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Model support studies toward the total synthesis of the stemona alkaloid stemocurtisine

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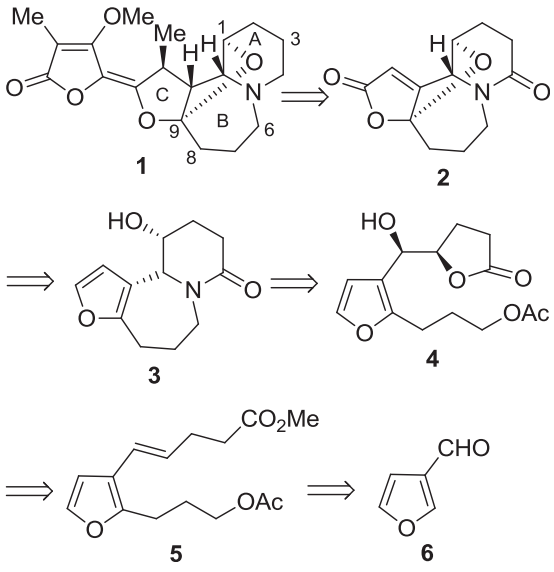
ABSTRACT

Herein we report the results of a furan-based approach toward the synthesis of the Stemona alkaloid, stemocurtisine **1** via the linearly fused tricyclic intermediate **3**, representing the key A,B,C-ring structural feature of the target molecule. A highly diastereoselective synthesis of compound **3** was achieved starting from 3-furfural **6**, in a synthetic sequence that involved; (1) a rapid *in situ* conversion of an *O*-mesylate to the corresponding chloride with inversion of configuration from assistance of the neighbouring 3-furanyl group; (2) an intramolecular aza-Wittig reaction to prepare the azepine ring; and (3) a base promoted lactam ring forming step. While methods were established to oxidize the furan ring of **3** to the corresponding γ-hydroxy-α,β-unsaturated lactone we were unable to affect cyclization of the lactam ring hydroxyl group to the γ-position of the lactone to create the cyclic ether feature of the natural product. Model studies were also unsuccessful.

1. Introduction

The extracts of roots of the Stemona species of plants have been used in traditional medicine in South–East Asia, China, and Japan to treat the symptoms of bronchitis, pertussis, and tuberculosis and have been used as anti-parasitics on humans and animals.[1,2] Some of the pure alkaloids derived from the extracts of the leaves and roots of Stemona species have been shown to have significant anti tussive activity in guinea pig after cough induction[3] as well as insect toxicity, antifeedant and repellent activities.[4–6] The Stemona group of alkaloids includes more than 120 different natural products, the majority of which have a common pyrrolo[1,2-*a*]azepine nucleus. Stemocurtisine **1** (Scheme 1) was the first Stemona alkaloid to be isolated with a pyrido[1,2-*a*]azepine A,B-ring system.[7]

Our retrosynthetic analysis of **1** (Scheme 1) indicated that the tricyclic intermediate **3**, representing the key A,B,C-ring structural feature of the target molecule, would be an attractive key intermediate toward this endeavour. We envisaged that oxidation of the furan moiety of **3** could give an intermediate that would allow for the introduction of the more synthetically challenging ether bridge between the A and B-rings and result in the tetracyclic compound **2** (Scheme 1). Our earlier attempts at the synthesis of a linearly fused tricyclic akin to compound **3** were unsuccessful. For example, the $Sc(OTf)_3$ catalysed cyclization reaction of the tethered furan-4,5-diacetoxypiperid-2-one **7** gave the spirotricyclic product **9** and not the desired linearly fused tricyclic compound **8** (Scheme 2).[8]



Scheme 1. Retrosynthetic analysis of stemocurtisine **1**.

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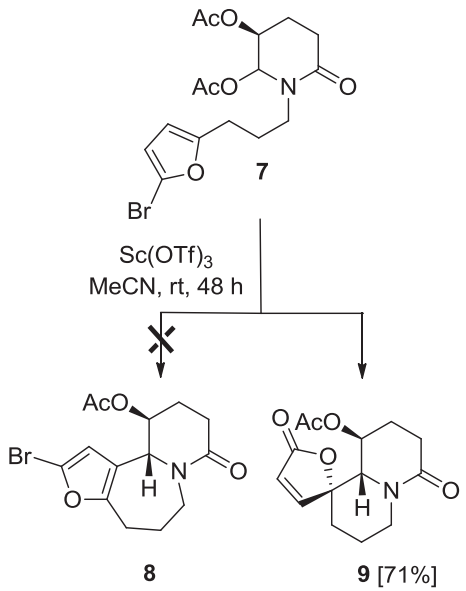
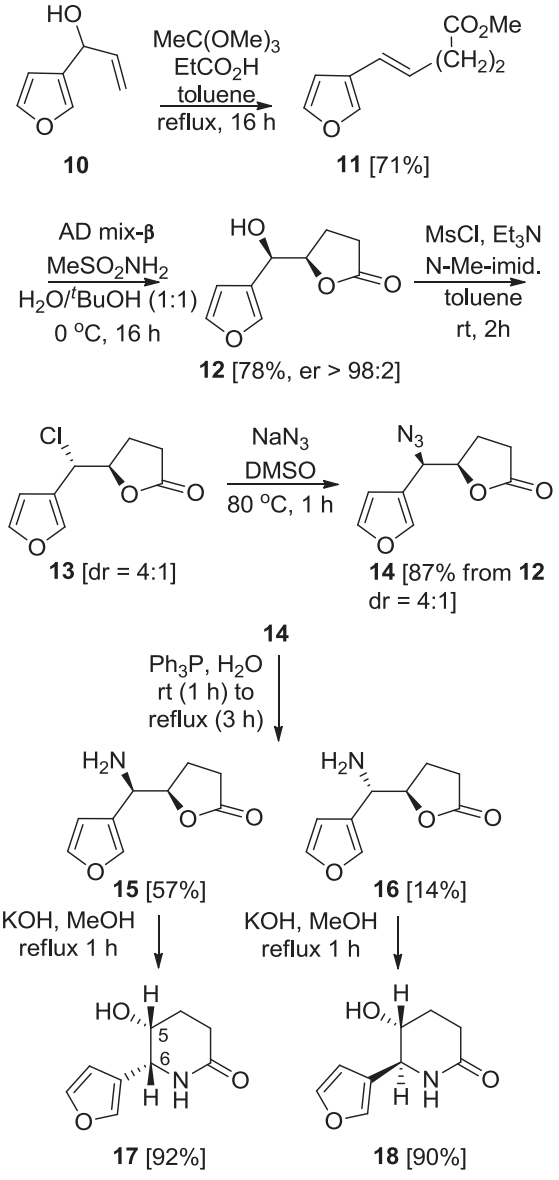


Scheme 2. Attempted synthesis of the linearly fused tricyclic compound **8**.

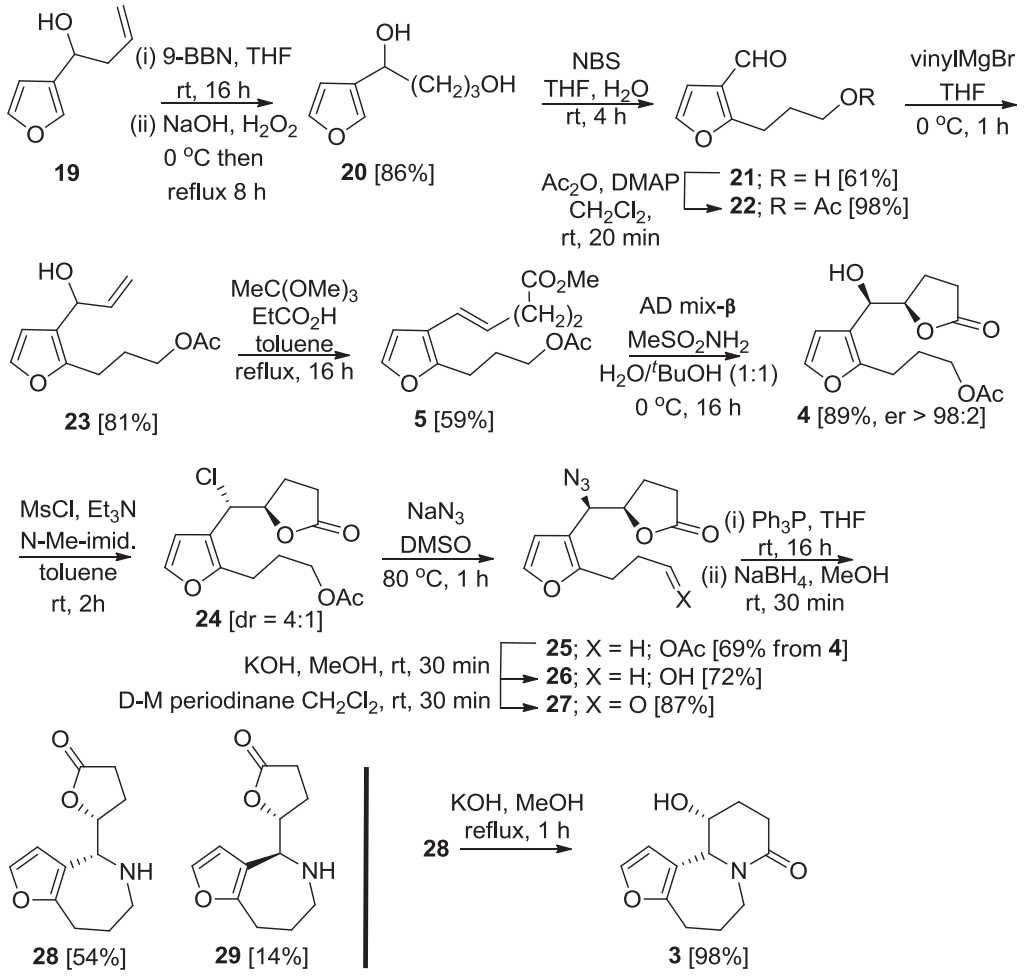
2. Results and discussion

To test the feasibility of securing the desired *cis*-configuration in our proposed synthesis of **3** we first examined the diastereoselective synthesis of (5*R*,6*R*)-6-(3-furyl)-5-hydroxy-piperidin-2-one **17** (Scheme 3). While the first two synthetic steps were similar to that reported by Sudalai[9] for the synthesis of (5*R*,6*S*)-5-hydroxy-6-phenylpiperidin-2-one from benzaldehyde, rather than 3-furanal in this synthesis, our synthesis required modification of the latter steps because of the presence of the more readily oxidisable furan ring in Schemes 3 and 4 and our requirement for lactams with the 6*R* configuration. The known vinyl alcohol **10**,[10] prepared by Grignard reaction of vinylmagnesium bromide with 3-furfural **6**, was subjected to a Johnson–Claisen rearrangement[9] to form the methyl ester **11** in 71% yield (Scheme 3). Asymmetric dihydroxylation[11] of the *trans* alkene of **11** with AD mix-β gave the lactone **12** in good yield (78%) and high enantioselectivity (*dr* >99:1 (from ^{1}H NMR); *er* >98:2 from Mosher's ester analysis). The desired 5,6-stereochemistry in the target molecule **17** required converting the secondary hydroxyl group in **12** into an amino group with overall retention of configuration. In pursuit of this result we first attempted to convert the secondary hydroxyl of **12** into the corresponding mesylate using standard conditions (MsCl, Et_3N, CH_2Cl_2, 0 °C).[12] All attempts were unsuccessful and only unreacted starting material was obtained. However we were very delighted to find that by using the conditions of Tanabe,[13] for the mesylation of secondary alcohols with MsCl and *N*-methylimidazole (*N*-MeIm) in toluene, the alcohol **12** was converted to the secondary chloride **13** with inversion. There is precedence for this type of *in situ* reaction of chloride with activated mesylates (e.g., mesylates of benzylic and allylic alcohols).[14] In contrast, the related phenyl analogue of **12** (i.e., **12** in which the 3-furyl group is replaced by a Ph) is readily converted to its corresponding mesylate, which is relatively stable under standard conditions.[9] The more electron rich 3-furanyl group in **12** is clearly responsible for this enhanced instability and can stabilize the expected S_N2 and S_N1 processes that lead to **12** and its epimer, respectively. When the diastereomeric mixture of the chlorides **13** was heated at 80 °C with sodium azide in DMSO the inverted azides **14** were obtained in 87% overall yield from **12** as a 4:1 mixture of inseparable diastereomers. The Staudinger reaction of this azide mixture with triphenylphosphine and water gave the primary amines **15** and **16**, which could be separated by column chromatography providing these compounds in yields of 57 and 14%, respectively. Compounds **15** and **16** were individually converted, in excellent yields (90–92%) to their respective piperidin-2-one derivatives, **17** and **18**, by heating a solution of these compounds in KOH/MeOH. The relative *cis* and *trans* 5,6-configurations of **17** and **18** were based on their respective ^{1}H NMR coupling constants $J_{5,6}$. For compound **17**, $J_{5,6}$ was 2.2 Hz, while that for **18** was 6.6 Hz. These values were consistent with those of *cis* ($J_{5,6}$=2.7 Hz)[15] and *trans*-5-hydroxy-6-phenylpiperidin-2-one ($J_{5,6}$=6.8 Hz),[16] respectively.



Scheme 3. Synthesis of *cis* and *trans*-6-(3-furyl)-5-hydroxy-piperidin-2-ones **17** and **18**.

This chemistry was then further developed to the synthesis of the more demanding tricyclic system **3** (Scheme 4). The known allyl alcohol **19**,[17] synthesized from the reaction of allylmagnesium bromide and 3-furfural, was converted to the diol **20** in 86% yield by hydroboration of the terminal alkene with 9-BBN followed by an oxidative work up with basic H_2O_2. Diol **20** was then subjected to the oxidative rearrangement reaction conditions developed by Walsh[18] by treatment with NBS in aqueous THF. This procedure

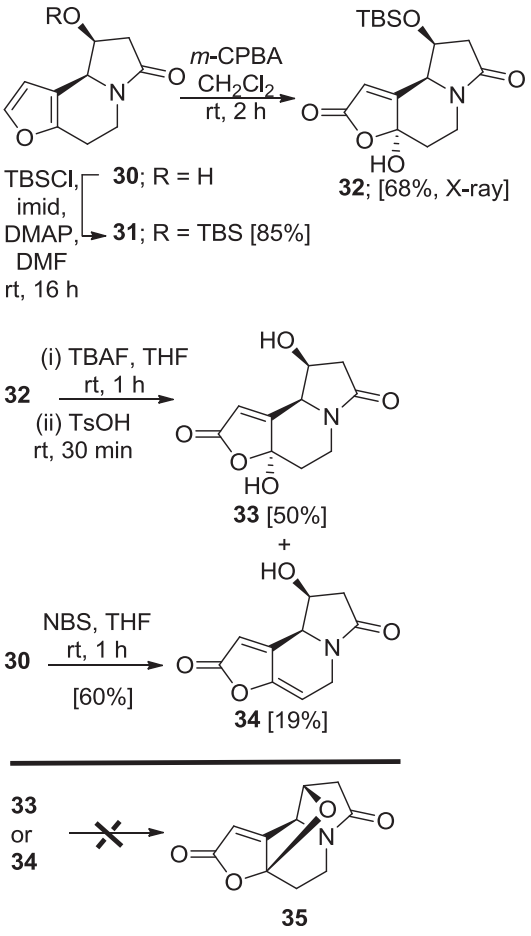


Scheme 4. Synthesis of the linearly fused tricyclic compound **3**.

provided the desired 2-substituted-3-furfural **21** in 61% yield. The primary alcohol of **21** was acetylated and the resulting ester **22** was converted to the allylic alcohol **23** when treated with vinylmagnesium bromide in THF. This was then converted to the ester **5** using an analogous Johnson–Claisen rearrangement procedure to that as described in Scheme 3. The asymmetric dihydroxylation of **5** with AD mix-β gave the lactone **4** in high yield (89%) and high enantioselectivity (*dr* >99:1 (from ^{1}H NMR); *er* >98:2 from Mosher's ester analysis). Lactone **4** was subsequently converted with inversion to chloride **24** (dr 4:1) and then with inversion to azide **25** (dr 4:1) using analogous chemistry to that described in Scheme 3. Hydrolysis of the acetate of **25** gave the primary alcohol, which was converted to the aldehyde **27** upon oxidation with the Dess–Martin periodinane reagent. The azido-aldehyde **27** was then treated under aza-Wittig reaction conditions[19] with triphenylphosphine in anhydrous THF and then the resulting cyclic imine intermediate was reduced with sodium borohydride. Separation by column chromatography gave the desired azepine-lactone **28** in 54% yield and its epimer **29** in 14% yield. Compound **28** was then converted to the long sought after tricyclic compound **3** in 98% by heating in KOH/MeOH. The relative *cis*-configuration of **3** is based on the ^{1}H NMR coupling constant $J_{1,10a}$ of 2.0 Hz (stemocurtisine numbering).

Before examining the oxidation chemistry of **3**, and the construction of the ether linkage in target molecule **2** (Scheme 1), we first studied the oxidation of compound **30**, which we had synthesized earlier.[20] The hydroxyl group of **30** was first protected as its TBS ether **31** in 88% yield (Scheme 5). Oxidation of the furan ring of **31** with *m*-CPBA in CH_2Cl_2 gave the γ-hydroxy-α,β-unsaturated lactone **32** as a single diastereoisomer. The configuration of the newly formed stereogenic center in compound **32** was confirmed by a single-crystal X-ray crystallographic analysis, which showed that the tertiary γ-hydroxyl group was *trans* to the two pyrrolidinone substituents (Fig. 1). The reaction of **32** with TBAF followed by *p*-TSA gave a separable mixture of the TBS deprotected compound **33** and dehydrated compound **34** but none of the desired cyclic ether product **35** was observed. Oxidation of the furan ring of **30** with NBS in THF gave the diene **34** in 60% yield. Our attempts to form the cyclic ether **35** from **33** by acid catalysed reactions (TsOH, toluene, reflux, 16 h or concd H_2SO_4, rt, 3 h) resulted in the isolation of only **34** in low yields (39 and 35%, respectively). While related acid catalysed intramolecular ketalization reactions of γ-hydroxy-α,β-unsaturated lactones are known,[21] we suspect that compound **35** did not form because of its expected high ring strain, made even more unfavourable by the three sp^2 hybridized carbons.2

Oxidation of the furan ring of **3** gave the γ-hydroxy-α,β-unsaturated lactone **36** in 54% yield as a single diastereomer (Scheme 6). We assigned the *trans*-configuration to the tertiary γ-hydroxyl group based on the stereochemical outcome of the oxidation of **31** to **33** (Scheme 5). Compound **36**, when subjected to acidic conditions (TsOH, CH_2Cl_2, rt, 16 h, or $BF_3\cdot OEt_2$, rt, 16 h, or anhydrous HCl in Et_2O, CH_2Cl_2, rt, 3 d) also failed to give the desired ether compound **2**, instead, starting material was recovered.



Scheme 5. Attempted synthesis of the cyclic ether **35**.

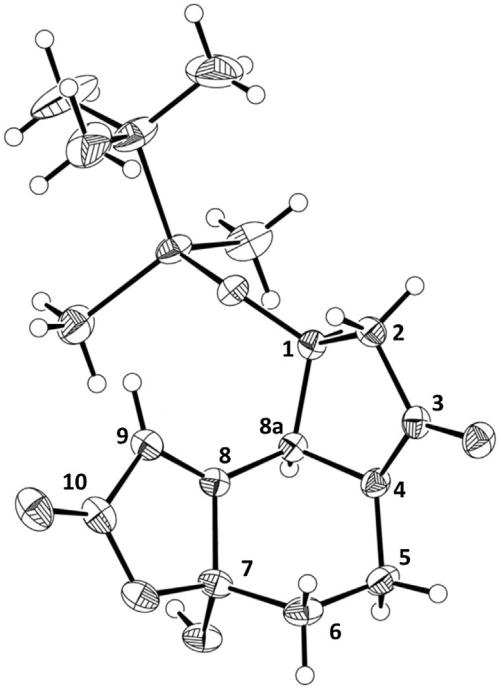
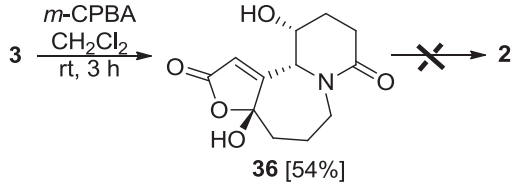
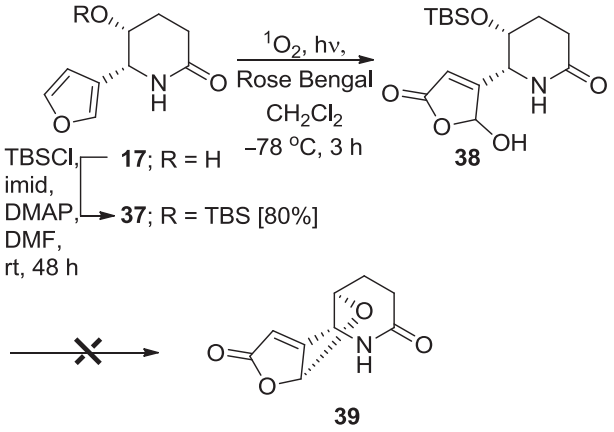


Fig. 1. Molecular structure of compound **32** ($C_{16}H_{25}NO_5Si$) with labelling of selected atoms, showing the major sites of disordered atoms (Si17 to C23, occupancy 0.84). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii (CCDC 924873).



Scheme 6. Attempted synthesis of the cyclic ether **2**.

An attempted oxidation of **37**, the OTBS ether derivative of **17**, using *m*-CPBA failed to proceed and returned only unreacted **37**. The singlet oxygen oxidation[21] of **37**, however, proceeded in high yield (91%) and gave the lactone **38** as a single diastereomer (Scheme 7). Protection of the hydroxyl group of **17** was necessary to afford a derivative that was soluble in CH_2Cl_2. Compound **38**, when subjected to $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 3 d led to the formation of TBS deprotected compound but failed to give any of the desired ether compound **39** (Scheme 7).



Scheme 7. Attempted synthesis of the cyclic ether **39**.

3. Conclusions

In conclusion, we have successfully prepared the linearly fused tricyclic compound **3**, which represents the key A,B,C-ring structural feature of the Stemona alkaloid, stemocurtisine **1**. A highly diastereoselective synthesis of compound **3** was achieved starting from 3-furfural **6**, in a synthetic sequence that involved; (1) a rapid *in situ* conversion of an *O*-mesylate to the corresponding chloride with inversion of configuration from assistance of the neighbouring 3-furanyl group; (2) an intramolecular aza-Wittig reaction to prepare the azepine ring; and (3) a base promoted lactam ring forming step. While methods were established to oxidize the furan ring of **3** to the corresponding γ-hydroxy-α,β-unsaturated lactone **36** we were unable to affect cyclization of the lactam ring hydroxyl group to the γ-position of the lactone to create the cyclic ether feature of the natural product. Model studies were also unsuccessful. This lack of success is most likely due to the strained nature of the hypothetical cyclic ether products and the reversible nature of our reaction conditions. We are currently examining a different strategy that involves less strained substrates, which have fewer sp^2 hybridised carbons and reactions that are under kinetic control (irreversible reactions).

4. Experimental section

4.1. General procedures

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 solution of

$CDCl_3$ unless otherwise noted. FCC is an abbreviation for flash column chromatography, which was performed with Merck silica gel 60 (40–60 μm) and under pressure from compressed air. Petrol refers to the hydrocarbon fraction of bp 40–60 °C. All the reagents were purchased from Sigma–Aldrich and used for reactions without further purification. Thin layer chromatography (TLC) was performed with precoated Merck silica gel 60 PF_{254} aluminium sheets, the spots were visualized under UV light (254 nm and 366 nm) and further by spraying with an acidified aqueous solution of ammonium molybdate and cerium(IV) sulphate then heating until charred. All air-sensitive reactions were carried out in predried glassware apparatus under a dry nitrogen atmosphere. HRMS data of all the new compounds was collected using Waters Xevo and optical rotations for all chiral compounds were measured on a Jasco P-2000 polarimeter.

4.2. 1-(Furan-3-yl)prop-2-en-1-ol (10)[10]

A solution of 3-furfual **6** (5.00 g, 52.0 mmol) in diethyl ether (50 mL) was cooled to 0 °C followed by dropwise addition of vinylmagnesium bromide (62.5 mL, 1 M solution in THF, 62.5 mmol). The reaction mixture was stirred at the same temperature for 1 h. A saturated solution of NH_4Cl (100 mL) was added and the reaction mixture was warmed to rt. The reaction mixture further extracted with EtOAc (3×100 mL) and the combined extracts were dried ($MgSO_4$) and concentrated to give a thick oil. The crude residue was further purified by FCC over silica gel using a gradient of 0:100–15:85 EtOAc/petrol to give **10** as light yellow oil (4.19 g, 65%). R_f 0.28 (1:9 diethyl ether/petrol); ^{1}H NMR δ 7.36 (br s, 1H), 7.35 (br s, 1H), 6.36 (br s, 1H), 6.06–5.99 (m, 2H), 5.32 (d, 1H, J=17.1 Hz), 5.18 (d, 1H, J=10.8 Hz), 5.11 (d, 1H, J=4.6 Hz).

4.3. (*E*)-Methyl 5-(furan-3-yl)pent-4-enoate (11)

To a stirred solution of **10** (2.00 g, 16.1 mmol) in toluene (50 mL) was added trimethyl orthoacetate (10 mL, 80.5 mmol), propionic acid (50 μL) and the reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The dark brown residue obtained was purified by FCC over silica gel using a gradient of 0:100–10:90 EtOAc/petrol to give **11** as thick oil (2.05 g, 71%). R_f 0.69 (20:80 EtOAc/petrol); IR ν_{max} (cm^{-1}): 2980, 1733, 1177, 1073, 1023, 964, 870, 775; ^{1}H NMR δ 7.32 (br s, 1H), 7.30 (s, 1H), 6.45 (br s, 1H), 6.25 (d, 1H, J=15.8 Hz), 5.88 (dt, 1H, J=6.3, 15.8), 3.62 (s, 3H), 2.60–2.45 (m, 4H); ^{13}C NMR δ 173.6, 156.0, 143.5, 139.9, 128.1, 120.8, 107.6, 51.7, 34.0, 28.2; HRMS (ESI +ve) calculated for $C_{10}H_{13}O_3$ ($M+H^+$) 181.0865, found 181.0858.

4.4. (5*R*)-5-(Furan-3-yl(hydroxy)methyl)dihydrofuran-2(3*H*)-one (12)

To a stirred solution of AD-mix-β (3.84 g) and methanesulfonamide (260 mg, 2.74 mmol) in water (14 mL) at 0 °C was added **11** (500 mg, 2.74 mmol dissolved in *tert*-butanol (14 mL)) and the reaction mixture was stirred at the same temperature for 16 h. The reaction mixture was warm to rt and extracted with EtOAc (3×50 mL). The combined extracts were dried ($MgSO_4$) then evaporated to give a thick yellow oil, which purified by FCC over silica gel using a gradient of 0:100–60:40 EtOAc/petrol to give **12** as a colourless oil (394 mg, 78%, er >98:2, (*S*) Mosher ester δ 3.40 (s, 3H, OMe), (*R*) Mosher ester δ 3.54 (s, 3H, OMe)). R_f 0.16 (1:1 EtOAc/petrol); $[\alpha]_D^{25}$ −34 (*c* 0.7, $CHCl_3$); IR ν_{max} (cm^{-1}): 3423, 1754, 1185, 1156, 1042, 1015, 989, 916, 799, 732, 698; ^{1}H NMR δ 7.46 (br s, 1H), 7.39 (s, 1H), 6.43 (br s, 1H), 4.66–4.60 (m, 2H), 2.64 (d, 1H, J=4.6 Hz, OH), 2.52–2.48 (m, 2H), 2.19–2.14 (m, 1H), 2.10–2.04 (m, 1H); ^{13}C NMR δ 177.2, 143.8, 140.6, 123.8, 109.1, 82.7, 69.3, 28.6, 24.0; HRMS (ESI +ve) calculated for $C_9H_{11}O_4$ ($M+H^+$) 183.0657, found 183.0665.

4.5. (5*R*)-5-(Azido(furan-3-yl)methyl)dihydrofuran-2(3*H*)-one (14)

To a stirred solution of **12** (300 mg, 1.64 mmol) in toluene (10 mL) was added triethylamine (0.68 mL, 4.92 mmol), *N*-methylimidazole (0.40 mL, 4.92 mmol), and mesyl chloride (0.40 mL, 4.92 mmol). The reaction mixture was stirred at the same temperature for 16 h. Water (5 mL) was added to the reaction mixture and extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried ($MgSO_4$) then evaporated to give the chloro compound **13**, which was used for the next reaction without further purification. Sodium azide (323 mg, 4.92 mmol) was added to a stirred solution of **13** in DMSO (5 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was cooled to rt followed by addition of water (5 mL) and then extracted with diethyl ether (3×50 mL). The combined organic extracts were dried ($MgSO_4$), evaporated and the residue obtained was purified by FCC over silica gel using a gradient of 0:100–30:70 EtOAc/petrol to give azide **14** as a colourless liquid (297 mg, 87% for two steps) and as a mixture of diastereoisomers (4:1). Major isomer: *Rf* 0.22 (2:3 EtOAc/petrol); IR ν_{max} (cm^{-1}): 2100, 1760, 1250, 1183, 1166, 1122, 1031, 996, 919, 870, 753; ^{1}H NMR δ 7.54 (br s, 1H), 7.44 (s, 1H), 6.47 (br s, 1H), 4.67–4.63 (m, 1H), 4.52 (d, 1H, J=4.6 Hz), 2.52–2.46 (m, 2H), 2.26–2.18 (m, 1H), 2.10–2.04 (m, 1H); ^{13}C NMR δ 176.4, 144.3, 141.5, 119.6, 109.6, 80.7, 60.4, 28.2, 24.6; HRMS (ESI +ve) calculated for $C_9H_{10}N_3O_3$ ($M+H^+$) 208.0722, found 208.0732.

4.6. (*R*)-5-((*R*)-Amino(furan-3-yl)methyl)dihydrofuran-2(3*H*)-one (15) and (*R*)-5-((*S*)-amino(furan-3-yl)methyl)dihydrofuran-2(3*H*)-one (16)

To a stirred solution of **14** (200 mg, 0.96 mmol) in dry THF (5 mL) was added triphenylphosphine (759 mg, 2.89 mmol) under a N_2 atmosphere and the reaction mixture stirred at rt for 1 h. Water (500 μL) was added to the reaction flask and the reaction mixture was heated at reflux for 3 h. The reaction was cooled to rt and the solvent was removed under reduced pressure. The residue obtained was purified by FCC over silica gel using a gradient of 0:100–8:92 MeOH/EtOAc to give first **15** and then **16** as colourless thick liquids (100 mg, 57% for **15** and 24 mg, 14% for **16**). Major isomer: R_f 0.28 (1:9 MeOH/EtOAc); $[\alpha]_D^{25}$ −31 (*c* 2.5, $CHCl_3$); IR ν_{max} (cm^{-1}): 3372, 1762, 1501, 1178, 1157, 1014, 911, 831, 795; ^{1}H NMR δ 7.39 (br s, 1H), 7.35 (s, 1H), 6.38 (br s, 1H), 4.84 (dd, 1H, J=7.3, 14.4 Hz), 3.94 (d, 1H, J=6.8 Hz), 2.47–2.40 (m, 2H), 2.12–2.06 (m, 1H), 2.00–1.90 (m, 1H); ^{13}C NMR δ 177.1, 143.8, 140.0, 125.1, 109.2, 82.7, 52.2, 28.8, 24.7; HRMS (ESI +ve) calculated for $C_9H_{12}NO_3$ ($M+H^+$) 182.0817, found 182.0827. Minor isomer: R_f 0.14 (1:9 MeOH/EtOAc); $[\alpha]_D^{25}$ 10 (*c* 0.6, $CHCl_3$); IR ν_{max} (cm^{-1}): 3372, 1762, 1501, 1178, 1158, 1021, 909, 838, 794; ^{1}H NMR δ 7.38 (br s, 2H), 6.34 (br s, 1H), 4.64–4.60 (m, 1H), 4.20 (d, 1H, J=3.6 Hz), 2.48–2.36 (m, 2H), 2.14–2.00 (m, 2H), 1.78 (br s, 2H); ^{13}C NMR δ 177.3, 143.8, 139.9, 124.8, 109.2, 83.3, 50.3, 28.7, 22.3; HRMS (ESI +ve) calculated for $C_9H_{12}NO_3$ ($M+H^+$) 182.0817, found 182.0820.

4.7. (5*R*,6*R*)-6-(Furan-3-yl)-5-hydroxypiperidin-2-one (17)

Potassium hydroxide (155 mg, 2.76 mmol) was added to a stirred solution of **15** (100 mg, 0.55 mmol) in methanol (5 mL) and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue obtained was purified by FCC over silica gel using a gradient of 0:100–8:92 MeOH/EtOAc to give **17** as a thick colourless oil (90 mg, 90%). R_f 0.24 (1:9 MeOH/EtOAc); $[\alpha]_D^{25}$ 5 (*c* 2.0,

$CHCl_3$); IR ν_{max} (cm^{-1}): 3266, 2922, 1654, 1628, 1387, 1311, 1213, 1158, 1064, 939, 873, 790; ^1H NMR δ 7.44 (br s, 1H), 7.40 (s, 1H), 6.53 (br s, 1H, N*H*), 6.37 (br s, 1H), 4.55 (d, 1H, *J*=2.2 Hz), 4.03–4.00 (m, 1H), 2.62–2.55 (m, 1H), 2.33–2.27 (m, 1H), 2.08–2.01 (m, 1H), 1.92–1.87 (m, 1H); ^{13}C NMR δ 172.7, 144.2, 140.6, 123.5, 109.5, 65.7, 54.6, 26.5 (×2); HRMS (ESI +ve) calculated for $C_9H_{12}NO_3$ ($M+H^+$) 182.0817, found 182.0815.

4.8. (5*R*,6*S*)-6-(Furan-3-yl)-5-hydroxypiperidin-2-one (18)

Compound **18** (18 mg, 92% as a thick colourless oil) was synthesized from **16** (20 mg, 0.11 mmol) using the method described above for the synthesis of **17**. R_f 0.12 (1:9 MeOH/EtOAc); $[\alpha]_D^{25}$ −27 (*c* 0.3, $CHCl_3$); IR ν_{max} (cm^{-1}): 3266, 2922, 1654, 1638, 1387, 1308, 1213, 1158, 1064, 935, 873, 790; ^1H NMR δ 7.42 (br s, 2H), 6.38 (br s, 1H), 5.91 (br s, 1H, N*H*) 4.31 (d, 1H, *J*=6.6 Hz), 3.86–3.82 (m, 1H), 2.62–2.55 (m, 1H), 2.49–2.42 (m, 1H), 2.11–2.05 (m, 1H), 1.92–1.84 (m, 1H); ^{13}C NMR δ 171.6, 144.6, 140.7, 124.8, 108.4, 69.6, 56.2, 28.6, 27.1; HRMS (ESI +ve) calculated for $C_9H_{12}NO_3$ ($M+H^+$) 182.0817, found 182.0815.

4.9. 1-(Furan-3-yl)but-3-en-1-ol (19)[17]

To a stirred solution of **6** (5.00 g, 52.0 mmol) in diethyl ether (50 mL) at 0 °C was added dropwise allylmagnesium bromide (63 mL, 1 M solution in THF, 62.5 mmol) over 10 min. The reaction mixture was stirred at the same temperature for 1 h. A saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the reaction mixture further extracted with EtOAc (3×100 mL). The combined organic extracts were dried ($MgSO_4$) then evaporated to give a thick light brown residue. The residue was purified by FCC over silica gel using a gradient of 0:100–25:100 EtOAc/petrol to give **19** as a colourless thick liquid (6.39 g, 89%). R_f 0.33 (1:9 diethyl ether/petrol); ^1H NMR δ 7.38 (br s, 2H), 6.40 (br s, 1H), 5.85–5.73 (m, 1H), 5.21–5.10 (m, 2H), 4.74–4.67 (m, 1H), 2.54–2.45 (m, 2H), 2.03 (d, 1H, *J*=3.8 Hz, OH).

4.10. 1-(Furan-3-yl)butane-1,4-diol (20)

To a stirred solution of **19** (4.50 g, 32.6 mmol) in THF (50 mL) was added 9-BBN (98 mL, 0.5 M solution in THF, 48.9 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was cooled to 0 °C and 6 M NaOH solution (12 mL) was added to the reaction mixture followed by dropwise addition of hydrogen peroxide (16 mL (30% aqueous solution), 151 mmol) at 0 °C over 30 min. The reaction mixture was warmed to rt and then heated at reflux for 8 h. The reaction mixture was cooled to rt and extracted with ethyl acetate (3×150 mL). The combined organic extracts were dried ($MgSO_4$) then evaporated and the residue obtained was purified by FCC over silica gel using a gradient of 50:50–100:0 EtOAc/petrol to give compound **20** as a thick colourless oil (4.37 g, 86%). R_f 0.36 (80:20 EtOA/petrol); IR ν_{max} (cm^{-1}): 3288, 2924, 1501, 1436, 1151, 1080, 1066, 988, 968, 907, 873, 794, 753; ^1H NMR δ 7.36 (br s, 2H), 6.38 (br s, 1H), 4.66 (dd, 1H, *J*=5.3, 7.0 Hz), 3.68–3.61 (m, 2H), 1.85–1.80 (m, 2H), 1.69–1.65 (m, 2H); ^{13}C NMR δ 143.4, 139.1, 129.3, 108.7, 67.0, 62.7, 35.2, 29.1; HRMS (ESI +ve) calculated for $C_8H_{13}O_3$ ($M+H^+$) 157.0786, found 157.0780.

4.11. 2-(3-Hydroxypropyl)furan-3-carbaldehyde (21)

To a stirred solution of **20** (1.00 g, 6.41 mmol) in a mixture of THF:H_2O (4:1, 20 mL) was added NBS (1.14 g, 6.41 mmol) in two portions over 10 min and the reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with water (5 mL) and then extracted with EtOAc (3×100 mL). The combined organic extracts were dried ($MgSO_4$) then evaporated to give a colourless liquid, which was purified by FCC over silica gel using a gradient of 0:100–40:60 EtOAc/petrol to give **21** as a colourless liquid (602 mg, 61%). R_f 0.28 (2:3 EtOAc/petrol); IR ν_{max} (cm^{-1}): 3398, 2943, 1670, 1655, 1422, 1123, 1090, 1036, 1014, 895, 722; ^1H NMR δ 9.93 (s, 1H), 7.30 (br s, 1H), 6.67 (br s, 1H), 3.63 (t, 2H, *J*=5.8 Hz), 3.07 (t, 2H, *J*=7.3 Hz), 1.94 (pent, 2H, *J*=6.8 Hz); ^{13}C NMR δ 185.7, 164.9, 142.4, 122.8, 108.5, 61.2, 30.9, 23.3; LRMS (ESI +ve) calculated for $C_8H_{11}O_3$ ($M+H^+$) 155, found 155.

4.12. 3-(3-Formylfuran-2-yl)propyl acetate (22)

To a stirred solution of **21** (1.80 g, 11.7 mmol) in CH_2Cl_2 (30 mL) was added DMAP (1.43 g, 11.7 mmol) and acetic anhydride (2.4 mL, 23.4 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with water (5 mL) and then extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$) then evaporated and the residue obtained was purified by FCC over silica gel using a gradient of 0:100–20:80 EtOAc/petrol to give **22** as a thick colourless liquid (2.24 g, 98%). R_f 0.52 (4:1 EtOAc/petrol); IR ν_{max} (cm^{-1}): 1734, 1677, 1422, 1366, 1235, 1123, 1040, 991, 753; ^1H NMR δ 9.90 (s, 1H), 7.29 (d, 1H, *J*=1.7 Hz), 6.66 (d, 1H, *J*=1.7 Hz), 4.06 (t, 2H, *J*=6.3 Hz), 3.02 (t, 2H, *J*=7.3 Hz), 2.05–2.00 (m, 2H), 2.01 (s, 3H); ^{13}C NMR δ 184.8, 171.1, 164.2, 142.5, 122.8, 108.4, 63.2, 27.2, 23.7, 21.0; LRMS (ESI +ve) calculated for $C_{10}H_{12}O_4Na$ ($M+Na^+$) 219, found 219 (100%).

4.13. 3-(3-(1-Hydroxyallyl)furan-2-yl)propyl acetate (23)

Compound **23** (1.11 g, 81% a thick colourless oil) was synthesized from **22** (1.20 g, 6.12 mmol) using the method described above for the synthesis of **10** except 1.1 equiv of vinylmagnesium bromide was used. R_f 0.62 (2:3 EtOAc/petrol); IR ν_{max} (cm^{-1}): 3445, 1734, 1719, 1239, 1038, 985, 919, 740; ^1H NMR δ 7.23 (br s, 1H), 6.28 (br s, 1H), 6.03–5.96 (m, 1H), 5.27 (d, 1H, *J*=17.1 Hz), 5.23 (d, 1H, *J*=10.2 Hz), 5.09 (d, 1H, *J*=4.8 Hz), 4.05–4.01 (m, 2H), 2.72 (t, 2H, *J*=7.3 Hz), 2.00 (s, 3H), 1.96–1.98 (m, 2H); ^{13}C NMR δ 171.4, 151.1, 141.1, 139.7, 121.7, 114.9, 109.4, 67.6, 63.6, 27.5, 22.9, 21.1; HRMS (ESI +ve) calculated for $C_{12}H_{16}O_4Na$ ($M+Na^+$) 247.0946, found 247.0947.

4.14. (*E*)-Methyl 5-(2-(3-acetoxypropyl)furan-3-yl)pent-4-enoate (5)

Compound **5** (737 mg, 59%, as a colourless oil.) was synthesized from **23** (1.00 g, 4.46 mmol) using the method described above for the synthesis of **11**. R_f 0.68 (80:20 EtOAc/petrol); IR ν_{max} (cm^{-1}): 1734, 1436, 1366, 1234, 1159, 1139, 1035, 1019, 960; ^1H NMR δ 7.20 (br s, 1H), 6.38 (br s, 1H), 6.18 (d, 1H, *J*=15.8 Hz), 5.80 (dt, 1H, *J*=6.6, 15.8 Hz), 4.03 (t, 2H, *J*=6.3 Hz), 3.66 (s, 3H), 2.69 (t, 2H, *J*=7.0 Hz), 2.48–2.42 (m, 4H), 2.03 (s, 3H), 1.95–1.90 (m, 2H); ^{13}C NMR δ 173.6, 171.3, 151.0, 141.3, 127.2, 120.9, 118.8, 108.0, 63.7, 51.8, 34.2, 28.5, 27.4, 22.7, 21.1; HRMS (ESI +ve) calculated for $C_{15}H_{21}O_5$ ($M+H^+$) 281.1389, found 281.1381.

4.15. 3-(3-((*R*)-Hydroxy((*R*)-5-oxotetrahydrofuran-2-yl)methyl)furan-2-yl)propyl acetate (4)

Compound **4** (448 mg, 89%) was synthesized from **5** (500 mg, 1.78 mmol, as a thick colourless oil, er >98:2 (*S*) Mosher ester δ 3.48 (s, 3H, OMe), (*R*) Mosher ester δ 3.57 (s, 3H, OMe)) using the method described above for the synthesis of **12**. R_f 0.23 (3:2 EtOAc/petrol); $[\alpha]_D^{25}$ −24 (*c* 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}): 3500, 1768, 1729, 1368, 1330, 1184, 1155, 1047, 1038, 1015, 982, 898; ^1H NMR δ 7.28 (d, 1H, *J*=1.3 Hz), 6.39 (d, 1H, *J*=1.3 Hz), 4.62–4.58 (m, 2H), 4.06 (t, 2H, *J*=6.3 Hz, 2H), 2.73 (t, 2H, *J*=7.3 Hz), 2.54–2.48 (m, 2H), 2.14–2.11 (m, 1H), 2.01 (s, 3H), 2.01–1.94 (m, 3H); ^{13}C NMR δ 177.0, 171.4, 152.4, 141.7, 117.9, 109.4, 83.0, 69.1, 63.6, 28.6, 27.4, 24.2, 23.1, 21.1; HRMS (ESI +ve) calculated for $C_{14}H_{18}O_6Na$ ($M+Na^+$) 305.1001, found 305.0999.

4.16. 3-(3-(Azido((*R*)-5-oxotetrahydrofuran-2-yl)methyl)furan-2-yl)propyl acetate (25)

Compound **25** (315 mg, 69% as a thick colourless oil) was synthesized from **4** (420 mg, 1.48 mmol) as a mixture of diastereoisomers (4:1) using the method described above for the synthesis of **14**. R_f 0.56 (3:2 EtOAc/petrol); Major isomer: IR ν_{max} (cm^{-1}): 2100, 1776, 1734, 1367, 1175, 1160, 1139, 1034, 1020, 989, 904; ^1H NMR δ 7.38 (d, 1H, J=1.4 Hz), 6.47 (d, 1H, J=1.4 Hz), 4.67–4.62 (m, 1H), 4.52 (d, 1H, J=5.3 Hz), 4.15–4.09 (m, 2H), 2.79–2.75 (m, 2H), 2.56–2.50 (m, 2H), 2.27–2.20 (m, 1H), 2.08 (s, 3H), 2.07–2.00 (m, 3H); ^{13}C NMR δ 176.1, 171.0, 153.2, 142.0, 113.8, 109.5, 80.8, 63.2, 60.1, 27.9, 27.4, 24.5, 22.8, 20.9; HRMS (ESI +ve) calculated for $C_{14}H_{17}N_3O_5Na$ ($M+Na^+$) 330.1066, found 330.1067.

4.17. (5*R*)-5-(Azido(2-(3-hydroxypropyl)furan-3-yl)methyl)dihydrofuran-2(3*H*)-one (26)

To a stirred solution of **25** (300 mg, 0.97 mmol) in methanol (8 mL) was added KOH (164 mg, 2.93 mmol) and the reaction mixture was stirred at rt for 1 h. The *p*H of the reaction mixture was made acidic by the addition of 2 M HCl in diethyl ether and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with water and then extracted with EtOAc (3×25 mL). The combined extracts were dried ($MgSO_4$) then evaporated and the residue obtained was purified by FCC over silica gel using a gradient of 0:100–30:70 EtOAc/petrol to give **26** as a thick colourless liquid (186 mg, 72%). R_f 0.52 (7:3 EtOAc/petrol); Major isomer: IR ν_{max} (cm^{-1}): 3417, 2957, 2099, 1768, 1243, 1220, 1181, 1157, 1043, 1003, 920, 877; ^1H NMR δ 7.33 (d, 1H, J=1.4 Hz), 6.41 (d, 1H, J=1.4 Hz), 4.65–4.61 (m, 1H), 4.58 (d, 1H, J=5.2 Hz), 3.63–3.61 (m, 2H), 2.78 (t, 2H, J=7.2 Hz), 2.52–2.45 (m, 2H), 2.24–2.12 (m, 1H), 2.08–1.98 (m, 1H), 1.94–1.82 (m, 2H); ^{13}C NMR δ 176.6, 153.9, 141.8, 113.7, 109.4, 81.0, 61.1, 60.1, 30.9, 28.0, 24.4, 22.3; HRMS (ESI +ve) calculated for $C_{12}H_{15}N_3O_4Na$ ($M+Na^+$) 288.0960, found 288.0962.

4.18. 3-(3-(Azido((*R*)-5-oxotetrahydrofuran-2-yl)methyl)furan-2-yl)propanal (27)

To a stirred solution of **26** (150 mg, 0.56 mmol) in dichloromethane (10 mL) was added Dess–Martin periodinane (360 mg, 0.84 mmol) and the reaction mixture was stirred at rt for 30 min. The reaction mixture was added to a beaker containing sodium thiosulphate (1.00 g) dissolved in a saturated solution of $NaHCO_3$ (10 mL). The mixture was stirred vigorously for 30 min, then extracted with CH_2Cl_2 (3×25 mL). The combined extracts were dried ($MgSO_4$) then evaporated and the residue obtained was purified by FCC over silica gel using a gradient of 0:100–15:85 EtOAc/petrol to give **27** (130 mg, 87%) as a thick colourless liquid. R_f 0.68 (1:1 EtOAc/petrol); Major isomer: IR ν_{max} (cm^{-1}): 2100, 1722, 1701, 1246, 1175, 1159, 1090, 1045, 1004, 918; ^1H NMR δ 9.78 (s, 1H), 7.30 (d, 1H, J=1.2 Hz), 6.42 (d, 1H, J=1.2 Hz), 4.67 (d, 1H, J=4.8 Hz), 4.64–4.60 (m, 1H), 2.98–2.92 (m, 2H), 2.89–2.84 (m, 2H), 2.54–2.42 (m, 2H), 2.26–2.18 (m, 1H), 2.12–2.04 (m, 2H); ^{13}C NMR δ 200.5, 176.6, 152.4, 142.2, 114.4, 109.9, 80.9, 60.1, 42.1, 28.2, 24.5, 18.7; LRMS (ESI +ve) calculated for $C_{12}H_{14}N_3O4$ ($M+H^+$) 264, found 264 (100%).

4.19. (*R*)-5-((*R*)-5,6,7,8-Tetrahydro-4*H*-furo[3,2-*c*]azepin-4-yl) dihydrofuran-2(3*H*)-one (28) and (*R*)-5-((*S*)-5,6,7,8-tetrahydro-4*H*-furo[3,2-*c*]azepin-4-yl)dihydrofuran-2(3*H*)-one (29)

To a stirred solution of **27** (120 mg, 0.45 mmol) in THF (5 mL) was added triphenylphosphine (478 mg, 1.82 mmol) and the reaction mixture was stirred under an argon atmosphere for 16 h. Methanol (18 μL, 0.45 mmol) and $NaBH_4$ (17 mg, 0.45 mmol) were added to the reaction mixture, which was stirred for another 30 min. The solvent was removed under reduced pressure and the residue obtained was purified by FCC over silica gel using a gradient of 0:100–10:90 MeOH/EtOAc to give **28** (54 mg, 54%) as major isomer and **29** as minor isomer (14 mg, 14%), both as thick colourless liquids. Major isomer (**28**): R_f 0.31 (5:95 MeOH/EtOAc); $[\alpha]_D^{25}$ −20 (*c* 0.4, $CHCl_3$) IR ν_{max} (cm^{-1}): 2900, 1751, 1437, 1185, 1149, 1060, 1019, 895, 799; ^1H NMR (CD_3OD) δ 7.22 (d, 1H, J=1.9 Hz), 6.30 (d, 1H, J=1.9 Hz), 4.90 (q, 1H, J=7.3 Hz), 3.80 (d, 1H, J=7.3 Hz), 3.30–3.26 (m, 1H), 3.05–3.00 (m, 1H), 2.87 (t, 2H, J=6.3 Hz), 2.62–2.46 (m, 2H), 2.24–2.10 (m, 2H), 1.86–1.78 (m, 2H); ^{13}C NMR (CD_3OD) δ 178.4, 154.0, 141.5, 119.5, 111.0, 80.2, 57.8, 46.3, 28.4, 27.1, 26.9, 25.1; HRMS (ESI +ve) calculated for $C_{12}H_{16}NO_3$ ($M+H^+$) 222.1130, found 222.1121. Minor isomer (**29**): R_f 0.18 (5:95 MeOH/EtOAc); $[\alpha]_D^{25}$ −6.0 (*c* 0.1, $CHCl_3$) IR ν_{max} (cm^{-1}): 2900, 1751, 1185, 1149, 1059, 1037, 895, 799, 721; ^1H NMR (CD_3OD) δ 7.20 (d, 1H, J=1.4 Hz), 6.30 (d, 1H, J=1.4 Hz), 4.94–4.86 (m, 1H), 3.92 (d, 1H, J=4.3 Hz), 3.00–2.88 (m, 3H), 2.84–2.76 (m, 1H), 2.56–2.46 (m, 1H), 2.44–2.28 (m, 2H), 2.20–2.10 (m, 1H), 1.84–1.74 (m, 2H); ^{13}C NMR (CD_3OD) δ 177.3, 153.6, 139.7, 119.4, 109.8, 82.2, 57.2, 47.7, 28.5, 27.8, 26.6, 23.1; HRMS (ESI +ve) calculated for $C_{12}H_{16}NO_3$ ($M+H^+$) 222.1130, found 222.1120.

4.20. (11*R*,11a*R*)-11-Hydroxy-5,6,9,10,11,11a-hexahydrofuro [3,2-*c*]pyrido[1,2-*a*]azepin-8(4*H*)-one (3)

Compound **3** (39 mg, 98% as thick colourless liquid) was synthesized from **28** (40 mg, 0.18 mmol) using the method described above for the synthesis of **17**. R_f 0.28 (5:95 MeOH/EtOAc); $[\alpha]_D^{25}$ −130 (*c* 0.4, $CHCl_3$); IR ν_{max} (cm^{-1}): 3250, 1701, 1640, 1239, 1120, 1100, 720; ^1H NMR δ 7.30 (br s, 1H), 6.28 (br s, 1H), 4.59 (d, 1H, J=2.0 Hz), 4.35 (dd, 1H, J=6.3, 13.7 Hz), 4.19–4.14 (m, 1H), 2.92–2.83 (m, 1H), 2.79–2.66 (m, 3H), 2.41–2.34 (m, 1H), 2.28–2.19 (m, 1H), 2.18–2.10 (m, 1H), 1.97–1.88 (m, 1H), 1.81–1.72 (m, 1H); ^{13}C NMR δ 170.2, 153.3, 141.6, 115.8, 109.3, 66.7, 62.6, 44.4, 27.1, 25.8, 23.6, 22.9; HRMS (ESI +ve) calculated for $C_{12}H_{16}NO_3$ ($M+H^+$) 222.1130, found 222.1120.

4.21. (9*S*,9a*S*)-9-((*tert*-Butyldimethylsilyl)oxy)-4,5,9,9a-tetrahydrofuro[2,3-*g*]indolizin-7(8*H*)-one (31)

To a stirred solution of **30** (800 mg, 4.14 mmol) in DMF was added imidazole (564 mg, 8.29 mmol), DMAP (1.00 g, 8.29 mmol) and TBSCl (1.25 g, 8.29 mmol) and the reaction mixture was stirred at rt for 2 days. The solvent was removed under reduced pressure and the residue obtained was dissolved in EtOAc (50 mL) and washed with water (3×50 mL). The organic extract was dried ($MgSO_4$) then evaporated and the residue obtained was purified by FCC over silica gel using a gradient of 20:80–50:50 EtOAc/petrol to give **31** as white solid (1.00 g, 85%). R_f 0.42 (1:1 EtOAc/petrol); Mp 78–80 °C; $[\alpha]_D^{25}$ 122 (*c* 1.0, $CHCl_3$); IR ν_{max} (cm^{-1}): 2931, 1670, 1428, 1252, 1179, 1110, 1081, 1057, 956, 949, 937, 841; ^1H NMR δ 7.28 (br s, 1H), 6.19 (br s, 1H), 4.6 (br s, 1H), 4.51–4.49 (m, 1H), 4.48 (dd, 1H, J=6.1, 12.9 Hz), 2.93–2.87 (m, 1H), 2.75–2.62 (m, 3H), 2.32 (d, 1H, J=16.6 Hz), 0.65 (s, 9H), −0.02 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 171.2, 149.8, 141.5, 113.7, 108.3, 68.2, 61.0, 42.6, 36.8, 25.5, 23.6, 17.8, −4.2, −4.9; HRMS (ESI +ve) calculated for $C_{16}H_{25}NO_3Si$ ($M+H^+$) 308.1682, found 308.1689.

4.22. (3a*R*,9S,9a*S*)-9-((*tert*-Butyldimethylsilyl)oxy)-3a-hydroxy-4,5,9,9a-tetrahydrofuro[2,3-*g*]indolizine-2,7(3a*H*,8*H*)-dione (32)

To a stirred solution of **31** (1.00 g, 3.25 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (1.69 g, 9.77 mmol) and the reaction mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue obtained was purified by FCC over silica gel using a gradient of 40:60–100:00 EtOAc/petrol to give **32** as a white solid (750 mg, 68%). R_f 0.36 (4:1 EtOAc/petrol); mp 191–193 °C; $[\alpha]_D^{25}$

−52 (*c* 0.4, MeOH); IR ν_{max} (cm^{-1}): 3078, 2932, 1757, 1661, 1464, 1421, 1246, 1159, 1129, 955, 910, 892, 797; ^1H NMR δ 6.10 (s, 1H), 5.27 (br s, 1H, OH), 4.78 (dd, 1H, *J*=6.9, 13.4 Hz), 4.52 (d, 1H, *J*=6.5 Hz), 4.18 (dd, 1H, *J*=4.9, 13.4 Hz), 3.04 (t, 1H, *J*=12.4 Hz), 2.64 (dd, 1H, *J*=7.4, 16.9 Hz), 2.39–2.34 (m, 2H), 1.77–1.73 (m, 1H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ 171.9, 170.5, 160.4, 115.4, 104.4, 66.8, 59.1, 39.7, 37.7, 36.6, 25.9, 18.2, −4.5, −4.7; HRMS (ESI +ve) calculated for $C_{16}H_{25}NO_5Si$ (M+H^+) 340.1580, found 340.1585.

4.23. (3a*R*,9*S*,9a*S*)-3a,9-Dihydroxy-4,5,9,9a-tetrahydrofuro[2,3-*g*]indolizine-2,7(3a*H*,8*H*)-dione (33) and (9*S*,9a*S*)-9-hydroxy-9,9a-dihydrofuro[2,3-*g*]indolizine-2,7(5*H*,8*H*)-dione (34)

To a stirred solution of **32** (60 mg, 0.17 mmol) in THF (5 mL) was added TBAF (0.25 mL, 0.25 mmol, 1 M in THF) and the reaction mixture stirred at the rt for 1 h. TsOH (58 mg, 0.34 mmol) was added and the reaction mixture was stirred at rt for 30 min. The solvent was removed under reduced pressure and the residue obtained was purified using FCC over silica gel using a gradient of 0:100–15:85 MeOH/EtOAc to give the diene **34** (7 mg, 19%) and then the diol **33** (20 mg, 50%), both as colourless thick liquids. **33**: R_f 0.35 (1:9 MeOH/EtOAc); $[\alpha]_D^{25}$ −18 (*c* 0.2, MeOH); IR ν_{max} (cm^{-1}): 3502, 2987, 1730, 1551, 1420, 1200, 1108, 980, 780; ^1H NMR (CD_3OD) δ 6.10 (s, 1H), 4.72–4.66 (m, 1H), 4.57 (d, 1H, *J*=2.9 Hz), 4.10 (dd, 1H, *J*=4.9, 13.2 Hz, 1H), 3.07 (t, 1H, *J*=12.9 Hz), 2.75 (dd, 1H, *J*=5.8, 17.1 Hz), 2.34–2.24 (m, 2H), 1.76–1.66 (m, 1H); ^{13}C NMR (CD_3OD) δ 173.1, 171.1, 161.0, 115.4, 104.4, 65.4, 59.8, 40.7, 36.2, 34.6; HRMS (ESI +ve) calculated for $C_{10}H_{12}NO_5$ (M+H^+) 226.0637, found 226.0637. **34**: R_f: 0.38 (1:9 MeOH/EOAc); $[\alpha]_D^{25}$ 95 (*c* 0.2, MeOH); IR ν_{max} (cm^{-1}): 3480, 3068, 2889, 1580, 1391, 1104, 980, 885, 760; ^1H NMR (CD_3OD) δ 6.08 (s, 1H), 6.01–5.99 (m, 1H), 4.97 (d, 1H, *J*=4.4 Hz), 4.79 (t, 1H, *J*=4.8 Hz), 4.69 (dd, 1H, *J*=5.3, 19.5 Hz), 3.84 (d, 1H, *J*=19.5 Hz), 2.86 (dd, 1H, *J*=4.3, 17.0 Hz), 2.36 (d, 1H, *J*=17.0 Hz); ^{13}C NMR (CD_3OD) δ 173.3, 169.3, 149.6, 148.3, 111.4, 105.3, 66.0, 60.1, 40.3, 37.7; HRMS (ESI +ve) calculated for $C_{10}H_{10}NO_4$ (M+H^+) 208.0532, found 208.0522.

*4.23.1. Synthesis of **34** from **30** using NBS.* To a stirred solution of **30** (50 mg, 0.26 mmol) in THF (5 mL) was added NBS (46 mg, 0.26 mmol) and the reaction mixture stirred at rt for 1 h. The solvent was removed under reduced pressure and the residue obtained was purified using FCC over silica gel using a gradient of 0:100–10:90 MeOH/EtOAc to give **34** (32 mg, 60%).

*4.23.2. Synthesis of **34** from **33** using TsOH.* To a stirred solution of **33** (30 mg, 0.13 mmol) in toluene (5 mL) was added TsOH-monohydrate (23 mg, 0.13 mmol) and the reaction mixture was heated at reflux for 16 h. The solvent was removed under reduced pressure and the residue obtained was purified using FCC over silica gel using a gradient of 0:100–10:90 MeOH/EtOAc to give **34** (11 mg, 39%).

*4.23.3. Synthesis of **34** from **33** using H_2SO_4.* Compound **33** (25 mg, 0.11 mmol) was dissolved in H_2SO_4 (3 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue obtained was purified using FCC over silica gel using a gradient of 0:100–10:90 MeOH/EtOAc to give **34** (8 mg, 35%).

4.24. (11*R*,11a*R*)-3a,11-Dihydroxy-3a,4,5,6,9,10,11,11a-octahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione (36)

Compound **36** (14 mg, 82% as thick colourless liquid) was synthesized from **3** (15 mg, 0.06 mmol) using the method described above for the synthesis **32**. R_f 0.28 (5:95 MeOH/EtOAc); $[\alpha]_D^{25}$ −110 (*c* 0.3, MeOH); IR ν_{max} (cm^{-1}): 3403, 2925, 1739, 1602, 1270, 947, 649; ^1H NMR (CD_3OD) δ 6.14 (s, 1H), 4.87 (d, 1H, *J*=3.9 Hz), 4.37–4.32 (m, 1H), 4.23–4.18 (m, 1H), 2.57–2.52 (m, 2H), 2.42–2.30 (m, 2H), 2.03–1.90 (m, 3H), 1.70–1.59 (m, 2H); ^{13}C NMR (CD_3OD) δ 170.7, 170.4, 168.0, 118.8, 109.3, 68.1, 62.3, 48.6, 38.5, 27.5, 26.2, 22.6; HRMS (ESI +ve) calculated for $C_{12}H_{16}NO_5$ (M+H^+) 254.1028, found 254.1025.

4.25. (5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-(furan-3-yl)piperidin-2-one (37)

To a stirred solution of **17** (100 mg, 0.55 mmol) in DMF (5 mL) was added imidazole (113 mg, 1.65 mmol) and TBSCl (249 mg, 1.65 mmol) and the reaction mixture was stirred at rt for 48 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (50 mL) and washed with water (3×50 mL). The solution was dried ($MgSO_4$) then evaporated and the residue obtained was purified using FCC over silica gel using a gradient of 20:80–80:20 EtOAc/petrol to give **37** as a white solid (130 mg, 80%). R_f 0.40 (4:1 EtOAc/petrol); Mp 88–90 °C; $[\alpha]_D^{25}$ −8 (*c* 0.6, $CHCl_3$); IR ν_{max} (cm^{-1}): 3243, 2933, 2857, 1654, 1618, 1468, 1069, 989, 830, 798; ^1H NMR δ 7.37 (br s, 1H), 7.36 (s, 1H), 6.36 (br s, 1H), 5.72 (br s, 1H, N*H*), 4.52 (d, 1H, *J*=2.1 Hz), 4.04–4.00 (m, 1H), 2.68–2.61 (m, 2H), 2.37–2.32 (m, 2H), 0.8 (s, 9H), −0.02 (s, 3H), −0.22 (s, 3H); ^{13}C NMR δ 172.0, 142.2, 140.4, 124.5, 110.3, 67.4, 55.2, 28.0, 26.7, 25.9, 18.2, −4.22, −4.90; HRMS (ESI +ve) calculated for $C_{15}H_{26}NO_3Si$ (M+H^+) 296.1682, found 296.1686.

4.26. (5*R*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-(2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl)piperidin-2-one (38)

To a stirred solution of **37** (80 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) was added Hunig's base (50 μL, 0.27 mmol) and Rose Bengal (3 mg) and the reaction mixture was cooled to −78 °C. Oxygen gas was bubbled through the reaction mixture, which was exposed to a 500 W flood light and stirred at the same temperature for 1 h. The reaction mixture was allowed to warm to rt followed by addition of saturated solution of oxalic acid (2 mL) and stirred at rt for 30 min. The reaction mixture was extracted with CH_2Cl_2 and the combined extracts were dried ($MgSO_4$) then evaporated and the residue obtained was purified by FCC over silica gel using a gradient of 0:100–10:90 MeOH/CH_2Cl_2 to give **38** (81 mg, 91%) as a thick oil and as a single diastereomer. R_f 0.25 (4:1 EtOAc/petrol); $[\alpha]_D^{25}$ −29 (*c* 0.3, $CHCl_3$); IR ν_{max} (cm^{-1}): 3232, 2929, 1759, 1655, 1630, 1471, 1252, 1121, 1084, 945, 852, 806; ^1H NMR δ 7.26 (br s, 1H, NH), 6.06 (br s, 2H), 4.49 (br s, 1H), 4.25 (br s, 1H), 2.53 (dt, 1H, *J*=7.3, 18.3 Hz), 2.35 (dt, 1H, *J*=6.3, 18.3 Hz), 1.89 (br s, 2H), 0.83 (s, 9H), −0.07 (br s, 6H); ^{13}C NMR δ 172.8, 170.1, 167.0, 120.8, 98.8, 66.3, 54.9, 27.4, 26.6, 25.6, 17.9, −4.79, −5.00; HRMS (ESI +ve) calculated for $C_{15}H_{26}NO_5Si$ (M+H^+) 328.1580, found 328.1574.

4.26.1. X-ray crystallographic data. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 924873). 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.

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