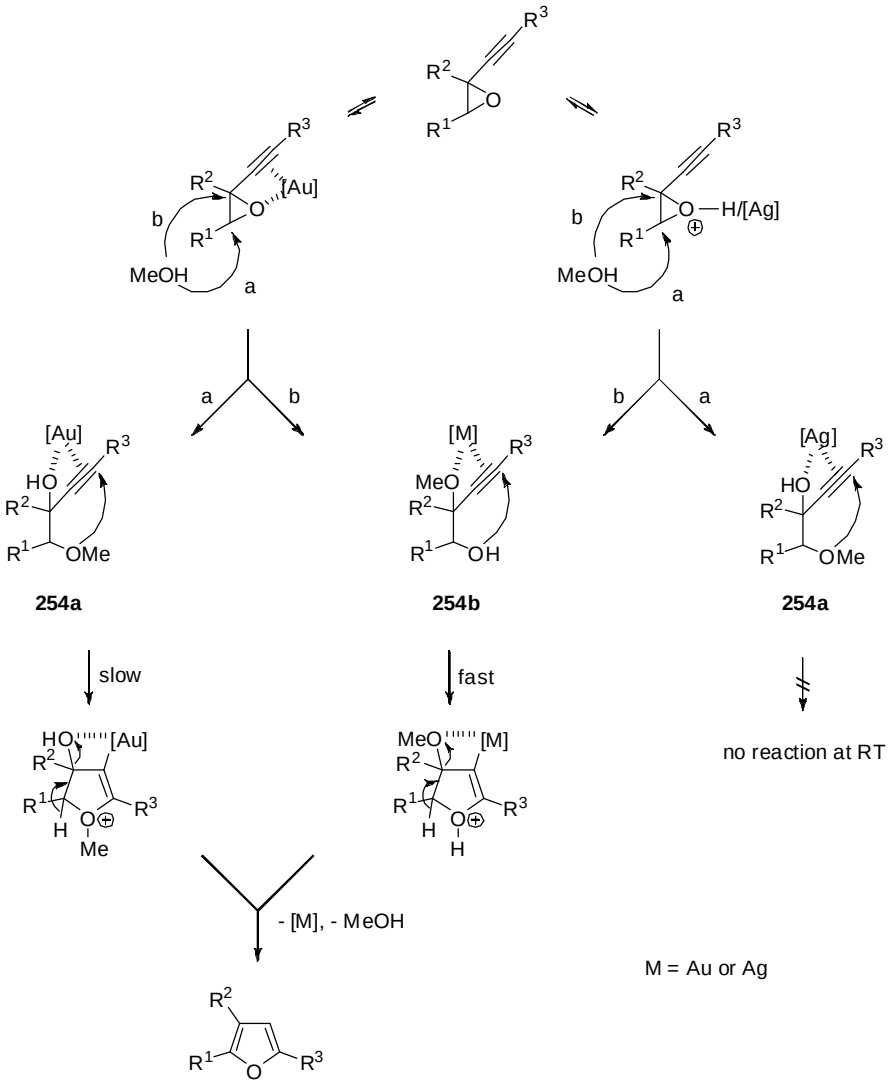
| Entry | Conditions | Yield / % |
|---|---|---|
| 1 | AgOTf, DCM | 30 |
| 2 | AgOTf, DCM/MeOH (9:1) | 73 |
| 3 | $AuCl_3$, MeCN | 31 |
| 4 | $AuCl_3$, DCM/MeOH (9:1) | 10 |
| 5 | $Ph_3PAuOTf$, DCM | 51 |
| 6 | $Ph_3PAuOTf$, DCM/MeOH (9:1) | 90 |

Performing the same experiments with Au catalysts, the Pale group found cyclisation using $AuCl_3$ gave poor conversion to furan **255** irrespective of the presence of methanol. Combining Au(I) complexes with the addition of methanol afforded far superior yields and reaction times (entries 5 and 6).

An interesting dichotomy exists between the mode of activation of Ag and Au catalysts. Whilst both methanol ring-opened products **254a** and **254b** may be produced in either reaction, Ag catalysts favour epoxide opening at the propargylic position to produce intermediate **254b**. Furthermore, Ag is only capable of promoting cyclisation of ring-opened product **254b**. In the Au-catalysed reaction, intermediates **254a** and **254b**

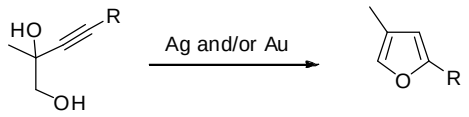
were produced in equal amounts and both were capable of evolving to the desired furan **255**.

**Scheme 4.10**: Pale's proposed mechanism for Ag/Au-catalysed furan formation from alkynyl oxiranes




Given these mechanistic insights, we decided to investigate the formation of furans from diol substrates of type **256** (Scheme 4.11).[187-189]

**Scheme 4.11**: Proposed formation of 4-methyl furans from diol precursors




**256**

Furan formation from diol precursors has been reported on a multi-mmol scale[187] using a variety of catalysts including the humble $AgNO_3$/silica gel.[189, 190] Our modified cyclisation precursor was synthesised in a similar manner as before, except that the alkynol was protected as its pivalate ester **257** prior to the Sonogashira coupling to enable easier handling of the diol substrate (Scheme 4.12). Dihydroxylation under standard Sharpless AD conditions[170] afforded diol **260** in good yield. Pivalate epoxide **259** was also synthesised to ascertain whether *O*-protection could enable more reliable yields than those obtained on the free alcohol **249**.

**Scheme 4.12**: Synthesis of modified cyclisation precursors

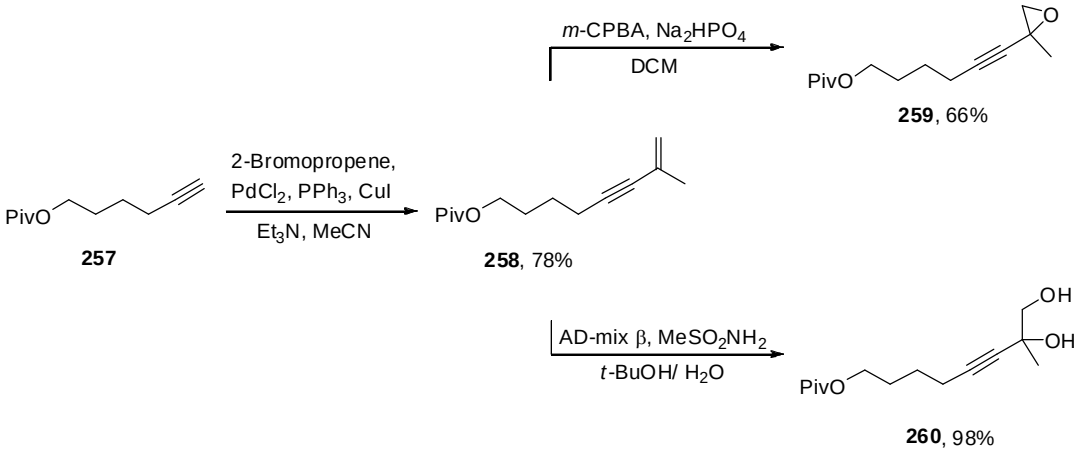
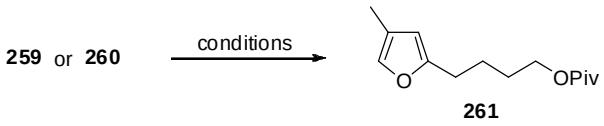


**Table 4.4**




**261**

| Entry | Precursor | Catalyst | Scale | Yield / % |
|---|---|---|---|---|
| **1** | **259** | 5 mol% AgOTf, 5 mol% PTSA, DCM/MeOH | 0.15 mmol | 66 |
| **2** | **259** | 5 mol% AgOTf, 5 mol% PTSA, DCM/MeOH | 0.50 mmol | decomposition |
| **3** | **260** | 5 mol% AgOTf, 5 mol% PTSA, DCM/MeOH | 0.10 mmol | decomposition |
| **4** | **260** | 5 mol% $AuCl_3$, DCM/MeOH | 0.10 mmol | decomposition |
| **5** | **260** | 5 mol% $AuCl_3$, MeOH | 0.10 mmol | 53 |
| **6** | **260** | 10 mol% $AgNO_3$/silica, DCM | 0.10 mmol | 95 |
| **7** | **260** | 4 mol% $AgNO_3$/silica, DCM | 1.20 mmol | 97 |
| **8** | **260** | silica, DCM, 2 weeks | 0.10 mmol | 33 |
| **9** | **260** | (neat at RT), 2 weeks | 1.00 mmol | 10 |

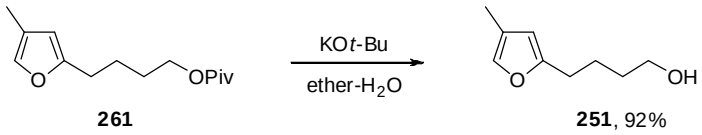
After screening a number of reaction conditions (Table 4.4), use of diol **260** with $AgNO_3$/silica catalyst proved to be the most effective system for the formation of **261** on milligram and multigram scale (entries 6 and 7) with no sign of substrate degradation. A

control experiment was carried out to ensure that $AgNO_3$, and not silica, was the active catalyst for the cyclisation. Indeed, although silica gel did catalyse the cyclisation, conversion was much slower than under the Ag-catalysed conditions and only 33% of **260** had converted to furan **261** after 2 weeks. Interestingly, storing diol **260** neat at RT also led to slow conversion to the desired furan **261** (entry 9).

## *4.3 Synthesis of aza-Bohlmann precursor*

With reproducible cyclisation conditions in place, the elaboration of pivalate ester **261** into our desired amine **242** and aldehyde **243** was explored.

**Scheme 4.13**

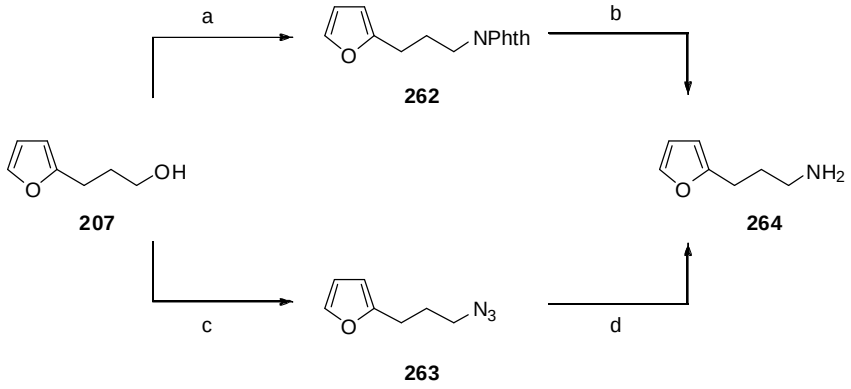



**261** **251**, 92%

Although the pivalate ester could be cleaved by treatment with $LiAlH_4$, this resulted in the formation of neopentyl alcohol that could not be separated from alcohol **251** during flash chromatography. Instead, hydrolysis of pivalate ester **261** with KO*t*-Bu (aq.) afforded alcohol **251** in high yield and the resulting by-product, pivalic acid, was easily removed during purification.

Conversion of hydroxyalkylfuran **251** into aminoalkylfuran **242** was investigated on a simpler model substrate: furylpropanol **207.** Attempts to access amine **264** *via* Mitsunobu chemistry were successful but low yielding. Upon treatment of alcohol **207** with DEAD, $PPh_3$ and phthalimide, imide **262** was obtained cleanly in moderate yield but subsequent hydrazinolysis resulted in substantial decomposition and amine **264** was recovered in a disappointing 36% yield.[191] Amine **264** could also be obtained by azide displacement and hydrogenation yet it proved difficult to achieve full reduction of azide **263** without competing reduction of the furan ring.

**Scheme 4.14**: Synthesis of furyl amine from furyl alcohol on model substrate

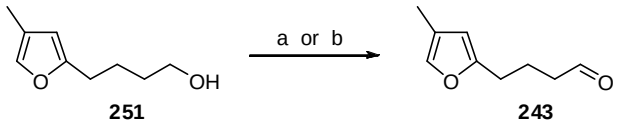



Conditions: (a) Phthalimide, DEAD, $PPh_3$, THF, 42%; (b) $N_2H_4.H_2O$, $CHCl_3$-EtOH (3:1), 60 °C, 36%; (c) (i) MsCl, $Et_3N$, DCM, (ii) $NaN_3$, DMF, 70 °C, 88% over 2 steps; (d) $H_2$, MeOH, 68%

Returning to the real system, brief attempts to oxidise alcohol **251** to aldehyde **243** under Swern or Parikh – Doering conditions gave unimpressive yields (Scheme 4.15). Whilst this transformation could have been optimised, we were wary of the difficulties encountered during large scale oxidations of furylpropanol **207** during our

conformational studies (Chapter 3). This, combined with the inefficient conversion of alcohol **207** to amine **264** in the model system, led us to consider an alternative route to 4-methylfuran amine **242** and aldehyde **243**.

**Scheme 4.15**

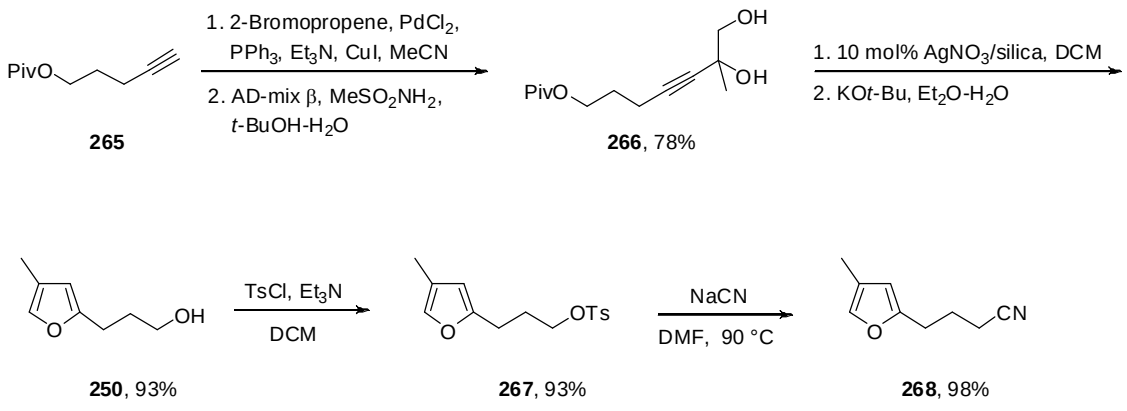



**251** **243**

Conditions: (a) $(COCl)_2$, DMSO, $Et_3N$, DCM, 35%; (b) $SO_3$•pyridine, DMSO, $Et_3N$, DCM, 40%

Effecting cyanide displacement on tosylate **267** would give access to both amine and aldehyde moieties by $LiAlH_4$ and DIBAL-H reductions respectively. Since the cyanide displacement would result in homologation of the chain, a slight modification to the route was required (Scheme 4.16): starting from pivalate ester **265** instead of hexynol **257**. The established chemistry proceeded as before to furnish hydroxyalkylfuran **250** in good yield.

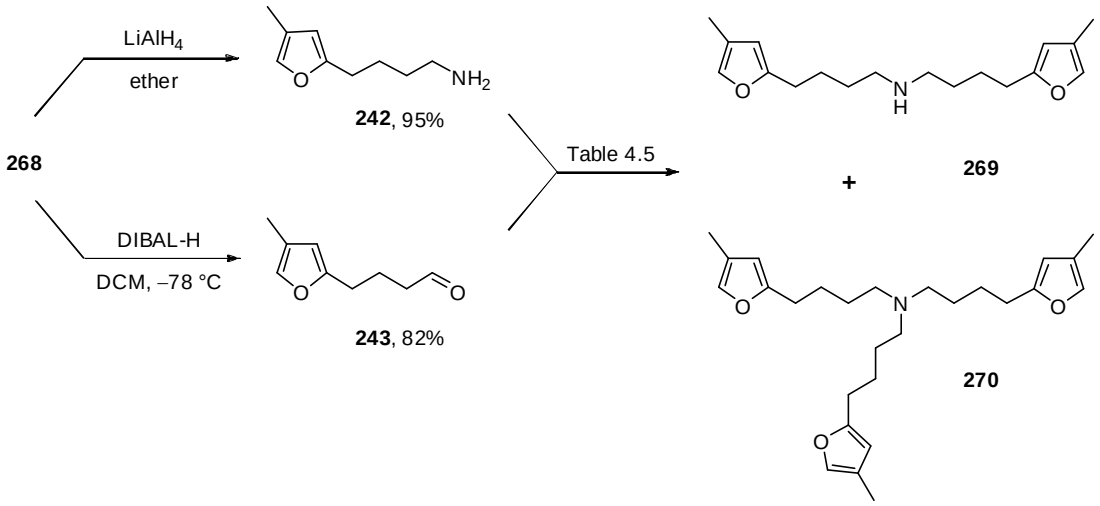
**Scheme 4.16**: Synthesis of nitrile **268**




**265** **266**, 78% **250**, 93% **267**, 93% **268**, 98%

Tosylation and cyanide displacement under standard protocols furnished nitrile **268**, which was smoothly converted to the desired amine **242** and aldehyde **243**. The coupling of **242** and **243** *via* reductive amination was then examined (Table 4.75).

**Scheme 4.17**




Despite the prevalence of one-pot strategies in the literature, reductive amination to form difuran amine **269** was most effectively carried out in a two-step process. Use of mild reducing agents (e.g. $NaBH(OAc)_3$) in a one-pot procedure resulted in the formation of substantial quantities of amine trimer **270**. Simply mixing amine **242** and aldehyde **243** alone in MeOH proved efficient; the addition of catalytic $Ti(O\textit{i}\text{-}Pr)_4$ led to decomposition,[192] and difuran amine **269** was obtained in 22% yield *vs*. 87% yield obtained in the absence of a catalyst.

**Table 4.5**: Survey of reductive amination conditions

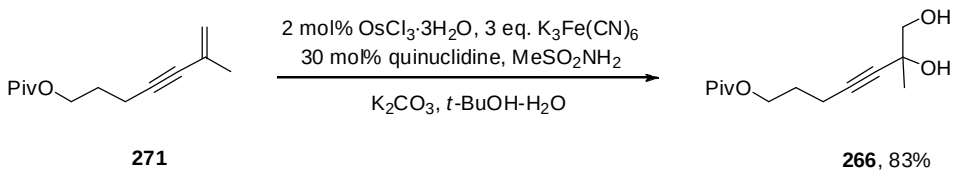
| Entry | Conditions | 269, Yield / % | 270, Yield / % |
|---|---|---|---|
| **1** | **242** (1.0 eq.), **243** (1.0 eq.), AcOH, $NaBH(OAc)_3$, DCE | 22 | 25 |
| **2** | **242** (1.1 eq.), **243** (1.0 eq.), $NaBH(OAc)_3$, THF | 24 | 18 |
| **3** | **242** (1.1 eq.), **243** (1.0 eq.), $NaBH(OAc)_3$, DCM | 15 | 30 |
| **4** | **242**(1.2 eq.), **243** (1.0 eq.), Ti(O*i*-Pr)$_4$, MeOH then $NaBH_4$ | 22 | 0 |
| **5** | **242** (1.1 eq.), **243** (1.0 eq.), MeOH then $NaBH_4$ | 87 | **0** |

### 4.3.1 Large scale synthesis of difuran amine 269

Before progressing amine **269** towards pandamarilactone-1 **1**, a large scale synthesis was undertaken. Although the established route was compatible with scale-up, it seemed sensible to investigate an alternative route to diol **266** since the use of AD-mix β at such an early point in the synthesis was not cost-effective. A brief exploration of alternative, cheaper dihydroxylation conditions proved unfruitful. The high cost of the commercially available AD-mixes derives partly from the inclusion of expensive chiral amine ligands DHQ and DHDQ-phal. As the configuration of the diol is irrelevant to the Ag-catalysed cyclisation step, Warren's analogous "racemic mix" methodology appeared to be an appealing alternative. Indeed, dihydroxylation of enyne **271** proceeded smoothly to afford diol **266** in high yield (Scheme 4.18). Surprisingly, on closer inspection of the cost of the reagents it was revealed that quinuclidine is even more

expensive than Sharpless' ligands [$(DHDQ)_2PHAL$ costs £45/g, quinuclidine costs £77/g] and so this reaction was not suitable for scale-up.

**Scheme 4.18**: Dihydroxylation under Warren's racemic dihydroxylation conditions



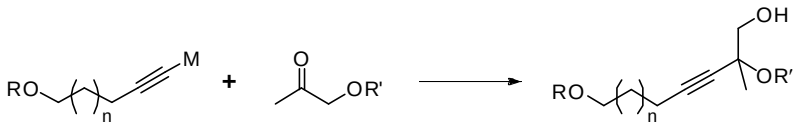

**271** **266**, 83%

A brief scoping of other dihydroxylation methodologies failed to offer satisfactory yields of diol **266** without high osmium loadings and so a different entry to this key substrate was explored: addition of a metallated alkyne to hydroxyacetone (Table 4.6). Although this type of addition is straightforward, we had two concerns: (i) we wanted to use *O*-pivaloyl protection for the alkynol as this was compatible with the Ag-catalysed cyclisation step yet ester moieties can be unstable to organometallic reagents; (ii) in order to conserve material, we wanted to react the two fragments in a 1:1 ratio yet this would require protection of the free hydroxyl of hydroxyacetone and mean another unwieldy protection/deprotection step was added to the sequence.

Addition of pivalate **265** to hydroxyacetone **272** was unsuccessful; reaction at –78 °C led to the recovery of the starting material, and allowing the temperature to rise to –40 °C resulted in a complex mixture of products. The addition of lithiated *O*-TBS alkynol **275** to

*O*-TBS hydroxyacetone **273** afforded the addition product **277** in excellent yield, though the prospect of using two TBS groups was unattractive.

**Table 4.6**: Synthesis of 4-methylfuran precursor *via* organometallic addition to hydroxyacetone



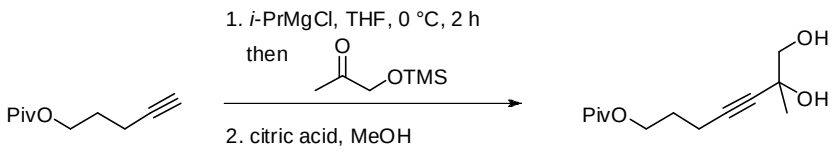

**272**: R' = H
**273**: R' = TBS
**274**: R' = TMS

| Entry | Alkyne | | | R' | Conditions | Product | Yield / % |
|---|---|---|---|---|---|---|---|
| | | R | n | | | | |
| 1 | **265** | Piv | 1 | H | (i) 2.2 eq. **265**, 2.0 eq. *n*-BuLi, THF, – 78 °C<br>(ii) 1.0 eq. **272**, – 78 °C | – | no reaction |
| 2 | **265** | Piv | 1 | H | (i) 2.2 eq. **265**, 2.0 eq. *n*-BuLi, THF, – 78 °C<br>(ii) 1.0 eq. **272**, – 78 °C to – 40 °C | – | decomposition |
| 3 | **265** | Piv | 1 | TBS | (i) 2.2 eq. **265**, 2.0 eq. *n*-BuLi, THF, – 78 °C<br>(ii) 1.0 eq. **273**, – 78 °C to – 40 °C | **276** | 5 |
| 4 | **275** | TBS | 2 | TBS | (i) 1.1 eq. **276**, 1.1 eq. *n*-BuLi, THF, 0 °C<br>(ii) 1.0 eq. **273**, – 78 °C to 0 °C | **277** | 83 |
| 5 | **265** | Piv | 1 | H | (i) 2.1 eq. **265**, 2.1 eq. *i*-PrMgCl, THF, 0 °C to RT<br>(ii) 1.0 eq. **272**, – 10 °C to RT | **266** | 43 |
| 6 | **265** | Piv | 1 | H | (i) 1.0 eq. **265**, 1.0 eq. *i*-PrMgCl, THF, 0 °C to RT<br>(ii) 1.0 eq. **272**, 1.0 eq. *i*-PrMgCl (pre-mixed), –10 °C to RT | **266** | 35 |
| 7 | **265** | Piv | 1 | TBS | (i) 1.0 eq. **265**, 1.0 eq. *i*-PrMgCl, THF, 0 °C to RT<br>(ii) 1.0 eq. **273**, 0 °C to RT | **276** | 89 |
| 8 | **265** | Piv | 1 | TMS | (i) 1.0 eq. **265**, 1.0 eq. *i*-PrMgCl, THF, 0 °C to RT<br>(ii) 1.0 eq. **274**, 0 °C to RT | **278** | 93 |

Switching the base to *i*-PrMgCl proved much more effective.[193] Deprotonation took place without decomposition of the pivalate ester and successful addition occurred in each case (entries 5 – 8). Addition to hydroxyacetone **272** proceeded cleanly though two equivalents of alkyne **265** were required. Excess alkyne **265** could be recovered from the reaction by a simple work-up procedure: after quenching the reaction and removal of THF *in vacuo*, extraction of the aqueous layer with petrol followed by ethyl acetate provided clean separation. Pure alkyne was recovered in the petrol fraction whilst the ethyl acetate fraction contained pure diol. However, diol **266** could not be obtained in yields greater than 43% and the throughput of material was deemed impractical for scale-up to multi-gram quantities.

In order to allow for a 1:1 ratio of reagents to be used, pre-deprotonation of hydroxyacetone prior to addition of the alkyne was investigated but this led to a decrease in yield (entry 6). In the end, addition to *O*-TMS hydroxyacetone **274** proved the most effective strategy. *O*-silyl ether **278** was easily deprotected on treatment with citric acid and the Ag-catalysed cyclisation progressed without the need for purification of any of the intermediates (Scheme 4.19).

**Scheme 4.19**: Large scale synthesis of diol **266**



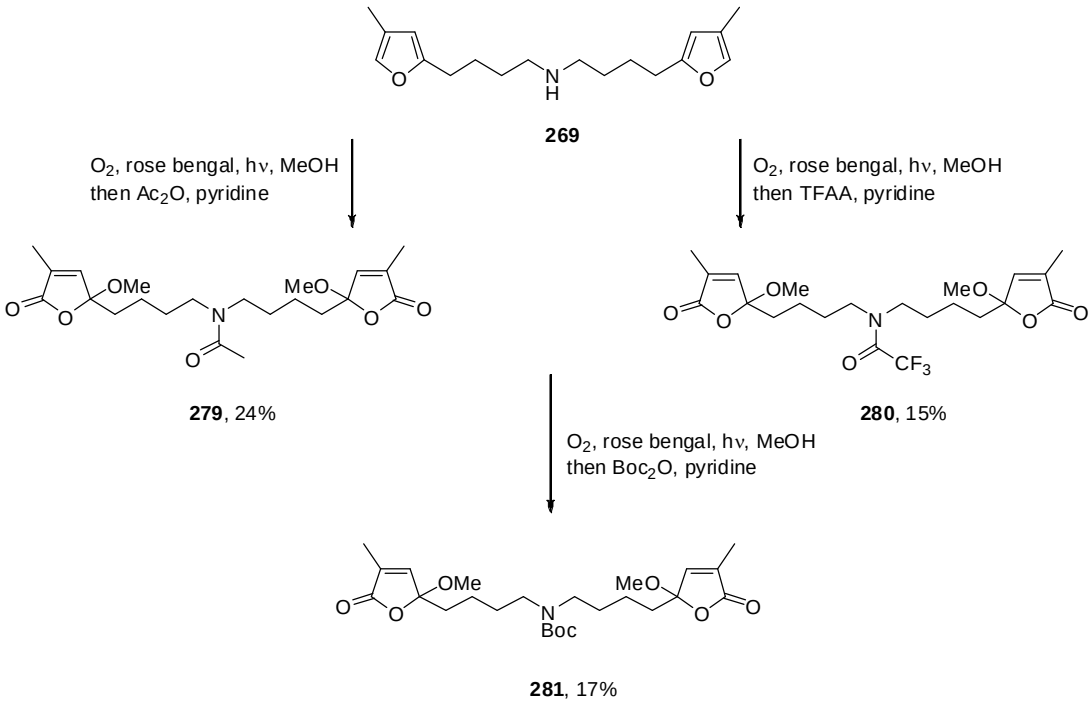

**265** **266**, 84%

Scale-up of the remainder of the route proceeded without event (*cf*. Scheme 4.16 and 4.17) and multi-gram quantities of amine dimer **269** were obtained ready for elaboration towards pandamarilactone-1 **1**.

## *4.4 Oxidation and cyclisation of difuran amine 269*

Oxidation of difuran amine **269** was initially attempted, in contrast to previous work, on the free amine (Scheme 4.20). Under our standard singlet oxygen oxidation conditions, the *N*-acetylated methoxybutenolide **279** was isolated in 24% yield.

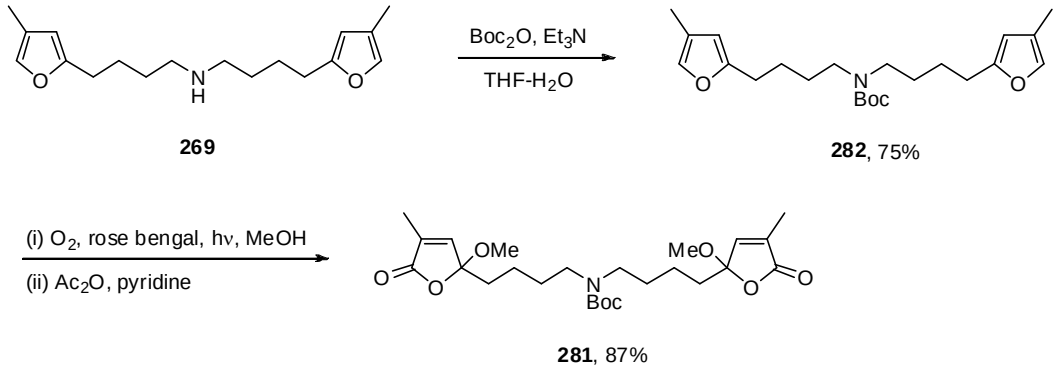
**Scheme 4.20**: Protecting group-free oxidation



Although the ability to perform the oxidation without the use of a protecting group is interesting, quite forcing conditions are required to cleave acetamide protecting groups and this may negate the convenience of being able to carry out the oxidation on the free amine. As an alternative, the use of TFAA to break down the hydroperoxide was explored. On addition of TFAA to the crude oxidation product, significant decomposition occurred and trifluoroacetamide methoxybutenolide **280** was obtained in only 15% yield.

Finally, we investigated the use of Boc anhydride in the oxidation work-up. Although *N*-Boc butenolide **281** was obtained, the low yield meant that we opted to perform the singlet oxygen oxidation of the pre-formed carbamate **282** instead (Scheme 4.21). Gratifyingly, oxidation of the *N*-Boc protected substrate proceeded smoothly to give methoxybutenolide **281** in 87% yield.

**Scheme 4.21**



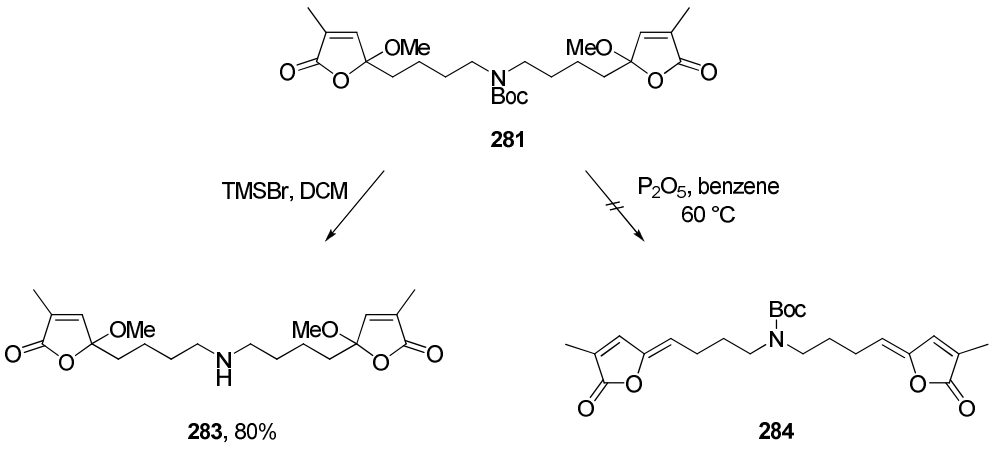

**269** **282**, 75%

**281**, 87%

Given the difficulties encountered in the spirocyclisation of *N*-ethyl butenolide **174** in our previous work (Chapter 2), we tentatively decided to aim towards the synthesis of pandanamine **32** before attempting elaboration to pandamarilactone-1 **1**. Accordingly, the elimination of methanol from methoxybutenolide **281** was investigated.

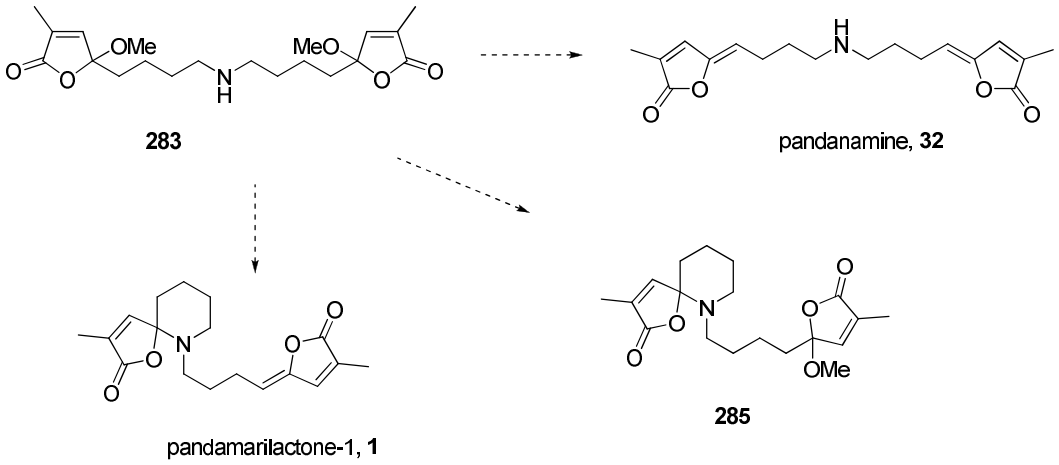
Subjecting butenolide **281** to $P_2O_5$ in benzene[194] gave mostly starting material along with a small amount of polymeric material. Based on work by the Burton group,[195] the elimination of methanol under TMSBr/DBU conditions was explored. Much to our delight, instead of providing γ-alkylidene butenolide **284**, treatment of dimethoxybutenolide **281** with TMSBr removed the Boc group and gave clean conversion to free amine **283**.

**Scheme 4.22**



Methoxybutenolide amine **283** was then screened against a number of mineral and Lewis acid reagents with a view to providing pandanamine **32**, methoxybutenolide spirocycle **285**, or indeed our primary target: pandamarilactone-1 **1** (Scheme 4.23).

**Scheme 4.23**




In stark contrast to *N*-ethyl butenolide **174** studied in our previous work, methoxybutenolide **283** proved to be remarkably stable. Exposure to a variety of Lewis acids only returned starting material, even at stoichiometric quantities and extended reaction times (Table 4.7). The addition of 4 Å molecular sieves to act as a methanol scavenger did nothing to promote reaction.

**Table 4.7**

| Entry | Conditions | Result |
|---|---|---|
| 1 | PTSA, 80 °C, benzene, 48 hr | no reaction |
| 2 | 20 mol% TMSOTf, DCM | decomposition |
| 3 | 20 mol% TMSOTf, 2,6-lutidine, DCM, –40 °C → 0 °C | no reaction |
| 4 | 1 eq. $Yb(OTf)_3$, THF, 10 d | no reaction |
| 5 | 1 eq. $Nd(OTf)_3$, MeCN, 4 Å MS, 10 d | no reaction |
| 6 | $H_2SO_4$ on silica,[196] PhMe, 100 °C | decomposition |
| 7 | $MgBr_2 \cdot OEt_2$, DCM, 4 Å MS | no reaction |

Inspired by the isolation conditions used to extract the *Pandanus* alkaloids,[0] and previous success to effect cyclisation, we investigated the use of $H_2SO_4$. In the first instance, methoxybutenolide **283** was subjected to 20 mol% of $H_2SO_4$ in DCM and the reaction left to run for 2 days. Although the majority of starting material was recovered, a small amount of pandamarilactonines-A **30** and B **31** were isolated. The reaction was repeated on a larger scale with 2 eq. $H_2SO_4$ and left to run for 5 days. Astonishingly, pandamarilactone-1 **1** was isolated together with methoxybutenolide spirocycle **285**, and pandamarilactonine-A,B **30**, **31**. This represents the first total synthesis of pandamarilactone-1 **1** and the first formal aza-Bohlmann cyclisation on a dialkyl amine substrate. Pandamarilactone-1 was obtained in 3% from 4-pentyn-1-ol over 13 linear steps.

**Scheme 4.24**: Synthesis of *Pandanus* alkaloids from methoxybutenolide **283**

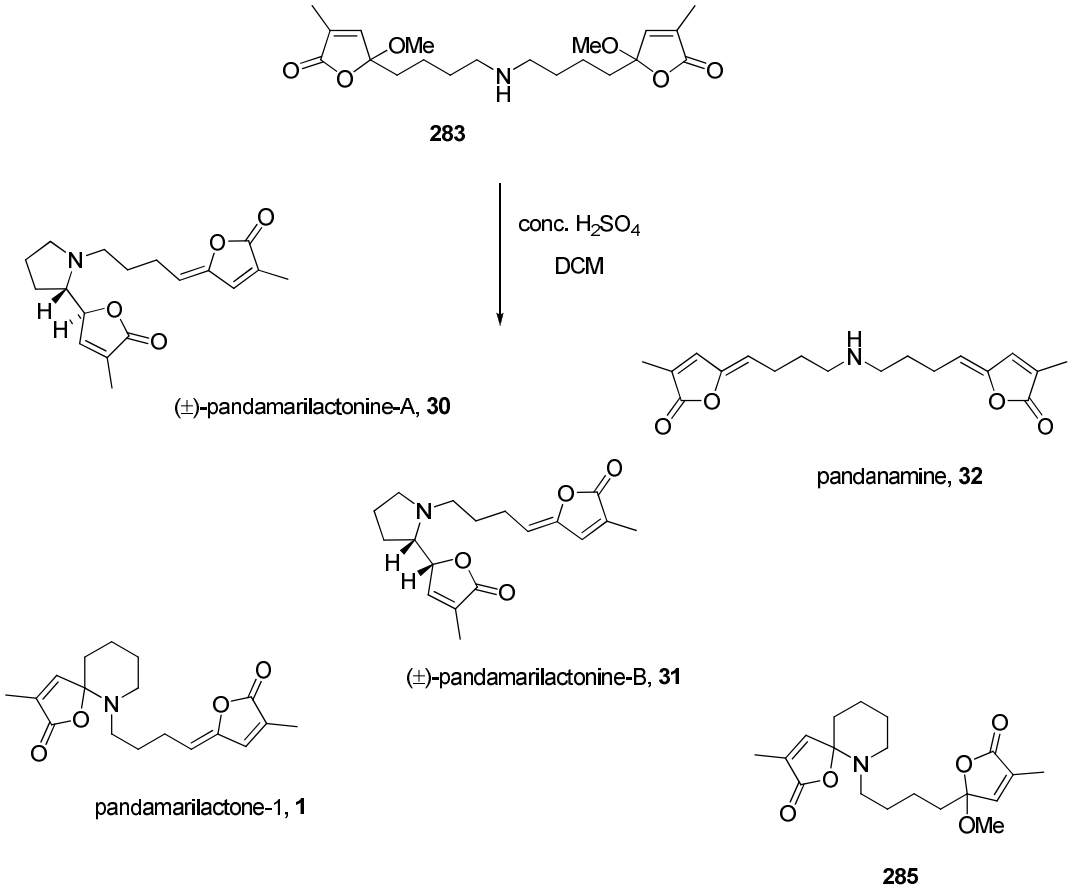
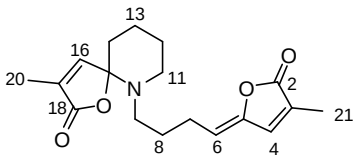



**Table 4.8**

| Conditions | Time | Result | Yield / % |
|---|---|---|---|
| 0.8 eq. conc. $H_2SO_4$, DCM | 2 h | (±)-pandamarilactonine-A **30** | 44 |
| | | (±)-pandamarilactonine-B **31** | 17 |
| 2.0 eq. conc. $H_2SO_4$, DCM | 2 d | (±)-pandamarilactonine-A **30** | 16 |
| | | (±)-pandamarilactonine-B **31** | 6 |
| | | (±)-pandamarilactone-1 **1** | 2 |
| | | **285** | 9 |
| 2.0 eq. conc. $H_2SO_4$, DCM | 5 d | (±)-pandamarilactonine-A **30** | 12 |
| | | (±)-pandamarilactonine-B **31** | 5 |
| | | (±)-pandamarilactone-1 **1** | 12 |
| | | **285** | 3 |

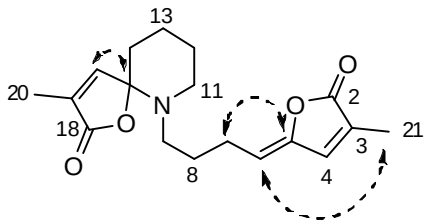
The $^{1}$H NMR spectrum of our synthetic pandamarilactone-1 **1** matches up well with the literature data, although the peaks for the piperidine ring protons **C**(11)–**C**(14) in the synthetic pandamarilactone-1 **1** suffer from broadening. The $^{13}$C NMR data matches up within 0.1 – 0.2 p.p.m., with the exception of **C**(9).

**Figure 4.1**: Comparison of NMR data with that reported by Nonato[0]




| | $^{1}$H NMR | | $^{13}$C NMR | |
|---|---|---|---|---|
| | **Reported** | **Found** | **Reported** | **Found** |
| **1** | - | - | - | - |
| **2** | - | - | **171.0** | **171.0** |
| **3** | - | - | **129.2** | **129.2** |
| **4** | **6.98** | **6.98** | **137.6** | **137.6** |
| **5** | - | - | **148.6** | **148.5** |
| **6** | **5.04** | **5.08** | **113.7** | **113.9** |
| **7** | **2.31** | **2.32** | **24.0** | **23.9** |
| **8** | **1.54** | **1.57 – 1.48** | **27.2** | **27.1** |
| **9** | **2.45** | **2.61 – 2.37** | **50.7** | **49.5** |
| **10** | - | - | - | - |
| **11** | **2.79** | **2.83 – 2.72** | **47.2** | **47.1** |
| **12** | **1.72** | **1.80 – 1.60** | **20.8** | **20.7** |
| **13** | **1.72** | **1.80 – 1.60** | **25.1** | **25.0** |
| **14** | **1.72** | **1.80 – 1.60** | **36.2** | **36.1** |
| **15** | - | - | **101.7** | **101.7** |
| **16** | **6.68** | **6.72** | **149.7** | **149.8** |
| **17** | - | - | **131.5** | **131.5** |
| **18** | - | - | **173.0** | **173.0** |
| **19** | - | - | - | - |
| **20** | **1.86** | **1.91** | **10.6** | **10.7** |
| **21** | **2.00** | **2.01** | **10.4** | **10.5** |

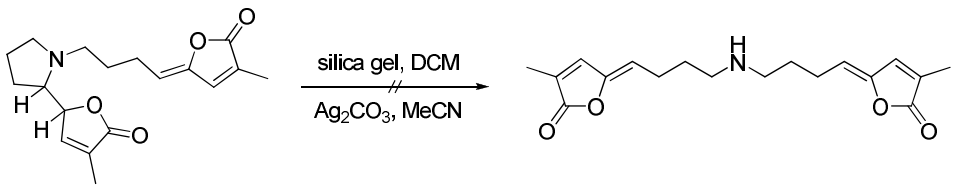
**Figure 4.2** HMBC correlations




We have requested a sample of natural pandamarilactone-1 **1** from Nonato and hope to confirm the identity of our synthetic pandamarilactone-1 **1** by performing a mixed sample NMR.

Trace amounts of what appeared to be pandanamine **32** were also recovered from the reaction yet this compound decomposed rapidly before sufficient data could be collected to verify its identity. Takayama *et al*. have reported the formation of pandanamine **32** from pandamarilactonines-A,B **30**, **31** by stirring with silica or $Ag_2CO_3$. In our hands, no conversion was observed and only starting material was recovered.

**Scheme 4.25**: Failed attempts to synthesise pandanamine from pandamarilactonine-A,B **30**, **31**




(±)-pandamarilactonine-A,B, **30**, **31** pandanamine, **32**

# Chapter 5 Conclusions and Further Work

## *5.1 Conclusions*

This project has demonstrated the development and scope of an aza-Bohlmann cyclisation process for the synthesis of [4.4]- and [4.5]-butenolide spiroaminoacetals. Two methods for the oxidation of 2-(ω-aminoalkyl)furan derivatives to the intermediate butenolide have been discussed: *m*-CPBA furnishes hydroxybutenolides whilst singlet oxygen generates methoxybutenolides. The latter method is considered superior due to the ease of isolation of the products and atom economy. In the simple furan derivatives, only *N*-sulfonamide protected 2-(3-aminoalkyl)- and 2-(4-aminoalkyl)furans tolerate the spirocyclisation conditions (30% aq. $H_2SO_4$).

However, upon application of our methodology to the synthesis of pandamarilactone-1 **1**, small amounts of the *N*-alkyl spiroaminoacetal natural product were generated by treatment of methoxybutenolide **283** with $H_2SO_4$ in DCM. The reaction was not selective and also produced a significant amount of the pyrrolidine natural products (±)-pandamarilactonine-A **30** and (±)-pandamarilactonine-B **31**.

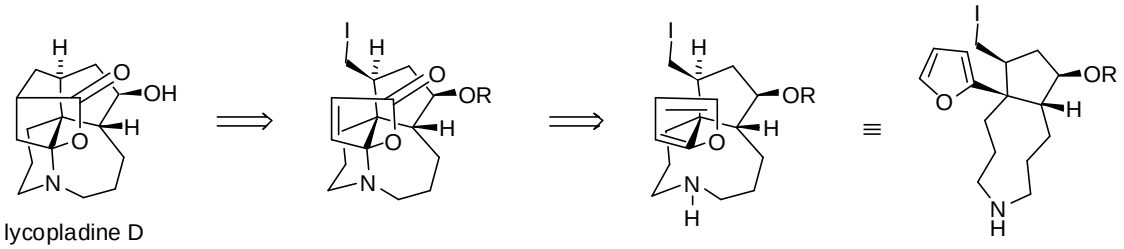
The synthesis and conformational preferences of 3-oxy-substituted spiroaminoacetals were investigated. The axial/equatorial preferences of 3-*O*-isovaleryl and 3-*O*-benzyl spiroaminoacetals were examined by an acid-catalysed thermodynamic relay of configuration between the spiro- and oxy- centres. Both oxy-substituents exhibited a preference for the axial site following equilibration in $CD_3CN$, which could be

rationalised by an attractive gauche interaction of the (C–H)σ–(C–O)σ* orbitals. The prospect of an analogous effect in the 3,4-diol spiroaminoacetal series warrants further investigation. To this end, the synthesis of 2-(β,γ-dihydroxy)aminofurans has been explored and could be envisaged as coming from a precursor aminoallylfuran *via* CM/Mitsunobu chemistry or an Overman rearrangement.

## *5.2 Further work*

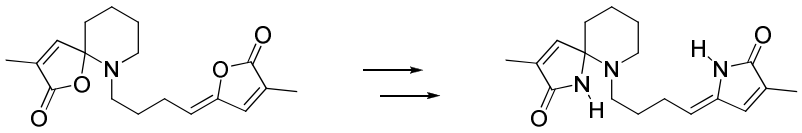
Based on the synthesis of pandamarilactone-1 **1**, the possibility of extending the aza-Bohlmann cyclisation methodology to a generalised synthesis of *N*-alkyl spiroaminoacetals is desirable. Whilst the yields and selectivity of the $H_2SO_4$/DCM conditions used in the pandamarilactone-1 **1** spirocyclisation are not synthetically attractive as a general method for the synthesis of spiroaminoacetals, application to niche targets such as lycopladine D could be investigated (Scheme 5.1).

**Scheme 5.1**



Furthermore, elaboration of the spiroaminoacetal moiety into spirolactams, for example the *Pandanus* alkaloid (±)-pandamarine **29**, could be investigated.

**Scheme 5.2**: Elaboration to spirolactams




pandamarilactone-1, **1** (±)-pandamarine, **29**

# Chapter 6 Experimental

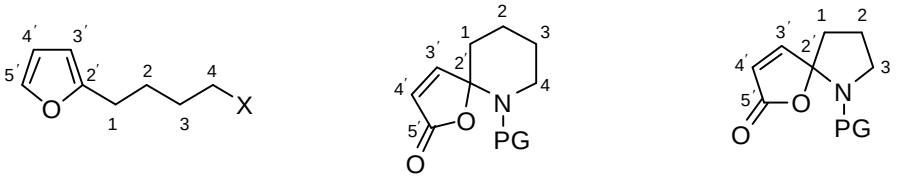
## *6.1 General experimental techniques*

**Melting points:** Melting points were recorded on a Griffin melting point apparatus and are uncorrected.

**Polarimetry:** Specific rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength of 589 nm and are quoted in $10^{-1}$ deg $cm^2$ $g^{-1}$. Concentrations are quoted in g 100 $mL^{-1}$.

**NMR spectra:** Proton ($^1H$) and carbon-13 ($^{13}C$) NMR spectra were recorded on Bruker AV400 and DPX400 spectrometers (400/100 MHz) or Bruker DRX500 or AVII500 spectrometers (500/125 MHz). Chemical shifts ($\delta_H$ or $\delta_C$) are reported in parts per million (ppm) downfield of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shifts, integrations and coupling constants using COSY, DEPT, HMBC, HMQC and HSQC data and comparison with spectra of related compounds. Multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), app. (apparent), m (multiplet) and br (broad). Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.5 Hz.

The numbering of atoms used to report $^{1}H$ and $^{13}C$ NMR data correspond to the following systems in the furan and spiroaminoacetal compounds.




All other compounds are numbered according to name unless otherwise specified.

**Infrared spectra:** Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as thin films on NaCl plates or using a diamond ATR module. Absorption maxima ($\nu_{max}$) are reported in wavenumbers ($cm^{-1}$) and are described as s (strong), m (medium), w (weak) or br (broad).

**Mass spectra:** Low resolution ESI mass spectra were recorded on a Micromass LCT Premier spectrometer (ESI) or using a Micromass GCT (CI). High resolution mass spectra (HRMS) were recorded either by the author using a Micromass GCT (CI) or by Colin Sparrow, Lingzhi Gong or James Wickens at the Chemistry Research Laboratory using a Micromass AutoSpec-oaTOF (CI or FI) or a Bruker Daltonics microTOF spectrometer (ESI). Mass to charge ratios (*m*/*z*) are reported in Daltons with percentage abundance in parentheses.

**Chromatography techniques:** Thin layer chromatography (TLC) was performed on Merck aluminium backed DC 60 $F_{254}$ 0.2 mm precoated plates. The spots were visualised by the quenching of ultraviolet light ($\lambda_{max}$ 254 nm) and/or staining with 5% anisaldehyde in ethanol or 5% potassium permanganate in 5% NaOH solution followed by heating. Flash

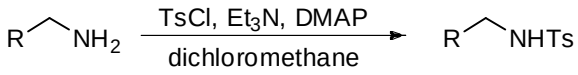
chromatography was performed using Merck 60 silica gel (particle size 40 – 63 Å) unless otherwise stated; the solvent system used is reported in parentheses. Basic alumina or neutral alumina (Sigma Aldrich, 58 Å, 10% deactivated) were used where specified.

**Solvents and reagents:** Solvents and commercially available reagents were dried and purified before use, as appropriate, using standard procedures. Ether, DCM, THF, MeCN and MeOH were obtained dry from solvent dispenser units having been passed through an activated alumina column under argon. Triethylamine was distilled from, and stored over, KOH. Petrol refers to the fraction of petroleum ether boiling at 30 – 40 °C, ether refers to diethyl ether.

**Reactions:** All non-aqueous reactions were carried out in oven-dried glassware under an atmosphere of argon where appropriate.

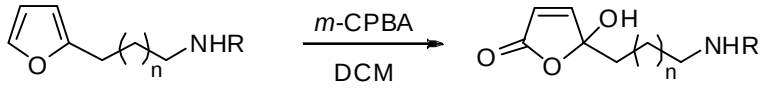
## *6.2 General procedures*

**General procedure A**




To a solution of amine (1.00 mmol) in dichloromethane (3 mL) at 0 °C was added triethylamine (2.20 mmol), 4-toluenesulfonyl chloride (2.00 mmol) and a crystal of 4-dimethylaminopyridine. The reaction was stirred at RT until complete as judged by TLC analysis (typically 10 h), then diluted with water (10 mL), the separated aqueous layer extracted with dichloromethane (3 × 10 mL), the combined organic layers washed with 1 N aq. HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the sulfonamide.

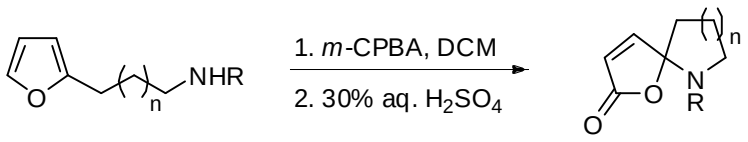
**General procedure B**




To a stirred solution of aminoalkylfuran (1.00 mmol) in dichloromethane (20 mL) at 0 °C was added *m*-chloroperbenzoic acid (2.20 mmol). The reaction was stirred at RT for 2h then sat. aq. $Na_2S_2O_3$ (50 mL) added. The layers were separated, the aqueous layer

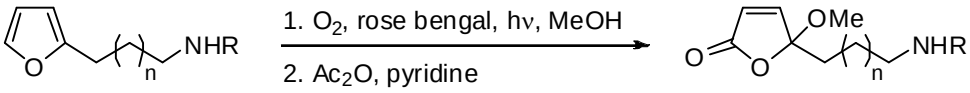
extracted with ethyl acetate (3 × 50 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the desired hydroxybutenolide.

**General procedure C**



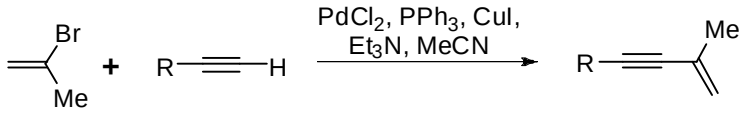

To a stirred solution of aminoalkylfuran (1.00 mmol) in dichloromethane (20 mL) at 0 °C was added *m*-chloroperbenzoic acid (2.20 mmol). The reaction was stirred at RT for 2h then sat. aq. $Na_2S_2O_3$ (50 mL) added. The layers were separated, the aqueous layer extracted with ethyl acetate (3 × 50 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. 30% aq. $H_2SO_4$ (3 mL) was added to the crude hydroxybutenolide and the reaction stirred at RT for 2 d. The reaction was basified with sat. aq. $NaHCO_3$ (100 mL) and the aqueous layer extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography to afford the desired spiroaminoacetal.

**General procedure D[197, 198]**




Oxygen was bubbled through a stirred solution of rose bengal ($1 \times 10^{-4}$ M) and aminoalkylfuran (1.00 mmol) in methanol (30 mL) for 2 min. Maintaining the stream of oxygen, the solution was cooled to 0 °C and irradiated with UV light (Exo-Terra PT-2056 200 W lamp) until complete consumption of the starting material had occurred as judged by TLC analysis (usually 10 min). The solvent was removed *in vacuo*, the resulting pink residue dissolved in pyridine (5 mL), acetic anhydride (94 µL, 102 mg, 1.00 mmol) added and the reaction stirred at RT for 15 min. The reaction was diluted with ethyl acetate (50 mL), the organic layer washed with water (50 mL), sat. aq. $CuSO_4$ (2 × 50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired methoxybutenolide.

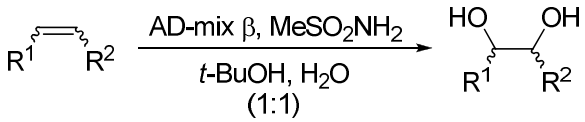
**General procedure E[199]**




To a stirred solution of 2-bromopropene (2.00 mmol) and triethylamine (3.00 mmol) in dry, degassed MeCN (4 mL) was added $PdCl_2$ (0.03 mmol), triphenylphosphine (0.05

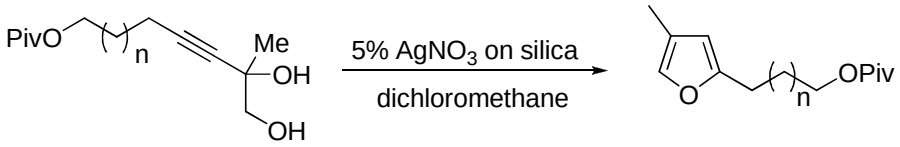
mmol) and CuI (0.04 mmol) sequentially. After stirring for 5 min at RT, the alkyne (1.00 mmol) was added and the reaction left to stir at RT. When the reaction was complete as judged by TLC, one of two work-ups was carried out: (i) for *O*-protected alkynols the reaction mixture was filtered through a pad of celite, the acetonitrile solution extracted with petrol (3 × 10 mL), and the petrol layer concentrated *in vacuo*; (ii) for alkynols with a free hydroxyl group the solvent was removed *in vacuo* and the residue partitioned between dichloromethane (20 mL) and 1N aq. HCl (20 mL). The separated aqueous layer was extracted with dichloromethane (2 × 20 mL), the combined organic layers washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the cross-coupled product.

**General procedure F[68]**



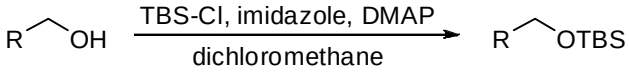

To a solution of olefin (0.594 mmol) in *t*-butanol/water (4 mL, 1:1) at 0 °C was added methanesulfonamide (0.594 mmol, 1 equiv.) and AD-mix β (832 mg, 0.2 mol% Os). The mixture was allowed to warm to RT and stirred for 20 h. Sodium sulfite (1.00 g) was added, the mixture stirred for 20 min, filtered through a pad of celite (washed with ethyl acetate) and concentrated *in vacuo*. Purification by flash chromatography (97:3, dichloromethane/methanol) afforded the diol.

**General procedure G[189]**




To a solution of diol (1.00 mmol) in dichloromethane (7.0 mL) at RT was added 5% $AgNO_3$ on $SiO_2$ (0.10 mmol). The reaction mixture was stirred in the absence of light until TLC analysis showed complete consumption of starting material (typically 2 h) then filtered through a short pad of celite and concentrated *in vacuo* to afford the desired *O*-pivaloyl alkylfuran.

**General procedure H[200]**



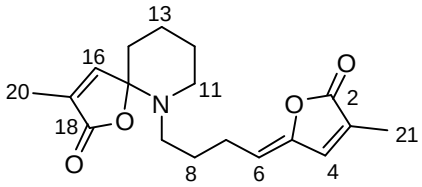

To a solution of alcohol (10.0 mmol) in dichloromethane (20 mL) at 0 °C was added *t*-butyldimethylsilyl chloride (11.0 mmol), imidazole (20.0 mmol) and 4-dimethylaminopyridine (0.10 mmol). After stirring at RT for 2 h, the reaction was diluted with sat. aq. $NH_4Cl$ (20 mL), the separated aqueous layer extracted with dichloromethane (2 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the silyl ether.

**General procedure I**

Equilibration experiment: To a solution of spiroaminoacetal (50 µmol) in $CD_3CN$ (0.65 mL) was added 40% aq. HI (1 mol%). The reaction was monitored by $^1H$ NMR spectroscopy.

## *6.3 Compounds*

**Pandamarilactone-1 (1)**

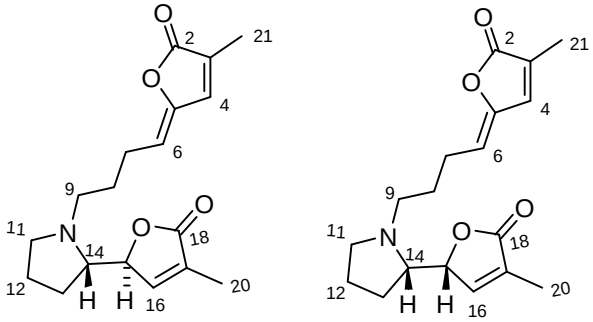



Conc. $H_2SO_4$ (20 mg, 0.21 mmol) was added to a solution of methoxybutenolide **283** (100 mg, 0.262 mmol) in dichloromethane (2 mL) and the reaction stirred at RT for 5 d. The reaction was diluted with sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (1:1, petrol/ether → 98:2, EtOAc/MeOH) afforded the title compound as a colourless oil (10 mg, 12 %); $R_f$ 0.29 (ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2941s, 2867s, 1763s, 1444m, 1308m, 1261s, 1159m, 1055m; $\delta_H$ (500 MHz, $CDCl_3$) 6.98 (1H, q, *J* 1.5, C(4)**H**), 6.72 (1H, q, *J* 1.5, C(16)**H**), 5.08 (1H, t, *J* 8.0, C(6)**H**), 2.83 – 2.72 (2H, m, C(11)$\mathbf{H_2}$), 2.61 – 2.37 (2H, m, C(9)$\mathbf{H_2}$), 2.32 (2H, q, *J* 7.5, C(7)$\mathbf{H_2}$), 2.01 (3H, s, C(21)$\mathbf{H_3}$), 1.91 (3H, d, *J* 1.5, C(20)$\mathbf{H_3}$), 1.80 – 1.60 (6H, m, C(12)$\mathbf{H_2}$, C(13)$\mathbf{H_2}$ and C(14)$\mathbf{H_2}$), 1.57 – 1.48 (2H, m, C(8)$\mathbf{H_2}$); $\delta_c$ (125 MHz, $CDCl_3$) 173.0 (**C**(18)), 171.0 (**C**(2)), 149.8 (**C**(16)), 148.5 (**C**(5)), 137.6 (**C**(4)), 131.5 (**C**(17)), 129.2 (**C**(3)), 113.9 (**C**(6)), 101.7 (**C**(15)), 49.5 (**C**(9)), 47.1 (**C**(11)), 36.1 (**C**(14)), 27.1 (**C**(8)), 25.0 (**C**(13)), 23.9 (**C**(7)), 20.7 (**C**(12)), 10.7 (**C**(20)), 10.5 (**C**(21)).

HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NNaO_4$ $[M+Na]^+$ : 340.1519

Found : 340.1519

**(±)-Pandamarilactone-A-B,[33] (±)-30 and (±)-31**




**(±)-30** **(±)-31**

Conc. $H_2SO_4$ (6 mg, 61.2 µmmol) was added to a solution of methoxybutenolide **283** (28 mg, 73.4 µmol) in dichloromethane (1 mL) and the reaction stirred at RT for 2 h. The reaction was diluted with sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc → 95:5, EtOAc/MeOH) to afford an inseparable mixture of (±)-pandamarilactonine-A **30** and (±)-pandamarilactonine-B **31** (**30**/**31** *d.r.*, 70:30) as a colourless oil (14 mg, 61 %); $R_f$ 0.16 (EtOAc); $\nu_{max}$ (thin film)/$cm^{-1}$ 2925m, 2821m, 1757s, 1673m, 1052s.

HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_4$ $[M+H]^+$ : 318.1700

Found : 318.1700

**NMR data for (±)-Pandamarilactonine-A ((±)-30)**

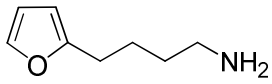
$\delta_H$ (500 MHz, $CDCl_3$) 7.09 (1H, quin, *J* 1.5, C(16)**H**), 7.00 (1H, s, C(4)**H**), 5.18 (1H, t, *J* 8.0, C(6)**H**), 4.82 – 4.78 (1H, m, C(15)**H**), 3.15 – 3.09 (1H, m, C(11)**H**H'), 2.95 – 2.86 (1H, m, C(9)**H**H', overlapping), 2.84 (1H, dt, *J* 9.0, 5.5, C(14)**H**, overlapping), 2.48 – 2.40 (1H, m, C(9)H**H'**, overlapping), 2.43 (2H, dt, *J* 8.0, 7.5, C(7)$\mathbf{H_2}$, overlapping), 2.29 – 2.18 (1H, m, C(11)H**H'**), 1.99 (3H, s, C(21)$\mathbf{H_3}$), 1.93 (3H, d, *J* 1.5, C(20)$\mathbf{H_3}$), 1.84 – 1.69 (2H, m, C(12)**H**H' and C(13)**H**H'), 1.68 – 1.58 (3H, m, C(8)$\mathbf{H_2}$ and C(13)H**H'**), 1.46 – 1.40 (1H, m, C(12)H**H'**); $\delta_c$ (125 MHz, $CDCl_3$) 174.3 (**C**(18)), 171.1 (**C**(2)), 148.5 (**C**(5)), 147.0 (**C**(16)), 137.7 (**C**(4)), 131.2 (**C**(17)), 129.1 (**C**(3)), 114.1 (**C**(6)), 83.4 (**C**(15)), 65.3 (**C**(14)), 55.0 (**C**(9)), 54.1 (**C**(11)), 28.3 (**C**(8)), 25.7 (**C**(12)), 23.9 (**C**(7)), 23.8 (**C**(13)), 10.7 (**C**(20)), 10.5 (**C**(21)).

**NMR data for (±)-Pandamarilactonine-B ((±)-30)**

$\delta_H$ (500 MHz, $CDCl_3$) 7.06 (1H, quin, *J* 1.5, C(16)**H**), 7.00 (1H, s, C(4)**H**), 5.17 (1H, t, *J* 8.0, C(6)**H**), 4.72 (1H, dt, *J* 5.5, 1.5, C(15)**H**), 3.15 – 3.09 (1H, m, C(11)**H**H'), 2.74 – 2.68 (2H, m, C(9)**H**H' and C(14)**H**, overlapping), 2.48 – 2.40 (1H, m, C(9)H**H'** and C(7)**H**H'), 2.39 – 2.32 (1H, m, C(7)H**H'**), 2.29 – 2.18 (1H, m, C(11)H**H'**), 2.00 (3H, s, C(21)$\mathbf{H_3}$), 1.93 (3H, d, *J* 1.5, C(20)$\mathbf{H_3}$), 1.84 – 1.69 (4H, m, C(12)$\mathbf{H_2}$ and C(13)$\mathbf{H_2}$), 1.68 – 1.58 (2H, m, C(8)$\mathbf{H_2}$); $\delta_c$ (125 MHz, $CDCl_3$) 174.3 (**C**(18)), 171.1 (**C**(2)), 148.5 (**C**(5)), 147.5 (**C**(16)), 137.7 (**C**(4)), 130.8

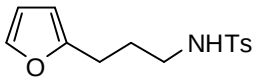
(**C**(17)), 129.1 (**C**(3)), 114.1 (**C**(6)), 83.4 (**C**(15)), 66.3 (**C**(14)), 55.7 (**C**(9)), 54.2 (**C**(11)), 28.4 (**C**(8)), 27.1 (**C**(12)), 24.0 (**C**(7)), 23.9 (**C**(13)), 10.8 (**C**(20)), 10.5 (**C**(21)).

**4-(Furan-2-yl)butan-1-amine[201] (118)**




To a stirred suspension of $LiAlH_4$ (2.22 g, 55.5 mmol, 95% by weight) in ether (100 mL) at 0 °C was added nitrile **287** (5.00 g, 37.0 mmol) in ether (30 mL). The reaction was stirred at RT for 0.5 h then cooled to 0 °C and water (2.2 mL), 15% aq. NaOH (2.2 mL), and a further portion of water (7.0 mL) added sequentially. The mixture was stirred at RT for 10 min, filtered through a pad of celite then concentrated *in vacuo* to afford the title compound as a yellow oil (4.89 g, 95%); $\nu_{max}$ (thin film)/$cm^{-1}$ 2936s, 2361w, 1572s, 1506s, 1326m, 1147m, 1007m, 730s; $\delta_H$ (400 MHz, $CDCl_3$) 7.26 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.24 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.95 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 2.67 (2H, t, *J* 7.0, C(4)$\mathbf{H_2}$), 2.61 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 1.64 (2H, app. quintet, *J* 7.5, C(2)$\mathbf{H_2}$), 1.46 (2H, quintet, *J* 7.5, C(3)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 156.1 (**C**(2')), 140.7 (**C**(5')), 110.0 (**C**(4')), 104.7 (**C**(3')), 41.9 (**C**(4)), 33.3 (**C**(3)), 27.8 (**C**(1)), 25.4 (**C**(2)).

**_N_-(3-Furan-2-yl-propyl)-4-methylbenzenesulfonamide[202] (119)**

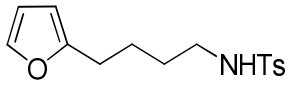



To a solution of *p*-toluenesulfonamide (6.75 g, 39.4 mmol) in dry DMSO (20 mL) was added KOH (1.25 g, 22.2 mmol). The reaction was stirred at 50 °C for 2 h, iodide **286** (4.04 g, 17.1 mmol) added, and the reaction stirred for a further 1.5 h at 50 °C. After cooling to RT, the reaction was diluted with water (100 mL) and the aqueous layer extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (2 × 150 mL), brine (50 mL), and dried over $MgSO_4$. Purification by flash chromatography (3:1→1:1, petrol/ethyl acetate) afforded the title compound as a pale yellow oil (3.74 g, 78%); $R_f$ 0.27 (1:1, petrol/ether), $\nu_{max}$ (thin film)/$cm^{-1}$ 3284br, 2929m, 1598m, 1434m, 1325s, 1159s, 1094s; $\delta_H$ (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.0, Ar**H**), 7.30 (2H, d, *J* 8.0, Ar**H)**, 7.27 – 7.26 (1H, m, C(5')**H**), 6.26 – 6.24 (1H, m, C(4')**H**), 5.94 (1H, d, *J* 3.0, C(3')**H**), 4.75 (1H, t, *J* 5.5, N**H**), 2.97 (2H, q, *J* 6.5, C(3)**$H_2$**), 2.63 (2H, t, *J* 7.0, C(1)**$H_2$**), 2.43 (3H, s, ArC**$H_3$**), 1.80 (2H, app. quin, *J* 7.0, C(2)**$H_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 154.5 (**C**(2')), 143.4 (Ar), 141.1 (**C**(5')), 136.9 (Ar), 129.7 (Ar), 127.1 (Ar), 110.2 (**C**(4')), 105.5 (**C**(3')), 42.4 (**C**(3)), 28.1 (**C**(1)), 24.9 (**C**(2)), 21.6 (Ar**C**$H_3$);

HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NO_3S$ $[M+Na]^+$ : 302.0821

Found : 302.0820

**_N_-[4-(Furan-2-yl)butyl]-4-methylbenzenesulfonamide[78] (120)**

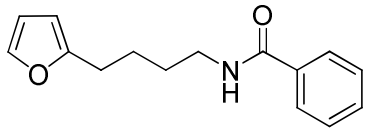



Synthesised by *general procedure A* from amine **118** (250 mg, 1.80 mmol). Purification by flash chromatography (4:1 → 1:1, petrol/ether) afforded the title compound as a colourless oil (481 mg, 91%); $R_f$ 0.31 (1:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3284br, 2942m, 2867m, 1598m, 1428m, 1325s, 1159s, 1094s; $\delta_H$ (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.0, Ar**H**), 7.31 (2H, d, *J* 8.0, Ar**H**), 7.29 – 7.27 (1H, m, C(5')**H**), 6.25 (1H, dd , *J* 3.0, 2.0, C(4')**H**), 5.94 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 4.37 (1H, t, *J* 6.0, N**H**), 2.95 (2H, app. q, *J* 7.0, C(4)**$H_2$**), 2.58 (2H, t, *J* 7.5, C(1)**$H_2$**), 2.44 (3H, s, ArC**$H_3$**), 1.67 – 1.58 (2H, m, C(2)**$H_2$**), 1.55 – 1.46 (2H, m, C(3)**$H_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 155.1 (**C**(2')), 143.3 (Ar), 140.8 (**C**(5')), 136.9 (Ar), 129.7 (Ar), 127.1 (Ar), 110.1 (**C**(4')), 105.0 (**C**(3')), 42.9 (**C**(4)), 28.9 (**C**(3)), 27.3 (**C**(1)), 24.9 (**C**(2)), 21.5 (Ar**C**$H_3$).

HRMS ($ESI^+$) *m/z* calcd for $C_{15}H_{19}NNaO_3S$ $[MNa]^+$ : 316.0978

Found : 316.0977

***N*-(4-(Furan-2-yl)butyl)benzamide**[78] (**122**)

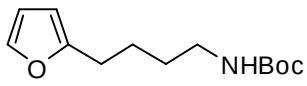


To a stirred biphasic mixture of amine **118** (150 mg, 1.08 mmol) in dichloromethane (6 mL) and NaOH (60 mg, 1.50 mmol) in water (3 mL) at 0 °C was added benzoyl chloride (151 µL, 183 mg, 1.30 mmol). The reaction was stirred at RT for 3.5 h, then diluted with water (25 mL) and the aqueous layer extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the title compound as a white solid (194 mg, 74%); $R_f$ 0.24 (1:1, petrol/ether); m.p. 50 – 53 °C (Lit. 51 – 53 °C); $\nu_{max}$ (thin film)/$cm^{-1}$ 3333br, 2929m, 2865m, 2244w, 1638s, 1541s, 1310m; $\delta_H$ (400 MHz, $CDCl_3$) 7.79 – 7.74 (2H, m, Ar**H**), 7.51 – 7.43 (1H, m, Ar**H**), 7.43 – 7.35 (2H, m, Ar**H**), 7.30 – 7.29 (1H, m, C(5')**H**), 6.53 (1H, br s, N**H**), 6.29 – 6.26 (1H, m, C(4')**H**), 6.00 – 5.96 (1H, m, C(3')**H**), 3.45 (2H, q, *J* 7.0, C(4)**$H_2$**), 2.66 (2H, t, *J* 7.0, C(1)**$H_2$**), 1.78 – 1.58 (4H, m, C(2)**$H_2$** and C(3)**$H_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 167.7 (**C**=O), 155.7 (**C**(2')), 140.8 (**C**(5')), 134.7 (Ar), 131.3 (Ar), 128.5 (Ar), 126.9 (Ar), 110.1 (**C**(4')), 105.0 (**C**(3')), 39.8 (**C**(4)), 29.1 (**C**(3)), 27.6 (**C**(1)), 25.5 (**C**(2)); *m/z* ($ESI^+$) 302 ($MNH_4^+$·MeCN, 100%), 266 ($MNa^+$, 40%).

HRMS ($ESI^+$) *m/z* calcd for $C_{15}H_{17}NNaO_2$ $[MNa]^+$ : 266.1151

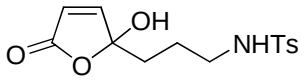
Found : 266.1144

**_tert_-Butyl 4-(furan-2-yl)butylcarbamate[78] (123)**



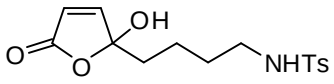

Di-*tert*-butyl dicarbonate (12.3 g, 56.4 mmol) was added to a solution of amine **118** (7.00 g, 50.3 mmol) and triethylamine (14.4 mL, 10.4 g, 103 mmol) in dichloromethane (100 mL) at 0 °C. The reaction stirred at RT for 16 h, diluted with water (100 mL) and the separated aqueous layer extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with 1M aq. HCl (100 mL), sat. aq. $NaHCO_3$ (100 mL), brine (100 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:1, petrol/ether) afforded the title compound as a colourless oil (11.07 g, 92%); $R_f$ 0.40 (3:1, petrol/ether), $\delta_H$ (400 MHz, $CDCl_3$) 7.28 (1H, d, *J* 2.0, C(5')**H**), 6.26 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.97 (1H, d, *J* 3.0, C(3')**H**), 4.50 (1H, br s, N**H**), 3.13 (2H, q, *J* 6.5, C(4)$\mathbf{H_2}$), 2.64 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 1.67 (2H, app. quin, *J* 7.0, C(2)$\mathbf{H_2}$), 1.52 (2H, app. quin, *J* 7.0, C(3)$\mathbf{H_2}$), 1.44 (9H, s, C(C$\mathbf{H_3}$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 156.0 (**C**=O), 155.8 (**C**(2')), 140.8 (**C**(5')), 110.1 (**C**(4')), 104.9 (**C**(3')), 79.0 (**C**$(CH_3)_3$), 40.3 (**C**(4)), 29.5 (**C**(3)), 28.4 (C(**C**$H_3)_3$), 27.6 (**C**(1)), 25.3 (**C**(2)).

**_N_-(3-(2-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)propyl)-4-methylbenzenesulfonamide[78] (124)**




Synthesised by *general procedure B* from sulfonamide **119** (100 mg, 0.358 mmol). Purification by flash chromatography (1:1, petrol/ethyl acetate) afforded the *title compound* as a yellow oil (94 mg, 84%); $R_f$ 0.11 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3287br, 2930s, 2256m, 2256w, 1756s, 1426s, 1324s, 1158s; $\delta_H$ (500 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.0, Ar**H**), 7.32 (2H, d, *J* 8.0, Ar**H**), 7.22 (1H, m, C(3')**H**), 6.12 (1H, d, *J* 6.0, C(4')**H**), 5.06 (1H, t, *J* 6.0, N**H**), 2.99 (2H, q, *J* 6.5, C(3)$\mathbf{H_2}$), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.06 – 2.03 (2H, m, C(1)$\mathbf{H_2}$), 1.72 – 1.63 (2H, m, C(2)$\mathbf{H_2}$); $\delta_C$ (125 MHz, $CDCl_3$) 171.3 (**C**(5')), 154.4 (**C**(3')), 143.6 (Ar), 136.6 (Ar), 129.8 (Ar), 127.0 (Ar), 123.2 (**C**(4')), 107.8 (**C**(2')), 42.6 (**C**(3)), 36.7 (**C**(1)), 23.6 (**C**(2)), 21.5 (Ar**C**$H_3$).

**_N_-(4-(2-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butyl)-4-methylbenzenesulfonamide[78] (125)**



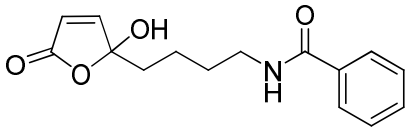

Synthesised by *general procedure B* from sulfonamide **120** (200 mg, 0.682 mmol). Purification by flash chromatography (1:1 → 2:1, ethyl acetate/petrol) afforded the *title compound* as a yellow oil (193 mg, 87%); $R_f$ 0.13 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin

film)/cm$^{-1}$ 3286s, br, 2950s, 2872m, 2256w, 1745s, 1598m, 1426s, 1323s, 1157s, 1093s; $\delta_H$ (500 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.0, Ar**H**), 7.31 (2H, d, *J* 8.0, Ar**H**), 7.32 (1H, m, C(3')**H**), 6.13 (1H, d, *J* 6.0, C(4')**H**), 4.71 (1H, t, *J* 6.0, N**H**), 2.96 (2H, q, *J* 7.0, C(4)**H$_2$**), 2.44 (3H, s, ArC**H$_3$**), 1.91 – 1.89 (2H, m, C(1)**H$_2$**), 1.60 – 1.42 (4H, m, C(2)**H$_2$** and C(3)**H$_2$**); $\delta_C$ (125 MHz, $CDCl_3$) 170.3 (**C**(5')), 154.3 (**C**(3')), 142.6 (Ar), 136.7 (Ar), 129.8 (Ar), 127.0 (Ar), 123.2 (**C**(4')), 107.8 (**C**(2')), 42.6 (**C**(4)), 36.7 (**C**(1)), 29.1 (**C**(3)), 21.5 (Ar**C**H$_3$), 20.2 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NNaO_5S$ $[M+Na]^+$ : 348.0876

Found : 348.0874

***N*-(4-(2-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butyl)benzamide[78] (127)**



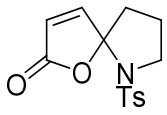

Synthesised according to *general procedure B* from amide **122** (10 mg, 41.1 μmol). Purification by flash chromatography (3:1, ethyl acetate/petrol) afforded the *title compound* as a colourless oil (8 mg, 71%); $R_f$ 0.28 (4:1, ethyl acetate/petrol); $\nu_{max}$ (thin film)/cm$^{-1}$ 3371br, 2958s, 1744s, 1630s, 1544s, 1259m, 1090m; $\delta_H$ (500 MHz, $(CD_3)_2CO$) 7.89 – 7.86 (2H, m, Ar**H**), 7.80 (1H, br s, N**H**), 7.54 – 7.43 (4H, m, C(3')**H** and Ar**H**), 6.12 (1H, d, *J* 6.0, C(4')**H**), 3.49 – 3.37 (2H, m, C(4)**H$_2$**), 2.05 – 1.95 (2H, m, C(1)**H$_2$**), 1.67 (2H, quin., *J* 7.0, C(3)**H$_2$**), 1.57 – 1.45 (2H, m, C(2)**H$_2$**); $\delta_C$ (125 MHz, $(CD_3)_2CO$) 171.1 (**C**(5')),

167.3 (N**C**=O), 156.2 (**C**(3')), 136.1 (Ar), 131.8 (Ar), 129.1 (Ar), 127.9 (Ar), 123.2 (**C**(4')), 108.9 (**C**(2')), 40.0 (**C**(4)), 38.1 (**C**(1)), 30.3 (**C**(3)), 21.7 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NNaO_4$ $[M+Na]^+$ : 298.1050

Found : 298.1039

**6-Tosyl-1-oxa-6-azaspiro[4.4]non-3-en-2-one[78] (128)**

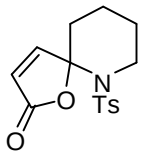



Synthesised by *general procedure C* from sulfonamide **119** (400 mg, 1.43 mmol). Purification by flash chromatography (3:1 → 1:1, petrol/ethyl acetate) afforded the *title compound* as brown oil (302 mg, 72%); $R_f$ 0.15 (1:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3102m, 2958s, 2925s, 1760s, 1597m, 1453m, 1349s, 1160s, 1134s, 1055s; $\delta_H$ (400 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.5, Ar**H**), 7.44 (1H, d, *J* 5.5, C(3')**H**), 7.31 (2H, d, *J* 8.5, Ar**H**), 6.16 (1H, d, *J* 5.5, C(4')**H**), 3.74 – 3.71 (1H, m, C(3)**H**H'), 3.57 – 3.50 (1H, m, C(3)H**H'**), 2.42 (3H, s, ArC**$H_3$**), 2.38 – 2.29 (1H, m, C(1)**H**H'), 2.10 – 2.02 (2H, m, C(2)**$H_2$**), 2.01 – 1.94 (1H, m, C(1)H**H'**); $\delta_C$ (100 MHz, $CDCl_3$) 170.0 (**C**(5')), 154.8 (**C**(3')), 144.3 (Ar), 135.3 (Ar), 129.7 (Ar), 127.6 (Ar), 121.8 (**C**(4')), 101.2 (**C**(2')), 49. 5 (**C**(3)), 39.2 (**C**(1)), 21.7 (Ar**C**$H_3$), 21.6 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NNaO_4S$ $[M+Na]^+$ : 316.0614

Found : 316.0611

**6-(4-Methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one[78] (129)**

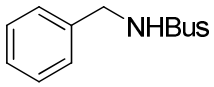



Synthesised by *general procedure C* from sulfonamide **120** (50 mg, 0.170 mmol). Purification by flash chromatography (3:1, petrol/ethyl acetate) afforded the *title compound* as a colourless solid (38 mg, 72 %); $R_f$ 0.61 (1:1, petrol/ethyl acetate); m.p. 118 – 120 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2950m, 1770s, 1598m, 1346s, 1165s; $\delta_H$ (400 MHz, $CDCl_3$) 7.79 (1H, d, *J* 5.5, C(3')**H**), 7.49 (2H, d, *J* 8.0, Ar**H**), 7.29 (2H, d, *J* 8.0, Ar**H**), 5.97 (1H, d, *J* 5.5, C(4')**H**), 4.13 – 4.07 (1H, m, C(4)**H**H'), 3.08 (1H, td, *J* 11.5, 2.5, C(4)H**H'**), 2.41 (3H, s, ArC**$H_3$**), 2.04 – 1.96 (1H, m, C(1)**H**H'), 1.94 – 1.71 (4H, m, C(2)**$H_2$** and C(3)**$H_2$**), 1.58 – 1.52 (1H, m, C(1)H**H'**); $\delta_C$ (100 MHz, $CDCl_3$) 169.9 (**C**(5')), 157.9 (**C**(3'), 144.4 (Ar), 135.3 (Ar), 129.9 (Ar), 127.3 (Ar), 118.2 (**C**(4')), 95.5 (**C**(2')), 45.7 (**C**(4)), 37.6 (**C**(1)), 24.5 (**C**(3)), 21.6 (Ar**C**$H_3$), 20.1 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{15}H_{17}NNaO_4S$ $[M+Na]^+$ : 330.0770

Found : 330.0767

**_N_-Benzyl-2-methylpropane-2-sulfonamide (142)**

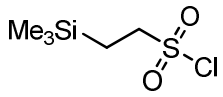



*m*-Chloroperbenzoic acid (162 mg, 0.561 mmol, 60% by weight) was added to a stirred solution of sulfinamide **288** (89 mg, 0.42 mmol) in dichloromethane (1 mL) at 0 °C. The reaction was stirred at RT for 2 h then sat. aq. $Na_2S_2O_3$ (5 mL) and sat. aq. $NaHCO_3$ (5 mL) added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless solid (94 mg, 98%); $R_f$ 0.18 (2:1, petrol/ether); m.p. 54 – 56 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3285s, 2972m, 1764s, 1454s, 1217s, 1129s; $\delta_H$ (400 MHz, $CDCl_3$) 7.37 – 7.26 (5H, m, Ar**H**), 4.36 (1H, d, *J* 6.0, PhC**H$_2$**), 4.30 (1H, t, *J* 6.0, N**H**), 1.42 (9H, s, C(C**H$_3$**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 137.8 (Ar), 128.8 (Ar), 127.9 (Ar), 127.7 (Ar), 60.0 (**C**$(CH_3)_3$), 48.5 (Ph**C**$H_2$), 24.3 (C(**C**$H_3)_3$).

HRMS (ESI$^+$) *m/z* calcd for $C_{11}H_{17}NNaO_2S$ $[MNa]^+$ : 250.0872

Found : 250.0874

**2-(Trimethylsilylethane)sulfonyl Chloride[87] (145)**

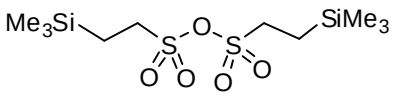


**Method A:** To a stirred solution of $PPh_3$ (2.54 g, 9.69 mmol) in dichloromethane (12 mL) at 0°C was added $SO_2Cl_2$ (865 µL, 1.44 g, 10.7 mmol). The reaction was allowed to warm to RT, 2-(trimethylsilyl)ethanesulfonic acid sodium salt (1.00 g, 4.85 mmol) added, and the reaction stirred for a further 3 h at RT. Ether in petrol (1:1, 500 mL) was added, the reaction allowed to stand until the solution was clear (1 h), the precipitate filtered off and the filtrate concentrated *in vacuo*. The residue was filtered through a silica plug (3:1, petrol/ethyl acetate) and concentrated *in vacuo* to afford the title compound as a colourless oil (662 mg, 68%).

**Method B:** 2-(Trimethylsilyl)ethanesulfonic acid sodium salt (1.00 g, 4.85 mmol) was suspended in $CCl_4$ (6.5 mL) and $PCl_5$ (3.00 g, 14.4 mmol) added in portions at 0°C. After stirring for 2 h at RT the reaction mixture was poured onto ice water (10 mL) and extracted with dichloromethane (3 × 15mL). The organic layer was washed with sat. aq. $NaHCO_3$ solution (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by Kugelrohr distillation (80-90°C at 4 Torr) afforded the title compound as a colourless oil (448 mg, 46%).

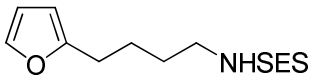
$\nu_{max}$ (thin film)/$cm^{-1}$ 2957s, 2520w, 2350w, 2317w, 1370s, 1254s, 1176s; $\delta_H$ (400 MHz, $CDCl_3$) 3.64 – 3.58 (2H, m, C**H₂**$SO_2$), 1.34 – 1.29 (2H, m, C**H₂**Si), 0.12 (9H, s, Si(C**H₃**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 63.4 (**C**$H_2SO_2$), 11.9 (**C**$H_2$Si), –2.0 (Si(**C**$H_3$)$_3$).

**2-(Trimethylsilyl)ethanesulfonic anhydride[87] (146)**



Formed as a by-product from the synthesis of chloride **145** by Method B, affording the title compound as a colourless oil (402 mg, 24%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2985s, 2903m, 1691m, 1371s, 1255s, 1176s, 1060s; $\delta_H$ (400 MHz, $CDCl_3$) 3.50 – 3.45 (2H, m, C**H$_2$**SO$_2$), 1.22 – 1.17 (2H, m, C**H$_2$**Si), 0.10 (9H, s, (C**H$_3$**)$_3$).

***N*-(4-(Furan-2-yl)butyl)-2-(trimethylsilyl)ethanesulfonamide (147)**



**Method A:** To a stirred solution of amine **118** (200 mg, 1.44 mmol) and triethylamine (602 μL, 437 mg, 4.32 mmol) in dichloromethane (10 mL) at –10 °C was added chloride **145** (577 mg, 2.88 mmol). The reaction was stirred at –10 °C for 1 h, then warmed to RT and stirred for a further 16 h. The reaction was diluted with water (30 mL), extracted with dichloromethane (3 × 30 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:1, petrol/ether) afforded the *title compound* as a pale yellow oil (360 mg, 82%).

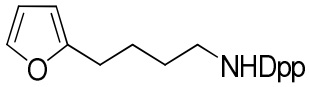
**Method B:** To a solution of amine **118** (200 mg, 1.44 mmol), triethylamine (402 µL, 292 mg, 2.88 mmol) and DMAP (18 mg, 0.144 mmol) in dichloromethane (10 mL) at –15 °C was added anhydride **146** (600 mg, 1.73 mmol). The reaction was stirred at –15 °C for 1 h, then warmed to RT and stirred for a further 16 h. The reaction was diluted with water (30 mL), the aqueous layer extracted with dichloromethane (3 × 30 mL), the combined organic layers washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:1, petrol/ether) afforded the *title compound* as a pale yellow oil (175 mg, 40%).

$R_f$ 0.26 (3:2, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3443br, 2953m, 1642m, 1320s, 1251m, 1141s; $\delta_H$ (400 MHz, $CDCl_3$) 7.30 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.28 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.00 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 4.21 (1H, t, *J* 6.0, N**H**), 3.12 (2H, app. q, *J* 6.5, C(4)**H$_2$**), 2.96 – 2.90 (2H, m, $SO_2C$**H$_2$**), 2.67 (2H, t, *J* 7.0, C(1)**H$_2$**), 1.76 – 1.67 (2H, m, C(3)**H$_2$**), 1.66 – 1.56 (2H, m, C(2)**H$_2$**), 1.04 – 0.98 (2H, m, C**H$_2$**Si$(CH_3)_3$), 0.06 (9H, s, $CH_2Si(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 155.4 (**C**(2')), 141.0 (**C**(5')), 110.1 (**C**(4')), 105.1 (**C**(3')), 48.7 ($SO_2$**C**$H_2$), 43.1 (**C**(4)), 29.8 (**C**(3)), 27.4 (**C**(1)), 25.0 (**C**(2)), 10.6 (**C**$H_2Si(CH_3)_3$), –2.0 ($CH_2Si$(**C**$H_3)_3$); *m/z* ($ESI^+$) 367 ($MNa^+$·MeCN, 100%), 326 ($MNa^+$, 57%).

HRMS (ESI) *m/z* calcd for $C_{13}H_{25}NNaO_3SSi$ $[M+Na]^+$ : 326.1217

Found : 326.1209

**_N_-(4-(Furan-2-yl)butyl)-_P_,_P_-diphenylphosphinic amide (148)**

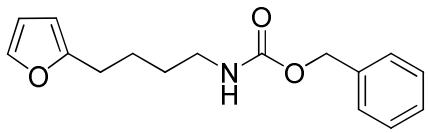



To a stirred solution of amine **118** (100 mg, 0.72 mmol) in dichloromethane (4 mL) at 0 °C was added triethylamine (0.11 mL, 80 mg, 0.79 mmol) and diphenylphosphinic chloride (151 µL, 187 mg, 0.79 mmol). The reaction was stirred for at 0 °C for 1 h, then allowed to warm to RT and stirred for a further 18 h. The reaction was diluted with water (20 mL) and the aqueous layer extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (1:1, ethyl acetate/petrol) afforded the *title compound* as a white solid (176 mg, 72%); $R_f$ 0.25 (2:1, ethyl acetate/petrol); m.p. 97 – 99 °C; $\nu_{max}$(thin film)/$cm^{-1}$ 3185br, 2939m, 2864m, 1592w, 1507w, 1438s, 1187s, 1123s, 1007m; $\delta_H$ (400 MHz, $CDCl_3$) 7.93 – 7.86 (4H, m, Ar**H**), 7.52 – 7.41 (6H, m, Ar**H**), 7.27 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.26 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.94 (1H, dd , *J* 3.0, 1.0, C(3')**H**), 3.00 – 2.92 (2H, m, C(4)$\mathbf{H_2}$), 2.84 (1H, t, *J* 6.5, N**H**), 2.60 (2H, t, *J* 7.0, C(1)$\mathbf{H_2}$), 1.71 – 1.57 (4H, m, C(2)$\mathbf{H_2}$ and C(3)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 152.7 (**C**(2')), 140.8 (**C**(5')), 133.1 (Ar), 132.1 (Ar), 132.0 (Ar), 128.5 (Ar), 110.1 (**C**(4')), 105.0 (**C**(3')), 40.5 (**C**(4)), 31.6 (**C**(3)), 31.5 (**C**(1)), 25.2 (**C**(2)); m/z ($ESI^+$) 679 ($2MH^+$, 100%), 340 ($MH^+$, 87%).

HRMS (ESI) *m/z* calcd for $C_{20}H_{23}NNaO_2P$ $[M+Na]^+$ : 340.1461

Found : 340.1455

**Benzyl 4-(furan-2-yl)butylcarbamate (149)**

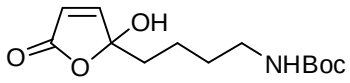


$NaHCO_3$ (180 mg, 2.16 mmol) and benzyl chloroformate (231 µL, 276 mg, 1.62 mmol) were added to a stirred solution of amine **118** (150 mg, 1.08 mmol) in dichloromethane (10 mL) at 0 °C. The reaction was stirred at RT for 16 h then filtered through a pad of celite and concentrated *in vacuo*. Purification by flash chromatography (8:1 → 3:1, petrol/ethyl acetate) afforded the *title compound* as a yellow oil (280 mg, 95%); $R_f$ 0.38 (1:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3355br, 3016m, 2944m, 1709s, 1521m, 1250m; $\delta_H$ (400 MHz, $CDCl_3$) 7.39 – 7.31 (5H, m, Ar**H**), 7.30 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.28 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.98 (1H, d, *J* 2.0, C(3')**H**), 5.10 (2H, s, PhC**H₂**), 4.74 (1H, br s, N**H**), 3.21 (2H, q, *J* 7.0, C(4)**H₂**), 2.65 (2H, t, *J* 7.5, C(1)**H₂**), 1.77 – 1.48 (4H, m, C(2)**H₂** and C(3)**H₂**); $\delta_C$ (100 MHz, $CDCl_3$) 156.4 (**C**=O), 155.7 (**C**(2')), 140.9 (**C**(5')), 136.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 110.1 (**C**(4')), 105.0 (**C**(3')), 66.6 (Ph**C**$H_2$), 40.8 (**C**(4)), 29.4 (**C**(3)), 27.5 (**C**(1)), 25.2 (**C**(2)); *m/z* ($ESI^+$) 296 ($MNa^+$, 100%), 274 ($MH^+$, 71).

HRMS (ESI$^+$) *m/z* calcd for $C_{16}H_{19}NNaO_3$ $[MNa]^+$ : 296.1257

Found : 296.1253

**_tert_-Butyl 4-(2-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butylcarbamate (151)**

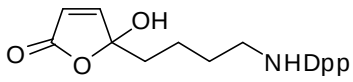



Synthesised according to *general procedure B* from carbamate **123** (100 mg, 0.418 mmol). Purification by flash chromatography afforded the *title compound* as a yellow oil (113 mg, 90%); $R_f$ 0.38 (ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 3352br, 2977s, 2934m, 1688s, 1596m, 1508s, 1271s, 1167s; $\delta_H$ (400 MHz, (MeOH-$d^4$) 7.40 (1H, d, *J* 5.5, C(3')**H**), 6.14 (1H, d, *J* 5.5, C(4')**H**), 3.04 (2H, t, *J* 6.5, C(4)**H$_2$**), 1.93 (2H, t, *J* 7.0, C(1)**H$_2$**), 1.55 – 1.37 (4H, m, C(2)**H$_2$** and C(3)**H$_2$**, overlapping), 1.44 (9H, s, C(C**H$_3$**)$_3$, overlapping); $\delta_C$ (100 MHz, MeOH-$d^4$) 172.1 (**C**(5')), 157.6 (N**C**=O), 156.1 (**C**(3')), 122.4 (**C**(4')), 109.3 (**C**(2')), 78.9 (**C**(CH$_3$)$_3$), 40.0 (**C**(4)), 37.3 (**C**(1)), 29.9 (**C**(3)), 27.8 (C(**C**H$_3$)$_3$), 19.8 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{13}H_{21}NNaO_5$ $[M+Na]^+$ : 294.1312

Found : 294.1313

**_N_-(4-(2-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butyl)-P,P-diphenylphosphinic amide (153)**

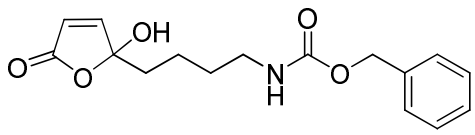



Synthesised according to *general procedure B* from phosphinamide **148** (100 mg, 0.295 mmol)**.** Purification by flash chromatography (1:1, petrol/ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (84 mg, 77%); $R_f$ 0.20 (4:1, ethyl acetate/petrol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3305br, 2938s, 1828s, 1703s, 1422s, 1125s; $\delta_H$ (500 MHz, $CDCl_3$) 7.91 – 7.82 (4H, m, Ar**H**), 7.51 (1H, d, *J* 6.0, C(3')**H**), 7.49 – 7.41 (6H, m, Ar**H**), 6.08 (1H, d, *J* 6.0, C(4')**H**), 3.09 – 2.91 (2H, m, C(4)$\mathbf{H_2}$), 2.26 – 2.11 (2H, m, C(1)$\mathbf{H_2}$), 1.91 – 1.54 (4H, m, C(2)$\mathbf{H_2}$ and C(3)$\mathbf{H_2}$); $\delta_C$ (125 MHz, $CDCl_3$) 170.9 (**C**(5')), 156.2 (**C**(3')), 132.1 (Ar), 131.9 (Ar), 128.8 (Ar), 128.6 (Ar), 122.5 (**C**(4')), 108.8 (**C**(2')), 39.6 (**C**(4)), 36.2 (**C**(1)), 30.2 (**C**(3)), 19.5 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{20}H_{22}NNaO_4P$ $[M+Na]^+$ : 394.1179

Found : 394.1168

**Benzyl 4-(2-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butylcarbamate (154)**

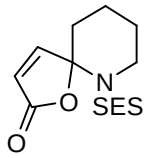



Synthesised by *general procedure B* from carbamate **149** (50 mg, 0.183 mmol). Purification by flash chromatography (3:1, ethyl acetate/petrol) afforded the *title compound* as a pale yellow oil (32 mg, 58%); $R_f$ 0.25 (4:1, ethyl acetate/petrol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3379s, br, 3026m, 2952m, 1735s, 1713, 1541m, 1246m; $\delta_H$ (500 MHz, ($CDCl_3$) 7.51 – 7.40 (5H, m, Ar**H**), 7.21 (1H, d, *J* 6.0, C(3')**H**), 6.10 (1H, d, *J* 6.0, C(4')**H**), 5.11 (2H, s, PhC$\mathbf{H_2}$), 5.02 (1H, br s, N**H**), 3.22 (2H, q, *J* 7.0, C(4)$\mathbf{H_2}$), 1.97 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 1.51 – 1.42 (4H, m, C(2)$\mathbf{H_2}$ and C(3)$\mathbf{H_2}$); $\delta_C$ (125 MHz, $CDCl_3$) 170.9 (**C**(5')), 156.2 (N**C**=O), 142.6 (**C**(3')), 137.1 (Ar), 129.0 (Ar), 128.8 (Ar) 128.7 (Ar), 124.2 (**C**(4')), 109.5 (**C**(2')), 66.9 (Ph**C**$H_2$), 40.1 (**C**(4)), 38.9 (**C**(1)), 30.1 (**C**(3)), 19.8 (**C**(2)); *m/z* ($ESI^+$) 369 ($MNa^+$·MeCN, 100%), 306 ($MH^+$, 45%).

HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NNaO_5$ $[M+Na]^+$ : 328.1155

Found : 328.1158

**6-(2-(Trimethylsilyl)ethylsulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (155)**

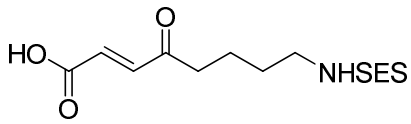



Synthesised by *general procedure C* from sulfonamide **147** (200 mg, 0.659 mmol). Purification by flash chromatography (3:1, petrol/ether) afforded the *title compound* as a colourless gum (186 mg, 89%); $R_f$ 0.22 (2:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3423br, 2361m, 2342m, 1770w, 1647, 1341w, 1249m; $\delta_H$ (400 MHz, $CDCl_3$) 7.73 (1H, d, *J* 6.0, C(3')**H**), 6.01 (1H, d, J 6.0, C(4')**H**), 4.02 (1H, dt, *J* 12.0, 3.0, C(4)**H**H'), 3.33 (td, *J* 12.0, 2.5, C(4)H**H'**), 2.88 – 2.75 (1H, m, $SO_2C$**H**H'), 2.70 – 2.57 (1H, m, $SO_2CH$**H'**), 2.06 – 1.95 (1H, m, C(1)**H**H'), 1.93 – 1.84 (3H, m, C(1)H**H'** and C(2)$\mathbf{H_2}$), 1.78 – 1.63 (2H, m, C(3)$\mathbf{H_2}$), 1.03 – 0.94 (2H, m, C$\mathbf{H_2}$Si$(CH_3)_3$), 0.02 (9H, s, $CH_2Si(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CDCl_3$) 170.2 (**C**(5')), 158.3 (**C**(3')), 118.1 (**C**(4')), 95.5 (**C**(2')), 50.0 ($SO_2$**C**$H_2$), 46.1 (**C**(4)), 37.2 (**C**(1)), 24.7 (**C**(3)), 20.3 (**C**(2)), 9.5 (**C**$H_2Si(CH_3)_3$), −2.18 ($CH_2Si($**C**$H_3)_3$); *m/z* ($ESI^+$) 318 ($MH^+$, 86%), 340 ($MNa^+$, 57%).

HRMS (ESI) *m/z* calcd for $C_{13}H_{23}NNaO_4SSi$ $[M+Na]^+$ : 340.1009

Found : 340.1018

**(*E*)-4-Oxo-8-(2-(trimethylsilyl)ethylsulfonamido)oct-2-enoic acid (**156**)**

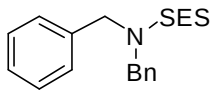



Formed as a by-product from the synthesis of **155** when the reaction was stirred in 30% aq. $H_2SO_4$ for 6 d, affording the *title compound* as a white solid (96 mg, 21%); $R_f$ 0.32 (95:5, ethyl acetate/methanol); m.p. 72 – 74 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3268s, 3067m, 2954s, 1684s, 1665s, 1624s, 1414s, 1315s, 1135s; $\delta_H$ (400 MHz, $CD_3OD$) 7.02 (1H, d, *J* 16.0, C(2)**H**), 6.69 (1H, d, *J* 16.0, C(3)**H**), 3.06 (2H, t, *J* 7.0, C(5)$\mathbf{H_2}$), 3.00 – 2.94 (2H, m, $SO_2C\mathbf{H_2}$), 2.77 (2H, t, *J* 7.0, C(8)$\mathbf{H_2}$), 1.71 (2H, quin, *J* 7.0, C(7)$\mathbf{H_2}$), 1.58 (2H, tt, *J* 8.0, 7.0, C(6)$\mathbf{H_2}$), 1.03 – 0.97 (2H, m, $C\mathbf{H_2}Si(CH_3)_3$), 0.09 (9H, s, $CH_2Si(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CD_3OD$) 200.8 (**C**(1)), 167.6 (**C**(4)), 139.7 (**C**(2)), 131.4 (**C**(3)), 47.9 ($SO_2\mathbf{C}H_2$), 42.7 (**C**(5)), 40.3 (**C**(8)), 29.7 (**C**(6)), 20.7 (**C**(7)), 10.4 ($\mathbf{C}H_2Si(CH_3)_3$), –2.9 ($CH_2Si(\mathbf{C}H_3)_3$).

HRMS (ESI) *m/z* calcd for $C_{13}H_{25}NNaO_5SSi$ $[M+Na]^+$ : 358.1115

Found : 358.1111

**_N_,_N_-Dibenzyl-2-(trimethylsilyl)ethanesulfonamide (159)**

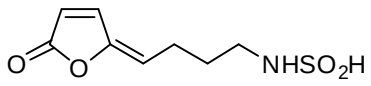



To a stirred solution of sulfonamide **289** (100 mg, 0.368 mmol) in acetonitrile (7 mL) was added benzyl bromide (47 µL, 67 mg, 0.390 mmol) and $K_2CO_3$ (511 mg, 3.70 mmol). The homogenous mixture was stirred at 80 °C for 18 h then cooled to RT, the solid base filtered off, and the solvent removed *in vacuo*. Purification by flash chromatography (5:1, petrol/ether) afforded the *title compound* as a yellow gum (113 mg, 85%); $R_f$ 0.31 (3:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3040m, 2952s, 2339m, 1495m, 1363s, 1322s, 1134s; $\delta_H$ (400 MHz, $CDCl_3$) 7.39 – 7.30 (10H, m, Ar**H**), 4.38 (4H, s, PhC**H$_2$**), 2.83 – 2.77 (2H, m, C**H$_2$**$SO_2$), 0.99 – 0.93 (2H, m, C**H$_2$**Si), −0.03 (9H, s, (C**H$_3$**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 136.0 (Ar), 128.8 (Ar), 128.7 (Ar), 128.0 (Ar), 50.4 (Ph**C**$H_2$), 50.1 (**C**$H_2SO_2$), 10.2 (**C**$H_2$Si), −2.03 ((**C**$H_3$)$_3$); *m/z* ($ESI^+$) 425 ($MNa^+$·MeCN, 100%), 379 ($MNH_4^+$, 44%).

HRMS (ESI) *m/z* calcd for $C_{19}H_{27}NNaO_2SSi$ $[M+Na]^+$ : 384.1424

Found : 384.1423

**(*E*)-4-(5-Oxofuran-2(5H)-ylidene)butylsulfurous acid (160)**

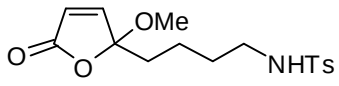



To a stirred solution of spiroaminoacetal **155** (120 mg, 0.378 mmol) in dichloromethane (1.5 mL) was added conc. $H_2SO_4$ (109 µL, 200 mg, 2.04 mmol). The reaction was stirred at RT for 24 h then diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as an orange oil (28 mg, 34%); $R_f$ 0.59 (90:10, ethyl acetate/methanol); $\nu_{max}$(thin film)/$cm^{-1}$ 3341m, 2934m, 1675s, 1602, 1525w, 1080m, 738m; $\delta_H$ (500 MHz, $CDCl_3$) 6.91 (1H, d, *J* 5.5, C(3')**H**), 6.17 (1H, d, *J* 5.5, C(4')**H**), 5.60 (1H, t, *J* 4.5, C(1)**H**), 3.68 – 3.64 (2H, m, C(4)$\mathbf{H_2}$), 2.38 (2H, td, *J* 6.0, 4.5, C(2)$\mathbf{H_2}$), 1.94 (2H, quin, *J* 6.0, C(3)$\mathbf{H_2}$); $\delta_C$ (125 MHz, $CDCl_3$) 169.1 (**C**(5')), 139.2 (**C**(2')), 133.7 (**C**(3')), 124.5 (**C**(4')), 113.0 (**C**(1)), 37.7 (**C**(4)), 22.9 (**C**(2)), 21.5 (**C**(3)).

HRMS (ESI) *m/z* calcd for $C_8H_{11}NNaO_4S$ $[M+Na]^+$ : 240.0301

Found : 240.0298

**_N_-[4-(2-Methoxy-5-oxo-2,5-dihydro-furan-2-yl)-butyl]-4-methyl-benzenesulfonamide (161)**




Synthesised according to *general procedure D* from sulfonamide **120** (25 mg, 85.2 µmol). Purification by flash chromatography (4:1 → 1:1, petrol/ethyl acetate) gave the *title compound* as a colourless oil (27 mg, 93%); $R_f$ 0.26 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3498m, 3281s, 2928s, 2872s, 1768s, 1711s, 1598m, 1495s, 1326s, 1159s, 1093s; $\delta_H$ (500 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.0, Ar**H**), 7.32 (2H, d, *J* 8.0, Ar**H**), 7.11 (1H, d, *J* 5.5, C(3')**H**), 6.22 (1H, d, *J* 5.5, C(4')**H**), 4.43 (1H, t, *J* 6.5, N**H**), 3.20 (3H, s, OC**H$_3$**), 2.93 (2H, app. q, *J* 7.0, C(4)**H$_2$**), 2.44 (3H, s, ArC**H$_3$**), 1.88 – 1.81 (2H, m, C(1)**H$_2$**), 1.51 (2H, quin, *J* 7.0, C(3)**H$_2$**), 1.41 (2H, quin, *J* 7.0, C(2)**H$_2$**); $\delta_C$ (125 MHz, $CDCl_3$) 169.8 (**C**(5')), 153.4 (**C**(3')), 143.5 (Ar), 136.8 (Ar), 129.7 (Ar), 127.1 (Ar), 125.0 (**C**(4')), 110.8 (**C**(2')), 51.1 (O**C**$H_3$), 42.8 (**C**(4)), 36.5 (**C**(1)), 29.4 (**C**(3)), 21.5 (Ar**C**$H_3$), 20.3 (**C**(2)).

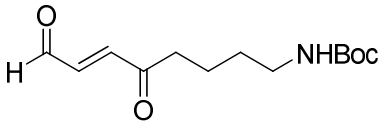
HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NNaO_5S$ $[M+Na]^+$ : 362.1033

Found : 362.1029

Also obtained from the reaction of spiroaminoacetal **129** (50 mg, 0.163 mmol) with Mg powder (20 mg, 0.823 mmol) in methanol (2 mL). The reaction mixture was sonicated

for 9 h, filtered through a pad of celite and concentrated *in vacuo* to afford the *title compound* as a colourless oil (21 mg, 38%). Spectroscopic data as above.

**(*E*)-*tert*-Butyl 5,8-dioxooct-6-enylcarbamate (162)**

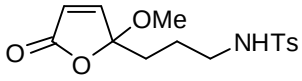



*N*-Bromosuccinimide (89 mg, 0.502 mmol) was added to a solution of carbamate **123** (100 mg, 0.418 mmol) in THF-$H_2O$ (5 mL, 3:1) at 0 °C and the reaction stirred at this temperature for 30 min. Sat. aq. $Na_2S_2O_3$ (10 mL) and sat. aq. $NaHCO_3$ (10 mL) were added, the aqueous layer extracted with ether (3 × 20 mL), the combined organic layers washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* as a brown oil (25 mg, 23%); $\nu_{max}$ (thin film)/$cm^{-1}$ 2975s, 2935s, 1758m, 1694s, 1519s, 1366s, 1249s, 1163s; $\delta_H$ (400 MHz, $CDCl_3$) 9.74 (1H, d, *J* 7.5, C(8)**H**), 6.86 (1H, d, *J* 16.5, C(6)**H**), 6.75 (1H, dd, *J* 16.5, 7.5, C(7)**H**), 4.72 (1H, br s, N**H**), 3.15 – 3.03 (2H, m, C(1)$\mathbf{H_2}$), 2.57 (2H, q, *J* 7.0, C(4)$\mathbf{H_2}$), 1.65 (2H, quin, *J* 7.0, C(2)$\mathbf{H_2}$), 1.48 (2H, quin, *J* 7.0, C(3)$\mathbf{H_2}$), 1.39 (9H, s, C($C\mathbf{H_3}$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 199.7 (**C**(5)), 193.4 (**C**(8)), 156.1 (N**C**=O), 144.7 (**C**(6)), 137.4 (**C**(7)), 79.2 (**C**($CH_3$)$_3$), 40.6 (**C**(1)), 40.1 (**C**(4)), 29.6 (**C**(2)), 28.4 (C(**C**$H_3$)$_3$), 20.5 (**C**(3)).

HRMS (ESI) *m/z* calcd for $C_{13}H_{21}NNaO_4$ $[M+Na]^+$ : 278.1363

Found : 278.1358

***N*-[3-(2-Methoxy-5-oxo-2,5-dihydro-furan-2-yl)-propyl]-4-methyl-benzene sulphonamide (168)**

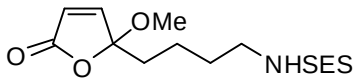



Prepared according to the *general procedure D* with sulfonamide **119** (100 mg, 0.360 mmol), affording the *title compound* as a yellow oil (101 mg, 86%); $R_f$ 0.24 (1:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3281br, 2940m, 1766s, 1327s, 1158s, 1092m; $\delta_H$ (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.0, Ar**H**), 7.30 (2H, d, *J* 8.0, Ar**H**), 7.10 (1H, d, *J* 5.5, C(3')**H**), 6.20 (1H, d, *J* 5.5, C(4')**H**), 5.00 (1H, t, *J* 6.5, N**H**), 3.16 (3H, s, OC**H$_3$**), 2.94 (2H, app. q, *J* 7.0, C(3)**H$_2$**), 2.42 (3H, s, ArC**H$_3$**), 1.97 – 1.80 (2H, m, C(1)**H$_2$**), 1.62 (2H, quin, *J* 7.0, C(2)**H$_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (**C**(5')), 153.5 (**C**(3')), 143.5 (Ar), 136.8 (Ar), 129.7 (Ar), 127.0 (Ar), 124.9 (**C**(4')), 110.6 (**C**(2')), 51.1 (O**C**$H_3$), 42.7 (**C**(3)), 34.0 (**C**(1)), 23.5 (**C**(2)), 21.5 (Ar**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NNaO_5S$ $[M+Na]^+$ : 348.0876

Found : 348.0873

***N*-(4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)butyl)-2-(trimethylsilyl) ethanesulfonamide (169)**

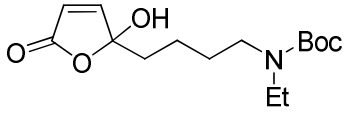



Prepared according to *general procedure D* from sulfonamide **147** (50 mg, 0.165 mmol), affording the *title compound* as a colourless oil (56 mg, 96%); $R_f$ 0.31 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3288br, 3092w, 2952s, 1767s, 1612w, 1421s, 1318s, 1167s; $\delta_H$ (400 MHz, $CDCl_3$) 7.15 (1H, d, *J* 6.0, C(3')**H**), 6.24 (1H, d, *J* 6.0, C(4')**H**), 4.39 (1H, t, *J* 6.0, N**H**), 3.21 (3H, s, OC**H$_3$**), 3.09 (2H, q, *J* 6.5, C(4)**H$_2$**), 2.95 – 2.89 (2H, m, C**H$_2$**$SO_2$), 1.97 – 1.86 (2H, m, C(1)**H$_2$**), 1.59 (2H, app. quin, *J* 7.5, C(3)**H$_2$**), 1.49 (2H, quin, *J* 7.5, C(2)**H$_2$**), 1.03 – 0.97 (2H, m, C**H$_2$**$Si(CH_3)_3$), 0.05 (9H, s, $CH_2Si(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (**C**(5')), 153.5 (**C**(3')), 125.0 (**C**(4')), 110.9 (**C**(2')), 51.2 (O**C**$H_3$), 48.7 (C**H$_2$**$SO_2$), 43.0 (**C**(4)), 36.5 (**C**(1)), 30.3 (**C**(3)), 20.3 (**C**(2)), 10.6 (**C**$H_2Si(CH_3)_3$), –2.0 ($CH_2Si(\mathbf{C}H_3)_3$).

HRMS (ESI) *m/z* calcd for $C_{14}H_{27}NNaO_5SSi$ $[M+Na]^+$ : 372.1271

Found : 372.1267

**Ethyl-[4-(2-hydroxy-5-oxo-2,5-dihydro-furan-2-yl)-butyl]-carbamic acid *tert*-butyl ester (173)**

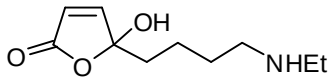



Prepared according to *general procedure B* from carbamate **290** (3.30 g, 12.3 mmol). Purification by flash chromatography on neutral alumina (3:1, petrol/ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (2.61 g, 71%); m.p. 64 – 66 °C; $R_f$ 0.27 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3307br, 2975s, 2933s, 1765s, 1660s, 1366s, 1160s; $\delta_H$ (400 MHz, MeOH-$d^4$) 7.39 (1H, d, *J* 5.5, C(3')**H**), 6.14 (1H, d, *J* 5.5, C(4')**H**), 3.25 – 3.21 (4H, m, NC**H₂**$CH_3$ and C(4)**H₂**), 1.95 (2H, t, *J* 7.0, C(1)**H₂**), 1.57 (2H, quin, *J* 7.5, C(3)**H₂**), 1.46 (9H, s, C(C**H₃**)$_3$), 1.39 (2H, quin, *J* 7.5, C(2)**H₂**), 1.11 (3H, t, *J* 7.0, $NCH_2$C**H₃**); $\delta_C$ (100 MHz, MeOH-$d^4$) 172.0 (**C**(5')), 156.3 (N**C**=O), 156.1 (**C**(3')), 122.4 (**C**(4')), 109.2 (**C**(2')), 79.8 (**C**($CH_3$)$_3$), 46.5 (**C**(4)), 41.9 (N**C**$H_2CH_3$), 37.3 (**C**(1)), 28.5 (**C**(3)), 27.8 (C(**C**$H_3$)$_3$), 20.9 (**C**(2)), 13.0 ($NCH_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{15}H_{25}NNaO_5$ $[M+Na]^+$ : 322.1625

Found : 322.1620

**5-[4-(Ethylamino)butyl]-5-hydroxyfuran-2(5*H*)-one (174)**

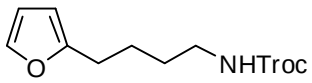



Hydroxybutenolide **173** (400 mg, 1.34 mmol) was dissolved in acetonitrile (2 mL) and $H_3PO_4$ (1.5 mL, 85% by weight in $H_2O$) added dropwise. The reaction was stirred at RT for 2 h then diluted with water (10 mL), the aqueous layer extracted with ethyl acetate (2 × 10 mL) and the combined organic layers discarded. The aqueous layer was then basified with sat. aq. $NaHCO_3$ (40 mL), re-extracted with ethyl acetate (3 × 50 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a pale yellow oil (61 mg, 23%); $R_f$ 0.16 (10:1:0.1, $CHCl_3$/MeOH/$NH_4OH$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3334m, 3087s, 2971s, 2937s, 1742s, 1663s. 1555s, 1365m, 1167s; $\delta_H$ (400 MHz, $CDCl_3$) 7.18 (1H, d, *J* 5.5, C(3')**H**), 6.06 (1H, d, *J* 5.5, C(4')**H**), 2.81 (2H, t, *J* 6.0, C(4)**H₂**), 2.52 (2H, q, *J* 7.0, NC**H₂**$CH_3$), 1.82 – 1.68 (6H, m, C(1)**H₂**, C(2)**H₂**, C(3)**H₂**), 0.97 (3H, t, *J* 7.0, $NCH_2C$**H₃**); $\delta_C$ (100 MHz, $CDCl_3$) 169.6 (**C**(5')), 157.1 (**C**(3')), 122.9 (**C**(4')), 104.4 (**C**(2')), 46.3 (**C**(4)), 44.7 (N**C**$H_2CH_3$), 36.0 (**C**(1)), 25.0 (**C**(3)), 20.6 (**C**(2)), 13.1 ($NCH_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{10}H_{17}NNaO_3$ $[M+Na]^+$ : 222.1101

Found : 222.1099

**2,2,2-Trichloroethyl 4-(furan-2-yl)butylcarbamate (176)**

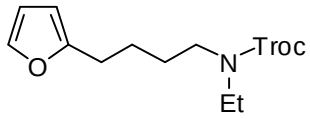



To a solution of amine **118** (500 mg, 3.59 mmol) in dichloromethane (30 mL) at 0 °C was added $NaHCO_3$ (603 mg, 7.18 mmol) and 2,2,2-trichloroethyl chloroformate (742 µL, 1.14 g, 5.39 mmol). The reaction mixture was stirred at RT for 8 h, diluted with water (50 mL) and the separated aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (10:1, petrol/ether) to afford the *title compound* as a colourless oil (723 mg, 64%); $R_f$ 0.23 (4:1, petrol/ether) $\nu_{max}$ (thin film)/$cm^{-1}$ 3341s, 2945s, 2865s, 1716s, 1521s, 1455s, 1239s; $\delta_H$ (400 MHz, $CDCl_3$) 7.30 (1H, s, C(5')**H**), 6.29 – 6.27 (1H, m, C(4')**H**), 6.00 – 5.98 (1H, m, C(3')**H**), 5.08 (1H, br s , N**H**), 4.72 (2H, s, OC**H₂**$CCl_3$), 3.26 (2H, q, *J* 6.5, C(4)**H₂**), 2.66 (2H, t, *J* 7.5, C(1)**H₂**), 1.70 (2H, app. quin, *J* 7.5, C(2)**H₂**)), 1.59 (2H, app. quin, *J* 7.0, C(3)**H₂**); $\delta_C$ (100 MHz, $CDCl_3$) 155.6 (N**C**=O), 154.6 (**C**(2')), 140.9 (**C**(5')), 110.1 (**C**(4')), 105.0 (**C**(3')), 95.7 ($OCH_2$**C**$Cl_3$), 74.4 (O**C**$H_2CCl_3$), 41.0 (**C**(4)), 29.2 (**C**(3)), 27.5 (**C**(1)), 25.1 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{11}H_{14}Cl_3NNaO_3$ $[M+Na]^+$ : 335.9931

Found : 335.9926

**2,2,2-Trichloroethyl ethyl(4-(furan-2-yl)butyl)carbamate (177)**

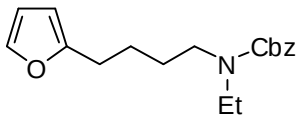



To a solution of carbamate **176** (212 mg, 0.674 mmol) in anhydrous DMF (2 mL) at 0 °C was added NaH (80 mg, 2.02 mmol, 60% dispersion in mineral oil). After stirring for 2 min, ethyl iodide (161 µL, 315 mg, 2.02 mmol) was added and the solution stirred at RT for 2 h. The reaction mixture was quenched with water (10 mL), the aqueous layer extracted with ether (2 × 10 mL), the combined organic layers washed with water (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography afforded the *title compound* as a colourless oil (111 mg, 48%); $R_f$ 0.35 (4:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2933s, 2865m, 1711s, 1424s, 1268s, 1169s; $\delta_H$ (400 MHz, $CDCl_3$) 7.30 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.28 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.99 (1H, d, *J* 3.0, C(3')**H**), 4.76 (2H, s, C**H$_2$**$CCl_3$), 3.35 – 3.31 (4H, m, C(4)**H$_2$** and NC**H$_2$**$CH_3$), 2.67 (2H, t, *J* 6.5, C(1)**H$_2$**), 1.71 – 1.61 (4H, m, C(2)**H$_2$** and C(3)**H$_2$**), 1.19 (3H, t, *J* 7.0, $NCH_2$C**H$_3$**); $\delta_C$ (100 MHz, $CDCl_3$) 155.8 (N**C**=O), 154.3 (**C**(2')), 140.9 (**C**(5')), 110.1 (**C**(4')), 104.9 (**C**(3')), 95.7 ($OCH_2$**C**$Cl_3$), 75.0 (O**C**$H_2CCl_3$), 47.2 (**C**(4)), 42.7 (N**C**$H_2CH_3$), 28.2 (**C**(1)), 27.6 (**C**(2)), 25.3 (**C**(3)), 13.9 ($NCH_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{13}H_{18}Cl_3NNaO_3^+$ $[M+Na]^+$ : 364.0244

Found : 364.0237

**Benzyl ethyl(4-(furan-2-yl)butyl)carbamate (178)**

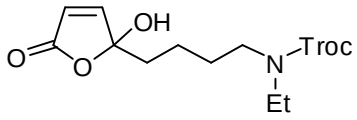



NaH (44 mg, 1.10 mmol, 60% dispersion in mineral oil) was added to a solution of carbamate **149** (100 mg, 0.366 mmol) in DMF (2 mL) at 0 °C and the reaction stirred at this temperature for 15 min. Ethyl iodide (88 µL, 172 mg, 1.10 mmol) was added, and the reaction stirred at RT for 14 h. After the addition of water (0.2 mL), the reaction mixture was diluted with ether (15 mL) and filtered through a pad of celite. The organic layer was washed with water (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1, petrol/ether) afforded the *title compound* as a colourless oil (84 mg, 76%); $R_f$ 0.34 (2:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3033w, 2929s, 2860s, 1699s, 1597m, 1422s, 1269s, 1172s, 1072s, 1006s; $\delta_H$ (400 MHz, $CDCl_3$) 7.39 – 7.29 (6H, m, Ar**H**, and C(5')**H**), 6.28 (1H, dd *J* 3.0, 2.0, C(4')**H**), 6.03 – 5.91 (1H, m, C(3')**H**), 5.14 (2H, s, OC**H₂**), 3.31 – 3.28 (4H, m, C(4)**H₂** and NC**H₂**$CH_3$), 2.65 (2H, t, *J* 6.0, C(1)**H₂**), 1.63 – 1.59 (4H, m, C(2)**H₂** and C(3)**H₂**), 1.14 – 1.12 (3H,m , $NCH_2C$**H₃**); $\delta_C$ (100 MHz, $CDCl_3$) 156.1 (N**C**=O), 155.9 (**C**(2')), 140.8 (**C**(5')), 137.1 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 110.1 (**C**(4')), 104.9 (**C**(3')), 66.8 (O**C**$H_2$), 46.8 (**C**(4)), 42.2 (N**C**$H_2CH_3$), 28.2 (**C**(3)), 27.7 (**C**(1)), 25.3 (**C**(2)), 13.9 ($NCH_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NNaO_3$ $[M+Na]^+$ : 324.1570

Found : 324.1560

**2,2,2-Trichloroethyl ethyl(4-(2-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butyl)carbamate (179)**

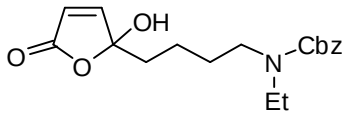



Synthesised according to *general procedure B* from carbamate **177** (300 mg, 0.876 mmol). Purification by flash chromatography (2:1, petrol/ethyl acetate) afforded the *title compound* as a colourless oil (171 mg, 52%); $R_f$ 0.37 (99:1, dichloromethane/methanol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3330br, 2937s, 1702s, 1478m, 1426s, 1267s, 1173s; $\delta_H$ (400 MHz, $CDCl_3$) 7.23 (1H, d, *J* 6.0, C(3')**H**), 6.10 (1H, d, *J* 6.0, C(4')**H**), 4.74 (2H, s, C$\mathbf{H_2}$C$Cl_3$), 3.36 (2H, t, *J* 7.0, C(4)$\mathbf{H_2}$), 3.32 (2H, q, *J* 6.5, NC$\mathbf{H_2}$C$H_3$), 1.98 (2H, t, *J* 7.0, C(1)$\mathbf{H_2}$), 1.62 (3H, q, *J* 7.0, C(3)$\mathbf{H_2}$), 1.56 – 1.38 (2H, m, C(2)$\mathbf{H_2}$), 1.15 (3H, t, *J* 6.5, NC$H_2$C$\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 169.2 (**C**(5')), 154.5 (**C**(3')), 153.9 (N**C**=O), 123.6 (**C**(4')), 108.1 (**C**(2')), 95.7 (C$H_2$**C**$Cl_3$), 75.0 (**C**$H_2$C$Cl_3$), 46.5 (**C**(4)), 42.1 (N**C**$H_2$C$H_3$), 38.2 (**C**(1)), 28.1 (**C**(3)), 20.6 (**C**(2)), 13.8 (NC$H_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{13}H_{18}Cl_3NNaO_5$ $[M+Na]^+$ : 396.0143

Found : 396.0137

**Benzyl ethyl(4-(2-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butyl)carbamate (180)**

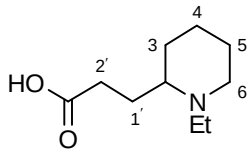



Synthesised according to *general procedure B* from carbamate **178** (76 mg, 0.252 mmol). Purification by flash chromatography (1:1, petrol/ethyl acetate) afforded the *title compound* as a colourless oil (72 mg, 86%); $R_f$ 0.23 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2935s, 1694s, 1481s, 1428s, 1178s, 1081s; $\delta_H$ (400 MHz, $CDCl_3$) 7.38 – 7.28 (5H, m, Ar), 7.20 (1H, d, *J* 5.0, C(3')**H**), 6.06 (1H, d, *J* 5.0, C(4')**H**), 5.11 (2H, s, PhC**H$_2$**), 3.37 – 3.17 (4H, m, C(4)**H$_2$** and NC**H$_2$**$CH_3$), 2.11 – 1.84 (2H, m, C(1)**H$_2$**), 1.67 – 1.45 (4H, m, C(2)**H$_2$** and C(3)**H$_2$**), 1.11 (3H, t, *J* 7.0, $NCH_2$C**H$_3$**); $\delta_C$ (100 MHz, $CDCl_3$) 168.8 (**C**(5')), 156.3 (**C**(3')), 154.6 (N**C**=O), 136.8 (Ar), 128.5 (Ar), 128.0 (Ar), 127.8 (Ar), 122.9 (**C**(4')), 108.3 (**C**(2')), 67.3 (Ph**C**$H_2$), 46.2 (**C**(4)), 41.9 (N**C**$H_2CH_3$), 36.3 (**C**(1)), 27.6 (**C**(3)), 20.3 (**C**(2)), 13.8 ($NCH_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NNaO_5$ $[M+Na]^+$ : 356.1468

Found : 356.1469

**3-(1-Ethylpiperidin-2-yl)propanoic acid (181)**

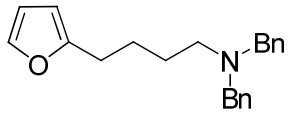



To a solution of hydroxybutenolide **180** (175 mg, 0.525 mmol) in methanol (5 mL) was added 10% Pd/C (20 mg). The airspace was evacuated and purged with argon (× 3) and a balloon of $H_2$ attached. After stirring for 0.5 h the reaction was filtered through a pad of celite and concentrated *in vacuo* to afford the *title compound* as a colourless oil (77 mg, 79%); $\nu_{max}$ (thin film)/$cm^{-1}$ 3042br, 2981m, 2944s, 2837m, 1722s, 1411m, 1209m, 1105m; $\delta_H$ (400 MHz, $CDCl_3$) 10.28 (1H, br s, O**H**), 3.09 – 2.94 (4H, m NC**H₂**$CH_3$, C(2)**H** and C(6)**H**H'), 2.87 – 2.76 (1H, m, C(6)H**H'**), 2.39 – 2.30 (1H, m, C(2')**H**H'), 2.19 – 2.16 (1H, m, C(2')H**H'**), 2.11 – 2.00 (1H, m, C(3)**H**H'), 1.93 – 1.82 (1H, m, C(3)H**H'**), 1.79 – 1.55 (5H, m, C(1')**H**H', C(4)**H₂** and C(5)**H₂**), 1.49 – 1.36 (1H, m, C(1')H**H'**), 1.19 (3H, t, *J* 7.0, $NCH_2C$**H₃**); $\delta_C$ (100 MHz, $CDCl_3$) 177.9 (**C**=O), 58.9 (**C**(2)), 48.4 (**C**(6)), 46.1 (N**C**$H_2CH_3$), 33.8 (**C**(2')), 26.2 (**C**(3)), 24.4 (**C**(1')), 22.0 (**C**(5)), 20.4 (**C**(4)), 8.9 ($NCH_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{10}H_{19}NNaO_2$ $[M+Na]^+$ : 208.1308

Found : 208.1307

**_N_,_N_-Dibenzyl-4-(2-furyl)butan-1-amine (185)**

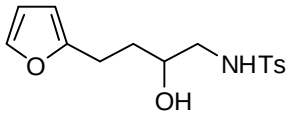



To a solution of amine **118** (100 mg, 0.72 mmol) in acetonitrile (15 mL) was added benzyl bromide (246 mg, 1.44 mmol) and $K_2CO_3$ (1 g, 7.20 mmol). The reaction mixture was heated at 70 °C for 24 h then cooled to RT and filtered through a pad of celite. The solution was concentrated *in vacuo* and the residue purified by flash chromatography (30:1, petrol/ether) to afford the *title compound* as a yellow oil (152 mg, 67%); $R_f$ 0.39 (15:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3424br, 2360m, 1647s, 1454m, 1006w; $\delta_H$ (400 MHz, $CDCl_3$) 7.47 – 7.33 (8H, m, Ar**H**), 7.32 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 7.29 – 7.26 (2H, m, Ar**H**), 6.30 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.95 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 3.58 (4H, s, PhC**$H_2$**), 2.57 (2H, t, *J* 7.0, C(4)**$H_2$**), 2.47 (2H, t, *J* 7.0, C(1)**$H_2$**), 1.69 – 1.66 (2H, m, C(2)**$H_2$**), 1.60 – 1.57 (2H, m, C(3)**$H_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 156.4 (**C**(2')), 140.7 (**C**(5')), 140.0 (Ar), 128.8 (Ar), 128.2 (Ar), 126.8 (Ar), 110.0 (**C**(4')), 104.7 (**C**(3')), 58.3 (Ph**C**$H_2$), 52.9 (**C**(4)), 27.7 (**C**(1)), 26.4 (**C**(2)), 25.59 (**C**(3)); *m/z* ($ESI^+$) 318 ($MH^+$, 86%), 340 ($MNa^+$, 57%).

HRMS (ESI) *m/z* calcd for $C_{22}H_{26}NO$ $[M+H]^+$ : 320.2009

Found : 320.1998

**_N_-(4-(Furan-2-yl)-2-hydroxybutyl)-4-methylbenzenesulfonamide (204)**

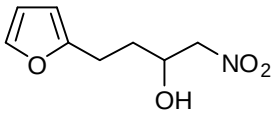



4-Toluenesulfonyl chloride (418 mg, 2.15 mmol) was added to a stirred solution of aminoalcohol **208** (328 mg, 2.11 mmol), triethylamine (427 mg, 588 µL, 4.22 mmol) and DMAP (13 mg, 0.106 mmol) in dichloromethane (13 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was diluted with water (50 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with 2N aq. HCl (100 mL), sat. aq. $NaHCO_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (0.5 → 4% MeOH in DCM) afforded the *title compound* as a beige solid (614 mg, 94%); Mpt: 70 – 72 °C; $R_f$ 0.13 (98:2, dichloromethane/methanol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3520s br, 3284s, 2925s, 1598s, 1508s, 1326s, 1160s, 1091m; $\delta_H$ (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 8.5, Ar**H**), 7.31 – 7.25 (3H, m, Ar**H** and C(5')**H**), 6.25 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.96 (1H, d, *J* 2.0, C(3')**H**), 5.44 (1H, t, *J* 5.5, N**H**), 3.81 – 3.62 (1H, m, C(3)**H**), 3.04 (1H, ddd, *J* 13.0, 7.0, 5.5, C(4)**H**H'), 2.86 – 2.60 (4H, m, C(4)H**H'**, C(1)**$H_2$** and O**H**), 2.42 (3H, s, ArC**$H_3$**), 1.72 (2H, q, *J* 7.5, C(2)**$H_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 155.0 (**C**(2')), 143.6 (Ar), 141.0 (**C**(5')), 136.6 (Ar), 129.8 (Ar), 127.1 (Ar), 110.2 (**C**(4')), 105.2 (**C**(3')), 69.6 (**C**(3)), 48.6 (**C**(4)), 32.7 (**C**(2)H), 23.9 (**C**(1)H), 21.5 (Ar**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NNaO_4S$ $[M+Na]^+$ : 332.0927

Found : 332.0926

**4-(Furan-2-yl)-1-nitrobutan-2-ol** (**205**)

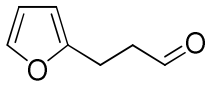



1*H*-Imidazole (27 mg, 0.403 mmol) was added to a solution of aldehyde **206** (200 mg, 1.61 mmol) and nitromethane (260 µL, 295 mg, 4.83 mmol) in water (3 mL) and the reaction mixture stirred at RT for 13 h. Water (30 mL) was added, the aqueous layer extracted with ether (3 × 40 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (4:1, petrol/ether) afforded the *title compound* as a colourless oil (191 mg, 64%); $R_f$ 0.11 (8:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3538m, 3396m, 2926m, 1551s, 1508s, 13832, 1096s, 1008s; $\delta_H$ (400 MHz, $C_6D_6$) 7.19 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.20 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.90 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 3.86 – 3.83 (1H, m, C(3)**H**), 3.72 (1H, dd, *J* 13.0, 9.0, C(4)**H**H'), 3.47 (1H, dd, *J* 13.0, 2.5, C(4)H**H'**), 2.78 (1H, br s, O**H**), 2.60 (1H, ddd, *J* 15.0, 9.0, 6.0, C(1)**H**H'), 2.49 (1H, dt, *J* 15.0, 8.0, C(1)H**H'**), 1.36 (1H, dddd, *J* 14.5, 9.0, 8.0, 6.0, C(2)**H**H'), 1.29 (1H, dddd, *J* 14.5, 9.0, 8.0, 4.0, C(2)H**H'**); $\delta_C$ (100 MHz, $C_6D_6$) 155.0 (**C**(2')), 141.3 (**C**(5')), 110.5 (**C**(4')), 105.6 (**C**(3')), 80.2 (**C**(4)), 67.5 (**C**(3)), 32.0 (**C**(2)), 23.8 (**C**(1)).

HRMS (ESI) *m/z* calcd for $C_8H_{10}NO_4$ $[M-H]^-$ : 184.0617

Found : 184.0615

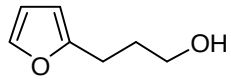
**3-(Furan-2-yl)propanal[39] (206)**



Zinc dust (1.00g, 15.4 mmol) was added to a stirred solution of bis(cyclopentadienyl)titanium(IV) dichloride (76 mg, 0.307 mmol) and triethylamine hydrochloride (4.23 g, 30.7 mmol) in degassed dichloromethane (120 mL) at RT. When the reaction mixture changed from a dark red to yellow colour (typically 2 min), 3-(2-furyl)acrolein (750 mg, 6.14 mmol) was added and stirring continued for 1 h. The reaction was then quenched with sat. aq. $NH_4Cl$ (100 mL), filtered through a pad of celite, the aqueous layer extracted with dichloromethane (3 × 100 mL) and the combined organic layers dried over $MgSO_4$. After removal of the solvent *in vacuo*, the title compound was obtained as a colourless oil (732 mg, 96%) that was used without further purification; $R_f$ 0.30 (8:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2918m, 2849s, 2729s, 1724s, 1508m; $\delta_H$ (400 MHz, $CDCl_3$) 9.83 (1H, s, C(3)**H**), 7.31 (1H, d, *J* 1.0, C(5')**H**), 6.28 (1H, dd, *J* 2.5, 2.0, C(4')**H**), 6.03 (1H, d, *J* 2.5, C(3')**H**), 2.99 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 2.80

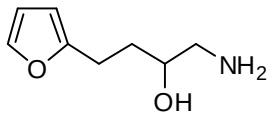
(2H, t, *J* 7.5, C(2)**H₂**); $\delta_C$ (100 MHz, $CDCl_3$) 201.0 (**C**(3)), 153.8 **C**(2'), 141.3 **C**(5'), 110.2 **C**(4'), 105.5 **C**(3'), 41.9 (**C**(2)), 20.7 (**C**(1)).

**3-(Furan-2-yl)propan-1-ol[203] (207)**




To a solution of furan (2.14 mL, 2.00 g, 29.4 mmol) in THF (30 mL) at 0 °C was added *n*-butyl lithium (18.4 mL, 29.4 mmol, 1.6 M solution in hexane) and the reaction mixture stirred at 0 °C for 1 h. After cooling to − 78 °C, boron trifluoride diethyl etherate (3.63 mL, 4.17 g, 29.4 mmol) and trimethylene oxide (955 µL, 853 mg, 14.7 mmol) were added, the solution allowed to warm to RT over 5 h, then quenched with sat. aq. $NH_4Cl$ (15 mL) and filtered through a celite pad. The solvent was removed *in vacuo*, the aqueous layer diluted with water (80 mL) and extracted with ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and the residue purified by flash chromatography (neutral alumina, 4:1 → 1:1, petrol/ether) to afford the title compound as a yellow oil (1.70 g, 92%); $R_f$ 0.27 (1:1, petrol/ether); $\delta_H$ (400 MHz, $CDCl_3$) 7.28 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.26 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.99 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 3.63 (2H, t, *J* 6.5, C(3)**H₂**), 2.86 (1H, br s, O**H**), 2.70 (2H, t, *J* 7.5, C(1)**H₂**), 1.87 (2H, tt, *J* 7.5, 6.5, C(2)**H₂**); $\delta_C$ (100 MHz, $CDCl_3$) 155.6 (**C**(2')), 140.9 (**C**(5')), 110.9 (**C**(4')), 104.9 (**C**(3')), 61.7 (**C**(1)), 30.9 (**C**(2)), 24.2 (**C**(3)).

**1-Amino-4-(furan-2-yl)butan-2-ol (208)**

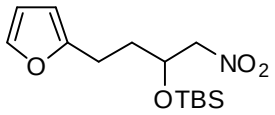



To a stirred solution of cyanohydrin **210** (1.65 g, 10.9 mmol) in ether (50 mL) at 0 °C was added $LiAlH_4$ (655 mg, 16.4 mmol, 95% by weight). The reaction was stirred at RT for 20 min then cooled to 0 °C and water (0.6 mL), 20% aq. NaOH (0.6 mL) and water (1.8 mL) added sequentially. The reaction mixture was stirred at RT for 10 min then filtered through a pad of celite and concentrated *in vacuo*. The *title compound* was obtained as a yellow oil (1.52 g, 90%) that was used in subsequent reactions without purification; $R_f$ 0.14 (10:1:0.1, $CHCl_3$/MeOH/$NH_4OH$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3297br, 3116m, 2926s, 2857m, 1655s, 1508s, 1446s, 1145s, 1074s; $\delta_H$ (400 MHz, MeOH-$d^4$) 7.34 (1H, d, *J* 2.0, C(5')**H**), 6.29 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.05 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 3.55 (1H, tt, *J* 8.0, 4.5, C(3)**H**), 2.85 – 2.63 (3H, m, C(1)**$H_2$** and C(4)**H**H'), 2.56 (1H, dd, *J* 13.0, 8.0, C(4)H**H'**), 1.86 – 1.75 (1H, m, C(2) **H**H'), 1.69 (1H, dtd, *J* 14.0, 9.0, 5.5, C(2)H**H'**); $\delta_C$ (100 MHz, MeOH-$d^4$) 156.0 (**C**(2')), 141.1 (**C**(5')), 110.1 (**C**(4')), 104.9 (**C**(3')), 71.7 (**C**(3)), 47.3 (**C**(4)), 33.3 (**C**(2)), 24.1 (**C**(1)).

HRMS (ESI) *m/z* calcd for $C_8H_{13}NNaO_2$ $[M+Na]^+$ : 178.0838

Found : 178.0841

**_tert_-Butyl(4-(furan-2-yl)-1-nitrobutan-2-yloxy)dimethylsilane (209)**

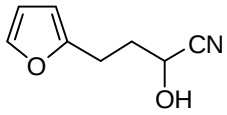



1*H*-Imidazole (44 mg, 0.646 mmol) and *tert*-butyldimethylsilyl chloride (89 mg, 0.592 mmol) were added to a solution of nitroalcohol **205** (50 mg, 0.269 mmol) in DMF (1 mL) and the resulting mixture stirred for 14 h at RT. Water (10 mL) was added, the aqueous layer extracted with ether (2 × 10 mL), the combined organic layers washed with water (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (30:1 → 10:1, petrol/ether) afforded the *title compound* as a colourless oil (73 mg, 90%); $R_f$ 0.23 (25:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2953s, 2844m, 1769s, 1718s, 1556s, 1008s; $\delta_H$ (400 MHz, $CDCl_3$) 7.33 – 7.32 (1H, m, C(5')**H**), 6.30 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.03 (1H, d, *J* 3.0, C(3')**H**), 4.51 – 4.43 (1H, m, C(3)**H**), 4.39 (2H, dd, *J* 11.5, 8.0, C(4)**H**H'), 4.32 (2H, dd, *J* 11.5, 4.0, C(4)H**H'**), 2.76 – 2.69 (2H, m, C(1)$\mathbf{H_2}$), 1.97 – 1.90 (2H, m, C(2)$\mathbf{H_2}$), 0.88 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.09 (3H, s, SiC$\mathbf{H_3}$), 0.03 (3H, s, SiC$\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 154.4 (**C**(2')), 141.2 (**C**(5')), 110.3 (**C**(4')), 105.4 (**C**(3')), 80.7 (**C**(4)), 69.2 (**C**(3)), 33.3 (**C**(2)), 25.6 (SiC(**C**$H_3$)$_3$), 22.3 (**C**(1)), 17.9 (Si**C**($CH_3$)$_3$), – 4.74 (Si**C**$H_3$), – 5.21 (Si**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{14}H_{25}NNaO_4Si$ $[M+Na]^+$ : 322.1445

Found : 322.1455

**4-(Furan-2-yl)-2-hydroxybutanenitrile (210)**

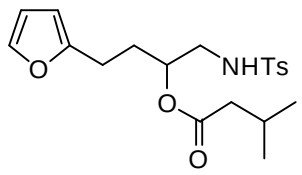



$K_2CO_3$ (92 mg, 0.666 mmol) and trimethylsilyl cyanide (2.33 mL, 1.84 g, 18.6 mmol) were added to a solution of aldehyde **206** (1.65 g, 13.3 mmol) in DMF (37 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 40 min then water (150 mL) and ether (150 mL) were added. The separated organic layer was washed with water (2 × 100mL), the aqueous layers back-extracted with ether (150 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (98:2, dichloromethane/methanol) afforded the *title compound* as a colourless oil (1.65 g, 82%); $R_f$ 0.15 (dichloromethane); $\nu_{max}$ (thin film)/$cm^{-1}$ 3441br, 2959s, 1718m, 1508m, 1255s, 1112s, 1009s; $\delta_H$ (400 MHz, $CDCl_3$) 7.73 (1H, s, C(5')**H**), 6.31 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.08 (1H, d, *J* 3.0, C(3')**H**), 4.49 (1H, td, *J* 7.0, 2.0, C(3)**H**), 3.24 (1H, br s, O**H**), 2.91 – 2.84 (2H, m, C(1)$\mathbf{H_2}$), 2.19 (2H, app. q, *J* 7.5, C(2)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 153.2 (**C**(2')), 141.6 (**C**(5')), 119.8 (**C**N), 110.3 (**C**(4')), 106.2 (**C**(3')), 60.2 (**C**(3)), 33.5 (**C**(2)), 23.1 (**C**(1)); *m/z* ($ESI^+$) 325 (2M+Na, 34%), 227 (71), 195 (47), 190 (M+K, 6).

HRMS (FI) *m/z* calcd for $C_8H_9NO_2$ $[M]^+$ : 151.0633

Found : 151.0629

**4-(Furan-2-yl)-1-(4-methylphenylsulfonamido)butan-2-yl 3-methylbutanoate (211)**



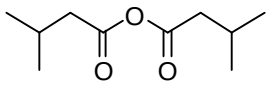

Trimethylsilyl trifluoromethanesulfonate (20 μL of 0.74 M solution of trimethylsilyl trifluoromethanesulfonate in dichloromethane, 14.8 μmol) was added to a solution of sulfonamide **204** (200 mg, 0.646 mmol) and anhydride **212** (193 μL, 180 mg, 0.969 mmol) in dichloromethane (0.5 mL) at –10 °C. After stirring at this temperature for 1 h, the reaction was quenched with sat. aq. $NaHCO_3$ (20 mL). The separated aqueous layer was extracted with dichloromethane (3 × 20 mL), the combined organic layers dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by flash chromatography (2:1, petrol/ether) afforded the *title compound* as a pale yellow oil (203 mg, 80%); $R_f$ 0.10 (4:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3284s, 2960s, 2872m, 1735s, 1598m, 1449s, 1333s, 1253m, 1162s, 1094s; $\delta_H$ (400 MHz, $CDCl_3$) 7.73 (2H,d, *J* 8.0, Ar**H**), 7.31 (2H, d, *J* 8.0, Ar**H**), 7.29 – 7.27 (1H, m, C(5')**H**), 6.26 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.96 (1H, d, *J* 3.0, C(3')**H**), 4.91 (1H, t, *J* 6.5, N**H**), 4.90 – 4.83 (1H, m, C(3)**H**), 3.13 – 3.08 (2H, m, C(4)$\mathbf{H_2}$), 2.64 – 2.61 (2H, m, C(1)$\mathbf{H_2}$), 2.42 (3H, s, ArC$\mathbf{H_3}$), 2.13 (2H, d, *J* 7.0, C(O)C$\mathbf{H_2}$), 2.10 – 2.01 (1H, m, C**H**$(CH_3)_2$), 1.98 – 1.84 (2H, m, C(2)$\mathbf{H_2}$), 0.94 (6H, d, *J* 6.5, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 172.9 (**C**(O)), 154.2 (**C**(2')), 143.6 (Ar), 141.1 (**C**(5')), 136.8 (Ar), 129.8 (Ar), 127.0

(Ar), 110.2 (**C**(4')), 105.4 (**C**(3')), 71.4 (**C**(3)), 46.1 (**C**(4)), 43.0 (C(O)**C**$H_2$), 29.9 (**C**(2)), 25.6 (**C**H$(CH_3)_3$, 23.7 (**C**(1)), 22.3 (CH(**C**$H_3)_2$), 21.5 (Ar**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NNaO_5S$ $[M+Na]^+$ : 416.1502

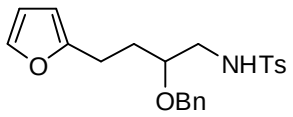
Found : 416.1500

**3-Methylbutanoic anhydride[204] (212)**



To a stirred solution of isovaleric acid (1.00 g, 9.79 mmol) in pyridine (2 mL) at RT was added benzylsulfonyl chloride (628 µL, 865 mg, 4.90 mmol) dropwise. Stirring is continued for 10 min then the reaction mixture poured onto ice-water. The aqueous layer was extracted with petrol (3 × 80 mL), the combined organics washed with sat. aq. $CuSO_4$ solution (2 × 80 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a colourless oil that was used without further purification (912 mg, 100%); $\delta_H$ (400 MHz, $CDCl_3$) 2.32 (4H, d, *J* 7.5, C(O)C**H$_2$**), 2.16 – 2.12 (2H, m, C**H**$(CH_3)_2$), 1.00 (12H, d, *J* 7.0, CH(C**H$_3$**$)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 168.8 (**C**=O), 44.1 (C(O)**C**$H_2$), 25.3 (**C**H$(CH_3)_2$), 22.2 (CH(**C**$H_3)_2$).

**_N_-(2-(Benzyloxy)-4-(furan-2-yl)butyl)-4-methylbenzenesulfonamide (213)**

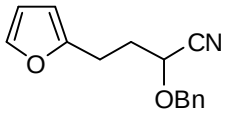



Prepared according to *general procedure H* from amine **216** (50 mg, 0.204 mmol). Purification by flash chromatography afforded the *title compound* as a yellow oil (66 mg, 81%); $R_f$ 0.52 (dichloromethane); $\nu_{max}$ (thin film)/$cm^{-1}$ 3288s, 3032s, 2926s, 1598m, 1496s, 1330s, 1162s, 1092s; $\delta_H$ (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.0, Ar**H**), 7.38 – 7.23 (8H, m, Ar**H** and C(5')**H**), 6.27 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.93 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 4.73 (1H, t, *J* 6.0, N**H**), 4.48 (1H, d, *J* 11.5, PhC**H**H'), 4.36 (1H, d, *J* 11.5, PhCH**H'**), 3.51 (1H, qd, *J* 6.0, 4.0, C(3)**H**), 3.15 (1H, ddd, *J* 13.0, 6.0, 4.0, C(4)**H**H'), 2.94 (1H, dt, *J* 13.0, 6.0, C(4)H**H'**), 2.65 (2H, t, *J* 7.5, C(1)**$H_2$**), 2.43 (3H, s, ArC**$H_3$**), 1.95 (1H, app. dq, *J* 14.0, 7.0, C(2)**H**H'), 1.81 (1H, dtd, *J* 14.0, 7.5, 6.0, C(2)H**H'**); $\delta_C$ (100 MHz, $CDCl_3$) 154.9 (**C**(2')), 143.4 (Ar), 141.0 (**C**(5')), 137.8 (Ar), 136.7 (Ar), 129.7 (Ar), 128.6 (Ar), 128.0 (Ar), 127.8 (Ar), 127.1 (Ar), 110.2 (**C**(4')), 105.2 (**C**(3')), 76.4 (**C**(3)), 71.5 (Ph**C**HH'), 45.5 (**C**(4)), 30.0 (**C**(2)), 23.6 (**C**(1)), 21.5 (Ar**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{22}H_{25}NNaO_4S$ $[M+Na]^+$ : 422.1397

Found : 422.1396

**2-(Benzyloxy)-4-(furan-2-yl)butanenitrile (214)**




**Method A:** Acetal **215** (651 mg, 2.02 mmol) and trimethylsilylcyanide (378 µL, 301 mg, 3.03 mmol) were added to a stirred solution of tetracyanoethylene (52 mg, 0.404 mmol) in acetonitrile (7.5 mL) and the reaction heated at 80 °C for 4 h. After cooling to RT, the acetonitrile layer was extracted with petrol (4 × 15 mL), the solvent removed *in vacuo*, and the residue purified by flash chromatography (30:1, petrol/ether) to afford the *title compound* as a colourless oil (327 mg, 67%).

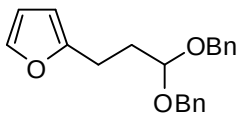
**Method B:** Trimethylsilyl trifluoromethanesulfonate (673 µL, 827 mg, 3.72 mmol) was added dropwise to a solution of tri(*o*-tolyl)phosphine (1.27 g, 4.17 mmol) and acetal **215** (600 mg, 1.86 mmol) in dichloromethane (15 mL) at –10 °C. The solution was stirred at RT for 1 h, then cooled to 0 °C and trimethylsilyl cyanide (699 µL, 554 mg, 5.58 mmol) added. After stirring at RT for 6 h, the reaction was quenched with sat. aq. $NaHCO_3$ solution (20 mL), the aqueous layer extracted with dichloromethane (3 × 20 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (100:1 → 40:1, petrol/ether) afforded the *title compound* as a colourless oil (328 mg, 73%).

$R_f$ 0.24 (10:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3033m, 2932s, 2871s, 2239w, 1599m, 1508s, 1455s, 1336s, 1145s, 1099s; $\delta_H$ (400 MHz, $CDCl_3$) 7.43 – 7.33 (5H, m, Ar**H**), 7.31 (1H, dd, *J* 2.0, 0.5, C(5')**H**), 6.28 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.98 (1H, dd, *J* 3.0, 0.5, C(3')**H**), 4.87 (1H, d, *J* 11.5, PhC**H**H'), 4.53 (1H, d, *J* 11.5, PhCH**H'**), 4.17 (1H, dd, *J* 7.5, 6.0, C(3)**H**), 2.86 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 2.30 – 2.15 (2H, m, C(2)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 153.3 (**C**(2')), 141.5 (**C**(5')), 135.8 (Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 118.0 (**C**N), 110.2 (**C**(4')), 106.0 (**C**(3')), 72.4 (Ph**C**HH'), 66.5 (**C**(3)), 32.0 (**C**(2)), 23.2 (**C**(1)).

HRMS (FI) *m/z* calcd for $C_{15}H_{15}NO_2$ $[M]^+$ : 241.1103

Found : 241.1102

**2-(3,3-Bis(benzyloxy)propyl)furan (215)**



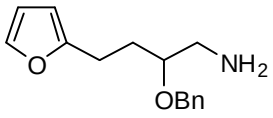

Aldehyde **206** (200 mg, 1.61 mmol) was added to a solution of *N*-chlorosuccinimide (11 mg, 0.082 mmol) and thiourea (3.0 mg, 0.039 mmol) in anhydrous benzyl alcohol (2 mL) at RT. After stirring for 4 h, the reaction mixture was poured onto a short column of silica and eluted with 30:1, petrol/ether. Evaporation of the solvent *in vacuo* afforded the *title compound* as a colourless oil (400 mg, 77%); $R_f$ 0.51 (7:1, petrol/ether); $\nu_{max}$

(thin film)/$cm^{-1}$ 3031s, 2933s, 2872s, 2360w, 2336w, 1598m, 1497m, 1454s, 1354s, 1124s, 1047s; $\delta_H$ (400 MHz, $CDCl_3$) 7.41 – 7.30 (11H, m, Ar**H** and C(5')**H**), 6.29 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.99 – 5.96 (1H, m, C(3')**H**), 4.81 (1H, t, *J* 6.0, C(3)**H**), 4.71 (2H, d, *J* 11.5, PhC**H**H'), 4.60 (2H, d, *J* 11.5, PhCH**H'**), 2.78 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 2.17 – 2.11 (2H, m, C(2)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 155.2 (**C**(2')), 141.0 (**C**(5')), 138.1 (Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 110.1 (**C**(4')), 105.0 (**C**(3')), 101.4 (**C**(3)), 67.5 (Ph**C**$H_2$), 31.7 (**C**(2)), 23.4 (**C**(1)).

HRMS (ESI) *m/z* calcd for $C_{21}H_{22}O_3$ $[M+Na]^+$ : 345.1461

Found : 345.1461

**2-(Benzyloxy)-4-(furan-2-yl)butan-1-amine (216)**



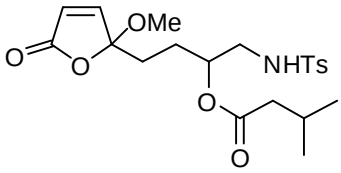

$LiAlH_4$ (79 mg, 2.02 mmol, 97% by weight) was added to a solution of nitrile **214** (326 mg, 1.35 mmol) in ether (4.5 mL) at 0 °C and the reaction stirred at RT for 10 min. The reaction was quenched at 0 °C by addition of water (0.1 mL), 20% aq. NaOH (0.1 mL), and a further portion of water (0.6 mL). The suspension was stirred at RT for 10 min then filtered through a pad of celite, and concentrated *in vacuo* to afford the *title compound* as a colourless oil (283 mg, 85%) that was used without purification; $R_f$ 0.32 (10:1:0.1, $CHCl_3$/MeOH/$NH_4OH$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3064w, 3031m, 2928s, 2864s,

1672s, 1596s, 1508s, 1497s, 1069s; $\delta_H$ (400 MHz, $CDCl_3$) 7.40 – 7.28 (6H, m, Ar**H** and C(5')**H**), 6.29 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 5.98 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 4.59 (1H, d, *J* 11.5, PhC**H**H'), 4.55 (1H, d, *J* 11.5, PhCH**H'**), 3.44 (1H, tt, *J* 6.5, 4.5, C(3)**H**), 2.88 (1H, dd, 13.5, 4.5, C(4)**H**H'), 2.77 – 2.71 (2H, m, C(1)$\mathbf{H_2}$), 2.76 (1H, dd, *J* 13.5, 6.5, C(4)H**H'**), 2.03 – 1.92 (1H, m, C(2)**H**H'), 1.92 – 1.82 (1H, m, C(2)H**H'**), 1.32 (2H, br s, N$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 155.7 (**C**(2')), 140.9 (**C**(5')), 138.6 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 110.1 (**C**(4')), 104.9 (**C**(3')), 79.8 (**C**(3)), 71.5 (Ph**C**HH'), 44.8 (**C**(4)), 30.2 (**C**(2)), 24.0 (**C**(1)).

HRMS ($ESI^+$) *m/z* calcd for $C_{15}H_{15}NO_2$ $[M]^+$ : 246.1489

Found : 246.1484

**4-(2-Methoxy-5-oxo-2,5-dihydrofuran-2-yl)-1-{[(4-methylphenyl)sulfonyl]amino}butan-2-yl 3-methylbutanoate (218)**



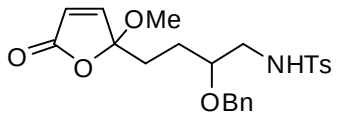

Prepared according to *general procedure D* from sulfonamide **211** (150 mg, 0.381 mmol). Purification by flash chromatography afforded the *title compound* as a 1:1 mixture of diastereomers as a viscous colourless oil (166 mg, 99%); $R_f$ 0.32 (99:1, dichloromethane/methanol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3277br, 2960m, 2873m, 1768s, 1733s,

1495s, 1453s, 1159s; $\delta_H$ (400 MHz, $C_6D_6$) 7.92 (2H,d, *J* 8.0, Ar**H**), 6.97 (2H, d, *J* 8.0, Ar**H**), 6.36 and 6.34 (1H, d, *J* 5.5, C(3')**H**), 5.76 and 5.74 (1H, d, *J* 5.5, C(4')**H**), 5.43 and 5.41 (1H, t, *J* 6.5, N**H**), 5.00 – 4.92 (1H, m, C(3)**H**), 3.06 – 2.99 (2H, m, C(4)$\mathbf{H_2}$), 2.87 (2 peaks, 3H, s, OC$\mathbf{H_3}$), 2.16 – 2.06 (3H, m, C(O)C$\mathbf{H_2}$ and C**H**$(CH_3)_2$), 2.04 (3H, s, ArC$\mathbf{H_3}$), 1.97 – 1.62 (4H, m, C(1)$\mathbf{H_2}$ and C(2)$\mathbf{H_2}$), 0.92 (2 peaks, 6H, d, *J* 6.5, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 172.5 (2 peaks, **C**(5)), 169.3 (2 peaks, **C**(5')), 152.8 (2 peaks, **C**(3')), 143.2 (Ar), 138.1 (Ar), 129.9 (Ar), 127.4 (Ar), 125.0 (**C**(4')), 110.1 (**C**(2')), 71.6 (2 peaks, **C**(3)), 50.6 (O**C**$H_3$), 46.1 and 46.0 (**C**(4)), 43.2 (C(O)**C**$H_2$), 33.2 (**C**(1)), 25.7 (**C**(2) and **C**H$(CH_3)_2$), 22.3 (CH(**C**$H_3)_2$), 21.1 (Ar**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{21}H_{29}NNaO_7S$ $[M+Na]^+$ : 462.1557

Found : 462.1543

**_N_-(2-(Benzyloxy)-4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)butyl)-4-methylbenzenesulfonamide (219)**



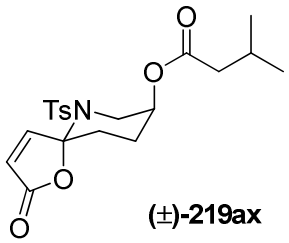

Prepared according to *general procedure D* from sulfonamide **213** (20 mg, 0.05 mmol). Purification by flash chromatography (99:1, dichloromethane/methanol) afforded the *title compound* as a 1:1 mixture of diastereomers as a colourless oil (17 mg, 76%); $R_f$

0.17 (199:1, dichloromethane/methanol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3288br, 3061m, 2928s, 1770s, 1599w, 1455m, 1333s, 1267s, 1163s, 1092s; $\delta_H$ (500 MHz, $CDCl_3$) 7.69 (2H, d, *J* 8.0, Ar**H**), 7.36 – 7.21 (7H, m, Ar**H**), 7.08 and 7.07 (1H, d, *J* 5.5, C(3')**H**), 6.20 (1H, d, *J* 5.5, C(4')**H**), 4.93 (1H, t, *J* 6.0, N**H**), 4.45 and 4.43 (1H, d, *J* 11.5, PhC**H**H'), 4.38 and 4.37 (1H, d, *J* 11.5, PhCH**H'**), 3.52 and 3.51 (1H, app. quin, *J* 5.5 C(3)**H**), 3.17 (3H, s, OC**$H_3$**), 3.10 – 3.04 (1H, m, C(4)**H**H'), 2.94 and 2.90 (1H, dd, *J* 13.0, 6.0, C(4)H**H'**), 2.42 (3H, s, ArC**$H_3$**), 1.98 – 1.78 (2H, m, C(1)**$H_2$**), 1.74 – 1.58 (2H, m, C(2)**$H_2$**); $\delta_C$ (125 MHz, $CDCl_3$) 169.7 (**C**(5')), 153.4 (2 peaks, **C**(3')), 143.5 (Ar), 137.7 (Ar), 136.7 (Ar), 136.6 (Ar), 129.8 (Ar), 128.5 (Ar), 127.9 and 127.8 (Ar), 127.0 (Ar), 125.0 (2 peaks, **C**(4')), 110.7 (2 peaks, **C**(2')), 76.6 (**C**(3)), 71.4 (2 peaks, O**C**$H_2$Ph), 51.2 (O**C**$H_3$), 45.4 and 45.3 (**C**(4)), 32.5 and 32.4 (**C**(1)), 25.3 (**C**(2)), 21.5 (Ar**C**$H_3$).

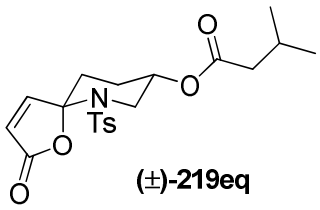
HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NNaO_6S$ $[M+Na]^+$ : 468.1451

Found : 468.1451

**(5*R**,8*S**)-8-Isovaleryloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (219ax) and (5*S**,8*S**)-8-Isovaleryloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (219eq)**




**(±)-219ax**




**(±)-219eq**

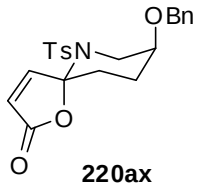
40% aq. $H_2SO_4$ (1.0 mL) was added to methoxybutenolide **217** (167 mg, 0.38 mmol) and the suspension stirred at RT for 5 d. The reaction mixture was diluted with sat. aq. $NaHCO_3$ solution (50 mL), the aqueous layer extracted with ethyl acetate (3 × 50 mL), and the combined organic layers washed with brine (50 mL) and dried over $MgSO_4$ then concentrated *in vacuo*. Purification by flash chromatography (99:1 → 97:3, dichloromethane/methanol) afforded both diastereomers of the *title compound* (**219ax/219eq**, *dr* = 65:35) as a yellow oil (42 mg, 27%); $R_f$ : 0.11 (dichloromethane); $\nu_{max}$ (thin film)/$cm^{-1}$ 2970s, 2922ms, 1766s, 1728s, 1345s, 1164s; $\delta_H$ (400 MHz, $CDCl_3$) 7.85 (1H, d, *J* 5.5, C(3')**H**, **ax**), 7.77 (1H, d, *J* 5.5, C(3')**H**, **eq**), 7.49 (2H, d, *J* 8.5, Ar**H**, **eq**), 7.48 (2H, d, *J* 8.5, Ar**H**, **ax**), 7.31 (2H, d, *J* 8.5, Ar**H**, **eq**), 7.29 (2H, d, *J* 8.5, Ar**H**, **ax**), 6.02 (1H, d, *J* 5.5, C(4')**H**, **ax**), 6.01 (1H, d, *J* 5.5, C(4')**H**, **eq**), 5.17 – 5.13 (1H, m, C(3)**H**, **ax**), 5.01 (1H, tdd, *J* 11.5, 5.5, 5.0, C(3)**H**, **eq**), 4.27 – 4.22 (2H, m, C(4)**H**H'**,** both) 3.27 (1H, dd, *J* 13.0, 2.0, C(4)H**H'**, **ax**), 3.06 (1H, t, *J* 11.0, C(4)H**H'**, **eq**), 2.43 (3H, s, ArC**$H_3$**, **eq**), 2.42 (3H, s, ArC**$H_3$**, **ax**), 2.40 – 1.61 (4H, m, C(1)**H**H', C(2)**$H_2$** and C**H**$(CH_3)_2$, both), 2.30 (2H, d, *J* 7.0,

C(O)C**H₂**, **ax**, overlapping), 2.29 (2H, d, *J* 7.0, C(O)C**H₂**, **eq**, overlapping), 1.52 – 1.47 (1H, m, C(1)H**H'**, both), 1.02 (6H, d, *J* 6.5, CH(C**H₃**)$_2$, **ax**), 0.97 (6H, d, *J* 6.5, CH(C**H₃**)$_2$, **eq**); $\delta_C$ (100 MHz, $CDCl_3$) 172.5 (**C**(5), **ax**), 171.9 (**C**(5), **eq**), 169.5 (**C**(5'), **ax**), 169.3 (**C**(5'), **eq**), 157.1 ((**C**(3'), **ax**), 156.6 ((**C**(3'), **eq**), 144.8 (Ar, **eq**), 144.6 (Ar, **ax**), 135.3 (Ar, **ax**), 135.0 (Ar, **eq**), 130.0 (Ar, **eq**), 129.9 (Ar, **ax**), 127.3 (Ar, **eq**), 127.2 (Ar, **ax**), 119.0 (**C**(4'), **eq**), 118.7 (**C**(4'), **ax**), 94.9 (**C**(2'), **ax**), 94.2 (**C**(2'), **eq**), 67.3 (**C**(3), **eq**), 64.7 (**C**(3), **ax**), 48.0 (**C**(4), **ax**), 47.6 (**C**(4), **eq**), 43.5 (**C**(6), **ax**), 43.3 (**C**(6), **eq**), 32.6 (**C**(1), **ax**), 31.9 (**C**(1), **eq**), 25.8 (**C**(2), **ax**), 25.7 (**C**H($CH_3$)$_2$, both), 25.6 (**C**(2), **eq**), 22.4 (CH(**C**H$_3$)$_2$, **ax**), 22.3 (CH(**C**H$_3$)$_2$, **eq**), 21.7 (Ar**C**H$_3$, **eq**), 21.6 (Ar**C**H$_3$, **ax**).

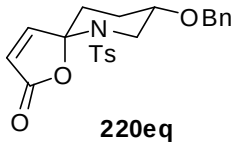
HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NNaO_6S$ $[M+Na]^+$ : 430.1293

Found : 430.1295

**(5*R**,8*S**)-8-Benzyloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (220ax) and (5*S**,8*S**)-8-Benzyloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (220eq)**




**220ax**




**220eq**

40% aq. $H_2SO_4$ (1.0 mL) was added to methoxybutenolide **218** (177 mg, 0.397 mmol) and the suspension stirred at RT for 2 d. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (20 mL), the aqueous layer extracted with ethyl acetate (3 × 20 mL), and the combined organic layers washed with brine (20 mL) and dried over $MgSO_4$ then concentrated *in vacuo*. Purification by flash chromatography (99:1, dichloromethane/methanol) afforded both diastereomers of the *title compound* (**220ax**/**220eq**, *dr* = 15:85) as a pale yellow solid (123 mg, 75%); $R_f$ 0.45 (98:2, dichloromethane/methanol); m.p. 164 – 166 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3030s, 2922s, 2360s, 1770s, 1580m, 1341s, 1161s, 1101s.

NMR data for **220ax**: $\delta_H$ (400 MHz, $CDCl_3$) $\delta_H$ (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 5.5, C(3')**H**), 7.52 (2H, d, *J* 8.5, Ar**H**), 7.44 – 7.30 (5H, m, Ar**H**), 7.29 (2H, d, *J* 8.5, Ar**H**), 5.99 (1H, d, *J* 5.5, C(4')**H**), 4.78 (1H, d, *J* 12.0, PhC**H**H') 4.55 (1H, d, *J* 12.0, PhCH**H'**), 4.39 (1H, ddd, *J*

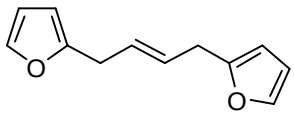
13.0, 3.0, 2.0, C(4)**H**H'), 3.82 – 3.73 (1H, m, C(3)**H**), 3.14 (1H, dd, *J* 13.0, 1.5, C(4)H**H'**), 2.50 (1H. td, *J* 13.5, 4.5, C(1)**H**H'), 2.42 (3H, s, ArC**H$_3$**), 2.03 – 1.97 (1H, m, C(2)**H**H'), 1.92 (1H, tdd, *J* 14.0, 4.5, 3.0, C(2)H**H'**), 1.40 (1H, ddd, *J* 13.5, 4.5, 2.5, C(1)H**H'**); $\delta_C$ (100 MHz, $CDCl_3$) 169.9 (**C**(5')), 157.5 (**C**(3')), 144.4 (Ar), 137.9 (Ar), 135.7 (Ar), 129.9 (Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 127.2 (Ar), 118.6 (**C**(4')), 95.4 (**C**(2')), 69.9 (Ph**C**H$_2$), 68.7 (**C**(3)), 46.6 (**C**(4)), 32.4 (**C**(1)), 25.2 (**C**(2)), 21.6 (Ar**C**H$_3$).

NMR data for **220eq**: $\delta_H$ (400 MHz, $CDCl_3$) 7.74 (1H, d, *J* 5.5, C(3')**H**), 7.46 (2H, d, *J* 8.5, Ar**H**), 7.41-7.31 (5H, m, Ar**H**), 7.29 (2H, d, *J* 8.5, Ar**H**), 5.99 (1H, d, *J* 5.5, C(4')**H**), 4.65 (2H, s, PhC**H$_2$**) 4.29 (1H, ddd, *J* 11.0, 4.5, 1.5, C(4)**H**H'), 3.72 (1H, tt, *J* 11.0, 4.5, C(3)**H**), 2.94 (1H, t, *J* 11.0, C(4)H**H'**), 2.42 (3H, s, ArC**H$_3$**), 2.17 – 2.11 (1H, m, C(2)**H**H'), 2.04 (1H, td, *J* 13.5, 4.5, C(1)**H**H'), 1.79 (1H, ddd, *J* 13.5, 13.0, 11.0, 4.0, C(2)H**H'**), 1.63 (1H, ddd, *J* 13.5, 4.0, 3.0, C(1)**H**H'); $\delta_C$ (100 MHz, $CDCl_3$) 169.5 (**C**(5')), 156.9 (**C**(3')), 144.7 (Ar), 138.0 (Ar), 135.0 (Ar), 129.9 (Ar), 128.5 (Ar), 127.9 (Ar), 127.6 (Ar), 127.3 (Ar), 118.8 (**C**(4')), 94.4 (**C**(2')), 72.8 (**C**(3)), 71.0 (**C**H$_2$Ph), 48.7 (**C**(4)), 36.1 (**C**(1)), 26.9 (**C**(2)), 21.6 (Ar**C**H$_3$).

HRMS (ESI) *m/z* calcd for $C_{22}H_{23}NNaO_5S$ $[M+Na]^+$ : 436.1189

Found : 436.1175

**(*E*)-1,4-Di(furan-2-yl)but-2-ene (229)**

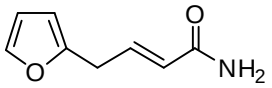


2-(Tributylstannyl)furan (5 mL, 15.9 mmol) was added to a stirred suspension of freshly purified copper(I) chloride (157 mg, 1.59 mmol) in DMF (54 mL). The mixture was warmed to 90 °C and (*E*)-1,4-dibromobut-2-ene (1.70 g, 7.94 mmol) added. After stirring for 16 h, the reaction mixture was cooled to RT and sat. aq. KF solution (20 mL) added. The suspension was diluted with ether (50 mL), filtered through a celite pad and the separated aqueous layer extracted with ether (2 × 50 mL). The combined organic layers were washed with water (2 × 100 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (99:1, petrol/ether) afforded the *title compound* as a colourless oil (1.12 g, 75%); $R_f$ 0.27 (petrol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3117br, 2958m, 2923s, 1596s, 1506m, 1148m, 1009s; $\delta_H$ (400 MHz, $CDCl_3$) 7.34 (2H, dd, *J* 2.0, 1.0, C(5')**H**), 6.32 (2H, dd, *J* 3.0, 2.0, C(4')**H**), 6.04 (2H, dd, *J* 3.0, 1.0, C(3')**H**), 5.74 – 5.70 (2H, m, C(2)**H** and C(3)**H**), 3.42 (4H, d, *J* 4.5, C(1)$\mathbf{H_2}$ and C(4)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 154.2 (**C**(2')), 141.2 (**C**(5')), 127.9 (**C**(2) and **C**(3)), 110.2 (**C**(4')), 105.3 (**C**(3'), 31.3 (**C**(1) and **C**(4)).

HRMS (ESI) *m/z* calcd for $C_{12}H_{12}O_2$ $[M]^+$ : 188.0837

Found **:** 188.0836

**(*E*)-4-(Furan-2-yl)but-2-enamide (230)**

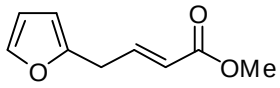


Acrylamide (100 mg, 1.41 mmol) was added to a solution of titanium(IV) isopropoxide (470 µL, 440 mg, 1.55 mmol) in dry, degassed dichloromethane (5 mL) and the mixture stirred for 1 h at 40 °C. Alkene **229** (200 mg, 1.06 mmol) and Grubbs' II catalyst (90 mg, 0.106 mmol) were added and stirring continued for a further 48 h at 40 °C. The solvent was removed *in vacuo* and the crude residue purified by flash chromatography (ethyl acetate → 98:2, ethyl acetate/methanol) to afford the *title compound* as a brown oil (51 mg, 16%); $R_f$ 0.15 (98:2, EtOAc/MeOH); $\nu_{max}$ (thin film)/$cm^{-1}$ 3352s, 3180s, 1672s, 1609s, 1422s, 1076m; $\delta_H$ (500 MHz, MeOH-$d^4$) 7.42 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.88 (1H, dt, *J* 15.5, 6.5, C(2)**H**), 6.35 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.14 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 6.01 (1H, d, *J* 15.5, 1.5, C(3)**H**), 3.56 (2H, d, *J* 6.5, C(1)$\mathbf{H_2}$); $\delta_C$ (100 MHz, MeOH-$d^4$) 170.7 (**C**=O), 153.3 (**C**(2'), 143.0 (**C**(5'), 141.8 (**C**(2), 126.0 (**C**(3), 111.4 (**C**(4'), 107.4 (**C**(3'), 31.4 (**C**(1).

HRMS (ESI) *m/z* calcd for $C_8H_9NNaO_2$ $[M+Na]^+$ : 174.0525

Found : 174.0525

**(*E*)-Methyl 4-(furan-2-yl)but-2-enoate (231)**

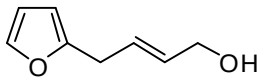



Hoveyda-Grubbs' II catalyst (33 mg, 53.1 µmol) was added to a stirred solution of alkene **229** (100 mg, 0.531 mmol) and methyl acrylate (145 µL, 137 mg, 1.59 mmol) in degassed DCM (6 mL). The reaction mixture was heated at 40 °C for 4 h then concentrated *in vacuo*. Purification by flash chromatography (98:2, petrol/ether) afforded the *title compound* as a colourless oil (127 mg, 72%); $R_f$ 0.25 (95:5, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2952m, 1724s, 1660s, 1437m, 1338m, 1277s, 1013m; $\delta_H$ (400 MHz, $CDCl_3$) 7.34 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 7.04 (1H, dt, *J* 15.5, 6.5, C(2)**H**), 6.32 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.09 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 5.89 (1H, dt, *J* 15.5, 2.0, C(3)**H**), 3.74 (3H, s, OC**H$_3$**), 3.55 (2H, d, *J* 6.5, C(1)**H$_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 166.7 (**C**=O), 151.2 (**C**(2'), 144.0 (**C**(2), 141.8 (**C**(5'), 122.8 (**C**(3), 110.4 (**C**(4'), 106.6 (**C**(3'), 51.5 (O**C**$H_3$), 30.8 (**C**(1).

HRMS (FI) *m/z* calcd for $C_9H_{10}O_3$ $[M]^+$ : 166.0630

Found : 166.0634

**(*E*)-4-(Furan-2-yl)but-2-en-1-ol (232)**

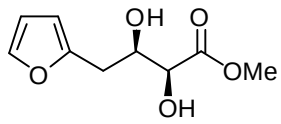



Boron trifluoride diethyletherate (33 µL, 37 mg, 0.264 mmol) was added to a stirred solution of ester **231** (20 mg, 0.12 mmol) in dichloromethane (0.5 mL) at –78 °C. The reaction was stirred at this temperature for 15 min, DIBAL-H (0.36 mL, 0.36 mmol, 1 M solution in hexane) added, the reaction stirred for a further 2 h at –78 °C, then quenched with acetic acid (70 µL) and sat. aq. potassium sodium tartrate (5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1, petrol/ether) afforded the *title compound* as a pale yellow oil (13 mg, 76%); $R_f$ 0.17 (2:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3333br s, 2919m, 2869s, 1718m, 1672s, 1596s, 1506s, 1424s, 1145m, 1074s; $\delta_H$ (400 MHz, $CDCl_3$) 7.33 (1H, d, *J* 2.0, C(5')**H**), 6.30 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.03 (1H, d, *J* 3.0, C(3')**H**), 5.88 – 5.72 (2H, m, C(2)**H** and C(3)**H**), 4.15 (2H, d, *J* 5.0, C(4)$\mathbf{H_2}$), 3.41 (2H, d, *J* 6.0, C(1)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 153.7 (**C**(2')), 141.3 (**C**(5')), 131.4 (**C**(2)), 127.9 (**C**(3)), 110.3 (**C**(4')), 105.6 (**C**(3')), 63.4 (**C**(4)), 31.1 (**C**(1)).

HRMS (FI) *m/z* calcd for $C_8H_{10}O_2$ $[M]^+$ : 138.0681

Found : 138.0675

**(2*S*,3*R*)-Methyl 4-(furan-2-yl)-2,3-dihydroxybutanoate (233)**

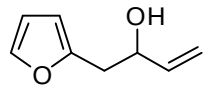



Synthesised by *general procedure F* from ester **231** (760 mg, 4.04 mmol). Purification by flash chromatography (97:3, dichloromethane/methanol) gave the *title compound* as a colourless oil (582 mg, 72%); $R_f$ 0.12 (1:1, petrol/ethyl acetate); $[\alpha]_D^{21}$ –1.90 (c = 1.0, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3421s, 2958m, 1735s, 1439m, 1261s, 1052s; $\delta_H$ (400 MHz, $CDCl_3$) 7.36 (1H, d, *J* 2.0, C(5')**H**), 6.32 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.16 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 4.28 (1H, app. qd, *J* 6.0, 2.0, C(2)**H**), 4.14 (1H, dd, *J* 6.0, 2.0, C(3)**H**), 3.83 (3H, s, OC**H$_3$**), 3.20 – 3.14 (1H, m, O**H**), 3.01 (2H, d, *J* 6.5, C(1)**H$_2$**), 2.32 – 2.24 (1H, m, O**H**); $\delta_C$ (100 MHz, $CDCl_3$) 173.7 (**C**=O), 151.6 (**C**(2')), 141.8 (**C**(5')), 110.4 (**C**(4')), 107.4 (**C**(3')), 72.2 (**C**(3)), 71.1 (**C**(2)), 52.9 (O**C**$H_3$), 32.6 (**C**(1)).

HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NNaO_4S$ $[M+Na]^+$ : 223.0577

Found : 223.0580

**1-(Furan-2-yl)but-3-en-2-ol[205] (235)**

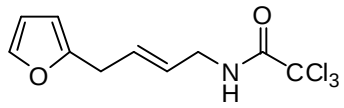



*n*-Butyllithium (1.67 mL, 2.67 mmol, 1.6 M solution in hexanes) was added to a solution of furan (200 mg, 214 μL, 2.94 mmol) in ether (4 mL) at 0 °C and the reaction stirred at this temperature for 1 h. After cooling to –78 °C, butadiene monoxide (94 mg, 108 μL, 1.34 mmol) was added, the reaction allowed to warm up to RT over 5 h and then quenched with sat. aq. $NHCl_4$ (20 mL). The suspension was filtered through a pad of celite, the aqueous layer was extracted with dichloromethane (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a pale yellow oil that was used without further purification (85 mg, 46%); $R_f$ 0.21 (dichloromethane); $\nu_{max}$ (neat)/$cm^{-1}$ 3419br, 2951s, 2860s, 1793s, 1360m, 1107s; $\delta_H$ (400 MHz, $CDCl_3$) 7.36 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.32 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.14 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 5.93 (1H, ddd, *J* 17.0, 10.5, 6.0, C(3)**H**), 5.30 (1H, dt, *J* 17.0, 1.5, C(4)H**H'**), 5.16 (1H, dt, *J* 10.5, 1.5, C(4)**H**H'), 4.46 – 4.43 (1H, m, C(2)**H**), 4.10 (1H, br s, O**H**), 2.93 (1H, dd, *J* 15.0, 5.0, C(1)**H**H'), 2.86 (1H, dd, *J* 15.0, 8.0, C(1)H**H'**); $\delta_C$ (100 MHz, $CDCl_3$) 152.0 (**C**(2')), 141.7 (**C**(5')), 139.7 (**C**(3)), 115.3 (**C**(4)), 110.3 (**C**(4')), 107.3 (**C**(3')), 71.4 (**C**(2)), 36.1 (**C**(1)).

HRMS (FI) *m*/*z*: calcd for $C_8H_{10}O_2$ $[M]^+$ : 138.0681

Found : 138.0687

**(*E*)-2,2,2-Trichloro-N-(4-(furan-2-yl)but-2-enyl)acetamide (236)**

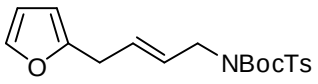


NaH (14 mg, 0.362 mmol, 60% dispersion in mineral oil) was added to stirred solution of alcohol **235** (100 mg, 0.724 mmol) in ether (5 mL) at RT. After the evolution of hydrogen ceased, the reaction was cooled to –15 °C and trichloroacetonitrile (157 mg, 109 µL, 1.09 mmol) added dropwise. The mixture was allowed to warm to RT over 2 h, concentrated *in vacuo*, pentane (4 mL containing 14 µL, 0.724 mmol of methanol) added with vigorous stirring, and the solution filtered through a pad of celite. The solvent was then removed *in vacuo*, the crude imidate taken up in *m*-xylene (5 mL) and the reaction stirred at 150 °C for 6 h. After cooling to RT, the solvent was evaporated *in vacuo* and the residue purified by flash chromatography (10:1 → 5:1, petrol/ether) to give the *title compound* as a colourless oil (78 mg, 38%); $R_f$ 0.37 (2:1, petrol/ether); $\nu_{max}$ (neat)/$cm^{-1}$ 3340br, 2927s, 1698s, 1596w, 1517s, 1430w, 1257m, 1010m, 823s; $\delta_H$ (400 MHz, $CDCl_3$) 7.33 (1H, s, C(5')**H**), 6.77 (1H, br s, N**H**), 6.31 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.04 (1H, d, *J* 3.0, C(3')**H**), 5.86 (1H, dt, *J* 15.5, 6.5, C(2)**H**), 5.62 (1H, dt, *J* 15.5, 6.0, C(3)**H**), 3.99 (2H, t, *J* 6.0, C(4)$\mathbf{H_2}$), 3.42 (2H, *J* 6.5, C(1)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 161.7 (**C**=O), 153.1 (**C**(2')), 141.4 (**C**(5')), 130.2 (**C**(3)), 126.1 (**C**(2)), 110.3 (**C**(4')), 105.8 (**C**(3')), 92.5 (**C**$Cl_3$), 42.9 (**C**(4)), 31.0 (**C**(1)).

HRMS ($ESI^+$) *m/z*: calcd for $C_{10}H_{10}Cl_3NNaO_2$ [$M+Na^+$] : 303.9669

Found : 303.9668

**(*E*)-*tert*-Butyl 4-(furan-2-yl)but-2-enyl(tosyl)carbamate (238)**



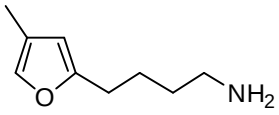

Triphenylphosphine (18 mg, 69.5 μmol) was added to a solution of diisopropylazodicarboxylate (13 μL, 13 mg, 66.6 μmol) in THF at –78 °C and the reaction stirred at this temperature for 40 min. Alcohol **232** (10 mg, 72.4 μmol) was added, followed by *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (18 mg, 66.6 μmol), and the reaction mixture stirred at RT for 12 h. The reaction was concentrated *in vacuo* and the crude residue purified by flash chromatography (20:1 → 10:1, petrol/ether) to afford the *title compound* as a yellow oil (11 mg, 42%); $R_f$ 0.43 (2:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2929s, 2860s, 1699s, 1422s, 1172s, 1006s; $\delta_H$ (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.5, Ar**H**), 7.33 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 7.28 (2H, d, *J* 8.5, Ar**H**), 6.31 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.04 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 5.90 (1H, dtt, *J* 15.5, 7.0, 1.5, C(2)**H**), 5.70 (1H, dtt, *J* 15.5, 6.5, 1.5, C(3)**H**), 4.43 (2H, dd, *J* 6.5, 1.5, C(4)**$H_2$**), 3.42 (2H, d, *J* 7.0, C(1)**$H_2$**), 2.44 (3H, s, ArC**$H_3$**), 1.33 (9H, s, C(C**$H_3$**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 153.5 (**C**=O), 150.7 (**C**(2')), 144.0 (Ar), 141.3 (**C**(5')), 137.3 (Ar), 130.3 (**C**(3)), 129.2 (Ar), 128.1 (Ar), 127.2 (**C**(2)),

110.3 (**C**(4')), 105.7 (**C**(3')), 84.3 (**C**$(CH_3)_3$), 47.9 (**C**(4)), 31.1 (**C**(1)), 27.9 (C(**C**$H_3)_3$), 21.6 (Ar**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NNaO_5S$ $[M+Na]^+$ : 414.1346

Found : 414.1331

**4-(4-Methylfuran-2-yl)butan-1-amine (242)**



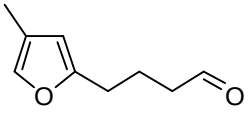

$LiAlH_4$ (443 mg, 11.1 mmol, 98% by weight) was added to a stirred solution of nitrile **268** (1.11 g, 7.41 mmol) in ether (30 mL) at 0 °C then the reaction stirred at RT for 15 min. After re-cooling to 0 °C, the reaction was quenched by the sequential addition of water (0.5 mL), 20% aq. NaOH (0.5 mL), a further portion of water (1.5 mL) and allowed to stir at RT for 20 min. The reaction mixture was then filtered through a pad of celite and concentrated *in vacuo* to afford the *title compound* as a pale yellow solid (1.08 g, 95%) that was used without further purification; $R_f$ 0.27 (10:1:0.1, $CHCl_3$/MeOH/$NH_4OH$); m.p. 44 – 46 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3297m, 2927s, 2845m, 1552s, 1459s, 1387m, 1320s, 1119m; $\delta_H$ (400 MHz, $CDCl_3$) 7.01 (1H, s, C(5')**H**), 5.82 (1H, s, C(3')**H**), 2.67 (2H, t, *J* 7.0, C(4)**H$_2$**), 2.54 (2H, t, *J* 7.5, C(1)**H$_2$**), 2.43 (2H, br s, N**H**), 1.94 (3H, s, C(4')C**H$_3$**), 1.61 (2H, quin, *J* 7.5, C(2)**H$_2$**), 1.46 (2H, app. quin, *J* 7.5, C(3)**H$_2$**); $\delta_c$ (100 MHz, $CDCl_3$) 156.0

(**C**(2')), 137.4 (**C**(5')), 120.4 (**C**(4')), 107.6 (**C**(3')), 41.6 (**C**(4)), 32.8 (**C**(3)), 27.8 (**C**(1)), 25.3 (**C**(2)), 9.7 (C(4')**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_9H_{16}NO$ $[M+H]^+$ : 154.1226

Found : 154.1223

**4-(4-Methylfuran-2-yl)butanal (243)**



To a stirred solution of nitrile **268** (500 mg, 3.35 mmol) in dichloromethane (30 mL) at –78 °C was added DIBAL-H (4.02 mL, 4.02 mmol, 1M solution in hexanes). After stirring at –78 °C for 1.5 h, the reaction mixture was poured onto sat. aq. potassium sodium tartrate (30 mL) and stirred at RT for 1 h. The separated aqueous layer was extracted with dichloromethane (2 × 30 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (40:1 → 30:1, petrol/ether) afforded the *title compound* as a colourless oil (418 mg, 82%); $R_f$ 0.22 (10:1, petrol/ether), $\nu_{max}$ (thin film)/$cm^{-1}$ 2930s, 2734w, 1724s, 1618w, 1552w, 1455w, 1389m, 1116s; $\delta_H$ (400 MHz, $CDCl_3$) 9.74 (1H, s, C(4)**H**), 7.06 (1H, s, C(5')**H**), 5.88 (1H, s, C(3')**H**), 2.63 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 2.47 (2H, td, *J* 7.5, 1.5, C(3)$\mathbf{H_2}$), 1.98 (3H, s, C(4')C$\mathbf{H_3}$, overlapping), 1.96 (2H, quin, *J* 7.5, C(2)$\mathbf{H_2}$, overlapping); $\delta_c$ (100 MHz, $CDCl_3$) 202.0 (**C**(4)),

154.8 (**C**(2')), 137.7 (**C**(5')), 120.5 (**C**(4')), 108.4 (**C**(3')), 43.0 (**C**(3)), 27.2 (**C**(1)), 20.6 (**C**(2)), 9.7 (C(4')**C**$H_3$).

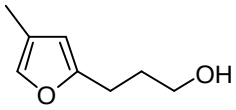
HRMS (FI) *m/z* calcd for $C_9H_{12}O_2$ $[M]^+$ : 152.0837

Found : 152.0839

**6-(2-Methyloxiran-2-yl)hex-5-yn-1-ol[184] (249)**

Prepared according to literature procedure.

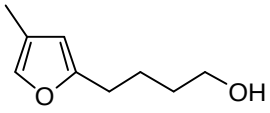
**3-(4-Methylfuran-2-yl)propan-1-ol[206] (250)**




To a solution of ester **291** (1.09 g, 4.86 mmol) in ether (25 mL) at 0 °C was added KO*t*-Bu (5.16 g, 45.9 mmol) and water (2.10 mL). The reaction was stirred at RT for 4 d then 1 M aq. HCl (50 mL) added and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and the crude residue purified by flash chromatography (2:1, petrol/ether) to afford the title compound as a pale yellow oil (647 mg, 95%); $R_f$ 0.18 (2:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3338br s, 2963s, 2882s, 1544s, 1118s, 1052s; $\delta_H$ (400 MHz, $CDCl_3$) 7.07 (1H, s,

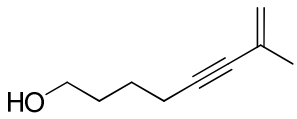
C(5')**H**), 5.88 (1H, s, C(3')**H**), 3.68 (2H, t, *J* 6.5, C(3)**H$_2$**), 2.68 (2H, t, *J* 7.5, C(1)**H$_2$**), 1.99 (3H, s, C(4')C**H$_3$**), 1.88 (2H, tt, *J* 7.5, 6.5, C(2)**H$_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 155.6 (**C**(2')), 137.5 (**C**(5')), 120.5 (**C**(4')), 107.9 (**C**(3')), 62.1 (**C**(3)), 31.0 (**C**(2)), 24.4 (**C**(1)), 9.8 (C(4')**C**$H_3$).

**4-(4-Methylfuran-2-yl)butan-1-ol[184] (251)**



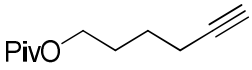

$AuCl_3$ (3 mg, 9.75 μmmol) was added to a stirred solution of oxirane **249** (30 mg, 0.195 mmol) in dry MeCN (0.3 mL) and the reaction stirred in the absence of light at RT. The reaction was stopped after 48 h as decomposition of the material had started to occur. The solvent was removed *in vacuo* and the crude residue purified by flash chromatography (2:1, petrol/ether) to afford the title compound as a colourless oil (12 mg, 40%); $R_f$ 0.16 (2:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3422s br, 2944s, 1751s, 1443m, 1234m, 1046s; $\delta_H$ (400 MHz, $CDCl_3$) 6.97 (1H, s, C(5')**H**), 5.79 (1H, s, C(3')**H**), 3.61 (2H, t, *J* 6.5, C(4)**H$_2$**), 2.53 (2H, t, *J* 7.5, C(1)**H$_2$**), 1.91 (3H, s, C(4')C**H$_3$**), 1.63 (2H, quin, *J* 7.5, C(2)**H$_2$**), 1.53 (2H, app. quin, *J* 7.0, C(3)**H$_2$**), 1.44 (1H, s, O**H**); $\delta_c$ (100 MHz, $CDCl_3$) 156.0 (**C**(2')), 137.2 (**C**(5')), 120.2 (**C**(4')), 107.6 (**C**(3')), 62.1 (**C**(4)), 32.1 (**C**(3)), 27.7 (**C**(1)), 24.2 (**C**(2)), 9.6 (C(4')**C**$H_3$).

**7-Methyloct-7-en-5-yn-1-ol[184] (252)**




Synthesised by *general procedure E* from 2-bromopropene (5.14 mL, 7.00 g, 57.9 mmol) and 5-hexyn-1-ol (2.12 mL, 1.89 g, 19.3 mmol). Purification by flash chromatography (4:1 → 2:1, petrol/ether) afforded the title compound as a pale yellow oil (2.51 g, 94%); $R_f$ 0.28 (3:1, petrol/ether); $\delta_H$ (400 MHz, $CDCl_3$) 5.18 – 5.15 (1H, m, C(8)**H**H'), 5.11 (1H, quin, *J* 1.5, C(8)H**H'**), 3.62 (2H, t, *J* 7.0, C(1)**$H_2$**), 2.31 (2H, t, *J* 7.0, C(4)**$H_2$**), 1.83 (3H, t, *J* 1.5, C(7)C**$H_3$**), 1.65 (2H, quin, *J* 7.0, C(2)**$H_2$**, overlapping), 1.58 (2H, quin, *J* 7.0, C(3)**$H_2$**, overlapping); $\delta_c$ (100 MHz, $CDCl_3$) 127.2 (**C**(7)), 120.4 (**C**(8)), 88.9 (**C**(5)), 82.1 (**C**(6)), 62.2 (**C**(1)), 31.7 (**C**(2)), 25.0 (**C**(3)), 23.8 (C(7)**C**$H_3$), 19.0 (**C**(4)).

**Hex-5-ynyl pivalate (257)**



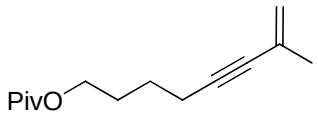

To a stirred solution of 5-hexyn-1-ol (300 mg, 3.06 mmol) and triethylamine (512 µL, 372 mg, 3.67 mmol) in dichloromethane (12 mL) at 0 °C was added trimethylacetyl chloride (413 µL, 405 mg, 3.36 mmol). The reaction was stirred at RT for 18 h then diluted with

sat. aq. $NaHCO_3$ (30 mL). The separated aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1, petrol/ether) afforded the *title compound* as a yellow oil (524 mg, 94%); $R_f$ 0.48 (5:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2958s, 2390w, 2219m, 1727s, 1480m, 1367m, 1284s, 1152s; $\delta_H$ (400 MHz, $CDCl_3$) 4.09 (2H, t, *J* 7.0, C(1)**H$_2$**), 2.24 (2H, td, *J* 7.0, 2.5, C(4)**H$_2$**), 1.96 (1H, t, *J* 2.5, C(6)**H**) 1.76 (2H, quin, *J* 7.0, C(2)**H$_2$**), 1.61 (2H, quin, *J* 7.0, C(3)**H$_2$**), 1.20 (9H, s, C(C**H$_3$**)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 178.5 (**C**=O), 83.9 (**C**(5)), 68.6 (**C**(6)), 63.8 (**C**(1)), 38.7 (**C**$(CH_3)_3$), 27.7 (**C**(2)), 27.2 (C(**C**$H_3)_3$), 25.0 (**C**(3)), 18.1 (**C**(4));

HRMS (ESI) *m/z* calcd for $C_{11}H_{18}NaO_2$ $[M+Na]^+$ : 205.1199

Found : 205.1192

**7-Methyloct-7-en-5-ynyl pivalate (258)**



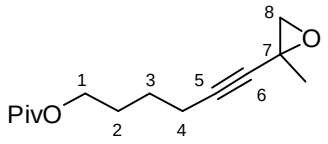

Synthesised by *general procedure E* from alkyne **257** (100 mg, 0.549 mmol) and 2-bromopropene (147 µL, 200 mg, 1.65 mmol). Purification by flash chromatography (10:1, petrol/ether) afforded the *title compound* as a colourless oil (95 mg, 78%); $R_f$ 0.55 (5:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3511w, 2959s, 2873s, 2215m, 1728s, 1679s, 1615m, 1480s, 1285s, 1156s, 1040m; $\delta_H$ (400 MHz, $CDCl_3$) 5.21 – 5.19 (1H, m, C(8)**H**H'),

5.14 (1H, quin, *J* 1.5, C(8)H**H'**), 4.08 (2H, t, *J* 6.5, C(1)$\mathbf{H_2}$), 2.34 (2H, t, *J* 7.0, C(4)$\mathbf{H_2}$), 1.88 – 1.85 (3H, m, C(7)C$\mathbf{H_3}$), 1.75 (2H, quin, *J* 7.0, C(2)$\mathbf{H_2}$), 1.61 (2H, quin, *J* 7.0, C(3)$\mathbf{H_2}$), 1.20 (9H, s, C(C$\mathbf{H_3}$)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 178.6 (**C**=O), 127.2 (**C**(7)), 120.5 (**C**(8)), 88.6 (**C**(5)), 82.3 (**C**(6)), 63.8 (**C**(1)), 38.7 (**C**$(CH_3)_3$), 27.8 (**C**(2)), 27. 2 (C(**C**$H_3)_3$), 25.2 (**C**(3)), 23.8 (C(7)**C**$H_3$), 18.9 (**C**(4)).

HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NaO_2$ $[M+Na]^+$ : 245.1512

Found : 245.1505

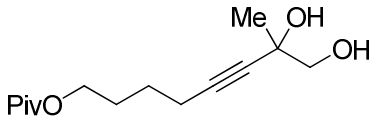
**6-(2-Methyloxiran-2-yl)hex-5-ynyl pivalate[207] (259)**




$Na_2HPO_4$ (160 mg, 1.13 mmol) and *m*-chloroperbenzoic acid (258 mg, 0.898 mmol, 60% by weight) were added to a stirred solution of enyne **258** (100 mg, 0.449 mmol) in dichloromethane (4 mL) at 0 °C. The reaction was stirred at RT for 3 h then diluted with sat. aq. $Na_2S_2O_3$ (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 20 mL), the combined organic layers washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash

chromatography (basic alumina, 5:1, petrol/ether) afforded the title compound as a colourless oil (71 mg, 66%); $R_f$ 0.14 (10:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2959s, 2873m, 1724s, 1481m, 1284s, 1152s, 1037m; $\delta_H$ (400 MHz, $CDCl_3$) 4.05 (2H, t, *J* 6.5, C(1)**H$_2$**), 2.94 (1H, d, *J* 5.5, C(8)**H**H'), 2.70 (1H, d, *J* 5.5, C(8)H**H'**), 2.22 (2H, t, *J* 7.0, C(4)**H$_2$**), 1.70 (2H, app. quin, *J* 7.0, C(2)**H$_2$**), 1.55 (2H, quin, *J* 7.0, C(3)**H$_2$**, overlapping), 1.51 (3H, s, C(7)C**H$_3$**, overlapping), 1.18 (9H, s, C(C**H$_3$**)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 178.5 (**C**=O), 82.3 (**C**(5)), 79.9 (**C**(6)), 63.8 (**C**(1)), 55.5 (**C**(8)), 47.4 (**C**(7)), 38.7 (**C**$(CH_3)_3$), 27.8 (**C**(2)), 27.2 (C(**C**$H_3$)$_3$), 24.9 (**C**(3)), 23.3 (C(7)**C**$H_3$), 18.3 (**C**(4)).

**7,8-Dihydroxy-7-methyloct-5-ynyl pivalate (260)**



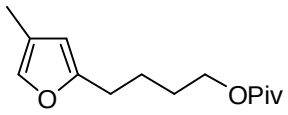

Synthesised according to *general procedure F* from enyne **258** (50 mg, 0.225 mmol). Purification by flash chromatography (neutral alumina, 96:4, dichloromethane/methanol) afforded the *title compound* as a yellow solid (56 mg, 98%); $R_f$ 0.13 (97:3, DCM/MeOH); $[\alpha]_D^{21}$ –0.04 (c = 1.0, $CHCl_3$); m.p. 78 – 80 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3428br, 2960s, 2936s, 2873m, 2173w, 1725s, 1481s, 1459s, 1285s, 1154s, 1040s; $\delta_H$ (400 MHz, $CDCl_3$) 4.09 (2H, t, *J* 6.5, C(1)**H$_2$**), 3.61 (1H, d, *J* 11.0, C(8)**H**H'), 3.46 (1H, d, *J* 11.0, C(8)H**H'**), 2.53 (2H, br s, O**H**), 2.25 (2H, t, *J* 7.0, C(4)**H$_2$**), 1.74 (2H, app.

quin, *J* 7.0, C(2)**H₂**), 1.57 (2H, quin, *J* 7.0, C(3)**H₂**), 1.43 (3H, s, C(7)C**H₃**), 1.19 (9H, s, C(C**H₃**)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 178.8 (**C**=O), 84.4 (**C**(5)), 82.4 (**C**(6)), 70.8 (**C**(1)), 68.6 (**C**(7)$CH_3$), 63.9 (**C**(8)), 38.7 (**C**$(CH_3)_3$), 27.7 (**C**(2)), 27.2 (C(**C**$H_3$)$_3$), 25.6 (C(7)**C**$H_3$), 24.9 (**C**(3)), 18.3 (**C**(4)).

HRMS (ESI) *m/z* calcd for $C_{14}H_{24}NaO_4$ $[M+Na]^+$ : 279.1567

Found : 279.1567

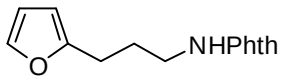
**4-(4-Methylfuran-2-yl)butyl pivalate[207] (261)**




Prepared according to *general procedure G* from diol **260** (300 mg, 1.17 mmol) to afford the title compound as a colourless oil (270 mg, 97%); $R_f$ 0.17 (6:1, petrol/ether); $\delta_H$ (400 MHz, $CDCl_3$) 7.06 (1H, s, C(5')**H**), 5.87 (1H, s, C(3')**H**), 4.08 (2H, t, *J* 6.0, C(4)**H₂**), 2.61 (2H, t, *J* 6.5, C(1)**H₂**), 1.99 (3H, s, C(4')C**H₃**), 1.73 – 1.66 (4H, m, C(2)**H₂** and C(3)**H₂**), 1.20 (9H, s, C(C**H₃**)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 178.6 (**C**=O), 155.8 (**C**(2')), 137.4 (**C**(5')), 120.4 (**C**(4')), 107.8

(**C**(3')), 64.0 (**C**(4)), 38.7 (**C**$(CH_3)_3$), 28.1 (**C**(3)), 27.6 (**C**(1)), 27.2 (C(**C**$H_3)_3$), 24.5 (**C**(2)), 9.8 (C(4')**C**$H_3$).

**2-(3-(Furan-2-yl)propyl)isoindoline-1,3-dione (262)**

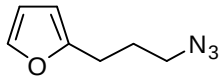



Diethyl azodicarboxylate (798 µL, 718 mg, 4.12 mmol) was added to a stirred suspension of triphenylphosphine (998 mg, 3.80 mmol) in THF (10 mL) at 0 °C. Alcohol **207** (400 mg, 3.17 mmol) was added after 15 min, followed by phthalimide (471 mg, 3.20 mmol) after a further 20 min. The reaction was stirred at RT for 48 h then concentrated *in vacuo*. Purification by flash chromatography (10:1 → 2:1, petrol/ether) afforded the *title compound* as a brown solid (340 mg, 42%); $R_f$ 0.43 (1:1, petrol/ether); m.p. 212 – 214 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3466w, 2943m, 2872m, 1772m, 1719s, 1614m, 1438m, 1396s, 1370s, 1024s; $\delta_H$ (400 MHz, $C_6D_6$) 7.54 (2H, dd, *J* 5.5, 3.0, Ar**H**), 7.15 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.99 (2H, dd, *J* 5.5, 3.0, Ar**H**), 6.15 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.02 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 3.58 (2H, t, *J* 7.0, C(3)**$H_2$**), 2.54 (2H, t, *J* 7.5, C(1)**$H_2$**), 1.96 (2H, app. quin, *J* 7.0, C(2)**$H_2$**); $\delta_C$ (100 MHz, $C_6D_6$) 167.9 (**C**=O), 155.0 (**C**(2')), 141.1 (**C**(5')), 133.3 (Ar), 132.6 (Ar), 122.9 (Ar), 110.3 (**C**(4')), 105.5 (**C**(3')), 37.4 (**C**(3)), 27.0 (**C**(2)), 25.6 (**C**(1)).

HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{13}NO_3$ $[M+Na]^+$ : 278.0788

Found : 278.0785

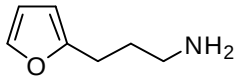
**2-(3-Azidopropyl)furan[208] (263)**




Methanesulfonyl chloride (1.03 mL, 1.52 g, 13.3 mmol) was added to a stirred solution of alcohol **207** (1.20 g, 9.51 mmol) and freshly distilled triethylamine (3.98 mL, 2.89 g, 28.5 mmol) in dichloromethane (40 mL) at 0 °C. The reaction was stirred at RT for 1 h then poured onto water (100 mL). The separated aqueous layer was extracted with dichloromethane (2 × 100 mL), the combined organic layers washed with 1 N aq. HCl (200 mL), sat. aq. $NaHCO_3$ (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in anhydrous DMF (20 mL), $NaN_3$ (884 mg, 13.6 mmol) added and the resulting solution stirred at 70 °C for 4 h. After cooling to RT, the solution was diluted with water (100 mL), the aqueous layer extracted with ether (2 × 100 mL), the combined organic layers washed with water (100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (99:1, petrol/ether) afforded the title compound as a yellow oil (1.27 g, 88%); $\nu_{max}$ (thin film)/$cm^{-1}$ 2935s, 2874m, 2093s, 1716m, 1597s, 1508m, 1286s, 1258s; $\delta_H$ (400 MHz, $CDCl_3$) 7.33 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.31 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.05 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 3.33 (2H, t, *J* 7.0, C(3)$\mathbf{H_2}$), 2.75 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 1.95 (2H, app. quin, *J* 7.0, C(2)$\mathbf{H_2}$); $\delta_C$ (100

MHz, $CDCl_3$) 154.5 (**C**(2')), 141.2 (**C**(5')), 110.2 (**C**(4')), 105.5 (**C**(3')), 50.6 (**C**(3)), 27.4 (**C**(2)), 25.0 (**C**(1)).

**3-(Furan-2-yl)propan-1-amine[201] (264)**




**Method A**: Hydrazine monohydrate (133 µL, 137 mg, 2.74 mmol) was added to a stirred solution of imide **262** (100 mg, 0.392 mmol) in $CHCl_3$-EtOH (4 mL, 3:1) and the reaction mixture heated at 60 °C for 18 h. After cooling to RT, the solid precipitate was filtered off, the filter cake washed with ether (20 mL), the filtrate washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil (18 mg, 36%).

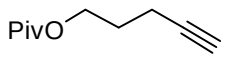
**Method B**: 10% Pd/C (13 mg) was added to a stirred solution of azide **263** (125 mg, 0.83 mmol) in MeOH (4 mL). The airspace was evacuated and purged with argon (× 3), the headspace filled with hydrogen and the reaction stirred at RT for 12 h. The reaction mixture was filtered through a pad of celite and concentrated *in vacuo* to afford the title compound as a colourless oil (71 mg, 68 %).

$\nu_{max}$ (thin film)/$cm^{-1}$ 3320br, 2938s, 2859s, 1580s, 1469s, 1297s, 1016s; $\delta_H$ (400 MHz, $CDCl_3$) 7.28 (1H, s, C(5')**H**), 6.26 (1H, s, C(4')**H**), 5.98 (1H, s, C(3')**H**), 2.73 (2H, t, *J* 7.0, C(3)$\mathbf{H_2}$), 2.67 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 1.79 (2H, app. quin, *J* 7.0, C(2)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 155.7 (**C**(2')), 140.8 (**C**(5')), 110.1 (**C**(4')), 104.9 (**C**(3')), 41.5 (**C**(3)), 31.9 (**C**(2)), 25.3 (**C**(1)).

HRMS (FI) *m/z* calcd for $C_7H_{11}NO$ $[M]^+$ : 125.0841

Found : 125.0842

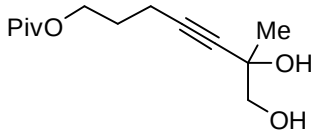
**Pent-4-ynyl pivalate[209] (265)**




To a solution of 4-pentyn-1-ol (3.24 mL, 2.93 g, 34.8 mmol) in dichloromethane (130 mL) at 0 °C was added triethylamine (6.79 mL, 4.93 g, 48.71 mmol), 4-dimethylaminopyridine (425 mg, 3.48 mmol) and trimethylacetyl chloride (5.57 mL, 5.45 g, 45.2 mmol). The solution was stirred at RT for 16 h then diluted with water (200 mL) and the separated aqueous layer extracted with dichloromethane (2 × 200 mL). The combined organic layers were washed with 1N aq. HCl (200 mL) and sat. aq. $NaHCO_3$ (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash

chromatography (15:1 → 10:1, petrol/ether) afforded the title compound as a colourless oil (5.50 g, 94%); $R_f$ 0.45 (5:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3297m, 2972s, 1729s, 1481m, 1284s, 1156s, 1039m; $\delta_H$ (400 MHz, $CDCl_3$) 4.13 (2H, t, *J* 6.0, C(1)**H₂**), 2.25 (2H, td, *J* 7.0, 2.5, C(3)**H₂**), 1.94 (1H, t, *J* 2.5, C(5)**H**), 1.83 (2H, app. quin, *J* 6.5, C(2)**H₂**), 1.17 (9H, s, C(C**H₃**)₃); $\delta_c$ (100 MHz, $CDCl_3$) 178.3 (**C**=O), 82.9 (**C**(4)), 68.9 (**C**(5)), 62.8 (**C**(1)), 38.7 (**C**$(CH_3)_3$), 27.6 (**C**(2)), 27.1 (C(**C**$H_3)_3$), 15.1 (**C**(3)).

**6,7-Dihydroxy-6-methylhept-4-ynyl pivalate (266)**




To a stirred solution of pent-4-ynyl pivalate (200 mg, 1.19 mmol) in THF (4 mL) at 0 °C was added *i*-propylmagnesium chloride (0.59 mL, 1.19 mmol, 2M solution in ether). The reaction stirred at RT for 90 min then cooled to –10 °C and hydroxyacetone (39 µL, 42 mg, 0.57 mmol) added. After stirring at this temperature for 2 h, the reaction was diluted with sat. aq. $NH_4Cl$ (5 mL) and brine (20 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 × 30 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography

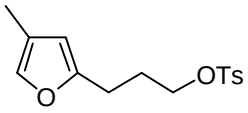
(97:3, dichloromethane/methanol) afforded the *title compound* as a colourless oil (59 mg, 43%); $R_f$ 0.22 (96:4, dichloromethane/methanol); $\nu_{max}$ (thin film)/$cm^{-1}$ 3419s, 2976s, 2267w, 1729s, 1482m, 1367m, 1286s, 1160s, 1057m; $\delta_H$ (400 MHz, $CDCl_3$) 4.18 (2H, t, *J* 6.0, C(1)**H$_2$**), 3.62 (1H, d, *J* 11.0, C(7)**H**H'), 3.46 (1H, d, *J* 11.0, C(7)H**H'**), 2.86 (1H, br s, O**H**), 2.58 (1H, br s, O**H**), 2.29 (2H, t, *J* 7.0, C(3)**H$_2$**), 1.84 (2H, app. quin, *J* 6.5, C(2)**H$_2$**), 1.42 (3H, s, C(6)C**H$_3$**), 1.20 (9H, s, C(C**H$_3$**)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 178.8 (**C**=O), 83.3 (**C**(4)), 82.8 (**C**(5)), 70.9 (**C**(7)), 68.6 (**C**(6)), 62.6 (**C**(1)), 38.8 (**C**$(CH_3)_3$), 27.5 (**C**(2)), 27.2 (C(**C**$H_3$)$_3$), 25.4 (C(6)**C**$H_3$), 15.2 (**C**(3)).

HRMS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $[M+Na]^+$ : 265.1410

Found : 265.1404

Also obtained from the deprotection of silyl ether **278**: Citric acid (144 mg, 0.687 mmol) was added to a solution of silyl ether **278** (21.6 g, 68.7 mmol) in methanol (100 mL) and the reaction stirred for 4 h at RT. The reaction was diluted with water (100 mL), the methanol removed *in vacuo* and the aqueous layer extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless oil (15.0 g, 90%) that was used in subsequent reactions without purification. Spectroscopic data as above.

**3-(4-Methylfuran-2-yl)propyl 4-methylbenzenesulfonate (267)**

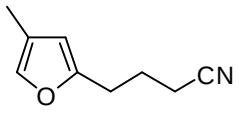



To a stirred solution of alcohol **250** (4.09 g, 29.2 mmol) in dichloromethane (150 mL) at 0 °C was added triethylamine (5.29 mL, 3.84 g, 37.9 mmol), 4-dimethylaminopyridine (160 mg, 1.31 mmol) and *p*-toluenesulfonyl chloride (6.81 g, 35.0 mmol). The reaction was stirred at RT for 16 h, then diluted with water (200 mL). The separated aqueous layer was extracted with dichloromethane (2 × 200 mL), the combined organic layers washed with 1N aq. HCl (200 mL) and sat. aq. $NaHCO_3$ (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 10:1, petrol/ether) afforded the *title compound* as a colourless oil (7.99 g, 93%); $R_f$ 0.26 (15:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2971m, 2926m, 1603m, 1353s, 1176s; $\delta_H$ (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.5, Ar**H**), 7.35 (2H, d, *J* 8.5, Ar**H**), 7.01 (1H, s, C(5')**H**), 5.75 (1H, s, C(3')**H**), 4.05 (2H, t, *J* 6.5, C(3)**$H_2$**), 2.62 (2H, t, *J* 7.5, C(1)**$H_2$**), 2.46 (3H, s, ArC**$H_3$**), 1.96 (2H, app. quin, *J* 7.0, C(2)**$H_2$**, overlapping), 1.95 (3H, s, C(4')C**$H_3$**, overlapping); $\delta_c$ (100 MHz, $CDCl_3$) 153.9 (**C**(2')), 144.7 (Ar), 137.7 (**C**(5')), 133.1 (Ar), 129.8 (Ar), 127.9 (Ar), 120.4 (**C**(4')), 108.5 (**C**(3')), 69.5 (**C**(3)), 27.4 (**C**(2)), 23.9 (**C**(1)), 21.7 (Ar**C**$H_3$), 9.7 (C(4')**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{15}H_{18}NaO_4S^+$ $[M+Na]^+$ : 317.0818

Found : 317.0810

**4-(4-Methylfuran-2-yl)butanenitrile (268)**

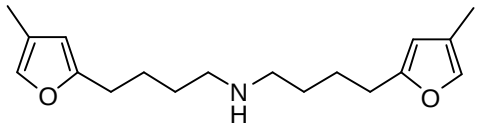



NaCN (5.45 g, 0.111 mol) was added to a solution of tosylate **267** (6.56 g, 22.3 mmol) in DMSO (70 mL) and the mixture stirred at 60 °C for 8 h. After cooling to RT, the mixture was diluted with water (300 mL), the aqueous layer extracted with ether (2 × 300 mL), the combined organic layers washed with water (2 × 300 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (50:1 → 30:1, petrol/ether) afforded the *title compound* as a colourless oil (3.27 g, 98%); $R_f$ 0.15 (30:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2931s, 2875w, 2844w, 2247m, 1798s, 1767s, 1619m, 1553m, 1432s, 1262m, 1112s; $\delta_H$ (400 MHz, $CDCl_3$) 7.08 (1H, s, C(5')**H**), 5.94 (1H, s, C(3')**H**), 2.74 (2H, t, *J* 7.0, C(1')$\mathbf{H_2}$), 2.36 (2H, t, *J* 7.0, C(3)$\mathbf{H_2}$), 1.99 (3H, s, C(4')C$\mathbf{H_3}$), 1.98 (2H, quin, *J* 7.0, C(2)$\mathbf{H_2}$); $\delta_c$ (100 MHz, $CDCl_3$) 153.3 (**C**(2')), 138.1 (**C**(5')), 120.6 (**C**(4')), 119.3 (**C**N), 109.1 (**C**(3')), 26.7 (**C**(1)), 24.0 (**C**(2)), 16.4 (**C**(3)), 9.7 (C(4')**C**$H_3$).

HRMS (GCT, $CI^+$) *m/z* calcd for $C_9H_{12}NO^+$ : 150.0919

Found : 150.0926

**Bis(4-(4-methylfuran-2-yl)butyl)amine (269)**



**Method A:** To a solution of amine **242** (48 mg, 0.311 mmol) and aldehyde **243** (43 mg, 0.283 mmol) in THF (1 mL) was added $NaBH(OAc)_3$ (99 mg, 0.444 mmol, 95%) and the reaction stirred at RT for 2 h. The reaction was diluted with sat. aq. $NaHCO_3$ (5 mL), the THF removed *in vacuo* and the aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (95:5:1, EtOAc/MeOH/$NH_4OH$) afforded the *title compound* as a yellow oil (20 mg, 24%).

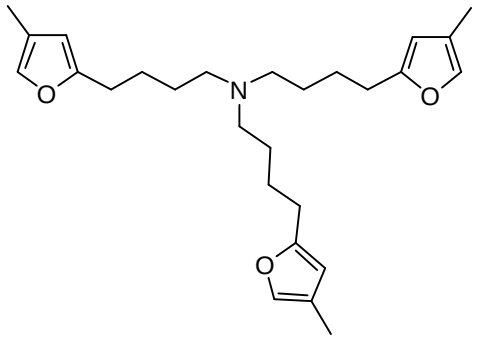
**Method B:** A solution of amine **242** (60 mg, 0.392 mmol) and aldehyde **243** (50 mg, 0.329 mmol) in methanol (1 mL) was stirred at RT for 4 h. $NaBH_4$ (20 mg, 0.529 mmol) was added and the reaction stirred for a further 40 min before diluting with 1M NaOH (2 mL). The methanol was removed *in vacuo*, the aqueous layer diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (95:5:1, EtOAc/MeOH/$NH_4OH$) gave the *title compound* as a yellow oil (83 mg, 87%).

$R_f$ 0.61 (10:1:0.1, $CHCl_3$/MeOH/$NH_4OH$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3305w, 2928s, 2863s, 1618m, 1552s, 1457s, 1120s; $\delta_H$ (400 MHz, $CDCl_3$) 7.05 (2H, s, C(5')**H**), 5.86 (2H, s, C(3')**H**), 2.66 (4H, t, *J* 7.0, C(4')**$H_2$**), 2.59 (4H, t, *J* 7.0, C(1)**$H_2$**), 2.23 (1H, br s, N**H**), 1.98 (6H, t, *J* 1.0, C(4')C**$H_3$**), 1.70 – 1.63 (4H, m, C(2)**$H_2$**), 1.63 – 1.53 (4H, m, C(3)**$H_2$**); $\delta_c$ (100 MHz, $CDCl_3$) 156.0 (**C**(2')), 137.3 (**C**(5')), 120.4 (**C**(4')), 107.7 (**C**(3')), 49.4 (**C**(4)), 29.0 (**C**(3)), 27.8 (**C**(1)), 25.8 (**C**(2)), 9.8 (C(4')**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{18}H_{28}NO_2$ $[M+H]^+$ : 290.2115

Found : 290.2109

**Tris(4-(4-methylfuran-2-yl)butyl)amine (270)**



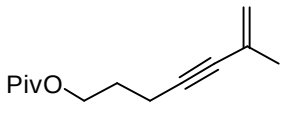

Obtained as a by-product in the synthesis of amine **269** by *method A* as a colourless oil (22 mg, 18%); $R_f$ 0.79 (10:1:0.1, $CHCl_3$/MeOH/$NH_4OH$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2927m, 1683s, 1552m, 1454m, 1112s; $\delta_H$ (400 MHz, $CDCl_3$) 7.05 (3H, s, C(5')**H**), 5.85 (3H, s, C(3')**H**), 2.57 (6H, t, *J* 7.5, C(1)**$H_2$**), 2.41 (6H, t, *J* 7.5, C(4)**$H_2$**), 1.99 (9H, s, C(4')C**$H_3$**), 1.61 (6H, quin, *J* 7.5, C(2)**$H_2$**), 1.47 (6H, quin, *J* 7.5, C(3)**$H_2$**); $\delta_c$ (100 MHz, $CDCl_3$) 156.3 (**C**(2')),

137.2 (**C**(5')), 120.4 (**C**(4')), 107.6 (**C**(3')), 53.7 (**C**(4)), 27.9 (**C**(1)), 26.5 (**C**(3)), 26.0 (**C**(2)), 9.8 (C(4')**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{27}H_{40}NO_3$ $[M+H]^+$ : 426.3003

Found : 426.2991

**6-Methylhept-6-en-4-ynyl pivalate (271)**

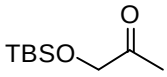



Synthesised by *general procedure E* from pivalate **265** (100 mg, 0.594 mmol) and 2-bromopropene (159 µL, 215 mg, 1.78 mmol). Purification by flash chromatography (30:1, petrol/ether) afforded the *title compound* as a colourless oil (117 mg, 94%); $R_f$ 0.18 (30:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2972s, 2874s, 1728s, 1679s, 1615m, 1481s, 1283s, 1152s; $\delta_H$ (400 MHz, $CDCl_3$) 5.18 – 5.16 (1H, m, C(8)**H**H'), 5.13 – 5.10 (1H, m, C(8)H**H'**), 4.12 (2H, t, *J* 6.5, C(1)**$H_2$**), 2.37 (2H, t, *J* 7.0, C(3)**$H_2$**), 1.84 (2H, app. quin, *J* 6.5, C(2)**$H_2$**, overlapping), 1.83 (3H, s, C(7)C**$H_3$**, overlapping), 1.20 (9H, s, C(C**$H_3$**)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 178.4 (**C**=O), 127. (**C**(6)), 120.6 (**C**(7)), 87.6 (**C**(4)), 82.4 (**C**(5)), 63.0 (**C**(1)), 38.7 (**C**$(CH_3)_3$), 27.8 (**C**(2)), 27. 1 (C(**C**$H_3$)$_3$), 23.7 (C(6)**C**$H_3$), 16.0 (**C**(3)).

HRMS (FI) *m/z* calcd for $C_{13}H_{20}O_2$ $[M]^+$ : 208.1463

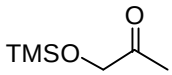
Found : 208.1466

**1-(*tert*-Butyldimethylsilyloxy)propan-2-one[193] (273)**



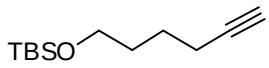

Synthesised according to *general procedure H* from hydroxyacetone (370 mg, 5.00 mmol). Purification by flash chromatography (10:1 → 8:1, petrol/ether) afforded the title compound as a colourless oil (931 mg, 99%); $R_f$ 0.36 (10:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2956s, 2856s, 1721s, 1473m, 1356s, 1255s, 1119s; $\delta_H$ (400 MHz, $CDCl_3$) 4.14 (2H, s, C**H**$_2$OSi), 2.16 (3H, s, C(O)C**H**$_3$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 0.09 (Si(C**H**$_3$)$_2$); $\delta_c$ (100 MHz, $CDCl_3$) 209.2 (**C**=O), 69.5 (**C**$H_2$OSi), 25.9 (C(O)**C**$H_3$), 25.7 (SiC(**C**$H_3$)$_3$), 18.3 (Si**C**$(CH_3)_3$), –5.6 (Si(**C**$H_3$)$_2$).

**1-(Trimethylsilyloxy)propan-2-one[210] (274)**



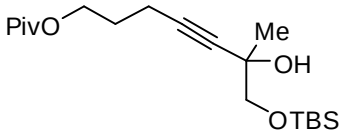

To a stirred solution of hydroxyacetone (2.00 g, 1.85 mL, 27.0 mmol), triethylamine (3.33 g, 4.59 mL, 32.9 mmol) and 4-dimethylaminopyridine (33 mg, 0.269 mmol) in dichloromethane (20 mL) at –10 °C was added chlorotrimethylsilane (2.93 g, 3.42 mL, 27.0 mmol). The reaction was stirred at RT for 15 min then diluted with water (30 mL), the separated aqueous layer extracted with dichloromethane (2 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting yellow liquid was filtered to remove $Et_3N{\cdot}HCl$ and then fractionally distilled under reduced pressure (b.p. 96 °C, 30 Torr) to afford the title compound as a colourless oil (2.84 g, 72%); $R_f$ 0.32 (3:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2959s, 2901s, 2837m, 1736s, 1437m, 1355s, 1253s, 1118s; $\delta_H$ (400 MHz, $CDCl_3$) 4.15 (2H, s, SiOC**H$_2$**), 2.14 (3H, s, C(O)C**H$_3$**), 0.14 (9H, s, Si(C**H$_3$**)$_3$); $\delta_c$ (100 MHz, $CDCl_3$) 208.2 (**C**=O), 68.9 (SiO**C**H$_2$), 25.7 (C(O)**C**H$_3$), –0.63 (Si(**C**H$_3$)$_3$).

**_tert_-Butyl(hex-5-ynyloxy)dimethylsilane[211] (275)**




Synthesised by *general procedure H* from 5-hexyn-1-ol (300 mg, 3.06 mmol). Purification by flash chromatography (50:1, petrol/ether) afforded the title compound as a colourless oil (591 mg, 91%); $R_f$ 0.44 (50:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3314s, 2954s, 2859s, 2120w, 1472m, 1388m, 1256s, 1108s; $\delta_H$ (400 MHz, $CDCl_3$) 3.64 (2H, t, *J* 6.0, C(1)**H$_2$**), 2.22 (2H, td, *J* 6.5, 2.5, C(4)**H$_2$**), 1.94 (1H, t, *J* 2.5, C(6)**H**), 1.68 – 1.55 (4H, m, C(2)**H$_2$**) and C(3)**H$_2$**), 0.90 (9H, s, SiC(C**H$_3$**)$_3$), 0.05 (6H, s, Si(C**H$_3$**)$_2$); $\delta_c$ (100 MHz, $CDCl_3$) 84.5 (**C**(5)), 68.3 (**C**(6)), 62.6 (**C**(1)), 31.8 (**C**(2)), 26.0 (SiC(**C**H$_3$)$_3$), 25.0 (**C**(3)), 18.3 (Si**C**(CH$_3$)$_3$), 18.2 (**C**(4)), –5.3 (Si(**C**H$_3$)$_2$).

**7-(_tert_-Butyldimethylsilyloxy)-6-hydroxy-6-methylhept-4-ynyl pivalate (276)**



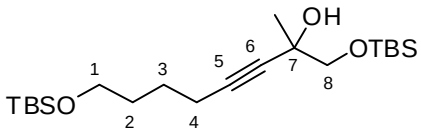

*i*-Propylmagnesium chloride (3.30 mL, 1.8 M solution in THF, 5.94 mmol) was added to a solution of pivalate ester **265** (1.00 g, 5.94 mmol) in THF (12 mL) at 0 °C. The solution

was stirred at RT for 1.5 h, then cooled to 0 °C and silyl ether **273** (1.12 g, 5.94 mmol) added. The reaction was stirred at RT for 16 h then diluted with sat. aq. $NH_4Cl$ (20 mL) and the solvent removed *in vacuo*. The aqueous layer was diluted with water (80 mL), extracted with ether (3 × 100 mL), the combined organic layers washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1 → 6:1, petrol/ether) afforded the *title compound* as a colourless oil (1.89 g, 89%); $R_f$ 0.10 (5:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3436m, 2953m, 2931s, 2852s, 2242w, 1731s, 1463m, 1284s, 1254s, 1153s, 1101s; $\delta_H$ (400 MHz, $CDCl_3$) 4.08 (2H, t, *J* 6.5, C(1)**H₂**), 3.58 (1H, d, *J* 9.5, C(7)**H**H'), 3.44 (1H, d, *J* 9.5, C(7)H**H'**), 2.85 (1H, s, O**H**), 2.24 (2H, t, *J* 7.0, C(3)**H₂**), 1.78 (2H, app. quin, *J* 7.0, C(2)**H₂**), 1.35 (3H, s, C(6)C**H₃**), 1.15 (9H, s, C(C**H₃**)₃), 0.88 (9H, s, SiC(C**H₃**)₃), 0.05 (3H, s, SiC**H₃**), 0.05 (3H, s, SiC**H₃**); $\delta_c$ (100 MHz, $CDCl_3$) 178.3 (**C**=O), 83.1 (**C**(4)), 82.1 (**C**(5)), 71.1 (**C**(7)), 67.9 (**C**(6)), 62.9 (**C**(1)), 38.7 (C(O)**C**$(CH_3)_3$), 27.8 (**C**(2)), 27.1 (C(**C**$H_3)_3$), 25.8 (SiC(**C**$H_3)_3$), 25.6 (C(6)**C**$H_3$), 18.3 (Si**C**$(CH_3)_3$), 15.3 (**C**(3)), –5.4 (Si**C**$H_3$). –5.5 (Si**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{19}H_{36}NaO_4Si$ $[M+Na]^+$ : 379.2275

Found : 379.2272

**1,8-Di(*tert*-butyldimethylsilyloxy)-2-methyloct-3-yn-2-ol (277)**

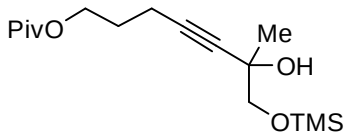



*n*-Butyllithium (0.23 mL, 0.368 mmol, 1.6 M in hexanes) was added to a stirred solution of 1-(*tert*-butyldimethylsilyloxy)hex-5-yne (78 mg, 0.368 mmol) in THF (1 mL) at 0 °C and the reaction stirred at this temperature for 1 h. The reaction was then cooled to –78 °C, a solution of silyl ether **273** (63 mg, 0.335 mmol) in THF (0.5 mL) added, and the reaction stirred at RT for 12 h. The reaction was diluted with sat. aq. $NH_4Cl$ (10 mL), the THF removed *in vacuo* and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1 → 6:1, petrol/ether) afforded the *title compound* as a viscous colourless oil (111 mg, 83%); $R_f$ 0.49 (3:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3420m, 2930s, 2858s, 1472m, 1253s, 1101s; $\delta_H$ (400 MHz, $CDCl_3$) 3.63 (1H, d, *J* 9.5, C(8)**H**H', overlapping), 3.62 (2H, t, *J* 6.0, C(1)$\mathbf{H_2}$, overlapping), 3.49 (1H, d, *J* 9.5, C(8)H**H'**), 2.81 (1H, s, O**H**), 2.21 (2H, t, *J* 7.0, C(4)$\mathbf{H_2}$), 1.66 – 1.50 (4H, m, C(2)$\mathbf{H_2}$ and C(3)$\mathbf{H_2}$), 1.40 (3H, s, C(7)C$\mathbf{H_3}$), 0.92 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.89 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.10 (3H, s, SiC$\mathbf{H_3}$), 0.09 (3H, s, SiC$\mathbf{H_3}$), 0.05 (6H, s, SiC$\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 83.6 (**C**(5)), 82.4 (**C**(6)), 71.1 (**C**(8)), 68.0 (**C**(7)), 62.6 (**C**(1)), 31.9 (**C**(2)), 25.9 (**C**(3), 25.8 (SiC(**C**$H_3$)$_3$), 25.7 (SiC(**C**$H_3$)$_3$), 25.1 (C(7)C$\mathbf{H_3}$), 18.4 (**C**(4)), 18.3 (2 × Si**C**$(CH_3)_3$), –5.3 (3 × Si**C**$H_3$), –5.4 (Si**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{21}H_{44}NaO_3Si_2$ $[M+Na]^+$ : 423.2721

Found : 423.2719

**6-Hydroxy-6-methyl-7-(trimethylsilyloxy)hept-4-ynyl pivalate (278)**



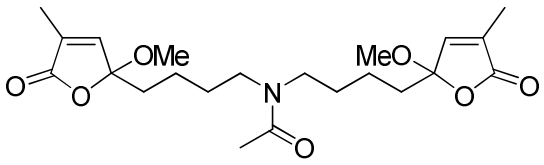

*i*-Propylmagnesium chloride (3.3 mL, 1.8 M solution in THF, 5.94 mmol) was added to a solution of pivalate ester **265** (1.00 g, 5.94 mmol) in THF (10 mL) at 0 °C. The reaction was stirred at RT for 1.5 h, then cooled to 0 °C and silyl ether **274** (869 mg, 5.94 mmol) added. The reaction was stirred at RT for 16 h then diluted with sat. aq. $NH_4Cl$ (20 mL) and the THF removed *in vacuo*. The aqueous layer was diluted with water (80 mL), extracted with ether (3 × 100 mL), the combined organic layers washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless oil (1.74 g, 93%). The product was taken on to the next step without further purification; $R_f$ 0.59 (97:3, dichloromethane/methanol), $\nu_{max}$ (thin film)/$cm^{-1}$ 3469s, 2959s, 2910s, 2872m, 2250m, 1721s, 1481s, 1285s, 1156s; $\delta_H$ (500 MHz, $CDCl_3$) 4.14 (2H, t, *J* 6.5, C(1)**H$_2$**), 3.60 (1H, d, *J* 9.5, C(7)**H**H'), 3.46 (1H, d, *J* 9.5, C(7)H**H'**), 2.30 (2H, t, *J* 7.5, C(3)**H$_2$**), 1.84 (2H, app. quin, *J* 7.0, C(2)**H$_2$**), 1.40 (3H, s, C(6)C**H$_3$**), 1.20 (9H, s, C(C**H$_3$**)$_3$),

0.15 (9H, s, Si(C**H$_3$**)$_3$); $\delta_c$ (125 MHz, $CDCl_3$) 178.5 (**C**=O), 83.1 (**C**(4)), 82.3 (**C**(5)), 70.5 (**C**(7)), 67.9 (**C**(6)), 62.9 (**C**(1)), 38.7 (**C**$(CH_3)_3$), 27.7 (**C**(2)), 27.2 (C(**C**$H_3$)$_3$), 25.7 (C(6)**C**$H_3$), 15.4 (**C**(3)), –0.5 (Si(**C**$H_3$)$_3$).

HRMS (ESI) *m/z* calcd for $C_{16}H_{30}NaO_4Si$ $[M+Na]^+$ : 337.1806

Found : 337.1805

***N*,*N*-Bis(4-(2-methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)butyl)acetamide (279)**



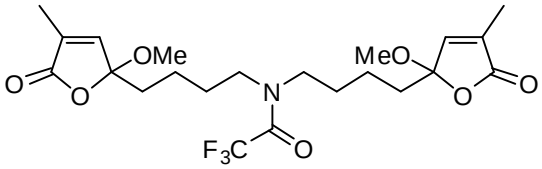

Prepared according to *general procedure D* from amine **269** (20 mg, 69.1 μmol). Purification by flash chromatography (0.5% $NH_4OH$ in EtOAc) afforded the *title compound* apparently as a 1:1 mixture of diastereomers as a brown oil (7 mg, 24%); $R_f$ 0.38 (99:1, ethyl acetate/$NH_4OH$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2939s, 2859m, 2828m, 1763s, 1637s, 1440s, 1318s, 1151m; $\delta_H$ (500 MHz, $CDCl_3$) 6.73 and 6.72 (2H, q, *J* 1.5, ($CH_3$)C=C**H**), 3.27 and 3.26 (4H, t, *J* 7.5, $CH_2$C**H$_2$**N), 3.19 (6H, s, OC**H$_3$**, 2 peaks), 2.06 (3H, s, NC(O)C**H$_3$**) 1.98 and 1.97 (6H, d, *J* 1.5, (C**H$_3$**)C=CH), 1.95 – 1.80 (4H, m, OCC**H$_2$**$CH_2$), 1.57 and 1.53 (4H, app. quin, *J* 7.5, C**H$_2$**$CH_2$N), 1.42 and 1.37 (4H, app. quin, *J* 8.0, OC$H_2$C**H$_2$**); $\delta_c$ (125MHz, $CDCl_3$) 171.4 and 171.2 (**C**=O), 170.1 (N**C**(O)$CH_3$), 145.9 and 145.7

(($CH_3$)C=**C**H), 134.1 and 133.8 (($CH_3$)**C**=CH), 109.0 and 108.6 (O**C**$CH_2CH_2$), 50.9 (O**C**$H_3$), 48.6 and 45.4 ($CH_2$**C**$H_2$N), 37.2 and 37.0 (OC**C**$H_2CH_2$), 28.8 and 27.5 (**C**$H_2CH_2$N), 21.5 (NC(O)**C**$H_3$), 20.8 and 20.7 (OCC$H_2$**C**$H_2$), 10.6 and 10.5 ((**C**$H_3$)C=CH).

HRMS (ESI) *m/z* calcd for $C_{22}H_{33}NNaO_7$ $[M+Na]^+$ : 446.2149

Found : 446.2146

**2,2,2-Trifluoro-N,N-bis(4-(2-methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)butyl)acetamide (280)**



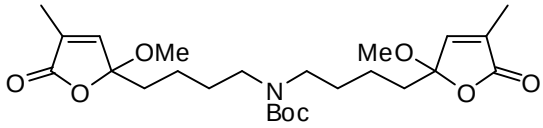

Prepared according to *general procedure D* from amine **269** (24 mg, 0.083 mmol) with modified work-up: After oxidation and removal of methanol *in vacuo*, the crude residue was dissolved in pyridine (1 mL) and trifluoroacetic anhydride (24 µL, 35 mg, 0.166 mmol) and the reaction stirred at RT for 15 min. The reaction was diluted with water (10 mL), the aqueous layer extracted with ethyl acetate (2 × 10 mL), the combined organic layers washed with sat. aq. $CuSO_4$ (2 × 20 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (1:1, petrol/ethyl acetate) afforded the *title compound* apparently as a 1:1 mixture of diastereomers as an orange

oil (6 mg, 15%); $R_f$ 0.19 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2943s, 1765s, 1686s, 1455m, 1317m, 1181s, 1142s; $\delta_H$ (500 MHz, $CDCl_3$) 6.73 – 6.71 (2H, m, $(CH_3)C=C\mathbf{H}$), 3.34 and 3.32 (4H, t, *J* 8.0, $CH_2C\mathbf{H_2}N$), 3.19 (6H, s, $OC\mathbf{H_3}$), 1.98 and 1.97 (6H, s, $(C\mathbf{H_3})C=CH$), 1.95 – 1.79 (4H, m, $OCC\mathbf{H_2}CH_2$), 1.62 and 1.61 (4H, q, *J* 8.0, $C\mathbf{H_2}CH_2N$), 1.43 and 1.41 (4H, quin, *J* 8.0, $OCCH_2C\mathbf{H_2}$); $\delta_c$ (125 MHz, $CDCl_3$) 171.3 and 171.1 (**C**=O), 156.6 (q, $^2J_{CF_3}$ 36.0, **C**(O)$CF_3$), 145.8 and 145.7 ($(CH_3)C=\mathbf{C}H$), 134.2 and 134.0 ($(CH_3)\mathbf{C}=CH$), 116.5 (q, $^1J_{CF_3}$ 288, C(O)**C**$F_3$), 108.8 and 108.6 (O**C**$CH_2CH_2$), 50.9 (O**C**$H_3$), 47.4 and 46.7 ($CH_2\mathbf{C}H_2N$), 37.0 and 36.9 ($OCC\mathbf{H_2}CH_2$), 28.5 and 26.6 (**C**$H_2CH_2N$), 20.6 and 20.5 ($OCCH_2\mathbf{C}H_2$), 10.6 and 10.5 ((**C**$H_3$)C=CH).

HRMS (ESI) *m/z* calcd for $C_{22}H_{30}F_3NNaO_7$ $[M+Na]^+$ : 500.1867

Found : 500.1860

**_tert_-Butyl bis(4-(2-methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)butyl)carbamate (281)**

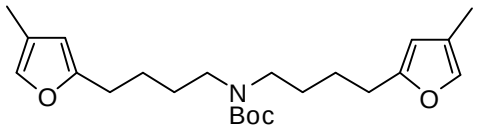



Synthesised by *general procedure D* from carbamate **282** (188 mg, 0.483 mmol). Purification by flash chromatography (1:1, petrol/ether) afforded the *title compound* as a colourless viscous oil apparently as a single diastereomer (202 g, 87%); $R_f$ 0.17 (1:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2937m, 1766s, 1686s, 1418s, 1252m, 1155s; $\delta_H$ (500 MHz, DMSO-$d^6$, 363K) 7.06 (2H, s, $(CH_3)C=C\mathbf{H}$), 3.12 (6H, s, $OC\mathbf{H_3}$), 3.11 (4H, t, *J* 7.5, $CH_2C\mathbf{H_2}N$), 1.88 (6H, s, $(C\mathbf{H_3})C=CH$), 1.85 (4H, t, *J* 8.0, $OCC\mathbf{H_2}CH_2$), 1.48 (4H, app. quin, *J* 7.5, $C\mathbf{H_2}CH_2N$), 1.40 (9H, s, $C(\mathbf{C}H_3)_3$) 1.28 (4H, app. quin, *J* 8.0, $OCH_2C\mathbf{H_2}$); $\delta_c$ (125 MHz, DMSO-$d^6$, 363K) 171.8 (**C**=O), 155.5 (N**C**(O)), 147.7 ($(CH_3)C=\mathbf{C}H$), 133.6 ($(CH_3)\mathbf{C}=CH$), 108.7 ($O\mathbf{C}CH_2CH_2$), 79.0 ($\mathbf{C}(CH_3)_3$), 51.4 ($O\mathbf{C}H_3$), 46.4 ($CH_2\mathbf{C}H_2N$), 37.2 ($OCC\mathbf{H_2}CH_2$), 28.8 ($C(\mathbf{C}H_3)_3$), 28.3 ($\mathbf{C}H_2CH_2N$), 21.1 ($OCCH_2\mathbf{C}H_2$), 11.0 ($(\mathbf{C}H_3)C=CH$).

HRMS (ESI) *m/z* calcd for $C_{25}H_{39}NNaO_8$ $[M+H]^+$ : 504.2568

Found : 504.2569

**_tert_-Butyl bis(4-(4-methylfuran-2-yl)butyl)carbamate (282)**

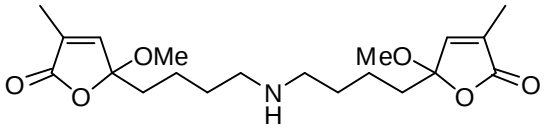



To a solution of amine **269** (200 mg, 0.691 mmol) in THF-$H_2O$ (4 mL, 3:1) was added triethylamine (125 μL, 91 mg, 0.899 mmol) and di-*tert*-butyl dicarbonate (196 mg, 0.899 mmol). The reaction mixture was stirred at RT for 2 h then diluted with water (10 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with dichloromethane (3 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (15:1, petrol/ether) afforded the *title compound* as a viscous colourless oil (202 mg, 75%); $R_f$ 0.22 (12:1, petrol/ether), $\nu_{max}$ (thin film)/$cm^{-1}$ 3340m, 2935s, 1764s, 1686s, 1421s, 1367s, 1421m, 1367m, 1167s; $\delta_H$ (400 MHz, DMSO-$d^6$, 363 K) 7.18 (2H, s, C(5')**H**), 5.93 (2H, s, C(3')**H**), 3.14 (4H, t, *J* 7.0, C(4')**$H_2$**), 2.57 (4H, t, *J* 7.0, C(1)**$H_2$**), 1.95 (6H, s, C(4')C**$H_3$**), 1.58 – 1.49 (8H, m, C(2)**$H_2$** and C(3)**$H_2$**), 1.40 (9H, s, C(C**$H_3$**)$_3$); $\delta_c$ (100 MHz, DMSO-$d^6$, 363 K) 156.5 (**C**(2')), 155.7 (N**C**=O), 138.3 (**C**(5')), 120.7 (**C**(4')), 108.6 (**C**(3')), 79.1 (**C**$(CH_3)_3$), 47.1 (**C**(4')), 29.9 (C(**C**$H_3$)$_3$), 28.4 (**C**(3')), 28.0 (**C**(1')), 25.8 (**C**(2')), 10.2 (C(4')**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{23}H_{35}NNaO_4$ $[M+Na]^+$ : 412.2454

Found : 412.2458

**5,5'-(4,4'-Azanediylbis(butane-4,1-diyl))bis(5-methoxy-3-methylfuran-2(5*H*)-one) (283)**

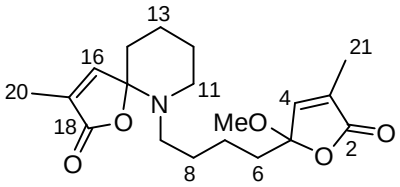



To a solution of methoxybutenolide **281** (144 mg, 0.299 mmol) in dichloromethane (2 mL) at 0 °C was added bromotrimethylsilane (375 µL, 435 mg, 2.84 mmol). The reaction was stirred for 2 h at RT then diluted with sat. aq. $NaHCO_3$ (15 mL) and the aqueous layer extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (95:5:0.5, $CHCl_3$/MeOH/$NH_4OH$) afforded the *title compound* apparently as a single diastereomer as a yellow oil (91 mg, 80%); $R_f$ 0.41 (10:1:0.1, $CHCl_3$/MeOH/$NH_4OH$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3422w, 2941s, 2781m, 1760s, 1688w, 1455s, 1319s, 1152s; $\delta_H$ (400 MHz, $CDCl_3$) 6.80 – 6.78 (2H, m, $(CH_3)C=C\mathbf{H}$), 3.27 (6H, s, $OC\mathbf{H_3}$), 2.93 (4H, t, *J* 7.5, $CH_2C\mathbf{H_2}N$), 1.97 (6H, s, $(C\mathbf{H_3})C=CH$), 1.95 – 1.81 (8H, m, $OCC\mathbf{H_2}CH_2$ and $C\mathbf{H_2}CH_2N$), 1.51 (4H, quin, *J* 8.0, $OCCH_2C\mathbf{H_2}$); $\delta_c$ (100 MHz, $CDCl_3$) 171.3 (**C**=O), 145.9 ($(CH_3)C=\mathbf{C}H$), 134.1 ($(CH_3)\mathbf{C}=CH$), 108.7 ($O\mathbf{C}CH_2CH_2$), 51.0 ($O\mathbf{C}H_3$), 47.4 ($CH_2\mathbf{C}H_2N$), 36.7 ($OC\mathbf{C}H_2CH_2$), 25.5 ($\mathbf{C}H_2CH_2N$), 20.7 ($OCCH_2\mathbf{C}H_2$), 10.6 ($(\mathbf{C}H_3)C=CH$).

HRMS (ESI) *m/z* calcd for $C_{20}H_{32}NO_6$ $[M+H]^+$ : 382.2224

Found : 382.2221

**6-(4-(2-Methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)butyl)-3-methyl-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (285)**



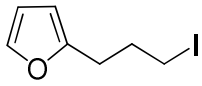

Isolated as a by-product from the synthesis of pandamarilactone-1 **1** (3 mg, 3%); $R_f$ 0.15 (ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2941s, 2864s, 1764s, 1445s, 1312s, 1157s, 1106m; $\delta_H$ (500 MHz, $CDCl_3$) 6.73 (1H, q, *J* 1.5, C(16)**H**), 6.71 (1H, q, *J* 1.5, C(4)**H**), 3.19 (3H, s, OC**H$_3$**), 2.82 – 2.77 (2H, m, C(11)**H$_2$**), 2.49 – 2.29 (2H, m, C(9)**H$_2$**), 1.98 (3H, d, *J* 1.5, C(20)**H$_3$**), 1.93 (3H, d, *J* 1.5, C(21)**H$_3$**), 1.88 – 1.78 (2H, m, C(6)**H$_2$**), 1.77 – 1.64 (6H, m, C(12)**H$_2$**, C(13)**H$_2$** and C(14)**H$_2$**), 1.37 (2H, quin, *J* 7.5, C(8)**H$_2$**), 1.33 – 1.28 (2H, m, C(7)**H$_2$**); $\delta_c$ (125 MHz, $CDCl_3$) 173.0 (**C**(18)), 171.3 (**C**(2)), 149.8 (**C**(16)), 145.9 (**C**(4)), 133.9 (**C**(3)), 131.5 (**C**(17)), 109.0 (**C**(5)), 101.8 (**C**(15)), 50.9 (O**C**$H_3$), 49.8 (**C**(9)), 47.1 (**C**(11)), 36.1 (**C**(14)), 27.6 (**C**(8)), 25.0 (**C**(13)), 21.0 (**C**(7)), 20.7 (**C**(12)), 10.7 (**C**(20)), 10.5 (**C**(21)).

HRMS (ESI) *m/z* calcd for $C_{19}H_{28}NO_5$ $[M+H]^+$ : 350.1962

Found : 350.1951

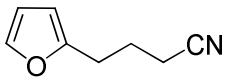
## *6.4 Additional compounds*

**2-(3-Iodopropyl)furan[212] (286)**



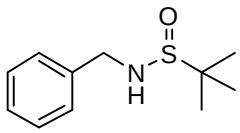
To a stirred solution of 2-(3-chloropropyl)furan (2.50 g, 17.4 mmol) in butan-2-one (28 mL) was added NaI (7.81 g, 52.1 mmol). The reaction mixture was heated at 80 °C for 6 h, cooled to RT and concentrated *in vacuo*. The crude oil was taken up in ether (200 mL), filtered, washed with sat. aq. $Na_2S_2O_3$ solution (2 × 150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as an orange oil (4.05 g, 99%), which was used in subsequent reactions without further purification; $R_f$ 0.75 (50:1, petrol/ether); $\delta_H$ (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* 2.0, C(5')**H**), 6.28 (1H, dd, *J* 3.0, 2.0, C(4')**H** ) 6.05 (1H, d, *J* 3.0, C(3')**H**), 3.20 (2H, t, *J* 7.0, C(3)$\mathbf{H_2}$), 2.76 (2H, t, *J* 7.0, C(1)$\mathbf{H_2}$), 2.14 (2H, quin, *J* 7.0, C(2)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 153.9 (**C**(2')), 141.15 (**C**(5')), 110.08 (**C**(4')), 105.69 (**C**(3')), 31.58 (**C**(2)), 28.55 (**C**(1)), 5.8 (**C**(3)).

**4-(Furan-2-yl)butanenitrile[213] (287)**




A solution of NaCN (373 mg, 7.61 mmol) in DMSO (5 mL) was heated to 80 °C, the heat removed whilst 2-(3-chloropropyl)furan (1.00 g, 6.92 mmol) in DMSO (1mL) was added dropwise with rapid stirring, and the reaction stirred at 80 °C for 5 h. The solution was cooled to RT, poured onto water (30 mL) and extracted with ether (3 x 30 mL). The ether layers were combined, washed with water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a pale yellow oil that was used in subsequent reactions without further purification (916 mg, 98%); $R_f$ 0.31 (5:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3120w, 2945m, 2247m, 1597m, 1508m, 1153m, 1007m, 738s; $\delta_H$ (400 MHz, $CDCl_3$) 7.31 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 6.28 (1H, dd, *J* 3.0, 2.0, C(4')**H**), 6.06 (1H, dd, *J* 3.0, 1.0, C(3')**H**), 2.78 (2H, t, *J* 7.0, C(1)$\mathbf{H_2}$), 2.34 (2H, t, *J* 7.0, C(3)$\mathbf{H_2}$), 1.98 (2H, quin, *J* 7.0, C(2)$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 153.3 (**C**(2')), 141.5 (**C**(5')), 119.4 (**C**N), 110.3 (**C**(3')), 106.3 (**C**(4')), 26.7 (**C**(1)), 24.0 (**C**(2)), 16.4 (**C**(3)).

**_N_-Benzyl-2-methylpropane-2-sulfinamide (288)**

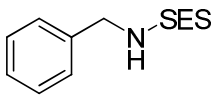


To a stirred solution of benzylamine (51 µL, 50 mg, 0.47 mmol) and triethylamine (131 µL, 95 mg, 0.94 mmol) in dichloromethane (2 mL) at –10 °C was added *t*-butylsulfinyl chloride (120 µL, 132 mg, 0.94 mmol). The reaction was allowed to warm to RT, stirred for 16 h, then diluted with sat. aq. $NaHCO_3$ (10 mL). The separated aqueous layer was extracted with DCM (3 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* as a colourless oil (89 mg, 90%) that was used without further purification; $R_f$ 0.34 (ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 3205s, 2980s, 2960s, 1455s, 1364m, 1303s, 1179m, 1053s; $\delta_H$ (400 MHz, $CDCl_3$) 7.36 – 7.26 (5H, m, Ar**H**), 4.36 (1H, dd, *J* 14.0, 5.0, PhC**H**H'), 4.25 (1H, dd, *J* 14.0, 8.0, PhCH**H'**), 3.54 (1H, dd, *J* 8.0, 5.0, N**H**), 1.25 (9H, s, C(C**H₃**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 138.5 (Ar), 128.6 (Ar), 128.1 (Ar), 127.7 (Ar), 55.9 (**C**$(CH_3)_3$), 49.4 (Ph**C**HH'), 22.7 (C(**C**$H_3)_3$).

HRMS ($ESI^+$) *m/z* calcd for $C_{11}H_{17}NNaOS$ $[MNa]^+$ : 234.0923

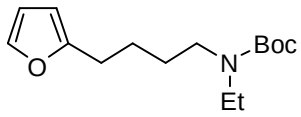
Found : 234.0926

**_N_-Benzyl-2-(trimethylsilyl)ethanesulfonamide[214] (289)**




To a stirred solution of benzylamine (204 µL, 200 mg, 1.87 mmol) and triethylamine (778 µL, 565 mg, 5.58 mmol) in dichloromethane (7 mL) at −10 °C was added 2-(trimethylsilylethane)sulfonyl chloride (747 mg, 3.72 mmol). After stirring for 1 h at −10 °C the solution was allowed to warm to RT and stirred for a further 16 h. The reaction was diluted with water (30 mL), extracted with dichloromethane (3 × 30 mL), the combined organic layers dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (4:1, petrol/ethyl acetate) afforded the title compound as a pale yellow oil (396 mg, 78%); $R_f$ 0.33 (3:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3299m, 2360m, 1645s, 1427w, 1310s, 1172m, 1135s; $\delta_H$ (400 MHz, $CDCl_3$) 7.40 – 7.30 (5H, m, Ar**H**), 4.52 (1H, t, *J* 6.5, N**H**), 4.31 (2H, d, *J* 6.5, PhC**H$_2$**), 2.84 – 2.79 (2H, m, $SO_2$C**H$_2$**), 0.97 – 0.92 (2H, m, C**H$_2$**Si($CH_3$)$_3$), 0.08 (9H, s, C**H$_2$**Si(C**H$_3$**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 137.1 (Ar), 128.9 (Ar), 128.1 (Ar), 128.0 (Ar), 49.6 ($SO_2$**C**$H_2$), 47.5 (PhC**H$_2$**), 10.5 (**C**$H_2$Si($CH_3$)$_3$), –2.1 ($CH_2$Si(**C**$H_3$)$_3$).

**Ethyl-(4-furan-2-yl-butyl)-carbamic acid *tert*-butyl ester (290)**

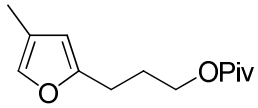



A solution of carbamate **123** (1.00 g, 4.18 mmol) in DMF (8 mL) was added dropwise to a suspension of NaH (502 mg, 12.54 mmol, 60% dispersion in mineral oil) in DMF (15 mL) at 0 °C. After stirring for 30 min, ethyl iodide (1.02 mL, 1.98 g, 12.7 mmol) in DMF (2mL) was added and the reaction stirred at RT for 16 h. The reaction was quenched with water (2 mL) at 0 °C, diluted with ether (100 mL) and filtered through a pad of celite. The separated organic layer was washed with water (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (9:1, petrol/ethyl acetate) afforded the *title compound* as a yellow oil (1.06 g, 95%); $R_f$ 0.20 (10:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3115w, 2974s, 2933s, 2867m, 1687s, 1478s, 1416s, 1356s, 1277s, 1160s; $\delta_H$ (400 MHz, $CDCl_3$) ) 7.29 (1 H, d, *J* 2.0, C(5')**H**), 6.27 (1 H, dd, *J* 3.0, 2.0, C(4')**H**), 5.97 (1 H, dd, *J* 3.0, 1.0, C(3')**H**),) 3.20 – 3.16 (4 H, m, C(4)$\mathbf{H_2}$ and NC$\mathbf{H_2}$$CH_3$), 2.64 (2 H, t, *J* 7.0, C(1)$\mathbf{H_2}$), 1.67 – 1.50 (4H, m, C(2)$\mathbf{H_2}$ and C(3)$\mathbf{H_2}$), 1.45 (9 H, s, C(C$\mathbf{H_3}$)$_3$), 1.08 (3 H, t, *J* 7.0, $NCH_2C\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 156.0 (**C**=O), 152.4 (**C**(2')), 140.7 (**C**(5')), 110.0 (**C**(4')), 104.7 (**C**(3')), 79.0 (**C**$(CH_3)_3$), 46.2 (**C**(4)), 41.7 (N**C**$H_2CH_3$), 28.5 (C(**C**$H_3$)$_3$), 28.0 (**C**(1)), 27.7 (**C**(2)), 25.3 (**C**(3)).

HRMS (ESI) *m/z* calcd for $C_{15}H_{25}NNaO_3$ $[M+Na]^+$ : 290.1726

Found : 290.1727

**3-(4-Methylfuran-2-yl)propyl pivalate (291)**

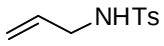



Prepared according to *general procedure G* from diol **266** (4.10 g, 16.9 mmol). The *title compound* was obtained as a colourless oil (3.68 g, 97%) that was used without further purification; $R_f$ 0.22 (6:1, petrol/ether); $\nu_{max}$ (thin film)/$cm^{-1}$ 2967s, 1726s, 1480m, 1364m, 1284s, 1154s, 1038m; $\delta_H$ (400 MHz, $CDCl_3$) 7.07 (1H, s, C(5')**H**), 5.88 (1H, s, C(3')**H**), 4.09 (2H, t, *J* 6.5, C(3)$\mathbf{H_2}$), 2.66 (2H, t, *J* 7.5, C(1)$\mathbf{H_2}$), 1.99 (3H, s, C(4')C$\mathbf{H_3}$, overlapping), 1.96 (2H, app. quin, *J* 7.0, C(2)$\mathbf{H_2}$, overlapping), 1.21 (9H, s, C(O)C(C$\mathbf{H_3}$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 178.5 (**C**=O), 154.9 (**C**(2')), 137.6 (**C**(5')), 120.5 (**C**(4')), 108.0 (**C**(3')), 63.5 (**C**(3)), 38.7 (C(O)**C**$(CH_3)_3$), 27.2 (C(O)C(**C**$H_3$)$_3$), 27.1 (**C**(2)), 24.5 (**C**(1)), 9.7 (C(4')**C**$H_3$).

HRMS ($FI^+$) *m/z* calcd for $C_{13}H_{20}O_3^+$ $[M]^+$ : 224.1412

Found : 224.1405

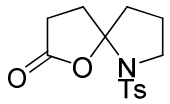
***N*-Allyl-4-methylbenzenesulfonamide[215] (292)**




Prepared according to *general procedure A* from allyl amine (1.00 g, 17.54 mmol) to afford the title compound as a colourless oil (3.68 g, 99%); $R_f$ 0.26 (3:1, petrol/ethyl

acetate); $\delta_H$ (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.0, Ar**H**), 7.30 (2H, d, *J* 8.0, Ar**H**), 5.70 (1H, dddd, *J* 17.0, 10.0, 6.0, **H**C=CHH'), 5.15 (1H, dd, *J* 17.0, 1.0, HC=C**H**H'), 5.07 (1H, dd, *J* 10.0, 1.0, HC=CH**H'**), 5.00 (1H, br s, N**H**), 3.56 (2H, tt, *J* 6.0, 1.0, C**$H_2$**NH), 2.42 (3H, s, ArC**$H_3$**); $\delta_C$ (100 MHz, $CDCl_3$) 143.5 (Ar), 136.9 (Ar), 133.0 (H**C**=CHH'), 129.7 (Ar), 127.1 (Ar), 117.6 (HC=**C**HH'), 45.7 (**C**$H_2$NH), 21.5 (Ar**C**$H_3$).

**6-Tosyl-1-oxa-6-azaspiro[4.4]nonan-2-one (293)**



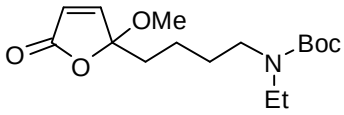

To a solution of 6-tosyl-1-oxa-6-azaspiro[4.4]non-3-en-2-one (10 mg, 35.8 µmol) in methanol (2 mL) was added 10% Pd/C (4 mg). The airspace was evacuated and purged with argon (× 3) and a balloon of $H_2$ attached. After stirring for 0.5 hr the reaction was filtered through a celite plug and concentrated *in vacuo* to give the *title compound* as a colourless oil (10 mg, 95%); $R_f$ 0.16 (2:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3286m, br, 2957s, 1776s, 1598m, 1454m, 1343s, 1157s, 1088m; $\delta_H$ (500 MHz, $CDCl_3$) 7.77 (2H, *J* 8.5, Ar**H**), 7.33 (2H, *J* 8.5, Ar**H**), 3.50 (1H, app. q, *J* 8.5, C(3)**H**H'), 3.32 (1H, dt, *J* 9.5, 5.5, C(3)H**H'**), 3.23 – 3.10 (2H, m, C(3')**H**H' and C(4')**H**H'), 2.63 – 2.56 (1H, m, C(4')H**H'**), 2.47-2.41 (4H, m, ArC**$H_3$** and C(3')H**H'**), 2.28 (1H, dt, *J* 13.5, 5.0, C(1)**H**H'), 2.17-2.10 (1H, m, C(1)H**H'**), 1.89-1.82 (2H, m, C(2)**$H_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 175.7 (**C**(5')), 144.0

(Ar), 135.6 (Ar), 129.6 (Ar), 127.9 (Ar), 102.5 (**C**(2')), 49.3 (**C**(3)), 42.7 (**C**(1)), 32.7 (**C**(3')), 29.0 (**C**(4')), 21.8 (Ar**C**), 21.6 (**C**(2)).

HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NNaO_4S$ $[M+Na]^+$ : 318.0770

Found : 318.0765

**Ethyl-[4-(2-methoxy-5-oxo-2,5-dihydro-furan-2-yl)-butyl]-carbamic acid *tert*-butyl ester (294)**

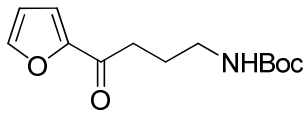



Prepared according to *general procedure D* from carbamate **290** (300 mg, 1.12 mmol). Purification by flash chromatography (2:1, petrol/ethyl acetate) gave the *title compound* as a colourless oil (256 mg, 73%); $R_f$ 0.31 (1:1, petrol/ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3087m, 2973s, 2935s, 1770s, 1683s, 1479m, 1417s, 1366s, 1253s, 1162s, 1078s; $\delta_H$ (400 MHz, $CDCl_3$) 7.09 (1H, d, *J* 5.5, C(3')**H**), 6.16 (1H, d, *J* 5.5, C(4')**H**), 3.16 (3H, s, OC**H$_3$**), 3.15 – 3.05 (4H, m, C(4)**H$_2$** and NC**H$_2$**$CH_3$), 1.88 (2H, t, *J* 8.0, C(1)**H$_2$**), 1.48 (2H, quin, *J* 7.5, C(3)**H$_2$**), 1.39 (9H, s, OC(C**H$_3$**)$_3$), 1.33 (2H, quin, *J* 8.0, C(2)**H$_2$**), 1.03 (3H, t, *J* 7.0, $NCH_2$C**H$_3$**); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (**C**(5')), 155.4 (**C**=O), 153.5 (**C**(3')), 124.8 (**C**(4')), 111.0 (**C**(2')), 79.0 (O**C**$(CH_3)_3$), 51.0 (O**C**$H_3$), 46.1 (**C**(4)), 41.7 (N**C**$H_2CH_3$), 36.7 (**C**(1)), 28.4 (OC(**C**$H_3)_3$), 28.3 (**C**(3)), 20.5 (**C**(2)), 13.6 ($NCH_2$**C**$H_3$).

HRMS (ESI) *m/z* calcd for $C_{16}H_{27}NNaO_5$ $[M+Na]^+$ : 336.1781

Found : 336.1768

**_tert_-Butyl 4-(furan-2-yl)-4-oxobutylcarbamate (295)**



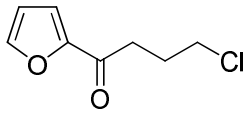

To a solution of furan (588 mg, 8.64 mmol) in THF (6 mL) was added *n*-BuLi (3.9 mL, 6.24 mmol, 1.6 M solution in hexanes) at −78°C. After stirring for 1 h at this temperature, the solution was added dropwise to a solution of *tert*-butyl 2-oxopyrrolidine-1-carboxylate (800 mg, 4.32 mmol) in THF (3 mL) and the mixture stirred at −78°C for 3 h. The reaction was allowed to warm to RT and quenched with sat. aq. $NH_4Cl$ solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (4:1, petrol/ether) afforded the *title compound* as a white solid (530 mg, 48 %); $R_f$ 0.13 (1:1 petrol:ether); m.p. 77 – 79 °C; $\nu_{max}$(thin film)/$cm^{-1}$ 3370s, 2984m, 1677s, 1517s, 1252s, 1167m; $\delta_H$ (400 MHz, $CDCl_3$) 7.59 (1H, dd, *J* 2.0, 1.0, C(5')**H**), 7.20 (1H, dd, *J* 3.5, 1.0, C(3')**H**), 6.54 (1H, dd *J* 3.5 , 2.0, C(4)**H**), 4.66 (1H, br s, N**H**), 3.22 (2H, q, *J* 6.5, C(4)$\mathbf{H_2}$), 2.89 (2H, t, *J* 7.0, C(2)$\mathbf{H_2}$), 1.93 (2H, app. quin, *J* 7.0, C(3)$\mathbf{H_2}$), 1.43 (9H, s, C(C$\mathbf{H_3}$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 189.9 (**C**=O), 156.0 (**C**=O), 152.6 (**C**(2')), 146.4 (**C**(5')), 117.1 (**C**(3')), 112.2 (**C**(4')), 79.14 (**C**$(CH_3)_3$), 40.0

(**C**(4)), 35.6 (**C**(2)), 28.36 (C(**C**$H_3$)$_3$), 24.34 (**C**(3)); *m/z* (ESI$^+$) 529 (2MNa$^+$, 100%), 276 (MNa$^+$, 90).

HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NNaO_4$ $[M+Na]^+$ : 276.1206

Found : 276.1211

**4-Chloro-1-(furan-2-yl)butan-1-one[216] (296)**




To a stirred solution of furan (267 µL, 3.67 mmol) and chlorobutyryl chloride (821 µL, 7.34 mmol) in nitromethane (3.5 mL) was added Sc(OTf)$_3$ (90 mg, 0.18 mmol) and MgO (296 mg, 7.34 mmol). The reaction was stirred at RT for 16 h, filtered through celite, washed with ether (20 mL) and concentrated *in vacuo*. Purification by flash chromatography (4:1, petrol/ether) gave the title compound as a yellow oil (155 mg, 25%); $R_f$ 0.22 (4:1 petrol:ether); $\delta_H$ (400 MHz, $CDCl_3$) 7.60 (1H, dd, *J* 1.5, 0.5, C(5')**H**), 7.23 (1H, dd, *J* 3.5, 0.5, C(3')**H**), 6.55 (1H, dd, *J* 3.5, 1.5, C(4')**H**), 3.66 (2H, t, *J* 6.5, C(4)**H$_2$**), 3.05 (2H, t, *J* 7.0, C(2)**H$_2$**), 2.21 (2H, app. quin, *J* 6.5, C(3)**H$_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 188.2 (**C**=O), 152.5 (**C**(2')), 146.5 (**C**(5')), 117.2 (**C**(3')), 112.28 (**C**(4')), 44.5 (**C**(4)), 35.1 (**C**(2)), 26.5 (**C**(3)).

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