1-1-2012

Synthesis of spirocyclic azacycles from the cyclization of furan tethered N-acyliminium ions

Sudhir R. Shengule
University of Wollongong, sudhir@uow.edu.au

Anthony Willis
Australian National University

Stephen G. Pyne
University of Wollongong, spyne@uow.edu.au

Synthesis of spirocyclic azacycles from the cyclization of furan tethered N-acyliminium ions

Abstract

The protic and Lewis acid promoted cyclization reactions of tethered furan-4,5-dihydroxypiperid-2-ones, furan-4,5-diacetoxypiperid-2-ones and furan-3,4-diacetoxypyrrolid-2-ones, via their corresponding N-acyliminium ion intermediates, have been studied. In the case of the furan-4,5-dihydroxypiperid-2-one 2a and its diacetate derivative 2b, macrocyclic products were formed from an initial intermolecular reaction between 2a or 2b, via the nucleophilic C5 furan carbon, and their corresponding N-acyliminium ion intermediates. When the furan C5 position of 2b was blocked by substitution with bromine then TFA or Sc(OTf)3 catalysed cyclization reactions gave a spirotricyclic product (a 5-6-6-tricycle) in a highly diastereoselective manner. Cyclization of the analogous C5-Br-furan-pyrrolidone 29 with TFA resulted in a related spirotricyclic (a 5-6-5 tricycle) product. Attempts to prepare an analogous azepine system, a 5-7-5 tricycle, were not successful. Cyclization reactions of the C5-PhS-furan- or C5-phenylsulfonyl-pyrrolidone analogues of 29 with TFA were also not successful.

Keywords

synthesis, ions, acyliminium, n, tethered, furan, cyclization, azacycles, spirocyclic, CMMB

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Shengule, S. R., Willis, A. & Pyne, S. G. (2012). Synthesis of spirocyclic azacycles from the cyclization of furan tethered N-acyliminium ions. Tetrahedron, 68 (4), 1207-1215.

Synthesis of spirocyclic azacycles from the cyclization of furan tethered *N*-acyliminium ions

Sudhir R. Shengule[a], Anthony Willis[b] and Stephen G. Pyne[a]*

[a]*School of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia*

[b] *Research School of Chemistry, Australian National University, Canberra, ACT, 0200, Australia.*

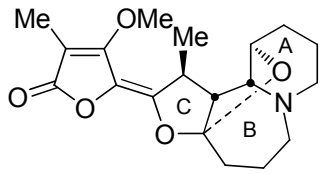
spyne@uow.edu.au

ABSTRACT

The protic and Lewis acid promoted cyclization reactions of tethered furan-4,5-dihydroxypiperid-2-ones, furan-4,5-diacetoxypiperid-2-ones and furan-3,4-diacetoxypyrrolid-2-ones, via their corresponding *N*-acyliminium ion intermediates, have been studied. In the case of the furan-4,5-dihydroxypiperid-2-one **2a**, and its diacetate derivative **2b**, macrocyclic products were formed from an initial intermolecular reaction between **2a** or **2b**, via the nucleophilic C5 furan carbon, and their corresponding *N*-acyliminium ion intermediates. When the furan C5 position of **2b** was blocked by substitution with bromine then TFA or $Sc(OTf)_3$ catalysed cyclization reactions gave a spirotricyclic product (a 5-6-6-tricycle) in a highly diastereoselective manner. Cyclization of the analogous C5-Br-furan-pyrrolidone **29** with TFA resulted in a related spirotricyclic (a 5-6-5 tricycle) product. Attempts to prepare an analogous azepine system, a 5-7-5 tricycle, were not successful. Cyclization reactions of the C5-PhS-furan- or C5-phenylsulfonyl-pyrrolidone analogues of **29** with TFA were also not successful.

1. Introduction

As part of a study aimed at the synthesis of the pyrido[1,2-*a*]azepine, Stemona alkaloid, stemocurtisine **1**[1] (Figure 1) we have investigated the cyclization reactions of the tethered furan-piperidones **2a-c** via generation of the corresponding *N*-acyliminium ion intermediates **3** (Scheme 1).[2]



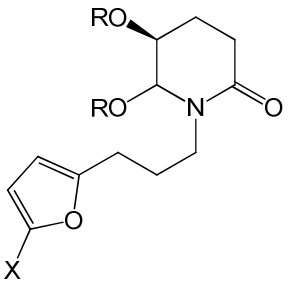
1

Figure 1. The structure of stemocurtisine **1**

These reactions could in principle give either the linearly fused tricyclic furan system **6**, with the desired A-B-C-ring structure of stemocurtisine **1**, or the spirocyclic products **7**, via the carbocationic intermediates **4** and **5**, respectively (Scheme 1). The intermediate **4** would be stabilized by the furan oxygen while the spirocyclic intermediate **5** would be stabilized by the furan substituent X, when X was an electron donating group, and destabilized when X was an electron withdrawing group. Consistent with this mechanistic scheme are the studies by Martin[3] and Tanis[4]. Martin found that the $LiClO_4$ promoted cyclization reactions of the highly activated TIPSO substituted furan substrates **8** gave exclusively the spirotricyclic products **9a,b** (Scheme 2) while Tanis disclosed the formation of linearly fused tricyclic adducts **11a,b** from substrates **10** in which the furan ring was only substituted at the tethered position (Scheme 3). Unfortunately, attempts by the latter group to prepare an azepine system **12b**, as desired by us, were unsuccessful (Scheme 3). However, a more recent report by Padwa showed that the formation of the azepine ring of **14** was possible employing a tethered 4-ethyl

substituted furan **13** (Scheme 4).[5] With this information in mind we decided to investigate the effect of various substituents on the furan ring on the cyclization reactions of the furan-aminols **2a-c**.

Scheme 1



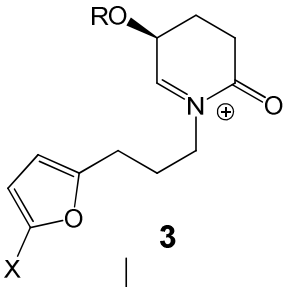
2a; R = X = H

2b; R = Ac, X = H

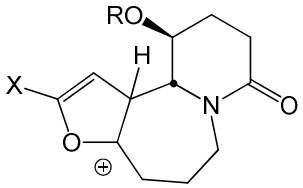
2c; R = Ac, X = Br

H^+ or

Lewis acid

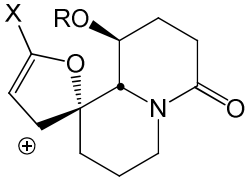


3



4

Stabilized by O



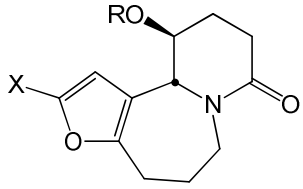
5

Stabilized by X when X = EDG

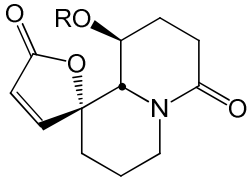
Destabilized by X when X = EWG

- H^+

X = OR, Br | H_2O

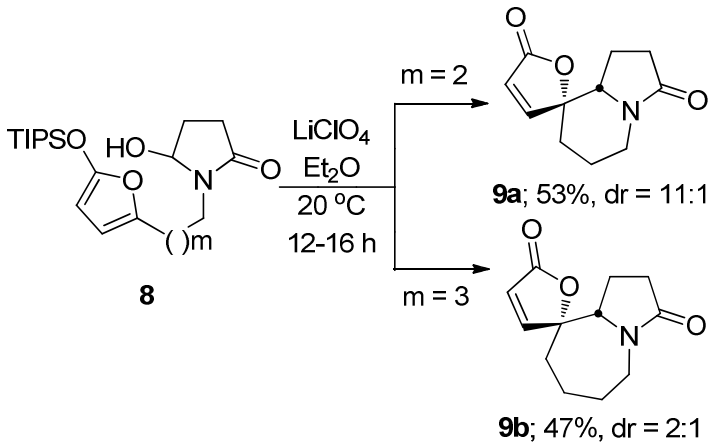


6

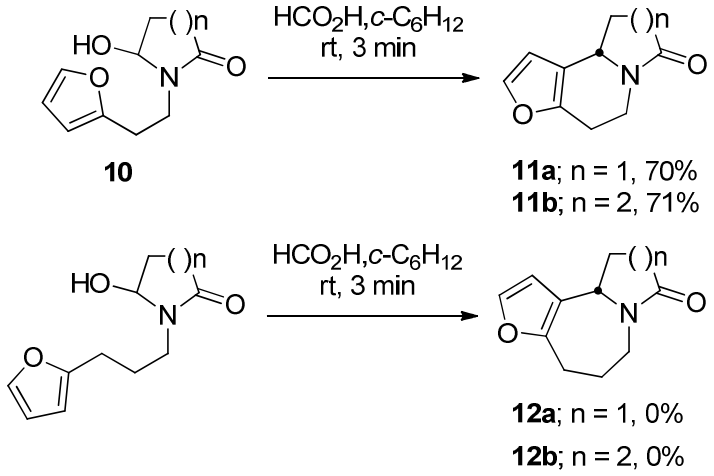


7

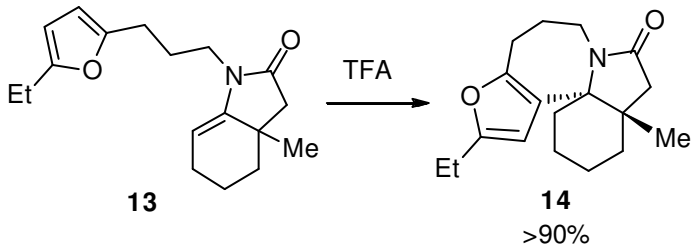
Scheme 2



Scheme 3



Scheme 4

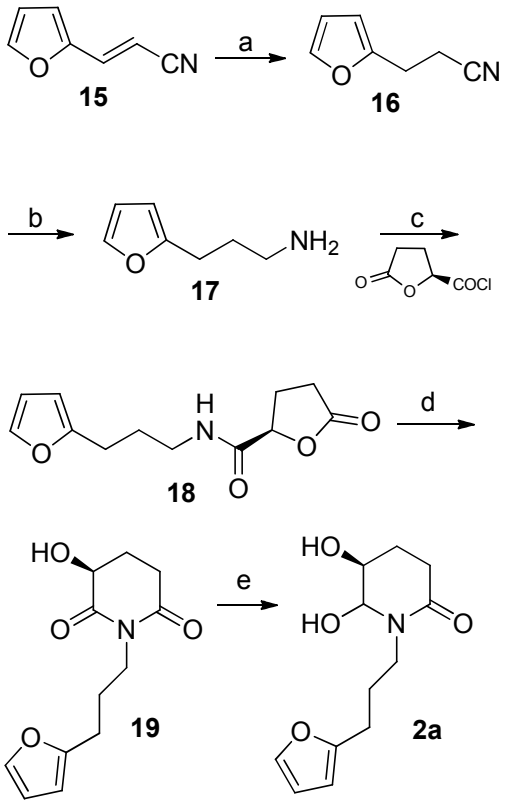


2. Results and discussion

The furyl amine **17**, that was required for the synthesis of **2a**, was synthesized from commercially available nitrile **15** in 81% yield over two steps as shown in Scheme 5.[6] Amine **17** was coupled with the acid chloride prepared from *L*-glutamic acid[7] to give amide **18** in 80% yield. Potassium *tert*-butoxide catalysed rearrangement of **18** provided glutarimide **19** in high yield (90%).[8] The C2 carbonyl group of **19** was regioselectively reduced using $NaBH_4$ to give the diol **2a**.[9] With the cyclization precursor in hand we further subjected **2a** to various Lewis acid or acid catalysed reaction conditions. Long exposure of **2a** to excess amounts of $BF_3{\cdot}Et_2O$ or TFA resulted in the formation of complex reaction mixtures with no traces of the requisite tricyclic products. However, treatment of **2a** with one equiv. of TFA in CH_2Cl_2 solution at rt for 2 h resulted in the self condensation product **20** as a single diastereomer in 54% yield (Scheme 6). Compound **20** had C_2 symmetry and was mostly likely formed from a dimerization reaction of the *N*-acyliminium ion intermediate **A**. While we did not comprehensively prove the stereochemistry of **20** the ^{1}H NMR coupling constant $J_{4a,10a}$ of 3.1 Hz suggested that the rings were *cis*-fused. When **2a** was treated with 1 equiv. of $BF_3{\cdot}Et_2O$ at rt for 2 d the macrocycle **21** was isolated in 29% yield after purification by column chromatography (Scheme 7). In this case, the furan moiety of **2a** acted as a nucleophile, in an intermolecular sense at C5, with the *N*-acyliminium ion **A**. While **20** was also likely to be formed initially in this reaction it would be expected to be in equilibrium with the *N*-acyliminium ion **A** and thus **20** would be slowly transformed into the more stable product **21**. Our attempts to achieve the transformation of **20** to **21**, however, were not successful. For example, exposure of **20** to $BF_3{\cdot}Et_2O$ resulted in a complex mixture of products. The yield of this macrocycle forming reaction was found to be better when carried out on the diacetate derivative **2b**. This substrate gave the macrocycle **22** in 58%

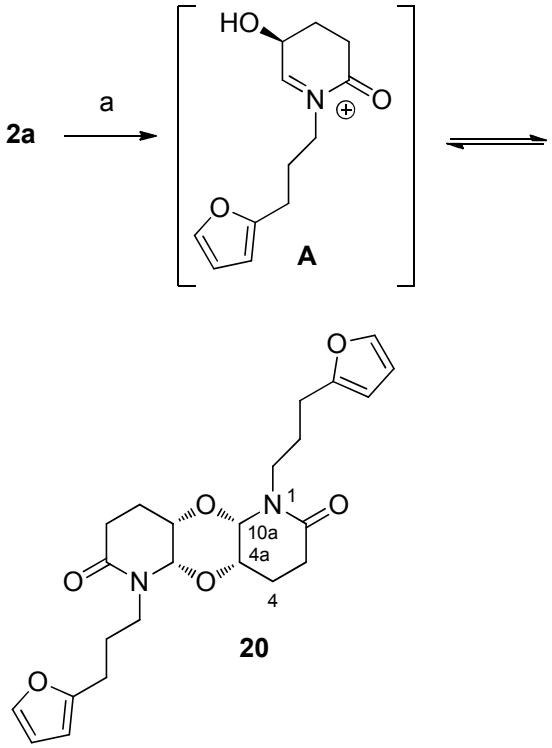
yield upon treatment with one equiv. of $BF_3{\cdot}Et_2O$ at rt for 16 h. Base catalysed hydrolysis of the acetate groups of **22** gave the same macrocycle **21**, in 98% yield, that was obtained from the reaction of **2a** (Scheme 7). The stereochemistry of **21** was assigned as *trans* based on its ^{1}H NMR coupling constant, $J_{5\text{-}6}$ (2.7 Hz), which is consistent in magnitude with that of related *trans* 5,6–disubstituted glutaramide derivatives.[9] The formation of the macrocycles **21** and **22**, rather than the desired linear tricyclic products similar to **12b**, (Scheme 3) is consistent with the results of Tanis[4] who found that formation of an azepine ring in an intramolecular sense was unrewarding in such types of reactions. Clearly in our case intermolecular reactions are more favourable. Formation of similar macrocycles have been previously reported by Padwa *et al.* while studying the *N*-acyliminium ion cyclization reactions of furans.[5]

Scheme 5



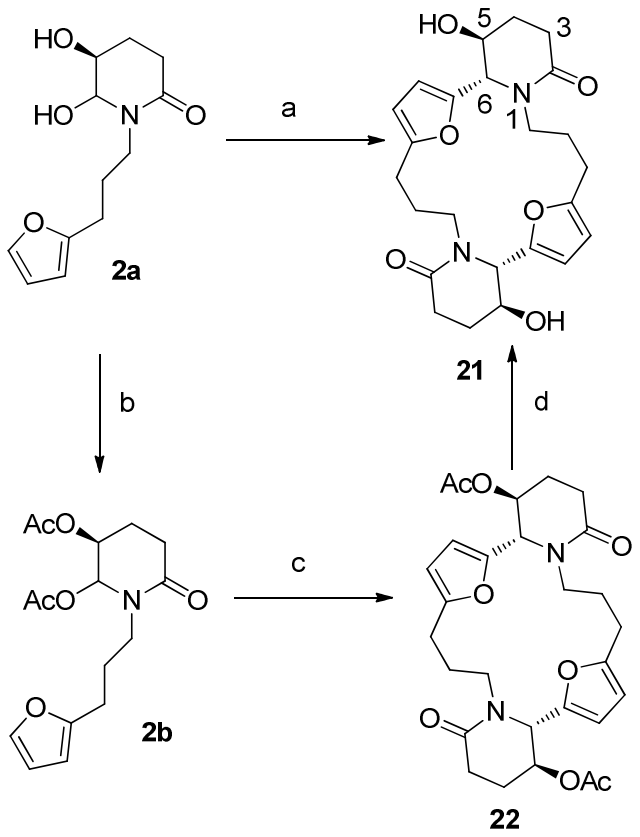
Reagents and conditions: (a) Pd/C, H_2, EtOH, rt, 16 h, 88% (b) $LiAlH_4$, THF, 0 °C, 1 h, 92% (c) acid chloride, TEA, CH_2Cl_2, rt, 16 h, 80% (d) *tert*-BuOK, THF, -78 °C to -40 °C, 1 h, 90% (e) $NaBH_4$, -30 °C, EtOH/CH_2Cl_2, 2 h, 47%.

Scheme 6



Reagents and conditions: (a) TFA, CH_2Cl_2, rt, 2 h, 54%.

Scheme 7



Reagents and conditions: (a) $BF_3{\cdot}Et_2O$ (1 eq.), MeCN, rt, 2 days, 29% (b) Ac_2O, pyridine, DMAP, 20 h, 98% (c) $BF_3{\cdot}Et_2O$ (1 eq.), MeCN, rt, 16 h, 58% (d) KOH, MeOH, rt, 16 h, 98%

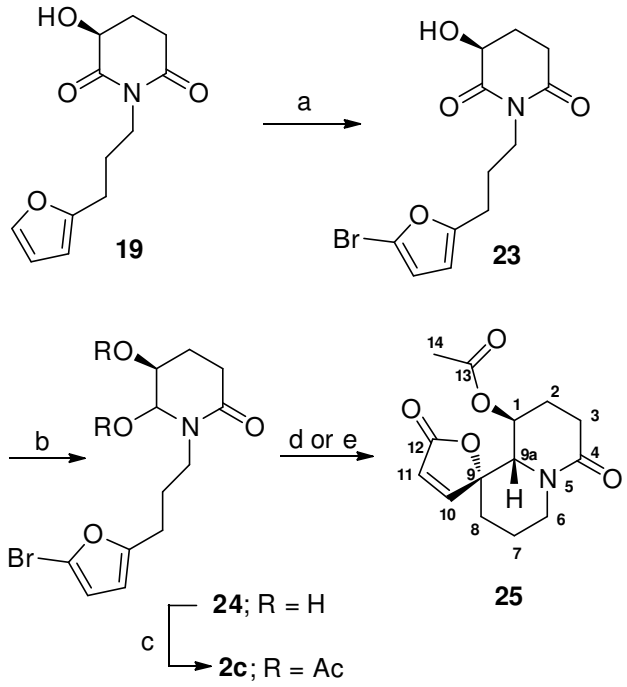
To avoid intermolecular reactions and thus favour intramolecular cyclization, we synthesized the cyclization precursor **2c**, in which both the potentially nucleophilic sites, the C5-hydroxyl group on the piperidinone ring and the C5 position on the furan ring were protected and blocked, respectively. We chose to block the C5 position of the furan moiety with bromine hoping that this weak electron withdrawing group would not

dramatically reduce the nucleophilicity of the furan towards cyclization. Thus compound **19** was treated with NBS in DMF[10] to give the corresponding bromo-furan **23** in 62% yield (Scheme 8). Regioselective carbonyl reduction of **23** using $NaBH_4$ gave the diol **24**, which was further protected by acetate groups giving **2c**. Compound **2c** when treated with TFA (3 equiv.) gave the spirocyclic butenolide **25** as a single diastereoisomer in 54% yield. A better yield (71%) of **25** was obtained when the reaction was carried out in the presence of scandium triflate (0.2 equiv.). In this study **25** was formed as a single diastereoisomer and we did not observe any products arising from cyclization at the C3 position of the furan moiety. The stereochemistry of **25** was confirmed by a single crystal, X-ray crystallographic analysis which indicated the *anti* relationship between H1-H9a and between H9a and the butenolide oxygen (Figure 1). The formation of **25** is consistent with the formation of carbocation intermediate **5** (X = Br) which is resonance stabilized by the Br atom. These results obtained here are similar to those of Martin in terms of the mode of cyclization and the relative stereochemical outcome between H9a and the butenolide oxygen (Scheme 2).[3]

We also investigated if this reaction could be used to synthesize a tricyclic spiro-butenolide with a 5-6-5 tricyclic ring skeleton by subjecting the tethered furan-pyrrolidinone **29** to acidic conditions. Compound **29** was synthesized in a similar way as **2a**, in this case starting with the furyl amine **17** and (*S*)-malic acid. Compound **29** when treated with 3 equiv. of TFA in CH_2Cl_2 at rt for 16 h formed the spirocyclic butenolide **30** as a single diastereomer in 59% yield. The configuration of C8a was expected to be the same as that of C9a in **25**. This was further supported by the magnitude of the ^1H NMR coupling constant $J_{8a,1}$ (1.3 Hz) which was consistent with the coupling constant observed for *trans*-4,5-disubstituted-pyrrolidinone derivatives.[9] Based on the

stereochemical outcomes observed by Martin[3] (Scheme 2) and a strong correlation between H8a and H9 in the NOE spectrum of **30** we have assigned the *trans* stereochemical relationship of H8a and the butenolide oxygen in this compound.

Scheme 8



Reagents and conditions: (a) NBS, DMF, 0 °C, 1 h, 62% (b) $NaBH_4$, EtOH, -30 °C, 2 h, 75% (c) Ac_2O, Pyridine, DMAP, rt, 16 h, 76% (d) TFA, CH_2Cl_2, rt, 16 h, 54 % (e) $Sc(OTf)_3$, MeCN, rt, 48 h, 71%.

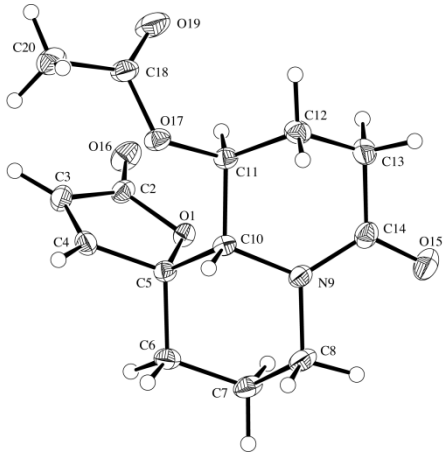
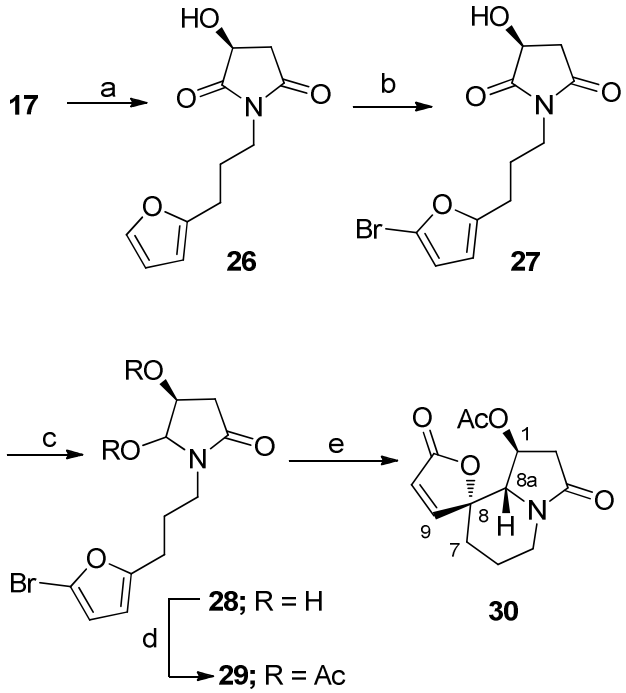


Figure 1. Molecular structure of compound **25** ($C_{14}H_{17}NO_5$) with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Compound numbering is different to the numbering used in Scheme 8.

Scheme 9



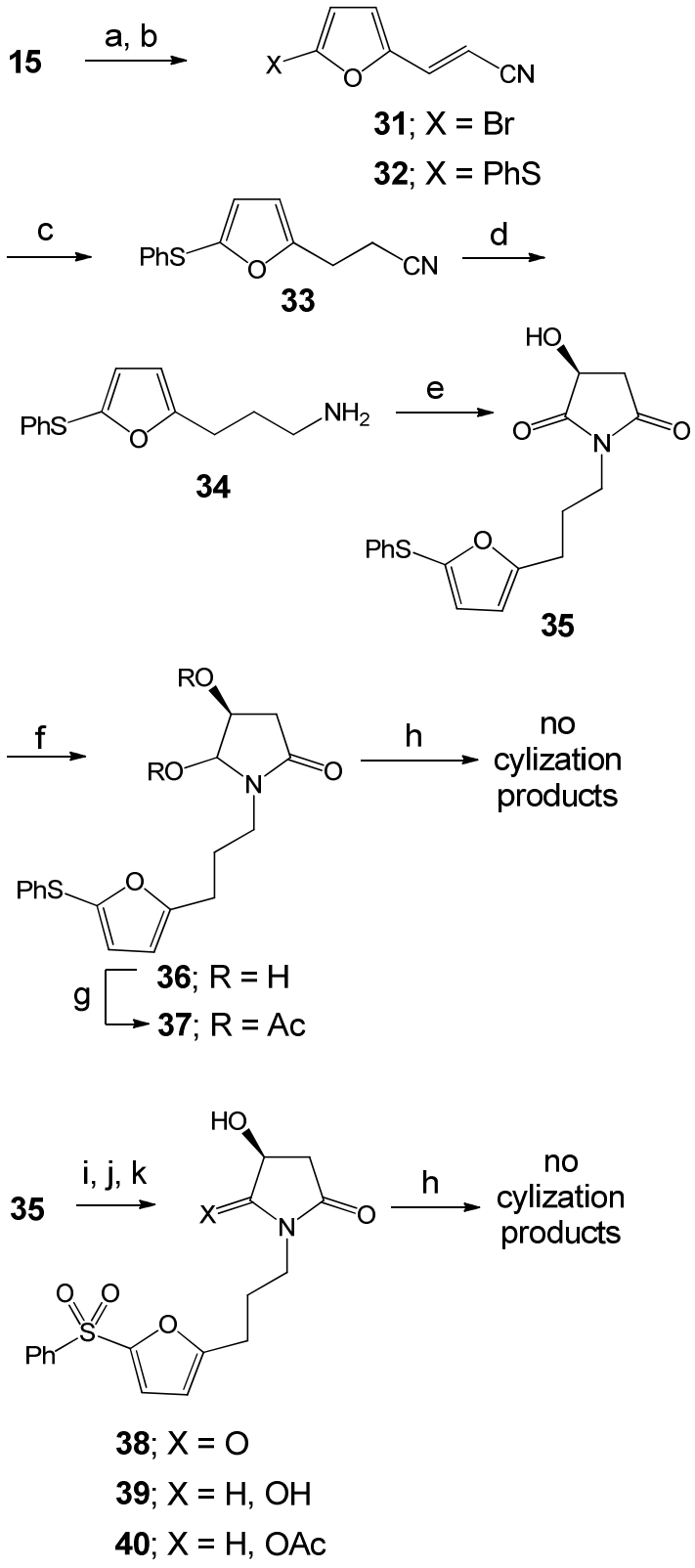
Reagents and conditions: (a) (*S*)-malic acid, xylene, 180 °C, 1.5 h, 69% (b) NBS, DMF, 0 °C, 1 h, 71% (c) $NaBH_4$, EtOH, –20 °C, 1 h, 62% (d) Ac_2O, pyridine, DMAP, rt, 16 h, 82% (e) TFA, CH_2Cl_2, rt, 16 h, 59%

Our attempts to preparing a spirocyclic 5-7-5 tricyclic ring structure using this methodology, akin to that found in many croomine-type Stemona alkaloids,[11-14] have not been successful.[15]

We further investigated the cyclization reactions of tethered furan-pyrrolidinones with an electron donating phenylthio and an electron withdrawing phenylsulfonyl group at the

C5 position of the furan ring. Target compounds **37** and **40** were synthesized from commercially available furyl nitrile **15** (Scheme 10). Bromination of **15** with NBS gave **31** which on treatment with the sodium salt of thiophenol gave the thioether **32** in a 69% yield. Compound **33** was synthesized by reduction of double bond of **32** using a mixture of a $NiCl_2/NaBH_4$ in the presence of $(Boc)_2O$,[16] in the anticipation of producing the *N*-Boc derivative of **34**, however, in our hands this only gave the conjugate reduction product **33**. Further reduction of the nitrile **33** with $LiAlH_4$ gave amine **34**. Compound **37** was synthesised from amine **34** in a similar fashion to the synthesis of **2c**. For the synthesis of **40**, the thioether **35** was oxidised with H_2O_2/HOAc giving sulfone **38** in excellent yield. The C2 carbonyl group of **38** was regioselectively reduced with $NaBH_4$ followed by acetate protection to give **40**. Unfortunately neither compound **37** nor **40**, when treated with TFA, gave any cyclization products and only their C5-hydroxypyrrolidinone derivatives could be isolated. The results obtained with **37** were surprising since we thought that the electron donating thioether group would make the furan ring more nucleophilic and thus favour the cyclization reaction. These results suggest that the thio ether group may have been protonated under the acidic conditions and thus has acted as a deactivating group, much like the sulfone group in **40**, resulting in no observed cyclization products. Indeed a ^1H NMR spectrum of **37** in $CDCl_3$ showed significant downfield shifts of the thiophenyl *ortho* and *para* proton resonances after the addition of 1 drop of TFA, consistent with protonation at sulfur.

Scheme 10



Reagents and conditions: (a) NBS, DMF, 0 °C, 1 h, 72% (b) PhSNa, MeOH, reflux, 16 h, 69% (c) $NiCl_2.6H_2O$, $NaBH_4$, $(Boc)_2O$, MeOH, rt, 16 h, 57% (d) $LiAlH_4$, Et_2O, 0 °C, 1h (e) (*S*)-malic

acid, xylene, 180 °C, 2 h, 39% (2 steps) (f) $NaBH_4$, EtOH, −40 °C, 1h, 50% (g) Ac_2O, pyridine, DMAP, 16 h, rt, 91% (h) TFA, CH_2Cl_2, rt, 3 days (i) H_2O_2, AcOH, rt, 2 days, 96% (j) $NaBH_4$, EtOH, -40 °C, 1 h, 54% (k) Ac_2O, pyridine, DMAP, rt, 16 h, 98%.

3. Conclusions

We have studied the protic and Lewis acid catalysed cyclization reactions of tethered furan-4,5-dihydroxypiperid-2-ones, furan-4,5-diacetoxypiperid-2-ones and furan-3,4-diacetoxypyrrolid-2-ones via their corresponding *N*-acyliminium ion intermediates. In the case of the furan-piperidone **2a** and its diacetate derivative **2b** a macrocyclic product arose from an initial intramolecular reaction between **2a** or **2b**, via the nucleophilic C5 furan carbon, and their corresponding *N*-acyliminium ion intermediates. When the furan C5 position of **2b** was blocked by substitution with a bromine atom then TFA or $Sc(OTf)_3$ catalysed cyclization gave a spirotricyclic product (a 5-6-6-tricycle) in a highly diastreoselective manner. The alternative cyclization product having the linearly fused tricyclic furan system required for the synthesis of stemocurtisine was not produced. Cyclization of the analogous C5-Br-furan-pyrrolidone **29** with TFA resulted in a related spirotricyclic (a 5-6-5 tricycle) product. Attempts to prepare an analogous azepine system, a 5-7-5 tricycle, were not successful. Cyclization reactions of the C5-PhS-furan-pyrrolidone or C5-phenylsulfonyl analogues of **29** with TFA were also not successful. The former case may have been deactivated to cyclization by protonation of the sulfur atom.

4. Experimental

4.1 General

All IR spectra were run as neat samples. All NMR spectra were run at 500 MHz (^{1}H NMR) or 125 MHz (^{13}C NMR) in solutions of $CDCl_3$ unless otherwise noted. FCC is an

abbreviation for flash column chromatography. Petrol refers to the hydrocarbon fraction of bp 40-60 °C.

*4.2 3-(Furan-2-yl)propanenitrile (**16**).*[17]

A solution of **15** (1.00 g, 8.40 mmol) in ethanol (10 mL) was flushed with N_2 for 5 min. followed by addition of 10 % Pd on C (200 mg) and the reaction mixture was stirred for 18 h under a H_2 atmosphere (H_2 balloons) at rt. The reaction mixture was filtered through celite, washed with ethanol (3 × 15 mL) and the solvent was removed under reduced pressure. The crude residue was purified by FCC over silica gel using a gradient of 0:100–12:88 EtOAc/petrol to give **16** as a colourless oil (894 mg, 88%). R_f: 0.48 (10:90, EtOAc/petrol). ^{1}H NMR δ 7.31 (bs, 1H), 6.28 (bs, 1H), 6.13 (d, 1H, *J* 3.2 Hz), 2.96 (t, 2H, *J* 7.4 Hz), 2.63 (t, 2H, *J* 7.4 Hz).

*4.2 3-(Furan-2-yl)propan-1-amine (**17**).*[6]

To a mixture of lithium aluminium hydride (471 mg, 12.3 mmol) in THF (10 mL) at 0 °C was added dropwise a solution of **16** (500 mg, 4.13 mmol) in THF (5 mL) under a N_2 atmosphere. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was cooled to −10 °C followed by the dropwise addition of water (2 mL) and 10 % NaOH (2 mL). The reaction mixture was slowly warmed to rt and then diluted with Et_2O (20 mL), filtered through celite and the solids were washed several times with Et_2O (3 × 10 mL). The filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give amine **17** as a thick colourless oil (516 mg, 92 %); ^{1}H NMR δ 7.22 (bs, 1H), 6.20 (bs, 1H), 5.92 (bs, 1H), 2.70–2.55 (m, 4H), 1.76–1.66 (m, 2H).

*4.3 (R)-N-(3-(Furan-2-yl)propyl)-5-oxotetrahydrofuran-2-carboxamide (**18**).*

To a solution of **17** (500 mg, 4.00 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (1.11 mL, 8.00 mmol) and the reaction mixture was cooled to 0 °C. After 5 min. a solution of 5-oxotetrahydrofuran-2-carbonyl chloride (592 mg, 8.00 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 30 min. The reaction was then stirred at rt for 18 h. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and then the solvent was removed under reduced pressure. The residue obtained was purified by FCC over silica gel using a gradient of 10:90–40:60 EtOAc/petrol to afford **18** as a colourless thick oil (758 mg, 80%); R_f: 0.31 (25:75, EtOAc/petrol); $[\alpha]_D^{25}$ -20.9 (*c* 1.1, $CHCl_3$); IR ν_{max} (cm^{-1}): 3341, 1778, 1650, 1542, 1178, 1139, 1045, 741; ^{1}H NMR δ 7.31 (bs, 1H), 6.47(bs, 1H), 6.30-6.36 (m, 1H), 6.02 (d, 1H, *J* 3.3 Hz), 4.82 (t, 1H, *J* 7.4 Hz), 3.42–3.28 (m, 2H), 2.68 (t, 2H, *J* 7.4 Hz), 2.65–2.58 (m, 1H), 2.55 (t, 2H, *J* 7.1 Hz), 1.89 (p, 2H, *J* 7.1 Hz);^{13}C NMR δ 175.9, 169.5, 154.8, 141.4, 110.4, 105.6, 77.3, 39.0, 27.9, 27.8, 26.0, 25.6. HRMS (ESI +ve) calculated for $C_{12}H_{16}NO_4$ ($M+H^+$) 238.1074, found 238.1080.

*4.4 (S)-1-(3-(Furan-2-yl)propyl)-3-hydroxypiperidine-2,6-dione (**19**).*

Compound **18** (100 mg, 0.421 mmol) was dissolved in THF (5 mL) and the reaction mixture was cooled to −78 °C. Potassium *tert*-butoxide (24 mg, 0.210 mmol) was added over 10 min. in small portions to the reaction mixture. The reaction mixture was slowly warmed to −40 °C and stirred at the same temperature until TLC analysis showed completion of the reaction. The reaction mixture was cooled to −78 °C and then quenched with a saturated solution of $NaHCO_3$ (2 mL). The reaction mixture was then diluted with water (5 mL) and then extracted with EtOAc (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by FCC using a gradient of 10:90–30:70 EtOAc/petrol to give **19** as

a white solid (90 mg, 90%); R_f: 0.62 (25:75, EtOAc/petrol); Mp: 78–82 °C; $[\alpha]_D^{25}$ -63 (*c* 1.7, $CHCl_3$); IR ν_{max} (cm^{-1}): 3402, 1731, 1650, 1363, 1334, 1319, 1245, 1093, 1077, 1035, 1007, 731; ^1H NMR δ 7.28 (bs, 1H), 6.27 (bs, 1H), 6.02 (d, 1H, *J* 3.1 Hz), 4.16 (dd, 1H, *J* 12.4, 5.7 Hz), 3.91–3.76 (m, 2H), 3.61 (bs, 1H), 2.89–2.81 (m, 1H), 2.65 (t, 2H, *J* 7.3 Hz), 2.64–2.54 (m, 1H), 2.34–2.36 (m, 1H), 1.95-1.79 (m, 3H); ^{13}C NMR δ 175.2, 171.1, 154.9, 140.9, 110.1, 104.9, 68.2, 40.0, 30.7, 25.8, 25.5, 25.2; HRMS (ESI +ve) calculated for $C_{12}H_{16}NO_4$ ($M+H^+$) 238.1074, found 238.1081.

*4.5 (5S)-1-(3-(Furan-2-yl)propyl)-5,6-dihydroxypiperidin-2-one (**2a**).*

Compound **19** (190 mg, 0.801 mmol) was dissolved in EtOH/CH_2Cl_2 (8:2, 5 mL) and the reaction mixture was cooled to −40 °C followed by addition of $NaBH_4$ (213 mg, 5.61 mmol) and the reaction mixture stirred at the same temperature for 1 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL) and the reaction mixture was warmed to rt. The reaction mixture was extracted with EtOAc (3 × 25 mL), and the combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by FCC over silica gel using a gradient of 0:100–10:90 MeOH/EtOAc to give **2a** as a thick colourless liquid as a single diastereoisomer (90 mg, 47%); R_f: 0.43 (10:90, MeOH/EtOAc); $[\alpha]_D^{25}$ +18.6 (*c* 3.2, MeOH); IR ν_{max} (cm^{-1}): 3423, 2940, 1718, 1654, 1636, 1617, 1508, 1481, 1039, 740; ^1H NMR (CD_3OD) δ 7.37 (bs, 1H), 6.27 (dd, 1H, *J* 3.0, 1.9 Hz), 6.04 (d, 1H, *J* 3.0 Hz), 4.73 (d, 1H, *J* 2.4 Hz), 3.87-3.82 (m, 1H), 3.71-3.62 (m, 1H), 3.26-3.16 (m, 1H), 2.64 (t, 2H, *J* 7.5 Hz), 2.58-2.49 (m, 1H), 2.31–2.24 (m, 1H), 2.21–2.12 (m, 1H), 1.95 (p, 2H, *J* 7.8 Hz), 1.80–1.73 (m, 1H); ^{13}C NMR δ 171.5, 155.5, 140.9, 109.9, 104.7, 83.6, 67.4, 44.9, 26.8, 26.1, 25.1, 22.2; HRMS (ESI +ve) calculated for $C_{12}H_{18}NO_4$ ($M+H^+$) 240.1231, found 240.1236.

*4.6. (4aS,5aR,9aS,10aR)-1,6-Bis(3-(furan-2-yl)propyl)octahydro-[1,4]dioxino[2,3-b:5,6-b']dipyridine-2,7(3H,8H)-dione (**20**).*

To a solution of **2a** (50 mg, 0.209 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.032 mL, 0.418 mmol) and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with a saturated solution of Na_2CO_3 (3 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was purified using FCC over silica gel using a gradient of 10:90–40:60 EtOAc/petrol to give **20** as a white solid and as a single diastereoisomer (25 mg, 54%); R_f: 0.50 (30:70, EtOAc/petrol); $[\alpha]_D^{25}$ +48 (*c* 0.3, $CHCl_3$); IR ν_{max} (cm^{-1}): 3000, 1639, 1476, 1035, 726; ^{1}H NMR δ 7.30 (bs, 2H), 6.28 (bs, 2H), 6.02 (bs, 2H), 4.75 (d, 2H, *J* 3.1 Hz), 4.03–3.95 (m, 2H), 3.81–3.71 (m, 2H), 3.30–3.20 (m, 2H), 2.63 (t, 4H, *J* 7.2 Hz), 2.62–2.52 (m, 2H), 2.32–2.22 (m, 2H), 2.20–2.10 (m, 2H), 2.00–1.85 (m, 4H), 1.85–1.75 (m, 2H); ^{13}C NMR δ 169.6 (2), 155.4 (2), 141.1 (2), 110.4 (2), 105.2 (2), 80.9 (2), 68.9 (2), 43.2 (2), 29.0 (2), 25.8 (2), 25.7 (2), 22.9 (2); HRMS (ESI +ve) calculated for $C_{24}H_{31}N_2O_6$ ($M+H^+$) 443.2177, found 443.2196.

*4.7 (3S)-1-(3-(Furan-2-yl)propyl)-6-oxopiperidine-2,3-diyl diacetate (**2b**).*

To a stirred solution of **2a** (120 mg, 0.50 mmol) in pyridine (5 mL) was added acetic anhydride (0.20 mL, 2.00 mmol) and DMAP (6 mg, 0.05 mmol). The reaction mixture was stirred at rt for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (15 mL) and washed with a saturated solution of $CuSO_4$ (3 × 15 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by FCC over silica gel using a gradient of 0:100–30:70 EtOAc/petrol to give **2b** as thick colourless oil (158 mg, 98%); R_f: 0.55

(20:80, EtOAc/petrol); $[\alpha]_D^{25}$ +69 (*c* 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}): 3000, 1746, 1666, 1369, 1210, 1184, 1013, 937, 748, 740, 732; ^{1}H NMR δ 7.29 (bs, 1H), 6.27 (t, 1H, *J* 2.4 Hz), 6.07 (bs, 1H), 6.01 (d, 1H, *J* 2.9 Hz), 5.01 (q, 1H, *J* 3.2 Hz), 3.80–3.71 (m, 1H), 3.16–3.06 (m, 1H), 2.64 (t, 2H, *J* 7.5 Hz), 2.61–2.45 (m, 2H), 2.30–2.20 (m, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.06-1.99 (m, 1H), 1.98–1.80 (m, 2H); ^{13}C NMR δ 170.0, 169.8 (2), 155.2, 141.2, 110.3, 105.2, 81.0, 67.2, 45.4, 27.4, 26.3, 25.3, 21.4, 21.1, 21.0; HRMS (ESI +ve) calculated for $C_{16}H_{22}NO_6$ ($M+H^+$) 324.1456, found 324.1446.

*4.8 Macrocycle **21***

To a solution of **2a** (100 mg, 0.418 mmol) in acetonitrile (3 mL) was added $BF_3{\cdot}OEt_2$ (0.052 mL, 0.418 mmol) and the reaction was stirred at rt for 2 d. The solvent was removed under reduced pressure and the dark brown residue was subjected to FCC over silica gel using a gradient of 0:100–25:90 MeOH/EtOAc to give **21** as light yellow solid and as a single diastereoisomer (54 mg, 29%); R_f: 0.32 (15:85, MeOH/EtOAc) Mp: 140–145 °C (decomposed); $[\alpha]_D^{25}$ +288 (*c* 0.3, MeOH); ^{1}H NMR (CD_3OD) δ 6.53 (d, 2H, *J* 5.9 Hz), 5.95 (d, 2H, *J* 5.9 Hz), 4.75 (d, 2H, *J* 13.1 Hz), 3.94-3.89 (m, 2H), 3.52 (d, 2H, *J* 2.7 Hz), 2.63–2.54 (m, 2H), 2.51–2.42 (m, 2H), 2.21 (dt, 2H, *J* 5.4, 17.5 Hz), 2.04–1.95 (m, 2H), 1.91–1.77 (m, 4H), 1.77–1.59 (m, 4H);^{13}C NMR (CD_3OD) δ 170.9 (2), 138.7 (2), 129.9 (2), 123.6 (2), 92.3 (2), 67.8 (2), 63.5 (2), 43.0 (2), 35.7 (2), 27.1 (2), 26.5 (2), 21.3 (2); HRMS (ESI +ve) calculated for $C_{24}H_{31}N_2O_6$ ($M+H^+$) 443.2177, found 443.2184.

*4.9 Macrocycle **22**.*

To a solution of **2b** (60 mg, 0.185 mmol) in acetonitrile (3 mL) was added $BF_3{\cdot}OEt_2$ (0.023 mL, 0.185 mmol) and the reaction was stirred at rt for 16 h. The solvent was removed under reduced pressure and the dark brown residue was subjected to FCC over

silica gel using a gradient of 0:100–10:90 MeOH/EtOAc to give **22** as light yellow solid and as a single diastereoisomer (28 mg, 58%); R_f: 0.65 (10:90, MeOH/EtOAc) Mp: 123–128 °C; $[\alpha]_D^{25}$ +473 (*c* 0.7, MeOH); IR ν_{max} (cm^{-1}): 3000, 1739, 1634, 1473, 1362, 1240, 1039, 748, 681; ^{1}H NMR (CD_3OD) δ 6.56 (d, 2H, *J* 6.1 Hz), 5.95 (d, 2H, *J* 6.1 Hz), 5.06–5.02 (m, 2H), 4.76 (d, 2H, *J* 13.1 Hz), 3.74 (d, 2H, *J* 2.3 Hz), 2.67–2.57 (m, 2H), 2.50–2.40 (m, 2H), 2.29 (dt, 2H, *J* 5.0, 17.3 Hz), 2.13–2.00 (m, 4H), 2.30 (s, 12H), 1.99–1.73 (m, 4H), 1.69–1.60 (m, 2H); ^{13}C NMR (CD_3OD) δ 170.5 (2), 170.1 (2), 138.6 (2), 129.5 (2), 123.7 (2), 92.2 (2), 66.9 (2), 64.6 (2), 42.7 (2), 35.4 (2), 27.0 (2), 23.6 (2), 21.1 (2), 19.8 (2); HRMS (ESI +ve) calculated for $C_{28}H_{35}N_2O_8$ ($M+H^+$) 527.2388, found 527.2376.

*4.10 Synthesis of macrocycle **21** from **22**.*

To a solution of **22** (25 mg, 0.047 mmol) in MeOH (3 mL) was added KOH (26 mg, 0.470 mmol) and the reaction mixture was stirred at rt for 16 h. The solvent was removed under reduced pressure and the crude residue was purified by FCC over silica gel using a gradient of 0:100–20:80 MeOH/EtOAc to give **21** as a light yellow solid (21 mg, 98%). This compound was identical to that obtained above from cyclization of **2a**.

*4.11 (S)-1-(3-(5-Bromofuran-2-yl)propyl)-3-hydroxypiperidine-2,6-dione (**23**).*

To a stirred solution of **19** (100 mg, 0.421 mmol) in DMF (5 mL) at 0 °C was added NBS (75 mg, 0.421 mmol) and the reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL) and then extracted with EtOAc (3 × 25 mL). The combined extracts were washed with water (3 × 20 mL) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was subjected to FCC over silica gel using a gradient of 10:90–30:70 EtOAc/petrol to give **23** as a thick colourless oil (82 mg, 62%); R_f: 0.62 (25:75,

EtOAc/petrol); $[\alpha]_D^{25}$ −38.6 (*c* 0.3, $CHCl_3$); IR ν_{max} (cm^{-1}): 3434, 1722, 1658, 1363, 1168, 1147, 1122, 1077, 1036, 796; ^{1}H NMR δ 6.14 (d, 1H, *J* 3.4 Hz), 5.98 (d, 1H, *J* 3.4 Hz), 4.16 (dd, 1H, *J* 12.5, 5.6 Hz), 3.86–3.71 (m, 2H), 2.87–2.80 (m, 1H), 2.64–2.53 (m, 3H), 2.32–2.23 (m, 1H), 1.90–1.78 (m, 3H); ^{13}C NMR δ 175.4, 171.5, 157.2, 119.5, 111.9, 108.2, 68.5, 40.0, 30.9, 26.0, 25.8, 25.5; HRMS (EI +ve) calculated for $C_{12}H_{14}Br^{79}NO_4$ ($M^{+\cdot}$) 315.0101, found 315.0109.

*4.12 (5S)-1-(3-(5-Bromofuran-2-yl)propyl)-5,6-dihydroxypiperidin-2-one (**24**).*

The title compound was synthesised from **23** (100 mg, 0.31 mmol) using the method described for the synthesis of **2a**. Compound **24** was isolated as a single diastereoisomer as a thick oil (75 mg, 75%); R_f: 0.43 (10:90, MeOH/EtOAc); $[\alpha]_D^{25}$ +31.8 (*c* 0.3, MeOH); IR ν_{max} (cm^{-1}): 3536, 1613, 1489, 1288, 1125, 1039, 962, 781; ^{1}H NMR (CD_3OD) δ 6.24 (d, 1H, *J* 2.5 Hz), 6.12 (bs, 1H), 4.74 (bs, 1H), 3.87 (bs, 1H), 3.73–3.63 (m, 1H), 3.29–3.19 (m, 1H), 2.66 (t, 2H, *J* 7.9 Hz), 2.62–2.50 (m, 1H), 2.30 (dd, 1H, *J* 5.2, 17.6 Hz), 2.24–2.13 (m, 1H), 1.93 (p, 2H, *J* 7.5 Hz), 1.83–1.75 (m, 1H);^{13}C NMR (CD_3OD) δ 171.5, 157.9, 119.0, 111.7, 107.9, 83.6, 67.4, 44.7, 26.8, 25.9, 25.2, 22.2; HRMS (EI +ve) calculated for $C_{12}H_{16}Br^{79}NO_4$ ($M^{+\cdot}$) 317.0258, found 315.0263.

*4.13 (3S)-1-(3-(5Bromofuran-2-yl)propyl)-6-oxopiperidine-2,3-diyl diacetate (**2c**).*

Using the method described for the synthesis of **2b** the title compound was isolated as colourless oil (59 mg, 78%); R_f: 0.55 (20:80, EtOAc/petrol); $[\alpha]_D^{25}$ 66.7 (*c* 0.7, $CHCl_3$); IR ν_{max} (cm^{-1}): 1745, 1665, 1369, 1211, 1154, 1125, 1057, 1012, 973, 940, 871, 785; ^{1}H NMR δ 6.16 (d, 1H, *J* 3.0 Hz), 6.03 (bs, 1H), 6.00 (d, 1H, *J* 2.8 Hz), 5.03–4.97 (m, 1H), 3.78–3.67 (m, 1H), 3.17-3.06 (m, 1H), 2.60 (t, 2H, *J* 7.3 Hz), 2.57–2.44 (m, 2H), 2.30–2.19 (m, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.06–1.97 (m, 1H), 1.97–1.77 (m, 2H);^{13}C NMR δ 170.0, 169.8 (2), 157.3, 119.6, 111.9, 108.2, 80.9, 67.2, 45.3, 27.4, 26.3, 25.5,

21.4, 21.1 (2); HRMS (EI +ve) calculated for $C_{16}H_{20}Br^{81}NO_6$ ($M^{+\cdot}$) 403.0449, found 403.0450.

*4.14 (2R,6'S)-5,9'-Dioxo-1',2',3',6',7',8',9',9a'-octahydro-5H-spiro[furan-2,4'-quinolizin]-6'-yl acetate (**25**).*

Method A: To a solution of **2c** (50 mg, 0.124 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.028 mL, 0.374 mmol) and the reaction mixture was stirred at rt for 16 h. The solvent was removed under reduced pressure and the residue was purified by FCC over silica gel using a gradient of 0:100–15:85 MeOH/EtOAc to give **25** as a white solid (19 mg, 54%).

Method B: To a stirred solution of **2c** (15 mg, 0.037 mmol) in acetonitrile (3 mL) was added scandium triflate (3.6 mg, 0.0074 mmol) and the reaction mixture was stirred at rt for 48 h. The solvent was removed under reduced pressure and the residue obtained was purified by FCC over silica gel using a gradient of 0:100–15:85 MeOH:EtOAc to give **25** as a white solid (7 mg, 71%).

R_f: 0.56 (10:90, MeOH/EtOAc);Mp: 195–200 °C; $[\alpha]_D^{25}$ −20.0 (*c* 0.3, MeOH); IR ν_{max} (cm^{-1}): 1753, 1741, 1642, 1632, 1276, 1361, 1258, 1230, 1174, 1061, 1039, 917, 846; ^1H NMR (CD_3OD) δ 7.75 (d, 1H, *J* 5.6 Hz), 6.19 (d, 1H, *J* 5.6 Hz), 4.82–4.76 (m, 1H), 4.69 (p, 1H, *J* 4.1 Hz), 4.01 (d, 1H, *J* 4.4 Hz), 2.69 (td, 1H, *J* 12.9, 4.9 Hz), 2.53–2.44 (m, 1H), 2.37–2.29 (m, 1H), 2.05 (s, 3H), 2.02–1.94 (m, 1H), 1.89–1.66 (m, 4H);^{13}C NMR (CD_3OD) δ 172.4, 170.2, 170.0, 158.8, 120.8, 87.2, 65.9, 62.8, 42.5, 34.3, 27.4, 23.8, 21.0, 19.7; HRMS (ESI +ve) calculated for $C_{14}H_{18}NO_5$ ($M+H^+$) 280.1180, found 280.1182.

*4.15 (S)-1-(3-(Furan-2-yl)propyl)-3-hydroxypyrrolidine-2,5-dione (**26**).*

To a solution of **17** (500 mg, 4.00 mmol) in xylene (15 mL) was added *L*-malic acid (804 mg, 6.00 mmol) and the reaction mixture was heated at 180 °C for 2 h in a flask having a Dean-Stark water trap. The solvent was removed under reduced pressure and the residue obtained was purified by FCC over silica gel using a gradient of 20:80–55:45 EtOAc/petrol to give **26** as a white solid (615 mg, 69%); R_f: 0.58 (25:75, EtOAc/petrol); Mp: 63–68 °C $[\alpha]_D^{25}$ −65.5 (*c* 0.9, $CHCl_3$); IR ν_{max} (cm^{-1}): 3513, 1700, 1406, 1341, 1249, 1152; ^{1}H NMR δ 7.28 (bs, 1H), 6.26 (dd, 1H, *J* 2.9, 1.8 Hz), 6.01 (d, 1H, *J* 2.9 Hz), 4.60–4.55 (m, 1H), 3.58 (t, 2H, *J* 7.2 Hz), 3.02 (dd, 1H, *J* 18.1, 8.6 Hz), 2.68–2.59 (m, 3H), 1.99–1.91 (m, 2H);^{13}C NMR δ 178.7, 174.4, 154.6, 141.3, 110.4, 105.5, 67.0, 38.7, 37.3, 25.8, 25.6; HRMS (ESI +ve) calculated for $C_{11}H_{14}NO_4$ ($M+H^+$) 224.0918, found 224.0914.

*4.16 (S)-1-(3-(5-Bromofuran-2-yl)propyl)-3-hydroxypyrrolidine-2,5-dione (**27**).*

The title compound was synthesized from **26** (120 mg, 0.538 mmol) using the method described for the synthesis of **23** (115 mg, 71%); R_f: 0.58 (25:75, EtOAc/petrol); $[\alpha]_D^{25}$ +54.4 (*c* 0.6, $CHCl_3$); IR ν_{max} (cm^{-1}): 3457, 1697, 1439, 1405, 1344, 1150, 1124, 1011; ^{1}H NMR δ 6.17 (d, 1H, *J* 3.2 Hz), 6.02 (d, 1H, *J* 3.2 Hz), 4.60 (dd, 1H, *J* 8.1, 4.8 Hz), 3.58 (t, 2H, *J* 6.7 Hz), 3.04 (dd, 1H, *J* 19.2, 9.1 Hz), 2.69–2.59 (m, 3H), 1.99–1.89 (m, 2H);^{13}C NMR δ 178.4, 174.2, 156.7, 119.8, 112.0, 108.5, 67.0, 38.5, 37.3, 25.8 (2); HRMS (EI +ve) calculated for $C_{11}H_{12}Br^{79}NO_4$ (M^+) 300.9945, found 300.9943.

*4.17 (4S)-1-(3-(5-Bromofuran-2-yl)propyl)-4,5-dihydroxypyrrolidin-2-one (**28**).*

The title compound was synthesized from **27** (100 mg, 0.33 mmol) using the method described for the synthesis of **24** as a thick colourless oil (62 mg, 62%); R_f: 0.40 (10:90, MeOH/EtOAc); $[\alpha]_D^{25}$ +6.3 (*c* 0.5, MeOH); IR ν_{max} (cm^{-1}): 3398, 1671, 1458, 1438, 1124, 1065, 1012; ^{1}H NMR (CD_3OD) δ 6.25 (d, 1H, *J* 3.3 Hz), 6.12 (d, 1H, *J* 3.3 Hz),

4.93 (s, 1H), 4.08 (d, 1H, *J* 6.0 Hz), 3.53–3.45 (m, 1H), 3.29–3.21 (m, 1H), 2.82 (dd, 1H, *J* 17.5, 6.2 Hz), 2.65 (t, 2H, *J* 8.0 Hz), 2.18 (dd, 1H, *J* 17.5, 1.5 Hz), 1.99–1.83 (m, 2H);^{13}C NMR (CD_3OD) δ 174.7, 157.7, 119.1, 111.7, 108.0, 89.9, 71.2, 39.2, 38.2, 25.8, 25.1; HRMS (ESI +ve) calculated for $C_{11}H_{15}Br^{79}NO_4$ ($M+H^+$) 304.0179, found 304.0186.

*4.18 (3S)-1-(3-(5-Bromofuran-2-yl)propyl)-5-oxopyrrolidine-2,3-diyl diacetate (**29**).*

The title compound was synthesized from **28** (60 mg, 0.154 mmol) using the same method used for the synthesis of compound **2b** as a colourless oil (63 mg, 82%); R_f: 0.48 (20:80, EtOAc/petrol); $[\alpha]_D^{25}$ +52.3 (*c* 0.8, $CHCl_3$); IR ν_{max} (cm^{-1}): 1681, 1607, 1374, 1466, 1233, 1071, 1041, 1012; ^{1}H NMR 6.18 (d, 1H, *J* 3.0 Hz), 6.12 (s, 1H), 6.01 (d, 1H, *J* 3.0 Hz), 5.12 (d, 1H, *J* 6.3 Hz), 3.62–3.53 (m, 1H), 3.19–3.10 (m, 1H), 2.92 (dd, 1H, *J* 18.1, 6.2 Hz), 2.61 (t, 2H, *J* 7.6 Hz), 2.37 (d, 1H, *J* 18.1 Hz), 2.11 (s, 3H), 2.10 (s, 3H), 1.99–1.79 (m, 2H);^{13}C NMR δ 173.3, 170.2, 169.9, 157.0, 119.7, 111.9, 108.4, 86.7, 71.1, 40.5, 36.1, 26.2, 25.5, 21.1, 21.0; HRMS (ESI +ve) calculated for $C_{15}H_{19}Br^{79}NO_6$ ($M+H^+$) 388.0391, found 388.0387.

*4.19 (1'S,2R)-3',5-dioxo-2',3',5',6',7',8a'-hexahydro-1'H,5H-spiro[furan-2,8'-indolizin]-1'-yl acetate (**30**).*

Compound **30** was synthesized from **29** (42 mg, 0.158 mmol) using the method (method A) described for synthesis of **25** (17 mg, 59%); R_f: 0.50 (10:90, MeOH/EtOAc); $[\alpha]_D^{25}$ −17.7 (*c* 0.1, MeOH); Mp: 172–178 °C; IR ν_{max} (cm^{-1}): 1763, 1743, 1677, 1466, 1255, 1231, 1183, 1039; ^{1}H NMR (CD_3OD) δ 7.70 (d, 1H, *J* 5.7 Hz), 6.26 (d, 1H, *J* 5.7 Hz), 4.69 (dt, 1H, *J* 7.7, 1.5 Hz), 4.22–4.16 (m, 1H), 4.06 (d, 1H, *J* 1.3 Hz), 2.97–2.88 (m, 1H), 2.74 (dd, 1H, *J* 18.2, 8.0 Hz), 2.39 (dt, 1H, *J* 18.3, 1.7 Hz), 2.23–2.11 (m, 1H), 2.01

(s, 3H), 1.80–1.68 (m, 3H);^{13}C NMR (CD_3OD) δ 172.1, 172.0, 170.6, 158.2, 121.5, 86.8, 66.4, 66.3, 38.8, 37.2, 32.6, 20.3, 19.5; HRMS (ESI +ve) calculated for $C_{13}H_{16}NO_5$ ($M+H^+$) 266.1023, found 266.1000.

*4.20 (E) and (Z)-3-(5-Bromofuran-2-yl)acrylonitrile (**31**).*[21]

To a solution of **15** (1.5 g, 12.6 mmol) in DMF (15 mL) at 0 °C was added NBS (2.23 g, 12.6 mmol) under a N_2 atmosphere and the reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was subjected to FCC over silica gel using a gradient of 0:100–10:90 EtOAc/petrol to give **31** as a thick colourless oil (1.77 g, 72%) and as a mixture of isomers (*trans*:*cis* = 10:4.5); R_f: 0.52 (5:95, EtOAc/petrol); *Trans* isomer: ^{1}H NMR δ 6.96 (d, 1H, *J* 16.4 Hz), 6.53 (d, 1H, *J* 3.5 Hz), 6.40 (d, 1H, *J* 3.5 Hz), 5.72 (d, 1H, *J* 16.4 Hz). *Cis* isomer: ^{1}H NMR δ 7.05 (d, 1H, *J* 3.6 Hz), 6.85 (d, 1H, *J* 12.3 Hz), 6.45 (d, 1H, *J* 3.6 Hz), 5.20 (d, 1H, *J* 12.3 Hz).

*4.21 (E)-3-(5-(Phenylthio)furan-2-yl)acrylonitrile (**32**).*

To a solution of **31** (1.00 g, 5.05 mmol) in methanol (20 mL) was added sodium thiophenolate (2.00 g, 15.1 mmol) and the reaction mixture heated at reflux for 16 h under a N_2 atmosphere. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was purified by FCC over silica gel using a gradient of 0:100–40:60 EtOAc/petrol to give **32** as a thick yellowish oil (791 mg, 69 %) and as a mixture of isomers (*trans:cis* = 10:4.3); R_f: 0.38 (30:70, EtOAc/petrol); IR ν_{max} (cm^{-1}): 2213, 1623, 1581, 1464, 1440, 1182, 1019, 950, 794;

Major isomer (*trans*):^{1}H NMR δ 7.35 – 7.20 (m, 5H), 7.00 (d, 1H, *J* 16.3 Hz), 6.65 (d, 1H, *J* 3.4 Hz), 6.60 (d, 1H, *J* 3.4 Hz), 5.73 (d, 1H, *J* 16.3 Hz); ^{13}C NMR δ 152.7, 148.8, 135.6, 134.0, 129.7, 129.6, 127.8, 120.2, 118.3, 117.1, 94.8; Minor isomer (*cis*): ^{1}H NMR δ 7.29 – 7.15 (m, 5H), 7.13 (d, 1H, *J* 3.7 Hz), 6.88 (d, 1H, *J* 12.2 Hz), 6.69 (d, 1H, *J* 3.7 Hz), 5.22 (d, 1H, *J* 12.2 Hz); ^{13}C NMR δ 152.8, 148.1, 134.7, 133.9, 130.1, 129.6, 127.8, 119.8, 117.3, 116.8, 92.5; HRMS (ESI +ve) calculated for $C_{13}H_{10}NOS$ ($M+H^+$) 288.0478, found 228.0501.

*4.22 3-(5-(Phenylthio)furan-2-yl)propanenitrile (**33**).*

To a solution of **32** (500 mg, 2.20 mmol) in MeOH (10 mL) was added $NiCl_2.6H_2O$ (52 mg, 0.220 mmol) and Boc_2O (959 mg, 4.40 mmol). The reaction mixture was cooled to 0 °C followed by addition of $NaBH_4$ (418 mg, 11.0 mmol) over 30 min. The reaction mixture was slowly warmed to rt and stirred at that tempertature for 16 h. A saturated solution of $NaHCO_3$ was added and the reaction mixture was further extracted with EtOAc (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and the residue was purified by FCC over silica gel using a gradient of 0:100–45:55 EtOAc/petrol to give **33** as a thick colourless oil (287 mg, 57%); R_f: 0.32 (30:70, EtOAc/petrol); IR ν_{max} (cm^{-1}): 2930, 1706, 1582, 1478, 1439, 1166, 1023, 792; ^{1}H NMR δ 7.27–7.09 (m, 5H), 6.67 (d, 1H, *J* 3.0 Hz), 6.26 (d, 1H, *J* 3.0 Hz), 2.99 (t, 2H, *J* 7.3 Hz), 2.67 (t, 2H, *J* 7.0 Hz); ^{13}C NMR δ 155.7, 142.7, 136.4, 129.3, 127.6, 126.6, 121.1, 118.6, 109.6, 24.9, 16.6; HRMS (ESI +ve) calculated for $C_{13}H_{12}NO_S$ ($M+H^+$) 230.0635, found 230.0656.

*4.23 (S)-3-Hydroxy-1-(3-(5-(phenylthio)furan-2-yl)propyl)pyrrolidine-2,5-dione (**35**).*

To a solution of lithium aluminium hydride (100 mg, 2.62 mmol) in Et_2O (10 mL) at 0 °C was added solution of **33** (200 mg, 0.873 mmol) in Et_2O (3 mL) over 15 min. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched by the dropwise addition of water (2 mL) followed by addition of 10% NaOH solution (2 mL). The reaction mixture was diluted with Et_2O (15 mL) and filtered through celite. The residue was washed with Et_2O (4 × 10 mL). The filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude amine (**34**) obtained was used in next reaction without any further purification. Compound **35** was synthesized from amine **34** using the method described for the synthesis of **26** (110 mg, 39% for 2 steps); R_f: 0.60 (20:80, EtOAc/petrol); $[\alpha]_D^{25}$ −22.24 (*c* 0.2, $CHCl_3$). IR ν_{max} (cm^{-1}): 3405, 2922, 1695, 1582, 1439, 1347, 1148, 1024, 793. ^{1}H NMR δ 7.27–7.20 (m, 2H), 7.16–7.10 (m, 3H), 6.63 (d, 1H, *J* 2.9 Hz), 6.11 (d, 1H, *J* 2.9 Hz), 4.55 (dd, 1H, *J* 4.8, 8.8 Hz), 3.56 (t, 2H, *J* 7.1 Hz), 3.00 (dd, 1H, *J* 8.0, 18.1 Hz), 2.65 (t, 2H, *J* 7.2 Hz), 2.62 (dd, 1H, *J* 4.8, 18.1 Hz), 1.94 (p, 2H, *J* 7.0 Hz).^{13}C NMR δ 178.2, 174.2, 159.2, 141.1, 137.0, 129.3, 127.3, 126.4, 121.2, 108.2, 67.1, 38.6, 37.3, 26.2, 25.9. HRMS (ESI +ve) calculated for $C_{17}H_{18}NO_4S$ ($M+H^+$) 332.0952, found 332.0953.

*4.24 (4S)-4,5-Dihydroxy-1-(3-(5-(phenylthio)furan-2-yl)propyl)pyrrolidin-2-one (**36**).*

The title compound was synthesised from **35** (80 mg, 0.256 mmol) using the same method described for the synthesis of **2a** (40 mg, 50%) and in a diastereomeric ratio of 10:8; IR ν_{max} (cm^{-1}): 3340, 2936, 1662, 1582, 1439, 1260, 1110, 1066, 1024, 792; Major isomer: R_f: 0.55 (10:90, MeOH/EtOAc); ^{1}H NMR (CD_3OD) δ 7.29-7.07 (m, 5H), 6.68 (d, 2H, *J* 3.0 Hz), 6.24–6.19 (m, 1H), 4.90 (s, 1H), 4.06 (d, 1H, *J* 6.4 Hz), 3.52–3.40 (m, 1H), 3.29–3.19 (m, 1H), 2.80 (dd, 1H, *J* 6.0, 17 Hz), 2.71–2.64 (m, 2H), 2.16 (dd, 1H, *J* 2.0, 17 Hz), 2.00–1.82 (m, 2H); ^{13}C NMR (CD_3OD) δ 174.7, 160.1, 140.8, 137.2, 128.9,

126.8, 125.9, 120.8, 107.7, 89.9, 71.2, 39.3, 38.2, 25.9, 25.4; Minor isomer: R_f: 0.50 (10:90, MeOH/EtOAc); ^{1}H NMR (CD_3OD) δ 7.29–7.07 (m, 5H), 6.68 (d, 2H, *J* 3.0 Hz), 6.24–6.19 (m, 1H), 5.03 (d, 1H, *J* 5.3 Hz), 4.26–4.20 (m, 1H), 3.52–3.40 (m, 1H), 3.29–3.19 (m, 1H), 2.54 (dd, 1H, *J* 6.8, 16.7 Hz), 2.71–2.64 (m, 2H), 2.34 (dd, 1H, *J* 6.0, 16.7 Hz), 2.00–1.82 (m, 2H); ^{13}C NMR (CD_3OD) δ 173.9, 160.2, 140.8, 137.1, 128.9, 126.9, 126.0, 120.8, 107.6, 83.4, 65.6, 39.5, 37.7, 25.8, 25.6; HRMS (ESI +ve) calculated for $C_{17}H_{20}NO_4S$ ($M+H^+$) 334.1108, found 334.1114.

*4.25 (3S)-5-Oxo-1-(3-(5-(phenylthio)furan-2-yl)propyl)pyrrolidine-2,3-diyl diacetate (**37**).*

The title compound was **37** synthesised from **36** (30 mg, 0.071 mmol) using the same method described for the synthesis of **2b** (34 mg, 91%). and in a diastereomeric ratio of 10:8; IR ν_{max} (cm^{-1}): 2800, 1751, 1717, 1479, 1370, 1220, 1142, 1007, 964, 751; Major isomer: R_f: 0.65 (20:80, EtOAc/petrol); ^{1}H NMR δ 7.29–7.19 (m, 3H), 7.12 (t, 2H, *J* 7.3 Hz), 6.64 (d, 1H, *J* 2.5 Hz), 6.11 (d, 1H, *J* 2.8 Hz), 6.0 (bs, 1H), 5.09 (d, 1H, *J* 6.3 Hz), 3.60–3.50 (m, 1H), 3.19–3.09 (m, 1H), 2.89 (dd, 1H, *J* 6.7, 17.7 Hz), 2.63 (t, 2H), *J* 7.8 Hz), 2.34 (d, 1H, *J* 17.7 Hz), 2.06 (s, 3H), 2.04 (s, 3H), 2.01–1.79 (m, 2H); ^{13}C NMR δ 173.3, 170.2, 169.9, 159.5, 140.9, 137.1, 129.2, 127.2, 121.1, 108.0, 86.8, 71.1, 40.5, 36.0, 29.9, 26.1, 25.8, 21.0, 20.9; HRMS (ESI +ve) calculated for $C_{21}H_{23}NO_6SNa$ ($M+Na^+$) 440.1139, found 440.1140.

*4.26 (S)-3-Hydroxy-1-(3-(5-(phenylsulfonyl)furan-2-yl)propyl)pyrrolidine-2,5-dione (**38**).*

To a solution of **35** (50 mg, 0.151 mmol) in acetic acid (5 mL) was added hydrogen peroxide (30% solution in water, 0.5 mL) and the reaction mixture was stirred at rt for 2

d. A saturated solution of $NaHCO_3$ (5 mL) was slowly added and the rmixture was extracted with EtOAc (3 ×20 mL). The extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was purified by FCC over silica gel using a gradient of 50:50–80:20 EtOAc/petrol to give **38** as a thick oil (52 mg, 96%); R_f: 0.43 (60:40, EtOAc/petrol); $[\alpha]_D^{25}$ −37.6 (*c* 2.0, $CHCl_3$); IR ν_{max} (cm^{-1}): 3443, 2942, 1696, 1499, 1325, 1139, 1082, 1015, 752; ^1H NMR δ 7.96 (d, 2H, 7.5 Hz), 7.60 (t, 1H, *J* 7.5 Hz), 7.52 (t, 2H, *J* 8.0 Hz), 7.09 (d, 1H, *J* 3.7 Hz), 6.17 (d, 1H, *J* 3.3 Hz), 4.61–4.54 (m, 1H), 3.53 (t, 2H, *J* 7.0 Hz), 3.01 (dd, 1H, *J* 8.4, 17.9 Hz), 2.64 (t, 2H, *J* 7.8 Hz), 2.65–2.58 (m, 1H), 1.92 (p, 2H, *J* 7.1 Hz); ^{13}C NMR δ 178.2, 174.2, 161.0, 148.2, 140.3, 133.8, 129.5, 127.9, 118.9, 108.1, 67.0, 38.3, 37.3, 25.9, 25.4; HRMS (ESI +ve) calculated for $C_{17}H_{18}NO_6S$ ($M+H^+$) 364.0850 found 364.0850.

*4.27 (4S)-4,5-Dihydroxy-1-(3-(5-(phenylsulfonyl)furan-2-yl)propyl)pyrrolidin-2-one (**39**).*

The title compound was synthesized from **38** (50 mg, 0.137 mmol) using the method described for the synthesis of **26** (27 mg, 54%) and in a diastereomeric ratio of 10:0.7; IR ν_{max} (cm^{-1}): 3310, 2954, 1653, 1447, 1320, 1140, 1058, 1018, 803; Major iomer: R_f: 0.35 (15:85, MeOH/EtOAc); ^1H NMR (CD_3OD) δ 7.94 (d, 2H, *J* 7.8 Hz), 7.67 (t, 1H, *J* 7.8 Hz), 7.59 (t, 2H, *J* 7.6 Hz), 7.18 (d, 1H, *J* 3.4 Hz), 6.32 (d, 1H, *J* 3.5 Hz), 4.87 (bs, 1H), 4.05 (d, 1H, *J* 5.8 Hz), 3.46–3.37 (m, 1H), 3.26–3.17 (m, 1H), 2.79 (dd, 1H, *J* 6.2, 17.5 Hz), 2.68 (t, 2H, *J* 7.5 Hz), 2.14 (d, 1H, *J* 17.6 Hz), 1.96–1.80 (m, 2H); ^{13}C NMR (CD_3OD) δ 174.8, 162.3, 148.0, 140.5, 133.7, 129.4, 127.4, 118.9, 107.8, 89.9, 71.2, 39.2, 38.2, 25.5, 25.1; HRMS (ESI +ve) calculated for $C_{17}H_{20}NO_6S$ ($M+H^+$) 366.1006, found 366.1007.

*4.28 (3S)-5-Oxo-1-(3-(5-(phenylsulfonyl)furan-2-yl)propyl)pyrrolidine-2,3-diyl diacetate (**40**).*

The title compound was synthesised from **39** (25 mg, 0.055 mmol) using the same method described for the synthesis of **2b** (30 mg, 98%); R_f: 0.40 (35:65, EtOAc/petrol); IR ν_{max} (cm^{-1}): 2952, 1714, 1447, 1373, 1328, 1216, 1141, 1042, 1013, 964; ^{1}H NMR δ 7.98 (d, 2H, *J* 8.5 Hz), 7.61 (t, 1H, *J* 7.2 Hz), 7.54 (t, 2H, *J* 7.2 Hz), 7.11 (d, 1H, *J* 3.8 Hz), 6.18 (d, 1H, *J* 3.4 Hz, 6.08 (bs, 1H), 5.11 (d, 1H, *J* 6.4 Hz), 3.59–3.48 (m, 1H), 3.17–3.08 (m, 1H), 2.91 (dd, 1H, *J* 6.2, 18.0 Hz), 2.64 (t, 2H, *J* 7.6 Hz), 2.36 (d, 1H, *J* 18.0 Hz), 2.09 (s, 3H), 2.07 (s, 3H), 1.98–1.78 (m, 2H); ^{13}C NMR δ 173.3, 170.2, 169.9, 161.3, 147.5, 140.0, 133.7, 129.4, 127.9, 118.9, 107.9, 86.6, 71.1, 40.4, 35.9, 25.8, 25.6, 21.0, 20.9; HRMS (ESI +ve) calculated for $C_{21}H_{24}NO_8S$ ($M+H^+$) 450.1232, found 450.1223.

4.3 X-ray crystallographic study.

4.3.1 Crystal data.

Compound **25**. $C_{14}H_{17}NO_5$, M = 279.29, T = 200 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 5.6983(1), b = 9.3734(2), c = 25.0005(4) Å, V =1335.34(4) Å^3, Dx = 1.389 g cm^{-3}, 1804 unique data (θ = 2.6–27.5°), R = 0.029 [for 1650 with $I > 2.0\sigma(I)$]; Rw = 0.074 (all data), S = 1.01.

4.3.2. Structure determination.

Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.[18] Structure solution was by direct methods (SIR92).[19] The structure was refined using the CRYSTALS program package.[20] Atomic coordinates, bond lengths and angles, and

displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 840569). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

5. Acknowledgements

We thank the Australian Research Council and the University of Wollongong for financial support.

6. References

1. Mungkornasawakul, P.; Pyne, S. G.; Jatisatienr, A.; Supyen, D.; Lie, W.; A.T. Ung, A. T.; Skelton, B.W.; White, A. H. *J. Nat. Prod*. **2003**, *66*, 980-982.
2. For reviews on *N*-acyliminium ion chemistry, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416; (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856; (c) Maryanoff, B. E.; Zhang, H.; J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628. (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368; (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541. (f) Martinez-Estibalez, U.; Gomez-SanJuan, A.; Garcia-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2011**, 20-21.
3. Martin, S. F.; Bur, S. K. *Tetrahedron Lett*. **1997**, *38*, 7641-7644. Martin, S. F.; Barr, K. J.; Smith, D. W.; and Scott K. Bur. S. K. *J. Am. Chem. Soc.* **1991**, *121*, 6990–6997.
4. Tannis, S. P.; Deaton, M. V.; Dixon, L. A.; McMills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914-6928.

5. Cassidy, M. P.; Oezdemir, A. D.; Padwa, A. *Org. Lett.* **2005**, *7*, 1339–1342.

6. Arutyunyan, N. S.; Akopyan, L. A.; Snkhchyan, G. M.; Papoyan, O. A.; Panosyan, G. A.; Gevorgyan, G. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 440–445.

7. Doolittle, R. E.; Heath, R. R. *J. Org. Chem.* **1984**, *49*, 5041–5050.

8. Huang, P.Q.; Liu, L. X.; Wei, B. G.; Ruan, Y. P. *Org. Lett*. **2003**, *5*, 1927–1929.

9. Morgan, I. R.; Yazici, A.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 1409–1419.

10. Tanis, S. P.; Chuang, Y. H.; *J. Org. Chem.* **1988**, *53*, 4929–4938.

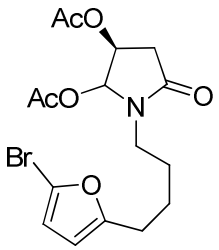
11. Lin, W.; Ye, Y.; Xu, R., *J. Nat. Prod*. **1992**, *55*, 571–576.

12. Lin, L.-G.; Leung, H. P.-H.; Zhu, J.-Y.; Tang, C.-P.; Ke, C.-Q.; Rudd, J. A.; Lin, G.; Ye, Y. *Tetrahedron* **2008**, *64*, 10155–10161.

13. Sanchez-Izquierdo, F.; Blanco, P.; Busque, F.; Alibes, R.; De March, P.; Figueredo, M.; Font, J.; Parella, T., *Org. Lett*. **2007**, *9*, 1769–1772.

14. Jiang, R.-W.; Hon, P.-M.; Zhou, Y.; Chan, Y.-M.; Xu, Y.-T.; Xu, H.-X.; Greger, H.;Shaw, P.-C.; But, P. P.-H. *J. Nat. Prod*. **2006**, *69*, 749–754.

15. We explored the possibility of preparing a spirocyclic 5-7-5 tricyclic ring structure from the cyclization reaction of **I**. Unfortunately no cyclised products could be isolated.



I

16. Caddick, S.; Judd, D.; Lewis, A.; Reich, M.; Williams, M. *Tetrahedron* **2003**, *59*, 5417–5423.

17. Maegawa, T.; Takahashi, T.; Yoshimura, M.; Suzuka, H.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2009**, *351*, 2091–2095.

18. Otwinowski, Z.; Minor, W. Processing of X-ray diffraction data collected in oscillation mode. In *Methods in Enzymology, Volume 276: Macromolecular Crystallography, Part A*; Carter Jr., C. W.; Sweet, R. M., Eds.; Academic Press: New York, 1997; pp 307–326.

19. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.

20. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr*. **2003**, *36*, 1487.

21. Jaehnisch, K.; Seeboth, H. *J. Prakt Chem.* **1981**, *323*, 26-32.

GRAPHICAL ABSTRACT

Synthesis of spirocyclic azacycles from the cyclization of furan tethered *N*-acyliminium ions

Sudhir R. Shengule, Anthony Willis and Stephen G. Pyne