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An unusual bicyclic aziridine, 1-azabicyclo[4.1.0]heptan-2-one, and its reaction with nucleophiles

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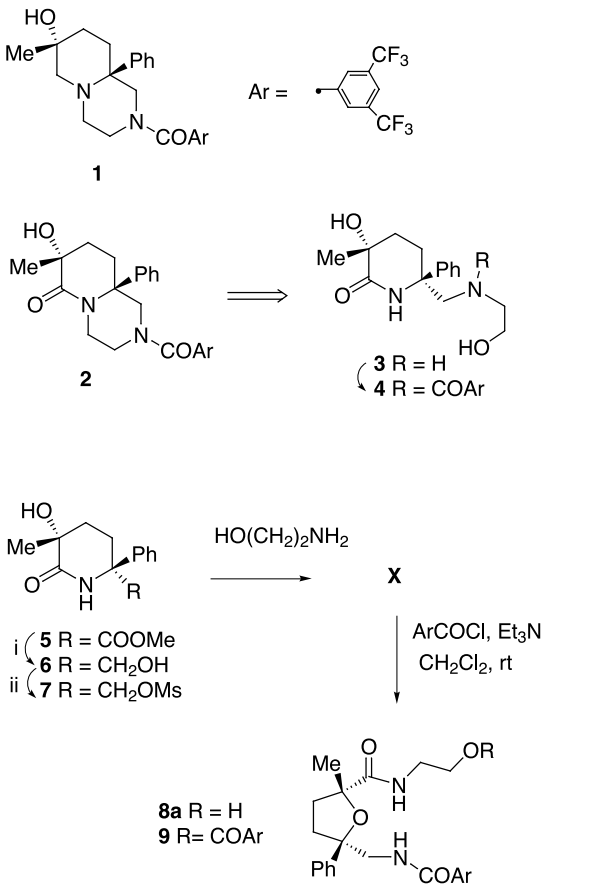
Abstract—Unexpected reaction pathways have been unravelled that are involved in the generation of 2,2,5,5-substituted tetrahydrofurans from the mesylate of 5-hydroxy-5-methyl-6-oxo-2-phenyl-2-piperidinemethanol (**7**). Upon treatment of **7** with amines under controlled conditions two reactive intermediates could be isolated. The first is a strained aziridine-fused lactam, 1-azabicyclo[4.1.0]heptan-2-one **10**, which reacts further with amines or methoxide at the lactam carbonyl group to form γ-hydroxyalkylaziridines. Final *N*-acylation results in internal OH attack to give the hydrofuran products. Reaction of **10** with some other nucleophiles led to 3,3,6,6-substituted 2-piperidinones.

1. Introduction

Recently, we reported the synthesis and a conformational study of the 9a-substituted perhydropyrido[1,2-*a*]pyrazine derivative **1**,[1] a potential substance P antagonist. In order to prepare the analogous bicyclic aminolactam **2**, we designed a synthetic route proceeding via intermediates **3** and **4**; the latter could be generated from compounds **5**–**7** as depicted in Scheme 1. However, following reduction of ester **5**, mesylation of the primary alcohol **6**, and reaction of mesylate **7** with ethanolamine, an initially unidentified product **X** was produced instead of the expected amine **3**. Treatment of **X** with 3,5-bis(trifluoromethyl)benzoyl chloride again did not yield the expected amide **4** but mainly tetrahydrofuran compounds **8** and **9**. In this report we unravel the structure of **X** and the pathways involved in the generation of **8** and **9**. Other nucleophiles and acid chlorides also were applied to produce comparable tetrahydrofuran analogues. It may be noticed that many natural and synthetic tetrahydrofuran derivatives are well known for a wide range of biological properties, e.g. (−)-virgatusin,[2] goniothalesdion,[3] and imifuramine.[4] Furthermore, lignans of the 2,5-diaryltetrahydrofuran series[5] have been identified as competitive PAF-receptor antagonists.[6] Many of the more than 200 isolated THF-ring containing acetogenins have potent antitumor and pesticidal activities.[7]



Scheme 1. *Reagents and conditions* (i): $NaBH_4$ (2 equiv.), MeOH, rt; (ii): CH_3SO_2Cl (1 equiv.), CH_2Cl_2, Et_3N; −15°C.

Keywords: aziridine; Nuclear Magnetic Resonance; tetrahydrofuran compounds.

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2. Results and discussion

2.1. Structural analysis of tetrahydrofuran products

Selective reduction of the ester group of compound **5**[8] could be effected using $NaBH_4$ (Scheme 1). The resulting alcohol **6** was converted to mesylate **7** and the latter submitted to reaction with ethanolamine (5 equiv.) and potassium carbonate (2 equiv.) in THF. After reflux for one day, the starting material had disappeared and a major product (for convenience named **X**) was observed whose MH^+ ion (*m/z* 279) corresponded to that expected for structure **3**. However, treatment of the crude product **X** with 3,5-bis(trifluoromethyl)benzoyl chloride did not provide lactam amide **4**, but two other diamide compounds. Finally these were characterised as the tetrasubstituted tetrahydrofuran compounds **8a** and **9**; the latter apparently was formed by further *O*-acylation of compound **8a**.

The ^1H NMR spectrum of **8a** displayed signals for two amide protons (δ 6.04, dd; δ 6.04, t), both of which revealed couplings with *vicinal* protons. The side-chain CH_2-NHCOAr was demonstrated by the ABX pattern appearing at δ 3.36 and 4.39. The EI mass spectrum revealed an MH^+=519 and an intense peak at *m/z* 248, corresponding to loss of the side-chain (see Section 4). The ^{13}C NMR spectrum also showed the existence of the tetrahydrofuran ring by the similar chemical shift values observed for the two quaternary carbons, i.e. 86.9 and 88.6 ppm. These values clearly agree with the two *O*-substituted carbons C-2 and C-5 present in the tetrahydrofuran ring, but not with the *O*- and *N*-substituted carbons C-3 and C-6 expected for piperidinone **4**.

2.2. Isolation and characterisation of a novel bicyclic aziridine 10

In this and the next section we are dealing with the structure elucidation of **X** and the reaction pathways leading to the tetrahydrofuran products. To unravel the reaction pathways followed, mesylate **7** was made to react with a lower amount of ethanolamine (1.5 equiv.). Besides the polar compound **X**, a new product **10** was isolated, which displayed a molecular ion at *m/z* 217 corresponding to the loss of HOMs from the original mesylate. Compound **10** was the only product isolated when the amine was replaced with other bases, i.e. K_2CO_3 in THF (72%) or NaH in THF (78%).

The spectral data of compound **10** indicated the bicyclic aziridine structure shown (Fig. 1). In the ^1H NMR spectrum, two singlets were observed at δ 2.37 and 2.52, corresponding to the geminal protons of the aziridine methylene group; the small geminal coupling (less than 1 Hz) is typical for aziridine protons.[9] The aziridine structure was also confirmed by the ^1H coupled ^{13}C NMR spectrum. Instead of the usual $^1J_{C-H}$ values (120–150 Hz) for a tetrahedral (sp^3) carbon, two larger $^1J_{C-H}$ values (178 and 169 Hz) were observed. Interestingly, the carbonyl function of the lactam ring showed spectral properties (^{13}C NMR: 194 ppm; IR 1700 cm^{-1}) that were closer to those of a ketone (195–200 ppm, 1705–1725 cm^{-1}) than of an amide group (ca. 170 ppm, 1630–1650 cm^{-1}).

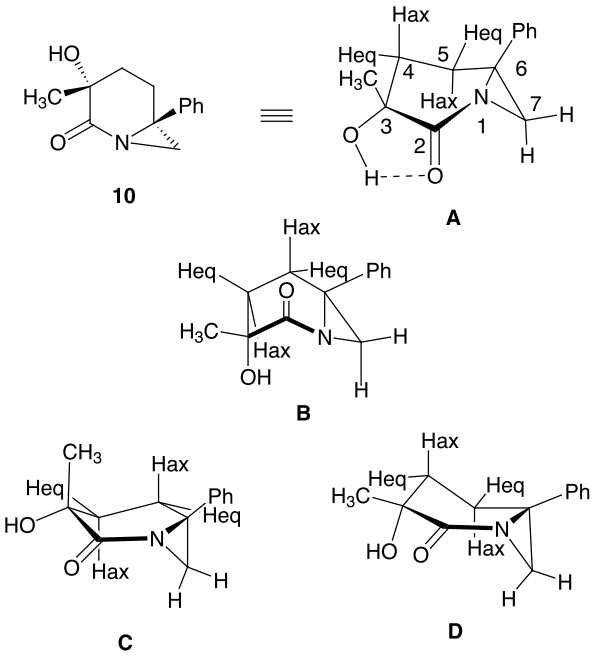


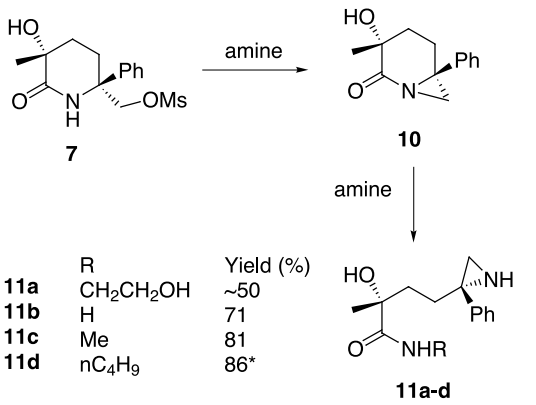
Figure 1.

The above observations led to the conclusion that under the basic conditions used the activated *neo*pentyl-like primary alcohol did not undergo substitution to provide **3** but rather internal displacement by the lactam NH-group to form a bicyclic aziridine system **10**. A similar intramolecular displacement has been reported by Kishi and co-workers.[10] Modelling analysis of bicyclic aziridine **10** revealed boat forms **A** and **B** as the lowest energy conformers. According to molecular mechanics calculations, boat form **A** is largely favoured over the usual half-chair forms **C** and **D** that are characteristic of unstrained six-membered ring lactams. Further intercomparison of boat forms **A** and **B** by AM1 indicated form **A** as the minimal energy conformer. Apparently, the piperidinone–aziridine ring fusion tends to force the atoms C5–C6–N1–C2 into one plane different from that of the aziridine ring, thus preventing a significant overlap of the sp^3 N lone pair and the carbonyl group.

The lack of conjugation between carbonyl and nitrogen in structure **A** agrees with the ketone-like properties of the carbonyl group mentioned above. In the NOESY spectrum of **10** in $CDCl_3$ and C_6D_6, a cross-peak between the phenyl *ortho*-protons and H-5*eq* (but not H-5*ax*) confirmed the predominance of boat form **A** over **B**. Moreover, the chemical shift of the OH-proton (δ 3.56 in $CDCl_3$ and δ 3.72 in C_6D_6) was only slightly affected by dilution or temperature changes, suggesting the existence of an intramolecular hydrogen bridge.

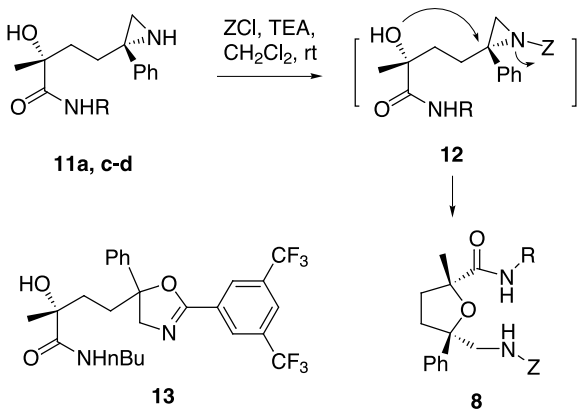
2.3. Regioselective opening of the bicyclic aziridine by amines: assignment of structure 11 to the unknown product X

In order to identify compound **X** and to verify whether it is formed via bicyclic aziridine **10**, the latter was treated with ethanolamine. This furnished the same product **X** (impure), to which was assigned the monocyclic aziridine structure **11a** based on the spectral data discussed below. Subsequent



	R	Yield (%)
11a	CH_2CH_2OH	~50
11b	H	71
11c	Me	81
11d	nC_4H_9	86*

Scheme 2. *Along with **11d**, a trace of product **18** (Scheme 5) was observed.



	R	Z	Yield (%)
8a	CH_2CH_2OH	$COC_6H_3(CF_3)_2$	48+39(**9**)
8b	Me	$SO_2C_6H_4NO_2$	81
8c	Me	COOEt	52
8d	nC_4H_9	$COC_6H_3(CF_3)_2$	35*

Scheme 3. *Along with **8d**, **13** was isolated in 50% yield.

N-acylation of **11a** with 3,5-bis(trifluoromethyl)benzoyl chloride yielded the final tetrahydrofuan product **8a**. Alternative treatment of mesylate **7** with ammonia (25% in water, rt, 2 days) and primary amines, i.e. methylamine (40% in water, rt, 2 days) or butylamine (10 equiv. in THF, reflux for 3 days), afforded the corresponding monocyclic aziridines **11b–d** in good yields (Scheme 2).

The electron-impact (EI) mass spectra of the monocyclic aziridines **11** displayed a base peak at *m/z* 132 and intense ions at *m/z* 190 and 146. These fragmentations probably are initiated by localisation of the positive charge on either the OH or aziridine NH group. The α-cleavage of the alcohol yields an ion at *m/z* 190. Opening of the charged aziridine gives an intermediate M^+ ion that can fragment through formation of a stable five-membered ring (*m/z* 146) or through β-cleavage (*m/z* 132). This agrees well with the results reported in an EI study of monocyclic aziridines.[11]

The monocyclic aziridine structure **11** also was confirmed by the NMR data. The two protons of the $CONH_2$ group of **11b** were observed as two singlets (δ: 7.22, 7.30) and the CONHMe of **11c** as a quartet (δ: 7.22). The large $^1J_{C-H}$ value (168 Hz) in the ^1H coupled ^{13}C NMR spectra of compounds **11b–d** provided further support for the aziridine structure. Based on these data structure **11a** finally could be assigned to the unknown product **X**.

The predominant attack of the amines on the carbonyl group of **10** can be related to the strain involved in ring fusion between the 2-pyridinone and aziridine rings. Upon addition of amine to the carbonyl group, the six-membered ring is opened releasing the strain in the bicyclic system.

2.4. Conversion of aziridine 11 into furan compounds 8

As described above, crude compound **X** (**11a**) was converted into tetrahydrofuran compound **8a** on treatment with 3,5-bis(trifluoromethyl)benzoyl chloride. Probably the *N*-acyl aziridine initially formed undergoes internal nucleophilic attack by the tertiary alcohol group to give the tetrahydrofuran derivative **8a**. Nosyl chloride and ethyl chloroformate also could be used to activate the aziridine ring of compound **11c** (Scheme 3).

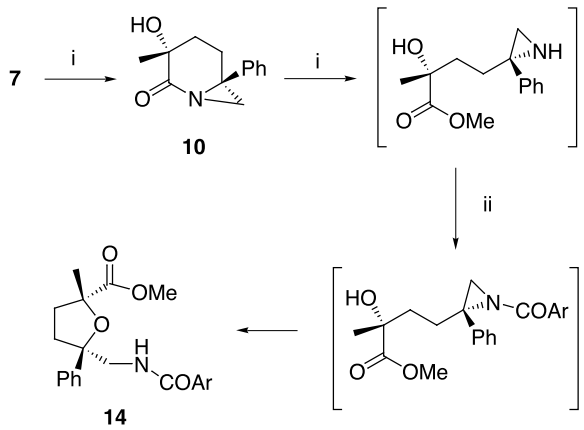
Treatment of the crude product **11d** with 3,5-bis(trifluoromethyl)benzoyl chloride gave the corresponding substituted tetrahydrofuran compound **8d** as a minor product in 35% yield; the major product (50%) was identified as the 2,5-substituted oxazoline **13** (Scheme 3), probably generated by an internal attack of the amide oxygen at the benzylic position. The assignment of **13** as the 2,5- and not the alternative 2,4-substituted structure that would result from attack of the amide oxygen at the methylene group of the aziridine, was based on the large $^2J_{C-H}$ values (15.2 Hz) observed for protons H-4. Although **13** was a single compound, the relative configuration of the stereocentre C-5 remains to be established.

The regioselectivity found for opening of the aziridine ring of **12** by internal attack of OH at the tertiary centre may be ascribed in part to the benzylic effect. Furthermore, the hydrofuran ring can be formed in a favourable 5-*exo-tet* process, according to Baldwin's rules for ring closure.[12] (Alternative S_N2 attack of OH on the aziridine methylene group to form the hydropyran ring constitutes a formal 6-*exo-tet* process with stereoelectronic requirements similar to that of 6-*endo-trig* when taking into account the partial π character of the C–C bond in the 3-membered ring.) Similar internal cyclisations involving regioselective opening of an aziridine or epoxide ring to form the corresponding O- and N-heterocycles have been reported previously.[13]

The combined ring opening–closing process was found to be completely stereoselective. The cross-peak found in the NOESY spectrum of **8** between the CH_3 protons and the Ph *ortho* protons clearly shows that the phenyl and methyl groups are *cis* oriented. This is consistent with an S_N2-like ring opening of the aziridine ring producing the tetrahydrofuran compounds as single diastereomers.

2.5. Further investigation of bicyclic aziridine 10

To investigate further the reactivity of this unknown bicyclic aziridine system, some other nucleophiles were applied. Thus ester compound **14** could be easily accessed

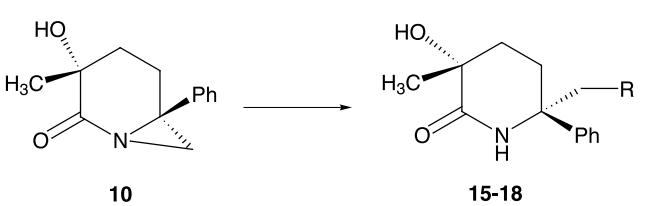


Scheme 4. *Reagents and conditions* (i): NaOMe (1 equiv.), MeOH, rt; (ii): 3,5-bis(trifluoromethyl)benzoyl chloride (ArCOCl), CH_2Cl_2, Et_3N.

by treating mesylate **7** with sodium methoxide (Scheme 4). Obviously, the methoxide reacts in the same way as the primary amines discussed above.

Unlike the lactam ring opening observed in the reaction of **10** with primary amines and methoxide, nucleophiles such as phenylthiolate, piperidine and azide were found to react with opening of the aziridine ring to give 2-piperidinones **15**–**18** (Scheme 5). The structures of **15**–**18** could easily be assigned from their EI mass spectra which displayed a characteristic base peak at *m/z* 204 due to α-cleavage. In the case of **17**, the base peak at *m/z* 98 corresponds to a methylene–piperidinium ion. In the ^{1}H NMR spectra of **15**–**18**, the piperidinone structure was confirmed by the AB patterns found for the methylene protons of the side-chain and by the singlet amide signal. Compound **18** was isolated as a side product of aziridine **11d** (see Scheme 2 before).

From the diverging results obtained in the reaction of bicyclic aziridine **10** with the various nucleophiles tested it appears that both the steric requirement and the 'hard–soft' character of the reagents determines the mode of attack of the incoming nucleophile at either one of two electrophilic sites. Soft nucleophiles like thiophenolate and azide prefer S_N2 displacement proceeding at the aziridine methylene carbon (soft electrophilic centre), rather than reaction with



Product	R	Conditions	Yields (%)
15	SPh	PhSH (2 eq), NaH, THF, 0°C	82
16	N_3	NaN_3 (2 eq), DMF, 90°C	75
17	piperidinyl	piperidine (5eq), THF, reflux	83
18	NHnBu	*n*-$BuNH_2$ (10 eq), THF, reflux	10

Scheme 5.

the carbonyl group (hard electrophilic centre). On the other hand reaction of primary amines and methoxide preferably occurs at the carbonyl centre. However, for the secondary amine piperidine (and to some extent also for *n*-butylamine), initial addition to the carbonyl group is impeded by the steric repulsion experienced from the heavily substituted vicinal positions N1 and C3; therefore attack at the less hindered aziridine methylene group is again preferred. The extent of the steric repulsion experienced in the addition reaction to the carbonyl group can be estimated from inspection of the structure of the more favourable boat conformer **A** (see Fig. 1).

3. Conclusion

On treatment with primary amines, the mesylate of 6-oxo-2-piperidinemethanol was converted to an unusual bicyclic lactam, 1-azabicyclo[4.1.0]heptan-2-one **10**, instead of undergoing an intermolecular displacement of the mesylate group. The amide carbonyl group of lactam **10** displayed properties corresponding to those of an unconjugated ketone and amino function. When applying primary amines or methoxide as nucleophilic reagents, preferential attack on the carbonyl group led to ring opening of the lactam to yield monocyclic γ-hydroxyalkylaziridines. By contrast, in the reaction of the bicyclic lactam **10** with phenylthiolate, piperidine or azide, preferred attack was found to occur on the methylene group of the aziridine, resulting in aziridine ring opening to give 3,3,6,6-substituted 2-piperidinones. Further *N*-acylation of the γ-hydroxyalkylaziridines led to stereoselective conversion into the 2,2,5,5-tetrahydrofuran ring system.

4. Experimental

4.1. General methods

Melting points were determined using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 297 grating IR spectrophotometer and a Perkin–Elmer 1720 Fourier transform spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. Analytical TLC was carried out using Alugram Sil G/UV_{254} plates and column chromatography by using 70–230 mesh silica gel 60 (E.M. Merck). Microanalyses were done by Janssen Pharmaceutica.

4.1.1. (3*R,6*S**)-3-Hydroxy-6-(hydroxymethyl)-3-methyl-6-phenyltetrahydro-2(1*H*)-pyridinone 6.** To a solution of 2.00 g methyl 6-oxo-2-piperidinecarboxylate **5**[8] (7.68 mmol) in methanol was added 590 mg $NaBH_4$ (15.4 mmol, 2 equiv.) powder in one portion. The reaction mixture was stirred at rt for 30 min. Then a saturated

ammonium chloride aqueous solution was added (pH 8.0–9.0). After removal of methanol, the residue was taken up in 30 mL water and extracted with 3×30 mL ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product that was purified by chromatography (silica gel, 10% MeOH/CH_2Cl_2) and crystallisation (hexane/dichloromethane). Yield: 1.68 g; 94%; white crystals; mp: 142–145°C; IR (KBr) cm^{-1}: 3363, 3188 (OH, NHCO), 1647 (CONH); ^1H NMR ($CDCl_3$): 1.33 (s, 3H, CH_3), 1.54 (m, 1H, ~J=31 Hz, H-4ax or H-3ax), 1.87–1.92 (m, 2H, H-3eq and H-4eq), 2.26 (m, 1H, ~J=30 Hz, H-3ax or H-4ax), 3.64 (dd, 1H, ^3J=5.0, 7.0 Hz, CH_2OH), 3.80 (dd, 1H, ^2J=12 Hz, ^3J=7.0 Hz, CH_2OH), 3.85 (dd, 1H, ^2J=12.0 Hz, ^3Jee=5.0 Hz, CH_2OH), 4.07 (s, 1H, OH), 7.26–7.38 (m, 6H, Ph-H and CONH); ^{13}C NMR ($CDCl_3$): 26.8 (CH_3), 28.8, 31.5 (C-3, C-4), 63.8 (C-2), 69.6 (C-5), 70.9 (CH_2OH), 125.6, 127.5, 128.8 (Ph-C), 142.4 (C-*ipso*), 176.6 (C-6); *m/z* (%) (CI): 236 (100, MH^+), 218 (25, MH^+-H_2O), 204 (18, MH^+−MeOH); exact mass for $C_{13}H_{18}O_3N_1$: (MH^+) 236.1287; found: 236.1289. Anal. calcd for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95; found: C 66.45, H 7.30, N 5.88.

4.1.2. [(2*S* *,5*R* *)-5-Hydroxy-5-methyl-6-oxo-2-phenylhexahydro-2-pyridinyl]methyl methanesulfonate 7. To a solution of 2.00 g (8.50 mmol) of 6-oxo-2-piperidinemethanol **6** and 2.40 mL Et_3N (2.0 equiv.) in dry dichloromethane at −15°C under N_2 atmosphere, was added 0.66 mL methanesulfonyl chloride (1.0 equiv.) via syringe over 10 min. The reaction mixture was stirred at this temperature for 1 h and then treated with 30 mL of a cold saturated aqueous $NaHCO_3$ solution. The mixture was extracted with 3×30 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product that was purified by column chromatography (10% MeOH/CH_2Cl_2) followed by crystallisation (hexane/dichloromethane). Yield: 92%; white crystals; mp: 143.0–143.6°C; IR (KBr) cm^{-1}: 3277 (OH), 1657 (CONH); ^1H NMR (DMSO-d_6): 1.14 (s, 3H, CH_3), 1.30 (td, 1H, ^2J=^3Jaa=13.8 Hz, ^3Jae=2.3 Hz, H-4ax or H-3ax), 1.68 (m, 1H, H-4eq or H-3eq), 1.93 (m, 1H, H-3eq or H-4eq), 2.35 (td, 1H, ^2J=^3Jaa=13.8 Hz, ^3Jae=3.0 Hz, H-3ax or H-4ax), 3.16 (s, 3H, SO_2CH_3), 4.26 (d, 1H, ^2J=10.0 Hz, CH_2OMs), 4.38 (d, 1H, ^2J=10.0 Hz, CH_2OMs), 5.18 (s, 1H, OH), 7.40–7.44 (m, 5H, Ph-H), 7.99 (s, 1H, NHCO); ^{13}C NMR: 26.5 (CH_3), 27.1, 31.8 (C-3, C-4), 36.6 (CH_3), 60.9 (C-2), 67.9 (C-5), 74.3 (CH_2OMs), 125.9, 127.4, 128.4 (Ph-C), 141.9 (C-*ipso*), 173.9 (C-6); *m/z* (%) (CI): 314 (100, MH^+), 296 (20, MH^+-H_2O); exact mass for $C_{13}H_{16}NO_5S$ [(M−Me)$^+$]: 298.0749; found: 298.0744.

4.1.3. [(2*S* *,5*R* *)-5-Methyl-5-methylsulfonyloxy-6-oxo-2-phenylhexahydro-2-pyridinyl]methyl methanesulfonate 6-diMs. This compound is a side product produced along with **7**. Yield: 7%; white crystals; ^1H NMR (DMSO-d_6): 1.56 (s, 3H, CH_3), 1.77 (ddd, 1H, ^2J=14.0 Hz, ^3J=9.0, 3.3 Hz, H-4 or H-3), 2.02 (ddd, 1H, ^2J=14.0 Hz, ^3J=8.8, 3.3 Hz, H-3 or H-4), 2.37 (ddd, 1H, ^2J=14.0 Hz, ^3J=9.0, 3.3 Hz, H-3 or H-4), 2.50 (ddd, 1H, ^2J=14.0 Hz, ^3J=8.8, 3.3 Hz, H-4 or H-3), 3.16 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 4.46 (s, 2H, CH_2OMs), 7.33–7.48 (m, 5H, Ph-H), 8.63 (s, 1H, NHCO); ^{13}C NMR (DMSO-d_6): 24.7 (CH_3), 28.2, 31.2 (C-3, C-4), 36.5, 40.5 (2×CH_3), 60.5 (C-2), 73.5 (CH_2OMs), 85.4 (C-5), 125.7, 127.6, 128.5 (Ph-C), 141.5 (C-*ipso*), 168.3 (C-6); *m/z* (%) (CI): 392 (7, MH^+), 296 (100, MH^+−MsOH), 200 (66, $MH^+-2\times$MsOH).

4.1.4. (3*S* *,6*R* *)-3-Hydroxy-3-methyl-6-phenyl-1-azabicyclo[4.1.0]heptan-2-one 10. *Method A*. To a solution of 370 mg (1.18 mmol) of mesylate **7** in dry THF at rt was added 326 mg K_2CO_3 (2.0 equiv.). The reaction mixture was heated at reflux for 2 days and then treated with 10 mL of water. The mixture was extracted with 3×10 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product that was purified by chromatography (2% MeOH/CH_2Cl_2).

Method B. To a solution of 500 mg of mesylate **7** (1.60 mmol) in dry THF at 0°C was added 65 mg (1.3 equiv.) NaH (80% dispersion in mineral oil). The reaction mixture was stirred at this temperature for 1 h and then a saturated aqueous solution of NH_4Cl was added (pH 8.0). The mixture was distributed between 10 mL water and 3×10 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product that was purified by chromatography (2% MeOH/CH_2Cl_2). Yield: 195 mg, 72% (Method A). Yield: 78% (Method B); colourless oil; IR (NaCl, film) cm^{-1}: 3470.9 (OH), 1700.1 (CO); ^1H NMR ($CDCl_3$): 1.52 (s, 3H, CH_3), 1.72 (ddd, 1H, ^2J=14.2 Hz, ^3Jaa=11.0 Hz, ^3Jae=4.4 Hz, H-5ax), 1.93 (ddd, 1H, ^2J=14.2 Hz, ^3Jea=4.5 Hz, ^3Jee=5.9 Hz, H-4eq), 2.12 (ddd, 1H, ^2J=14.2 Hz, ^3Jaa=11.0 Hz, ^3Jae=4.4 Hz, H-4ax), 2.37 (s, 1H, H-7), 2.52 (s, 1H, H-7), 2.54 (ddd, 1H, ^2J=14.2 Hz, ^3Jea=4.4 Hz, ^3Jee=5.9 Hz, H-5eq), 3.56 (s, 1H, OH), 7.26–7.42 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): 27.2 (CH_3), 28.7, 37.7 (C-4, C-5), 42.7 (C-7), 46.8 (C-6), 73.2 (C-3), 125.7, 127.6, 128.6 (Ph-C), 139.0 (C-*ipso*), 194.0 (CO); *m/z* (%): 216 (6, M^+−H), 198 (1, M^+-H_2O), 188 (4, M^+−CO); exact mass for $C_{13}H_{14}NO_2$ [(M−H)$^+$]: 216.1025; found: 216.1030.

4.2. Reaction of 3-hydroxy-3-methyl-6-phenyl-1-azabicyclo[4.1.0]heptan-2-one 10 with primary amines; conversion into monocyclic aziridines 11

4.2.1. (2*R* *)-2-Hydroxy-N^1-(2-hydroxyethyl)-2-methyl-4-[(2*S* *)-2-phenylaziranyl]butanamide 11a. To a solution of 1.07 g (3.41 mmol) of mesylate **7** in 20 mL THF were added 1.04 mL ethanolamine (5 equiv.) and 0.95 g K_2CO_3 (2 equiv.). The reaction mixture was heated at reflux temperature for 1 day. After concentration the residue was treated with 20 mL water and the mixture extracted with 3×20 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product that was purified by chromatography (10% MeOH/CH_2Cl_2). Yield: 460 mg, 48%; colourless oil; *m/z* (%) (CI): 279 (100, MH^+); *m/z* (%): 279 (10, MH^+), 248 (53, M^+-CH_2OH), 190 (55, $M^+-CONHCH_2CH_2OH$), 132 (100, [CH_2-C(Ph)NH=CH_2]$^+$); ^1H NMR (300 MHz, $CDCl_3$): 1.1 (br., 1H, NH), 1.4 (s, 3H, CH_3), 1.5–2.2 (m, 4H, CH_2CH_2), 2.1 (s, 2H, CH_2 aziridine), 3.5–3.7 (m, 4H, CH_2CH_2), 3.8–4.2 (br., 2H, OH), 7.3 (br., 1H, NHCO), 7.3–7.4 (m, 5H, Ph-H).

4.2.2. (2*R* *)-2-Hydroxy-2-methyl-4-[(2*S* *)-2-phenylaziranyl]butanamide 11b. To a solution of 660 mg (2.10 mmol) of mesylate **7** in 10 mL THF was added

20 mL 25% ammonia solution. The reaction mixture was stirred at rt for 2 days and then concentrated. The work-up and chromatography was done as mentioned for **11a**. Yield: 350 mg, 71%; colourless oil; IR (NaCl, film) cm^{-1}: 3286 (OH, NH), 1668 (CONH); ^1H NMR ($CDCl_3$): 1.00 (br., 1H, NH), 1.36 (s, 3H, CH_3), 1.49 (m, 1H, $\sim J$=30.0 Hz), 1.96 (m, 1H, $\sim J$=30.0 Hz), 2.10 (m, 1H, $\sim J$=30.0 Hz) (CH_2CH_2), 2.08 (s, 2H, *CH*$_2$ aziridine), 2.23 (m, 1H, $\sim J$=30.0 Hz), 5.55 (s, 1H, OH), 7.22 (br., 1H, NH_2CO), 7.30 (s, 1H, NH_2CO), 7.25–7.34 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): 27.6 (CH_3), 30.1 (br., CH_2NH), 31.8, 34.1 (CH_2CH_2), 41.0 (CNH), 74.8 (COH), 126.9, 127.6, 128.6 (Ph-C), 142.6 (Ph-C*ipso*), 180.0 (CO); *m/z* (%): 233 (46, M^+-H), 216 (18, M^+-H_2O), 190 (52, M^+-CONH_2), 146 (59, $M^+-NH_2COCMeOH$), 132 (100, $[CH_2C(Ph)NH{=}CH_2]^+$); exact mass for $C_{13}H_{18}N_2O_2$: 234.1368; found: 234.1357.

4.2.3. (2*R* *)-2-Hydroxy-N^1,2-dimethyl-4-[(2*S* *)-2-phenylaziranyl]butanamide 11c. To a solution of 1.36 g (4.34 mmol) of mesylate **7** in 20 mL THF was added 20 mL 40% $MeNH_2$ aqueous solution. The reaction mixture was stirred at rt for 2 days and then was concentrated. The work-up and chromatography was done as mentioned for **11a**. Yield: 872 mg, 81%; white semi-solid; IR (NaCl, film) cm^{-1}: 3285 (OH, NH), 1653, 1542 (CONH); ^1H NMR ($CDCl_3$): 1.00 (br., 1H, NH), 1.33 (s, 3H, CH_3), 1.48 (m, 1H, $\sim J$=30.0 Hz), 1.90 (m, 1H), 2.10 (m, 2H) (CH_2CH_2), 2.07 (s, 2H, *CH*$_2$NH), 2.83 (d, 3H, ^3J=5.0 Hz, *CH*$_3$NHCO), 7.22 (br.q, 1H, NHCO), 7.25–7.34 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): 25.8 (CH_3NH), 27.5 (CH_3), 30.4 (br., CH_2NH), 31.6, 34.2 (CH_2CH_2), 41.0 (C–NH), 74.8 (C–OH), 125.3–128.6 (Ph-C), 142.6 (Ph-C*ipso*), 177.4 (CONH); *m/z* (%): 247 (21, M^+-H), 190 (55, $M^+-CONHCH_3$), 146 (61, $[CH_2CH_2C(Ph)NH{=}CH_2]^+$), 132 (100, $[CH_2C(Ph)NH{=}CH_2]^+$); exact mass for $C_{14}H_{20}N_2O_2$: 248.1525; found: 248.1525.

4.2.4. (2*R* *)-N^1-Butyl-2-hydroxy-2-methyl-4-[(2*S* *)-2-phenylaziranyl)butanamide 11d. To a solution of 1.46 g (4.66 mmol) of mesylate **7** in 40 mL THF were added 4.6 mL *n*-butylamine (10.0 equiv.) and 0.71 g K_2CO_3 (1.1 equiv.). The reaction mixture was heated at reflux temperature for 3 days and then was concentrated. The work-up and chromatography was done as mentioned for **11a**. Yield: 1.32 g, 98% (composition 88% **11d** and 12% **18** from NMR); oil; IR (NaCl, film) cm^{-1}: 3342, 3337 (OH, NH), 1651 (CONH); ^1H NMR ($CDCl_3$, 50°C): 0.90 (t, 3H, ^3J=7.3 Hz, *CH*$_3$CH$_2$), 1.31 (s, 3H, CH_3), 1.33 (br., 1H, NH), 1.35 (m, 2H, $CH_3CH_2CH_2$), 1.48 (m, 3H, $CH_3CH_2CH_2$ and H-3 or H-4), 1.80 (m, 1H, $\sim J$=30.0 Hz, H-3 or H-4), 1.98 (s, 1H, CH_2 aziridine), 1.99 (s, 1H, CH_2 aziridine), 2.02 (m, 1H, $\sim J$=30.0 Hz, H-3 or H-4), 2.14 (m, 1H, $\sim J$=30.0 Hz, H-3 or H-4), 3.22 (m, 2H, COHN*CH*$_2$CH$_2$), 7.10 (br., 1H, NHCO), 7.28–7.34 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, 45°C): 13.5 (CH_3–*n*Bu), 19.8 (CH_2–*n*Bu), 27.1 (CH_3), 31.0 (br., $^1J_{C-H}$=169 Hz, $CH_2NH_{aziridine}$), 31.6 (CH_2–*n*Bu), 31.9 (C-3 or C-4), 34.7 (C-3 or C-4), 38.6 ($CONHCH_2$–*n*Bu), 40.9 (C–NH), 74.8 (C–OH), 127.0, 127.1, 128.6 (Ph-C), 143.0 (C-*ipso*), 176.3 (CONH); *m/z* (%): 291 (100, $M^+-H^\cdot$), 274 (30, M^+-OH), 190 (55, $M^+-CONHC_4H_9$), 146 (45, $[CH_2CH_2C(Ph)NH{=}CH_2]^+$), 132 (70, $[CH_2C(Ph)NH{=}CH_2]^+$).

4.3. General procedure for conversion of compounds 11 into tetrahydrofuran compounds 8 and 9

To a solution of 1.5 mmol (for **11c–d**) or 3.0 mmol (for **11a**) monocyclic aziridine **11** and 1.5 equiv. triethylamine in dry CH_2Cl_2 at −15°C was added 1.5 equiv. 3,5-bis(trifluoromethyl)benzoyl chloride (for **8a**,**d**) or 1.5 equiv. *p*-nitrobenzenesulfonyl chloride (for **8b**) or 1.5 equiv. ethoxycarbonyl chloride (for **8c**). The reaction mixture was stirred at this temperature for 1 h and then 10 mL water was added. The mixture was extracted with 3×10 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product that was purified by chromatography (5–10% MeOH/CH_2Cl_2).

4.3.1. (2*R* *,5*R* *)-5-({[3,5,-Bis(trifluoromethyl)benzoyl]-amino}methyl)-N^2-hydroxyethyl-2-methyl-5-phenyl-tetrahydro-2-furancarboxamide (8a). Yield: 750 mg, 48.3%; white powder; mp: 188–190°C; IR (KBr) cm^{-1}: 3370, 3286 (OH, NHCO), 1645, 1553, 1532 (CONH); ^1H NMR ($CDCl_3$): 1.51 (s, 3H, CH_3), 1.73 (td, 1H, ^2J=^3J=12.0, 7.0 Hz, H-3 or H-4), 2.23 (td, 1H, ^2J=^3J=12.0, 7.0 Hz, H-4 or H-3), 2.38 (ddd, 1H, ^2J=12.0 Hz, ^3J=7.0, 2.6 Hz, H-4, or H-3), 2.54 (ddd, 1H, ^2J=12.0 Hz, ^3J=7.0, 2.6 Hz, H-3 or H-4), 3.36 (dd, 1H, ^2J=14.0 Hz, ^3J=4.0 Hz, *CH*$_2$NHCO), 3.45 (dq, 1H, ^2J=14.0 Hz, ^3J=4.8 Hz, CONH*CH*$_2$CH$_2$OH), 3.65 (m, 1H, CONH*CH*$_2$CH$_2$OH), 3.75 (t, 1H, OH), 3.85 (q, 2H, ^3J=4.8 Hz, CONHCH$_2$*CH*$_2$OH), 4.39 (dd, 1H, ^2J=14.0 Hz, ^3J=9.0 Hz, *CH*$_2$NHCO), 6.40 (br.dd, 1H, CH$_2$N*H*CO), 7.35–7.50 (m, 5H, Ph-H), 7.98 (s, 1H, Ar-H*para*), 8.03 (s, 2H, Ar-H*ortho*), 8.24 (br.t, 1H, CON*H*CH$_2$CH$_2$OH); ^{13}C NMR ($CDCl_3$): 25.17 (CH_3), 35.7, 36.2, 42.9, 51.0 and 62.4 (5×CH_2), 86.9 and 88.6 (C-2 and C-5), 122.8 (q, $^1J_{C-F}$=273 Hz, 2×CF_3), 125.3 (Ar-C*para*), 127.4 (Ar-C*ortho*), 125.5, 128.7 and 127.9 (Ph-C), 132.4 (Ar-C*meta*), 136.3 and 143.5 (2×C-*ipso*), 166.2 and 176.7 (2×CONH); *m/z* (%) (CI): 519 (100, MH^+), 430 (7, $MH^+-HCONHCH_2CH_2OH$); *m/z* (%): 430 (50, $M^+-CONHCH_2CH_2OH$), 372 (23, $M^+-CONHCH_2CH_2OH$, −MeCOMe), 248 (71, $M^+-CH_2NHCOAr$), 241 (45, ^+COAr); exact mass for $C_{24}H_{24}F_6N_2O_4$: 518.1640; found: 518.1637. Anal. calcd for $C_{24}H_{24}F_6N_2O_4$: C 55.60, H 4.67, N 5.40; found: C 55.76, H 4.64, N 5.32.

4.3.2. (2*R* *,5*R* *)-5-({[3,5-Bis(trifluoromethyl)benzoyl]-amino}methyl)-N^2-[3,5-bis(trifluoromethyl)benzoyloxy-ethyl]-2-methyl-5-phenyltetrahydro-2-furancarboxa-mide 9. Compound **9** was isolated along with **8a**. Yield: 900 mg, 39.6%; white crystals; mp: 160–161°C; IR (KBr) cm^{-1}: 3275 (NHCO), 1732, 1666, 1646, 1559 (CONH); ^1H NMR ($CDCl_3$): 1.49 (s, 3H, CH_3), 1.71 (td, 1H, ^2J=^3J=12.0, 7.0 Hz, H-3 or H-4), 2.14 (td, 1H, ^2J=^3J=12.0, 7.0 Hz, H-4 or H-3), 2.35 (ddd, 1H, ^2J=12.0 Hz, ^3J=7.0, 2.5 Hz, H-4 or H-3), 2.54 (ddd, 1H, ^2J=12.0 Hz, ^3J=7.0, 2.5 Hz, H-3 or H-4), 3.25 (dd, 1H, ^2J=14.0 Hz, ^3J=4.0 Hz, *CH*$_2$NHCO), 3.72 (m, 1H, CONH*CH*$_2$CH$_2$O), 3.93 (m, 1H, CONH*CH*$_2$CH$_2$O), 4.36 (dd, 1H, ^2J=14.0 Hz, ^3J=9.0 Hz, *CH*$_2$NHCO), 4.66 (m, 2H, CONHCH$_2$*CH*$_2$O), 6.28 (dd, 1H, ^3J=9.0, 4.0 Hz, CH$_2$N*H*CO), 7.35–7.50 (m, 5H, Ph-H), 7.94 (s, 2H, Ar-H), 7.99 (s, 2H, Ar-H), 8.52 (s, 2H, Ar-H), 8.64 (br. t, 1H, ^3J=6.0 Hz, CON*H*CH$_2$CH$_2$OH); ^{13}CNMR ($CDCl_3$): 25.01 (CH_3), 35.7, 36.3, 38.6, 50.9 and 65.1

(5×CH_2), 86.8 and 88.6 (C-2 and C-5), 123.0 (4×CF_3), 125.3-129.8 (Ph-C and Ar-C), 132.5, 136.5 and 143.5 (3×C*ipso*), 163.9, 165.9 and 176.4 (3×CO); *m/z* (%): 759 (3, MH^+), 488 (82, $M^+-CH_2NHCOAr$), 430 (100, $M^+-CONHCH_2CH_2OCOAr$), 241 (53, ^+COAr); exact mass for $C_{33}H_{26}F_{12}N_2O_5$: 758.1650; found: 758.1648. Anal. calcd for $C_{33}H_{26}F_{12}N_2O_5$: C 52.25, H 3.45, N 3.69; found: C 52.21, H 3.39, N 3.66.

4.3.3. (2*R* *,5*R* *)-N²,2-Dimethyl-5-({[(4-nitrophenyl)sulfonyl]amino}methyl)-5-phenyltetrahydro-2-furancarboxamide 8b. Yield: 530 mg, 81%; white crystals; mp: 202°C; IR (KBr) cm^{-1}: 3396, 3313 (NH), 1672, 1539, 1440, 1175 (CONH, SO_2, NO_2); ^1H NMR (DMSO-d_6): 1.29 (s, 3H, CH_3), 1.59 (dt, 1H, ^2J=12.0 Hz, ^3J=7.5 Hz, H-3 or H-4), 2.11 (m, 2H, H-4 or H-3), 2.21 (dt, 1H, ^2J=12.0 Hz, ^3J=6.5 Hz, H-3 or H-4), 2.66 (d, 3H, ^3J=5.0 Hz, CH_3NH), 3.02 (d, 1H, ^2J=13.5 Hz, CH_2NHSO_2), 3.25 (d, 1H, ^2J=13.5 Hz, CH_2NHSO_2), 7.21 (t, 1H, Ph-H*para*), 7.28 (t, 2H, Ph-H*meta*), 7.38 (d, 2H, Ph-H*ortho*), 7.90 (m, 1H, NHCO), 7.94 (d, 2H, Ar-H), 8.10 (s, 1H, *NH*Ns), 8.36 (d, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): 25.3 (CH_3), 25.5 (CH_3), 34.8, 35.2 (C-3 and C-4), 51.9 (NCH_3), 85.6, 87.5 (C-2 and C-5), 124.4–127.8 (Ph-C, Ar-C), 144.2, 146.0 and 149.4 (other Ar-C), 174.9 (CONH); *m/z* (%): 434 (5, MH^+), 375 (64, $M^+-CONHCH_3$), 317 (12, $M^+-CONHCH_3-MeCOMe$), 218 (100, M^+-CH_2NHNs), 189 (91, ^+Ns); exact mass for $C_{20}H_{24}N_3O_6S$ (MH): 434.1386; found: 434.1382.

4.3.4. (2*R* *,5*R* *)-5-[(Ethoxycarbonylamino)methyl]-N²,2-dimethyl-5-phenyl-tetrahydro-2-furancarboxamide 8c. Yield: 410 mg, 52%; oil; IR (NaCl, film) cm^{-1}: 3316 (NHCO), 1710, 1656, 1546 (CONH); ^1H NMR ($CDCl_3$): 1.25 (t, 3H, ^3J=7.0 Hz, CH_3CH_2), 1.49 (s, 3H, CH_3), 1.69 (dt, ^2J=^3J=11.4, 7.0 Hz, H-3 or H-4), 2.06 (dt, 1H, ^2J=^3J=11.4, 7.0 Hz, H-4 or H-3), 2.22 (ddd, 1H, ^2J=11.4 Hz, ^3J=7.0, 3.4 Hz, H-4 or H-3), 2.46 (ddd, 1H, ^2J=11.4 Hz, ^3J=7.0, 3.4 Hz, H-3 or H-4), 2.86 (d, 3H, ^3J=4.5 Hz, CH_3NH), 3.26 (dd, 1H, ^2J=14.0 Hz, ^3J=4.0 Hz, CH_2NHCO), 3.78 (dd, 1H, ^2J=14.0 Hz, ^3J=10.0 Hz, CH_2-NHCO), 4.08 (q, 2H, ^3J=7.0 Hz, OCH_2), 4.88 (dd, 1H, HNCOO), 7.23–7.43 (m, 5H, Ph-H), 8.23 (br., 1H, Me*NH*CO); ^{13}C NMR ($CDCl_3$):14.3 (CH_3CH_2), 25.0 (CH_3), 25.8 (CH_3), 35.4, 36.0 (C-3 and C-4), 51.4 (NCH_2), 60.8 (OCH_2), 86.5, 88.3 (C-2 and C-5), 125.4, 127.0, 128.1 (Ph-C), 143.9 (C-*ipso*), 157.6 (NHCOO), 176.2 (*CO*$NHCH_3$); *m/z* (%): 321 (12, MH^+), 262 (56, $M^+-CONHCH3$), 218 (100, $M^+-CH_2NHCOOEt$); exact mass for $C_{17}H_{24}N_2O_4$: 320.1735; found: 320.1728.

4.3.5. (2*R* *,5*R* *)-5-({[3,5-Bis(trifluoromethyl)benzoyl]amino}methyl)-N²-butyl-2-methyl-5-phenyltetrahydro-2-furancarboxamide 8d. Yield: 160 mg, 25%; colourless oil; IR (NaCl, film) cm^{-1}: 3287 (NHCO), 3088 (NHCO), 1644, 1551 (CONH); ^1H NMR ($CDCl_3$): 0.92 (t, 3H, CH_3CH_2), 1.35 (m, 2H, CH_3CH_2), 1.48 (s, 3H, CH_3), 1.66 (m, 2H, $CH_2CH_2CH_3$), 1.71 (m, 1H, ~J=30.0 Hz), 2.22 (m, 1H), 2.33 (m, 1H), 2.40 (m, 1H) (CH_2CH_2), 3.29 (m, 2H, $NHCH_2CH_2$), 3.39 (dd, 1H, ^2J=14.0 Hz, ^3J=3.6 Hz, CH_2-NHCO), 4.23 (dd, 1H, ^2J=14.0 Hz, ^3J=8.4 Hz, CH_2-NHCO), 7.29 (t, 1H), 7.38 (t, 1H), 7.46 (d, 2H) (Ph-H), 7.60 (br.dd, 1H, $CONHCH_2$), 7.87 (br.t, 1H, $CONHCH_2$), 7.95 (s, 1H), 8.22 (s, 2H) (Ar-H); ^{13}C NMR ($CDCl_3$): 13.6 (CH_3), 20.0 (CH_2), 25.1 (CH_3), 31.6, 35.4, 36.1, 39.3 (CH_2), 50.5 (CH_2N), 86.0, 88.6 (C-2, C-5), 122.9 (q, 2×CF_3), 124.7–132.0, 136.5, 143.9 (Ph-C, Ar-C), 165.4 (CONH), 175.9 (CO); *m/z* (%): 531 (11, MH^+), 430 (100, $M^+-CONHC_4H_9$), 372 (35, $M^+-CONHC_4H_9-MeCOMe$), 260 (74, $M^+-CH_2NHCOAr$), 241 (45, ^+COAr); exact mass for $C_{26}H_{28}F_6N_2O_3$: 530.2004; found: 530.1990.

4.3.6. N¹-Butyl-4-{2-[3,5-bis(trifluoromethyl)phenyl]-5-phenyl-4,5-dihydro-1,3-oxazol-5-yl}-2-hydroxy-2-methylbutanamide 13. Compound **13** was isolated along with **8d**. Yield: 320 mg, 50%; colourless oil; IR (NaCl, film) cm^{-1}: 3336 (s, two bands, OH, NHCO), 1654, 1533 (CONH, C=N); ^1H NMR ($CDCl_3$): 0.87 (t, 3H, CH_3CH_2), 1.37 (s, 3H, CH_3), 1.26–1.34, 1.40–1.46 (m, 4H, CH_2CH_2-CH_3), 1.50 (m, 1H, H-3 or H-4), 1.96 (m, 2H, H-3 or H-4), 2.27 (ddd, 1H, H-3 or H-4), 2.65 (s, 1H, OH), 3.22 (m, 1H, $NHCH_2CH_2$), 4.16 (d, 1H, ^2J=15.2 Hz, CH_2N=), 4.23 (d, 1H, ^2J=15.2 Hz, CH_2N=), 6.62 (t, 1H, ^3J=5.6 Hz), 7.26–7.39 (m, 5H, Ph-H), 8.00 (s, 1, Ar-H*para*), 8.47 (s, 2H) (Ar-H*ortho*); ^{13}C NMR ($CDCl_3$): 13.6 (CH_3), 19.9 (CH_2), 27.1 (CH_3), 31.6, 34.7, 35.5, 38.9 (CH_2), 67.5 (CH_2N), 75.0 (C–O), 90.2 (C–O), 123.0 (q, 2×CF_3), 125.0–132.6, 143.6 (Ph-C, Ar-C), 160.6 (C=N), 174.8 (CO); *m/z* (%): 531 (8, MH^+), 430 (100, $M^+-CONHC_4H_9$), 372 (44, $M^+-CONHC_4H_9-MeCOMe$); exact mass for $C_{26}H_{28}F_6N_2O_3$: 530.2004; found: 530.2006

4.3.7. Methyl (2*R* *,5*R* *)-5-{[3,5-bis(trifluoromethyl)-benzoylamino]methyl}-2-methyl-5-phenyltetrahydro-2-furancarboxylate 14. To a solution of 1.00 g mesylate **7** (3.19 mmol) in 10 mL pure methanol was added 377 mg NaOMe (2.2 equiv.) at 0°C. The reaction mixture was stirred at rt for 5 days and was then concentrated. The residue was treated with 1.05 g (0.69 mL) 3,5-bis(trifluoromethyl)benzoyl chloride (1.2 equiv.) and 0.66 mL triethylamine (1.5 equiv.). After reaction for 30 min, 20 mL water was added and the mixture was extracted with 3×20 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product that was purified by chromatography (10% MeOH/CH_2Cl_2). Yield: 800 mg, 52%; white crystals; mp: 127.8°C; IR (KBr) cm^{-1}: 3330 (NHCO), 1724 (COO), 1664, 1534 (CONH); ^1H NMR ($CDCl_3$): 1.64 (s, 3H, CH_3), 1.84 (ddd, 1H, ^2J=12.0 Hz, ^3J=7.7 Hz, H-3 or H-4), 2.24–2.34 (m, 3H, H-3 and H-4), 3.36 (d, 1H, ^2J=14.0 Hz, CH_2NH), 3.78 (s, 3H, COOMe), 4.23 (dd, 1H, ^2J=14.0 Hz, ^3J=8.0 Hz, CH_2NH), 7.29 (t, 1H, Ph-H*para*), 7.38 (t, 2H, Ph-H*meta*), 7.50 (d, 2H, Ph-H*ortho*), 8.00 (s, 1H, Ar-H4), 8.63 (s, 2H, Ar-H2,6), 8.80 (d, 1H, ^3J=8.0 Hz, HNCO); ^{13}C NMR (CDCl3): 24.8 (CH3), 32.7, 37.3 (C-3 and C-4), 48.8 (CH_2N), 52.8 (OMe), 84.0, 88.9 (C-2, C-5), 122.8 (q, 2×CF_3), 124.6, 125.2, 127.3, 127.6, 128.2, 128.4, 132.0, 136.4, 144.1 (Ph-C, Ar-C), 164.6 (CONH), 177.8 (COO); *m/z* (%): 490 (10, MH^+), 430 (11, $M^+-COOMe$), 241 (24, ^+COAr), 219 (100, M^+-CH_2-NHCOAr); exact mass for $C_{23}H_{21}F_6NO_4$: 489.1375; found: 489.1384.

4.4. Generation of 3,3,6,6-tetrasubstituted 2-piperidinones

4.4.1. (3*R* *,6*S* *)-3-Hydroxy-3-methyl-6-phenyl-6-[(phenylsulfanyl)methyl]tetrahydro-2(1*H*)-pyridinone 15. To

a stirred suspension of 225 mg NaH (2.6 equiv.) in 5 mL THF was added 0.51 mL thiophenol (2.6 equiv.) at 0°C. After 10 min a solution of 420 mg bicyclic aziridine **10** in 3 mL dry THF was added. The reaction mixture was stirred for 30 min, then saturated aqueous ammonium chloride solution was added (pH 8.5) and 10 mL water was added. The aqueous layer was extracted with 3×20 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product which was purified by chromatography (5% MeOH/CH_2Cl_2). Yield: 520 mg, 82%; white crystals; mp: 165°C; IR (KBr) cm^{-1}: 3366 (OH), 1656 (CON); ^1H NMR ($CDCl_3$): 1.36 (s, 3H, CH_3), 1.57 (ddd, 1H, ^2J=14.2 Hz, ^3Jaa=10.0 Hz, ^3Jae=3.4 Hz, H-4ax), 1.90 (ddd, 1H, ^2J=14.2 Hz, ^3Jee=7.3 Hz, ^3Jea=3.4 Hz, H-4eq), 2.10 (dddd, 1H, ^2J=14.0 Hz, ^3Jee=7.3 Hz, ^3Jea=3.3 Hz, ^4Jee=1 Hz, H-5eq), 2.35 (ddd, 1H, ^2J=14.0 Hz, ^3Jaa=10.0 Hz, ^3Jae=3.3 Hz, H-5ax), 3.19 (s, 1H, OH), 3.32, 3.74 (2×d, 2H, ^2J=13.0 Hz, CH_2S), 6.70 (s, 1H, HNCO), 7.17–7.29 (m, 10H, Ph-H); ^{13}C NMR ($CDCl_3$): 27.2 (CH_3), 31.4, 33.5 (C-5, C-4), 48.9 (CH_2S), 62.0 (C-6), 69.8 (C-3), 125.4 (C-*ortho*), 126.9, 127.6 (C-*para*), 128.5 (C-*ortho*), 129.0, 130.8 (C-*meta*), 135.4, 142.7 (C-*ipso*), 175.6 (CONH); *m/z* (%): 328 (<1, M^+), 204 (100, M^+-CH_2SPh), 186 (30, $M^+-CH_2SPh-H_2O$), 176 (32, $M^+-CH_2SPh-CO$); exact mass for $C_{12}H_{14}NO_2$ (M^+-CH_2SPh): 204.1026; found: 204.1030.

4.4.2. (3*R,6*S**)-6-(Azidomethyl)-3-hydroxy-3-methyl-6-phenyltetrahydro-2(1*H*)-pyridinone 16.** To a stirred solution of 108 mg **10** in 1 mL dry DMF and 2 mL dry THF was added 35 mg sodium azide (1.1 equiv.). The reaction mixture was heated at 80°C (oil bath temperature) for 7 days, then 5 mL saturated ammonium chloride aqueous solution and 5 mL water were added. The aqueous layer was extracted with 3×10 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product which was purified by chromatography (5% MeOH/CH_2Cl_2). Yield: 102 mg, 75%; white powder; IR (KBr) cm^{-1}: 3334, 3279 (OH, NH); ^1H NMR (DMSO-d_6): 1.37 (s, 3H, CH_3), 1.61 (td, 1H, ^2J 14 Hz, ^3Jaa=12.0 Hz, ^3Jae=3.2 Hz, H-4ax), 1.93 (ddd, 1H, ^2J=14.0 Hz, ^3Jee=7.5 Hz, ^3Jee=3.2 Hz, H-4eq), 2.04 (ddd, 1H, ^2J=14.0 Hz, ^3Jee=7.5 Hz, ^3Jea=3.2 Hz, H-5eq), 2.23 (ddd, 1H, ^2J=14.0 Hz, ^3Jaa=12.0 Hz, ^3Jae=3.2 Hz, H-5ax), 3.17 (s, 1H, OH), 3.62, 3.88 (2×d, 2H, ^2J=12.2 Hz, CH_2N_3), 6.51 (s, 1H, HNCO), 7.33–7.43 (m, 5H, Ph-H); ^{13}C NMR (DMSO-d_6): 27.1 (CH_3), 30.7, 31.2 (C-5, C-4), 61.4 (CH_2N_3), 62.1 (C-6), 69.7 (C-3), 125.3 (C-*ortho*), 128.0 (C-*para*), 129.0 (C-*meta*), 141.9 (C-*ipso*), 175.8 (CONH); *m/z* (%): 260 (1, M^+), 204 (100, $M^+-CH_2N_3$), 186 (38, $M^+-CH_2N_3-H_2O$), 176 (53, $M^+-CH_2N_3-CO$); exact mass for $C_{12}H_{14}NO_2$ ($M^+-CH_2N_3$): 204.1026; found: 204.1028.

4.4.3. (3*R,6*S**)-3-Hydroxy-3-methyl-6-phenyl-6-(piperidinomethyl)tetrahydro-2(1*H*)-pyridinone 17.** To a stirred solution of 0.4 mL piperidine (4 equiv.) in 8 mL dry THF was added 217 mg **10** (1 equiv.) in 2 mL dry THF. The reaction mixture was heated at reflux temperature for 3 days, then the solvent was evaporated. The residue was subjected to column chromatography (Et_3N/MeOH/EtOAc 2:8:90) followed by crystallisation (dichloromethane/hexane). Yield: 250 mg, 83%; white powder; IR (KBr) cm^{-1}: 3358 (OH), 1649 (CON); ^1H NMR ($CDCl_3$): 1.31 (s, 3H, CH_3), 1.25–1.36 (m, 6H), 1.50 (m, 1H, ~J=31.0 Hz), 1.81 (m, 1H), 1.99–2.05 (m, 4H), 2.17 (m, 2H), 2.62, 2.86 (2×d, 2H, 2J=13.5 Hz, CH_2N), 3.40 (br.s, 1H, OH), 7.09 (br.s, 1H, HNCO), 7.23–7.33 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): 27.1 (CH_3), 23.7, 26.0, 31.4, 32.7 (5×CH_2), 56.3, 70.1 (3×CH_2N), 60.7 (C-6), 70.0 (C-3), 125.4 (C-*ortho*), 126.8 (C-*para*), 128.4 (C-*meta*), 144.6 (C-*ipso*), 175.5 (CONH); *m/z* (%): 303 (17, MH^+), 98 (100, $^+CH_2N(CH_2)_5$; exact mass for $C_{18}H_{28}N_2O_2$ (M^+): 302.1994; found: 302.1991.

4.4.4. (3*R,6*S**)-6-[(Butylamino)methyl]-3-hydroxy-3-methyl-6-phenyl-2(1*H*)-pyridinone 18.** Compound **18** was observed as a side product generated along with main product **11d**. Yield: 10%, oil; ^1H NMR ($CDCl_3$, 50°C): 0.82 (t, 3H, CH_3-nBu), 1.26–1.50 (m, 4H, $CH_3CH_2CH_2$), 1.31 (s, 3H, CH_3), 1.80 (m, 2H, H-4 or H-5), 2.00 (m, 1H, H-4 or H-5), 2.15 (m, 1H, H-4 or H-5), 2.45 (t, 2H, $CH_3CH_2CH_2$-CH_2NH), 2.48 (d, 1H, ^2J=13.5 Hz, CH_2NH), 2.70 (d, 1H, ^2J=13.5 Hz, CH_2NH), 3.00–3.20 (br.s, 2H, OH and NH), 7.10 (br.s, 1H, HNCO), 7.20–7.40 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, 45°C): 13.6 (CH_3-nBu), 19.9 (CH_2-nBu), 26.9 (CH_3), 31.5 (C-4 or C-5), 31.6 (C-4 or C-5), 38.0 (CH_2-nBu), 49.4 (CH_2CH_2N), 60.2 (CH_2NHnBu), 61.6 (C-6), 69.8 (C-3), 125.6, 125.7, 128.6 (Ph-C), 143.2 (C-*ipso*), 175.3 (CONH).

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