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# X=Y–ZH systems as potential 1,3-dipoles. Part 55: Cascade 1,3-azaprotio cyclotransfer–cycloaddition reactions between ketoximes and divinyl ketone

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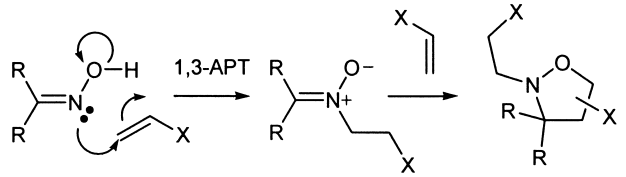
**Abstract**—The cascade 1,3-azaprotio cyclotransfer–1,3-dipolar cycloaddition reaction between ketoximes and divinyl ketone [or its equivalent bis(2-chloroethyl) ketone] affords high yields of substituted 1-aza-7-oxabicyclo[3.2.1]octan-4-ones and 1-aza-8-oxabicyclo-[3.2.1]octan-4-ones where the cycloaddition regioselectivity is controlled by a judicious choice of experimental conditions. The N–O bonds in the products are reductively cleaved to form piperidones and perhydroazepinones and the ketone moiety undergoes stereoselective sodium cyanoborohydride reduction to afford anti-1-aza-7-oxa-4-hydroxybicyclo[3.2.1]octanes and *anti*-1-aza-8-oxa-4-hydroxybicyclo-[3.2.1]octanes. 

The 1,3-azaprotio cyclotransfer reaction (1,3-APT) between an oxime and an alkene results in the formation of a nitrone (Scheme 1).[1] The resulting nitrone can undergo a 1,3-dipolar cycloaddition reaction (1,3-DC) with a second molecule of alkene to generate an isoxazolidine.[2] Nitrone cycloadditions have attracted much attention since they often proceed with a high degree of regio- and stereoselectivity, establishing multiple stereocentres in a single step and have been used to access the frameworks of a range of natural products.[2–4] Interfacing 1,3-APT with nitrone cycloaddition chemistry presents the opportunity for a potentially flexible route to complex heterocycles. We have pursued the development of such cascade 1,3-azaprotio cyclotransfer–cycloaddition reactions during the last decade.[5a–e] Such processes can be categorised into four distinct synthetic variants, depending on the intra- or intermolecular nature of each step (Table 1).[1]




**Scheme 1.**

**Table 1**. Synthetic variants of cascade 1,3-APT-cycloaddition reactions[1]

| Class | 1,3-APT | 1,3-DC |
|---|---|---|
| 1 | Intermolecular | Intermolecular |
| 2 | Intermolecular | Intramolecular |
| 3 | Intramolecular | Intermolecular |
| 4 | Intramolecular | Intramolecular |

The reaction between ketoximes **1** and divinyl ketone **2** represents a Class 2a process where both the azaprotiophile (nitrone generating functionality) and dipolarophile are located in the same bifunctional molecule (Scheme 2).[5d] We recently reported that such processes lead to the formation of 1-aza-7-oxabicyclo[3.2.1]octan-4-ones **3** and 1-aza-8-oxabicyclo[3.2.1.]octan-4-ones **4** where control of the cascade outcome is achieved by a judicious choice of experimental conditions.[6] We now present a full report of our findings.

Symmetrical ketoxime **1** and divinyl ketone **2** may, in principle, react in a number of ways including the synthetically less useful *O*-Michael addition. The desired 1,3-APT process leads to the formation of a nitrone that can undergo intramolecular cycloaddition via two different pre-transition state conformers where the enone moiety is in either the *s-cis* (**A**) or *s-trans* (**B**) conformation leading to **3** and **4**, respectively (Scheme 2).

The first task in developing the cascade protocol was to circumvent the thermal instability of divinyl ketone. Initial experiments revealed the cascade process to be low yielding

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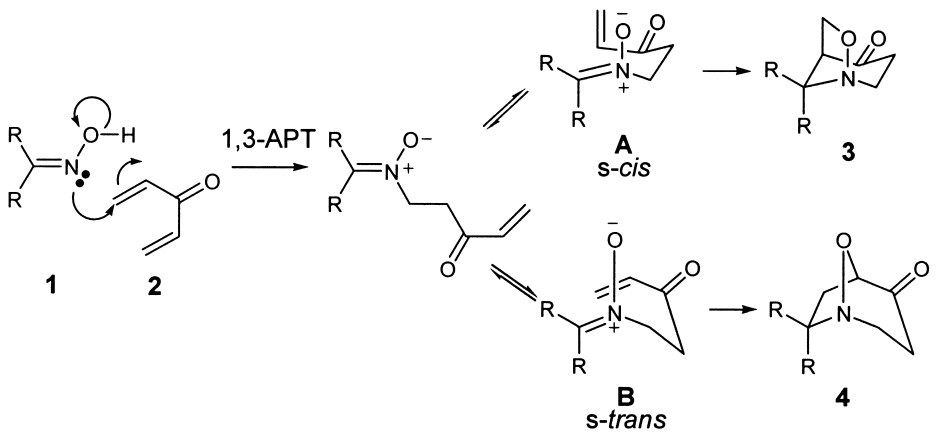
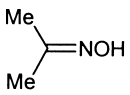
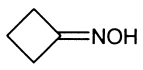
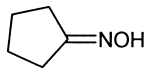
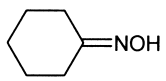
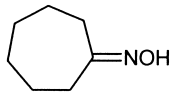



**Scheme 2.**

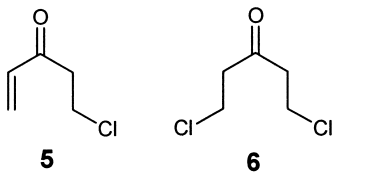
due to polymerisation of divinyl ketone proceeding more rapidly than 1,3-APT. Generating divinyl ketone[7] in situ from 2-chloroethyl vinyl ketone[8] (**5**) or bis(2-choroethyl) ketone[9] (**6**) was investigated since alternative strategies, such as generating the nitrone as a distinct step or using excess oxime, were unrewarding. The most promising results were obtained by employing base mediated dehydrohalogenation of **6** as the source of divinyl ketone, since **5** was found to spontaneously and rapidly dehydrohalogenate under thermal conditions, resulting in polymerisation. Anhydrous potassium carbonate was selected as the most favourable base for the dehydrohalogenation; anhydrous sodium carbonate resulted in sluggish dehydrohalogenation (ca. 10% conversion of **6** after 48 h in acetonitrile at reflux) while DBU initiated the process too rapidly. Employing preformed divinyl ketone was possible when the solvent: oxime ratio was increased from 2:1 mL mmol$^{-1}$ (used in our analogous divinyl sulfone cascades[5d]) to 20:1 mL mmol$^{-1}$ and resulted in the desired 1,3-APT–1,3-DC cascade. Accordingly, two general procedures have been adopted for the preparation of **3** and **4**. Mode 1 employs potassium carbonate mediated dehydrohalogenation of **6** whereas Mode 2 uses preformed divinyl ketone under high dilution conditions. Employing Mode 1, oximes **1a–e** afforded high yields (up to 85%) of the corresponding isoxazolidinones (Table 2). In most cases, aside from cyclopentanone oxime **1c**, type **4** isomers were the major products (Fig. 1).

**Table 2**. Mode 1 reactions of symmetrical ketoximes

| Oxime | Ratio **3**/**4**[a] | Yield (%)[b] |
|---|---|---|
|  **1a** | 1:4 | 45 |
|  **1b** | 1:3 | 74 |
|  **1c** | 1:1 | 85 |
|  **1d** | 1:4 | 67 |
|  **1e** | 1:4 | 62 |

Reaction conditions: Mode 1: bis(2-chloroethyl ketone) (1.2 mol equiv.), $K_2CO_3$ (2 mol equiv.), acetonitrile (5 mL mmol$^{-1}$), reflux, 20 h.
[a] Measured from the $^1$H NMR spectra of the crude products.
[b] Combined yield isolated after column chromatography.

The $^1$H NMR of **3** and **4** are distinguished by diagnostic ABX systems in their respective spectra. In **3** (Fig. 2) H6′



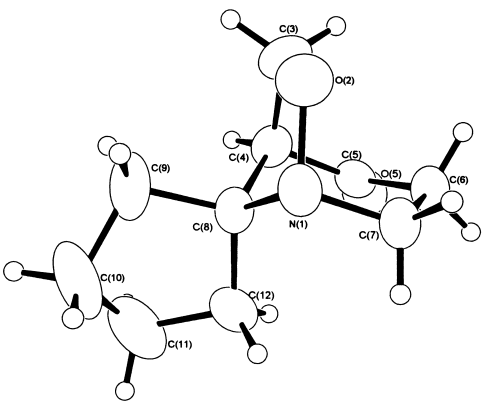




**Figure 1.** X-Ray crystal structure of **3c**.

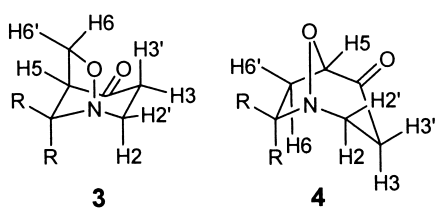



**Figure 2.**

**Table 3**. Effect of solvent on regioselectivity of reaction between cyclohexanone oxime **1d** and **2**

| Entry | Solvent | Dielectric constant $\varepsilon$[10] | Time (h) | Ratio **3d/4d**[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Cyclohexane | 2.02 | 48[c] | 1:1 | 68 |
| 2 | Toluene | 2.38 | 48[d] | 1:2 | 61 |
| 3 | THF | 7.58 | 72[d] | 1:4 | 70 |
| 4 | Acetonitrile | | 20[d] | 1:4 | 67 |
| 5 | HMPA | 29.60 | 48[c] | 1:9 | 30 |
| 6 | Methanol | 32.70 | 48[c] | 1:4 | 69 |
| 7 | DMF | 37.00 | 48[c] | 1:3 | 81 |
| 8 | Sulfolan | 43.30 | 48[c] | 1:4 | 73 |
| 9 | DMSO | 46.68 | 48[c] | 1:8 | 89 |
| 10 | Propylene carbonate | 65.10 | 48[c] | 1:8 | 45 |
| 11 | *N*-Methyl acetamide | 191.3 | 48[c] | 1:2 | 78 |

[a] Measured from the $^1$H NMR spectra of the crude products.
[b] Combined yield isolated after column chromatography.
[c] Reaction conditions: Mode 2: divinyl ketone (1.1 mol equiv.), solvent (20 mL mmol$^{-1}$), reflux.
[d] Reaction conditions: Mode 1: bis(2-chloroethyl) ketone (1.2 mol equiv.), $K_2CO_3$ (2 mol equiv.), solvent (5 mL mmol$^{-1}$), reflux.

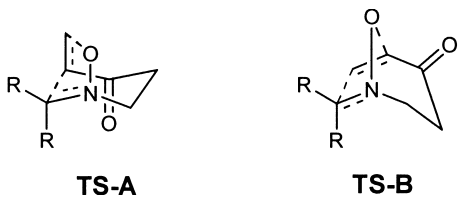
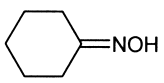
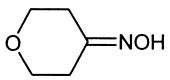
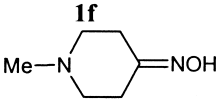
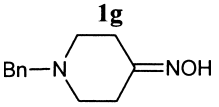
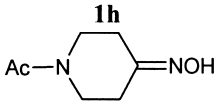
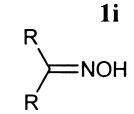



**Figure 3.**

and H6 are the most deshielded protons. The signal for H6 appears at $\delta$ 4.1–4.2 as a doublet ($J$=8.0–8.3 Hz) (dihedral angle H5–H6≈90°) and that for H6′ appears at $\delta$ 4.0–4.1 as a double doublet ($J$=8.0–8.3, 5.1–5.4 Hz), while H5 occurs as a doublet at $\delta$ 2.8–3.0. In **4**, H5 is the most deshielded proton and appears as a doublet ($J$=8.3–8.7 Hz) at $\delta$ 4.35–4.44 (dihedral angle H5–H6≈90°). In those isomers the signals for H6 and H6′ are frequently obscured due to overlap with other proton signals.

**Table 4**. Effect of remote heteroatom on regioselectivity

| Oxime | Dipole moment (De)[a] | p$K_a$[a] | Mode[b] | Time (h) | Ratio **3/4**[c] | Yield (%)[d] |
|---|---|---|---|---|---|---|
|  **1d** | 0.875 | 11.81 | 1 | 20 | 1:4 | 67 |
|  **1f** | 0.729 | 12.79 | 1 | 20 | 1:7 | 55 |
|  **1g** | 0.943 | 13.14 | 2 | 48 | 1:15 | 65 |
|  **1h** | 0.762 | 13.13 | 2 | 48 | 1:10 | 77 |
|  **1i** | 3.137 | 12.89 | 2 | 48 | 1:7 | 76 |
|  R=2-pyridyl **1j** | 2.571 | 7.91 | 2 | 48 | 1:>20 | 46 |

[a] Calculated using the ACD/I-lab service, version 4.5.
[b] Reaction conditions: Mode 1: bis(2-chloroethyl ketone) (1.2 mol equiv.), $K_2CO_3$ (2 mol equiv.), acetonitrile (5 mL mmol$^{-1}$), reflux; Mode 2: divinyl ketone (1.1 mol equiv.), acetonitrile (20 mL mmol$^{-1}$), reflux.
[c] Measured from the $^1$H NMR spectra of the crude products.
[d] Combined yield isolated after column chromatography.

**Table 5**. Lewis acid promoted reactions of **1d**

| Entry | Lewis acid | Temperature (°C) | Time (h) | Ratio **3/4**[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | None | Reflux | 72 | 20:80 | 70 |
| 2 | $ZnCl_2$ | Reflux | 48 | 90:11 | 30[c] |
| 3 | $ZnBr_2$ | Reflux | 48 | 95:5 | 48 |
| 4 | $ZnI_2$ | Reflux | 48 | 92:8 | 55[c] |
| 5 | $TiO_2$ | Reflux | 24 | 79:21 | – |
| 6 | ZnO | Reflux | 24 | 82:18 | – |
| 7 | $MgBr_2$ | Rt | 24 | 79:21 | – |

Reaction conditions: Mode 1: bis(2-chloroethyl) ketone (1.2 mol equiv.), $K_2CO_3$ (2 mol equiv.), Lewis acid (1.0 mol equiv.), THF (5 mL $mmol^{-1}$), reflux.

[a] Measured from the $^1H$ NMR spectra of the crude products.

[b] Combined yield isolated after column chromatography.

[c] Estimated yield after column chromatography, impurity present in isolated material.

We next sought to explore the effect of solvent polarity on the regiochemical outcome of the process using the reaction between cyclohexanone oxime **1d** and divinyl ketone as a model (Table 3). Polar solvents promote the formation of **4**: the ratio of **3d/4d** is 1:8 when the reaction is performed in DMSO (entry 9) compared with 1:1 in cyclohexane (entry 1). Though HMPA (entry 5) and propylene carbonate (entry 10) match the levels of regioselectivity obtained with DMSO, the products were obtained in disappointing yield. Inspection of molecular models revealed that the dipole moment of **TS-B** (Fig. 3) leading to **4**, ought to be greater than that of **TS-A** leading to **3**, on the basis that the opposing dipoles in **TS-A** would cancel each other out to some extent, leading to a lower dipole moment than that obtained in **TS-B**. Mopac AM1 calculations support these views with a predicted dipole moment of 2.55 De for **TS-A** and 5.52 De for **TS-B**[†].

The presence of a β-heteroatom in the ketoxime favours formation of **4** (Table 4). Oximes **1f–j** afford significantly higher degrees of regioselectivity than oxime **1d**. The combined products were obtained in good yields (up to 77%). Oximes containing a basic nitrogen atom (**1g–i**) were reacted using Mode 2 conditions since the formation of an ammonium salt was found to inhibit the reaction of **1g** under Mode 1 conditions. The regioselectivity of the cascades involving aliphatic ketoximes (**1d–i**) follows the order of

**Table 6**. $ZnBr_2$ promoted Mode 1 and Mode 2 reactions

| Entry | Oxime | Mode | Time (h) | Ratio **3/4**[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1c** | 1[c] | 18 | 95:5 | 84 |
| 2 | **1d** | 1[c] | 18 | 95:5 | 61 |
| 3 | **1e** | 1[c] | 24 | 61:39 | 87 |
| 4 | **1c** | 2 | 6 | >95:5 | 95 |
| 5 | **1d** | 2 | 6 | 97:3 | 97 |
| 6 | **1e** | 2 | 16 | 91:9 | 96 |

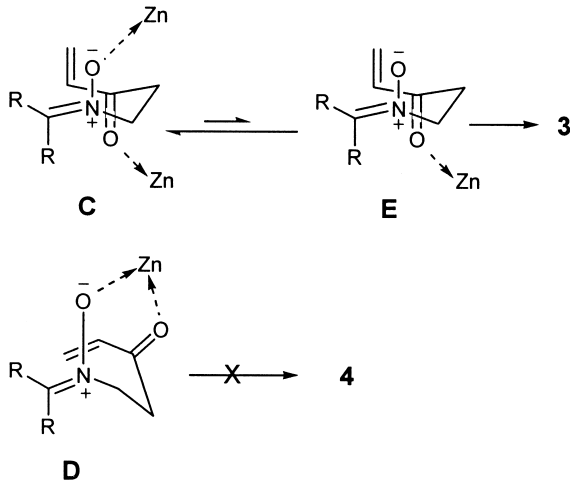
Reaction conditions: Mode 1: bis(2-chloroethyl) ketone (1.2 mol equiv.), $K_2CO_3$ (2 mol equiv.), $ZnBr_2$ (1.0 mol equiv.), THF (5 mL $mmol^{-1}$), reflux; Mode 2: divinyl ketone (1.1 mol equiv.), $ZnBr_2$ (1.5 mol equiv.), THF (40 mL $mmol^{-1}$), reflux.

[a] Measured from the $^1H$ NMR spectra of the crude products.

[b] Combined yield isolated after column chromatography.

[c] High purity bis(2-chloroethyl) ketone employed.

[†] Studies on the cycloreversion of **3** and **4** indicate that the products arise from a kinetically controlled process.




**Scheme 3.**

the calculated p$K_a$s of the oxime OH group (Table 4) but show no correlation with the calculated dipole moment of the product. Di(2-pyridyl)oxime **1j** does not follow the former trend.

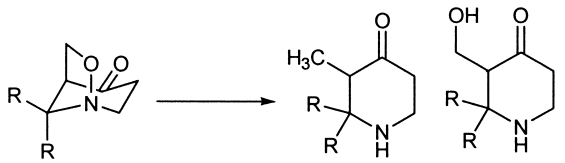
We then investigated the effect of Lewis acids on the Mode 1 process of oxime **1d**. Zinc, titanium and magnesium salts bias the regioselectivity of the reaction towards **3d** (Table 5). However, $TiO_2$ (entry 5), ZnO (entry 6) and $MgBr_2$ (entry 7) resulted in decomposition. Owing to the high degree of regioselectivity and promising yield, $ZnBr_2$ (entry 3) was selected as the Lewis acid of choice. By using high purity bis(2-chloroethyl) ketone the yield of **3d** was increased from 48% (Table 5, entry 3) to 61% (Table 6, entry 2). Similar development of a Mode 2-$ZnBr_2$ catalysed process indicated that high dilution conditions were necessary (40 mL solvent:1 mmol oxime) and that 1.5 equiv. of Lewis acid were required. Mode 1 and Mode 2-$ZnBr_2$-catalysed protocols were then evaluated for a range of oximes (Table 6). A difference in regioselectivity between Mode 1 and Mode 2 is evident and is exemplified by the case of **1e** (Table 6, entries 3 and 6). The formation of $H_2ZnX_4$ from zinc bromide and HCl liberated in the dehydrohalogenation step may promote competition from a Brønsted acid catalysed pathway.

The precise role of the zinc salt is a matter of conjecture. Zinc halides form 2:1 complexes with nitrones[11] [(nitrone)$_2$ $ZnX_2$] and there is also strong evidence for many organozinc species existing as dimeric or polymeric species in solution (e.g. Reformatsky reagents[12]). Nitrones are stronger bases than aldehydes or ketones and this property has been a major impediment to the development of Lewis acid catalysed intermolecular nitrone cycloadditions to carbonyl containing dipolarophiles, dictating that dipolarophiles with chelate type auxiliaries are employed.[13] Pre-transition state conformer **B** (Scheme 2) has favourable geometry for chelation of both oxygen moieties as in **D** (Scheme 3) and such chelation would be expected to suppress cycloaddition. Similar chelation in pre-transition state conformer **A** cannot occur although coordination of two Zn(II) ions as in **C** (Scheme 3) is possible. Equilibration of **C** with **E** would provide the necessary activation of the dipolarophile. This particular cycloaddition is expected to

**Table 7**. Reductions of type **3** isoxazolidinones

| Entry | Isoxazolidinone | Temperature (°C) | Time (h) | Ratio **5/6**[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **3c** | 65 | 3 | >20:1 | 61 |
| 2 | **3c** | 0–5 | 1.1 | 1:>20 | 98 |
| 3 | **3a** | 0–5 | 1.5 | 1:>20 | 47 |
| 4 | **3f** | 0–5 | 2 | 1:>20 | 86 |

Reaction conditions: zinc dust (<10 micron), acetic acid.
[a] Measured from the $^1$H NMR spectra of the crude products.
[b] Yield isolated after column chromatography.

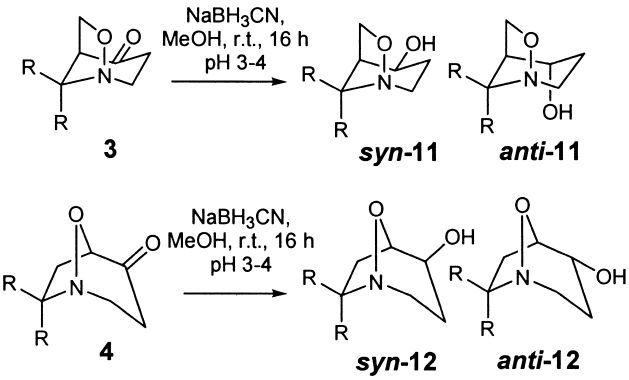



**a**. R,R=$CH_3$; **c**. R,R=$(CH_2)_4$;
**f**. R,R = 4-tetrahydropyran

**Scheme 4.**

be $HOMO_{nitrone}$–$LUMO_{alkene}$ controlled and this type of interaction is predicted to result in bond formation between the oxygen of the nitrone and the terminal alkene carbon as in **A**, ultimately leading to **3**.[14] Coordination of Zn(II) to the carbonyl moiety (as in **E**) enhances the electrophilicity of the β-carbon atom, leading to preferential bond formation between the oxygen atom and the β-carbon atom.[15]

With selective processes for the formation of **3** and **4** to hand, we explored the reductive cleavage of the N–O bond to unlock functionalised piperidone and azepinone ring systems respectively. Attempts to effect the reductive cleavage by catalytic hydrogenation[16] resulted in sluggish reactions whereas the use of zinc–acetic acid[17] proved more successful. Treatment of **3c** with Zn/HOAc at 65°C resulted in over-reduction to **5** (Table 7, entry 1). Lowering the reaction temperature resulted in formation of the 1,3-amino alcohol **6c** in quantitative yield (Table 7, entry 2). This




**c**. R,R = $(CH_2)_4$; **d**. R,R = $(CH_2)_5$;
**e**. R,R = $(CH_2)_6$ **f**. R,R = 4-tetrahydropyran

**Scheme 7.**

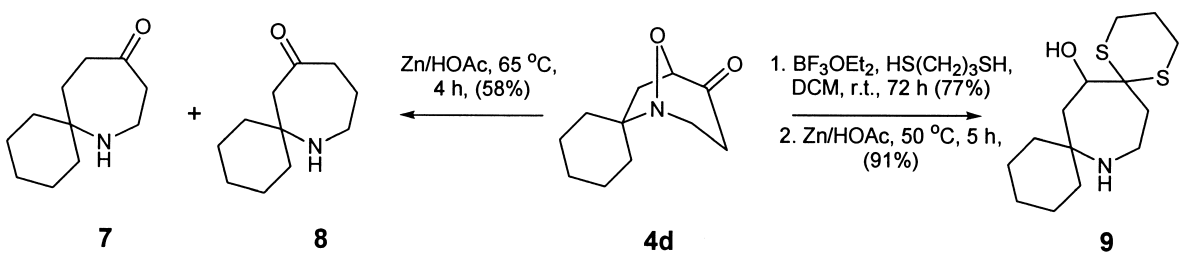
**Table 8**. $NaBH_3CN$ mediated reduction of **3** and **4**

| Entry | Isoxazolidinone | Time (h) | Product | *syn*/*anti*-Ratio[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **3c** | 2 | **11c** | 1:>20 | 88 |
| 2 | **3d** | 3 | **11d** | 1:7 | 94 |
| 3 | **3f** | 3 | **11f** | 1:15 | 62 |
| 4[c] | **4d** | 5 | **12d** | 1:3 | 89 |
| 5 | **4d** | 4 | **12d** | 1:10 | 79 |
| 6 | **4e** | 3.5 | **12e** | 1:9 | 74 |
| 7 | **4f** | 4 | **12f** | 1:12 | 58 |

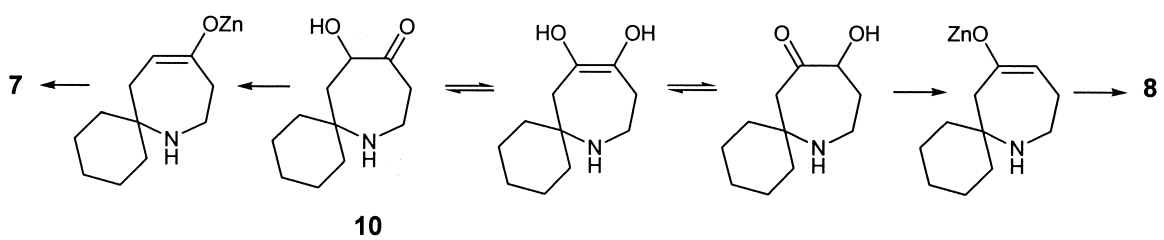
Reaction conditions, $NaBH_3CN$ (6 mol equiv.), pH 3–4, methanol, room temperature.
[a] Measured from the $^1$H NMR spectra of the crude products.
[b] Combined yield isolated after column chromatography.
[c] $NaBH_4$ (6 mol equiv.) in isopropanol used as the reducing agent.

protocol also proved effective for the reduction of **3a** and **3f** (Scheme 4).

Reduction of **4** with Zn/HOAc at 65°C proved more problematic resulting in the formation of a 1:1 mixture of regioisomeric perhydroazepinones **7** and **8** (Scheme 5). Transposition of the ketone and loss of hydroxy functionality presumably occurs via acid catalysed formation of an enediol intermediate from the intermediate amino alcohol




**Scheme 5.**




**Scheme 6.**

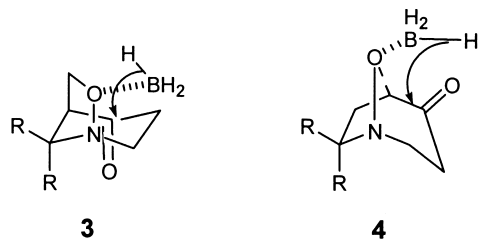



**Figure 4.**

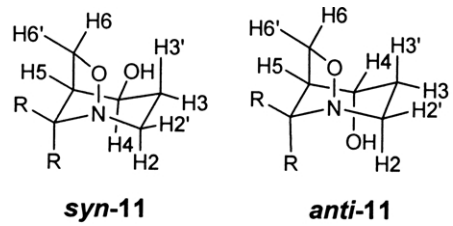



**Figure 5.**

**10** (Scheme 6). Alternative conditions were investigated, including lowering the reaction temperature and using Zn/$NH_4Cl$ but none were satisfactory in terms of yield or regioselectivity. However, dithiane protection of the ketone prior to reduction of **4d** afforded **9** in 70% overall yield.

Stereoselective reduction of the ketone moiety favours the *anti*-isomer in both **3** and **4** using sodium cyanoborohydride in methanol at pH 3–4 (Scheme 7, Table 8). Reduction using sodium borohydride afforded much lower degrees of *anti* selectivity (entry 4). The *anti*/*syn* ratios vary from 7:1 to >20:1 with sodium cyanoborohydride. The *anti* selectivity may be a result of coordination of borane (generated from $NaBH_3CN$ and HCl) to the oxygen bridge atom (Fig. 4) and, in the case of **3** may involve the boat conformer of cyclohexanone moiety (Fig. 5).

The stereochemistry of *anti*-**11c** (Fig. 6) and *anti*-**12d** (Fig. 7) was established by X-ray crystallography. In the $^1H$ NMR spectrum of *anti*-**11d** the H4 signal appears as a double doublet at $\delta$ 4.14 with $J$=6.1, 4.0 Hz ($J_{H4-H5}$ and $J_{H4-H3'/H3}$) whereas in the *syn*-isomer this signal is predicted to contain one large *trans* diaxial coupling constant 9–12 Hz ($J_{H4-H3'}$) and two smaller ones ($J$=2–5 Hz, $J_{H4-H3}$ and $J_{H4-H5}$). In *anti*-**12d** the signal of H4 appears as at $\delta$ 3.99 as a doublet of doublets of doublets ($J_{H4-H3}$ ca. 10.2 Hz, $J_{H4-H3'}/J_{H4-H5}$ ca. 4.0 and 6.2 Hz), consistent with the *anti* product whereas in *syn*-**12** H4 is predicted to consist of three small coupling constants. Insufficient amounts of *syn*-isomers were obtained for NMR studies.

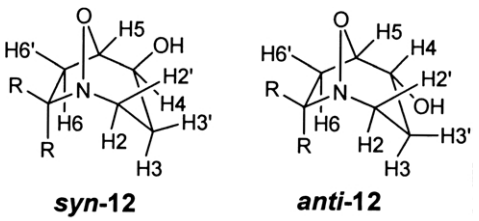



**Figure 5.**

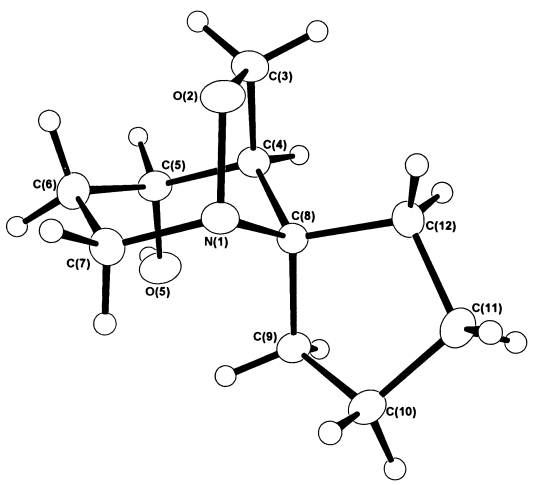



**Figure 6.** X-Ray crystal structure of *anti*-**11c**.

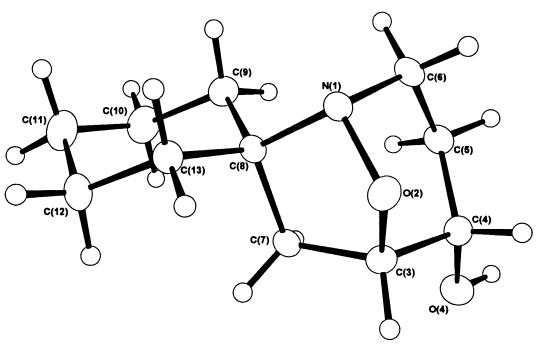



**Figure 7.** X-Ray crystal structure of *anti*-**12d**.

In summary, the Class 2a cascade 1,3-APT–1,3-DC process between divinyl ketone and ketoximes affords high yields of the bridged bicyclic isoxazolidinones that can be reductively cleaved at the N–O bond to form piperidones and perhydroazepinones or stereoselectively reduced at the carbonyl group to form *anti*-alcohols as the major products.

## 1. Experimental

Nuclear magnetic resonance spectra were determined at 300 MHz on a QE 300 instrument except where higher field (400 MHz on Bucker AM400 and 500 MHz on Brucker DRX500) is specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, brs=broad singlet. Infra red spectra were recorded in solution (dichloromethane) on a PU9706 IR spectrophotometer. Mass spectra were recorded at 70 eV on a VG Autospec mass spectrometer. X-Ray analyses were performed on a Stoe STADI 4-circle machine or a Nonius Kappa CCD area-detector diffractometer. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Petroleum ether refers to that fraction with bp

40–60°C. Melting points were obtained using a Koffler hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carbo-Erba Model 1106 instrument. Oximes **1a**, **1c** and **1d** were obtained from commercial sources. Oximes **1b**, **1e**, **1f**–**i** were prepared according to literature methods.[18–22] Divinyl ketone,[7] 2-chloroethyl vinyl ketone[8] and bis(2-choroethyl) ketone[9] were prepared according to literature methods.

In **3** and **4** the protons are labelled as depicted in Fig. 2, whilst in **11** and **12** the protons are labelled as depicted in Fig. 5.

### 1.1. General procedure for the preparation of ketoximes

The appropriate ketone was added to a solution of hydroxylamine hydrochloride and sodium acetate in 2:1 v/v acetonitrile–water. The resulting mixture was stirred at ambient temperature for 18 h. The mixture was extracted with chloroform, the combined organic extracts were washed with water, dried ($MgSO_4$), filtered, the filtrate concentrated in vacuo and the residue crystallised from an appropriate solvent.

### 1.2. General procedures for 1,3-APT–1,3-DC cascades

*Mode 1*. Anhydrous potassium carbonate (0.55 g, 4.0 mmol) was added to a stirred solution of bis(2-chloroethyl) ketone (0.37 g, 2.4 mmol) and the appropriate oxime (2.0 mmol) in dry solvent under a nitrogen atmosphere. The resulting mixture was stirred and heated at reflux for 16–72 h. After cooling the reaction mixture was filtered, the residue washed with a copious amount of dichloromethane and the filtrate concentrated in vacuo. The residue was purified by flash chromatography.

*Mode 2*. A solution of divinyl ketone (99 μL, 1.1 mmol) and the appropriate oxime (1 mmol) in dry solvent (20 mL) was stirred and heated at reflux for 48 h. After cooling the mixture was concentrated in vacuo and the residue purified by column chromatography.

### 1.3. General procedure for $ZnBr_2$ catalysed tandem 1,3-APT–1,3-DC cascades

*Mode 1*. Anhydrous potassium carbonate (0.55 g, 4.0 mmol) was added to a stirred solution of bis(2-chloroethyl) ketone (0.37 g, 2.4 mmol), the appropriate oxime (2.0 mmol) and anhydrous zinc bromide (0.45 g, 2.0 mmol) in dry tetrahydrofuran (15 mL) under a nitrogen atmosphere. The resulting mixture was stirred and heated at reflux for 18–24 h. After cooling the reaction mixture was quenched by the addition of 0.02 M sodium bicarbonate (100 mL), filtered and extracted with dichloromethane (3×100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography.

*Mode 2*. A solution of divinyl ketone (134 μL, 1.5 mmol), oxime (1 mmol) and anhydrous zinc bromide (0.35 g, 1.5 mmol) in dry tetrahydrofuran (40 mL) was heated at reflux with stirring under a nitrogen atmosphere for 6–96 h. After cooling the mixture was quenched by the addition of 0.02 M sodium bicarbonate (100 mL) and extracted with dichloromethane (3×100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography. Yields for $ZnBr_2$ catalysed Mode 1 and Mode 2 processes are reported in Table 6.

**1.3.1. 8,8-Dimethyl-1-aza-7-oxa-4-oxobicyclo[3.2.1]octane (3a) and 7,7-dimethyl-1-aza-8-oxa-4-oxobicyclo[3.2.1]-octane (4a).** Acetone oxime (**1a**) and bis(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 20 h. Subsequent work up afforded the crude product as a pale brown amorphous solid, comprising a 1:4 mixture of **3a** and **4a**. Flash chromatography, eluting with 2:1 v/v diethyl ether–ethyl acetate afforded **3a** (0.029 g, 9%) and **4a** (0.11 g, 36%).

Compound **3a**. Obtained as colourless plates from hexane, mp 91–93°C. Found C, 61.75; H, 8.55; N, 8.85; $C_8H_{13}NO_2$ requires C, 61.9; H, 8.45; N, 9.05%; $\delta_H$ (400 MHz) 4.10 (d, 1H, $J$=8.1 Hz, H6), 4.06 (dd, 1H, $J$=8.1, 5.2 Hz, H6′), 3.56 (dd, 1H, $J$=15.0, 10.1 Hz, H2′), 3.22 (ddd, 1H, $J$=15.0, 9.7, 6.9 Hz, H2), 2.80 (d, 1H, $J$=5.2 Hz, H5), 2.58 (dt, 1H, $J$=16.9, 9.9 Hz, H3′), 2.17 (ddd, 1H, $J$=16.9, 6.9 Hz, H3), 1.25 (s, 3H, $CH_3$) and 1.20 (s, 3H, $CH_3$); $m/z$ (%) 155 ($M^+$, 18), 138 (19), 98 (15), 83 (61), 73 (46), 55 (100) and 41 (45); $\nu$ (C=O) 1720 $cm^{-1}$.

Compound **4a**. Obtained as colourless plates from diethyl ether, mp 62–64°C. Found C, 62.1; H, 8.55; N, 8.95; $C_8H_{13}NO_2$ requires C, 61.9; H, 8.45%; N, 9.05%; $\delta_H$ (400 MHz) 4.34 (d, 1H, $J$=8.7 Hz, H5), 3.63 (ddd, 1H, $J$=14.7, 10.6, 6.4 Hz, H2′), 3.46 (dd, 1H, $J$=14.7, 8.6 Hz, H2), 2.52–2.43 (m, 1H, H3), 2.39 (dd, 1H, $J$=13.0, 8.7 Hz, H6′), 2.21 (dd, 1H, $J$=17.0, 6.4 Hz, H3′), 1.88 (dd, 1H, $J$=13.0, 2.0 Hz, H6), 1.39 (s, 3H, $CH_3$) and 1.30 (s, 3H, $CH_3$); $m/z$ (%) 156 (M+1, 10), 155 ($M^+$, 45), 138 (17), 112 (10), 98 (14), 83 (53), 73 (48), 70 (65), 55 (100) and 41 (52); $\nu$ (C=O) 1730 $cm^{-1}$.

**1.3.2. 8,8-Cyclobutyl-1-aza-7-oxa-4-oxobicyclo[3.2.1]-octane (3b) and 7,7-cyclobutyl-1-aza-8-oxa-4-oxobicyclo-[3.2.1]octane (4b).** Cyclobutanone oxime (**1b**) and bis-(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 20 h. Subsequent work up afforded the crude product as a brown gum, comprising a 1:3 mixture of **3b** and **4b**. Flash chromatography, eluting with 2:1 v/v diethyl ether–ethyl acetate afforded partial separation in 74% combined yield.

Compound **3b**. Data were obtained as an enriched 4:1 mixture with **4b**. Found, C 64.7; H, 7.6; N, 8.65; $C_9H_{13}NO_2$ requires C 64.65; H, 7.85; N, 8.4%; $\delta_H$ (300 MHz) 4.15 (d, 1H, $J$=8.0 Hz, H6), 3.97 (dd, 1H, $J$=8.0, 5.1 Hz, H6′), 3.52 (dd, 1H, $J$=14.5, 9.5 Hz, H2′), 3.15–3.06 (m, 2H, H2 and H5), 2.61 (dt, 1H, $J$=16.1, 10.2 Hz, H3′) and 2.34–1.85 (m, 7H, H3 and 6×cyclobutyl-H); $m/z$ (%) 167 ($M^+$, 90), 150 (16), 139 (20), 124 (58), 85 (62), 69 (55), 55 (100) and 41 (81); $\nu$ (C=O) 1715 $cm^{-1}$.

Compound **4b**. Obtained as colourless oil. Found, C, 64.6; H, 8.0; N, 8.4; $C_9H_{13}NO_2$ requires C 64.65; H, 7.85; N, 8.4%; $\delta_H$ (300 MHz) 4.37 (d, 1H, $J$=8.4 Hz, H5), 3.63–3.53

(m, 2H, H2′ and H2), 2.83 (dd, 1H, *J*=13.3, 8.4 Hz, H6′), 2.50–2.23 (m, 6H, H3′, H3 and 4×cyclobutyl-H), 2.11–2.03 (m, 1H, cyclobutyl-H) and 1.95–1.84 (m, 2H, H6 and cyclobutyl-H); *m/z* (%) 167 ($M^+$, 4), 139 (31), 122 (34), 83 (27), 69 (100), 55 (39) and 41 (86); $\nu$ (C=O) 1730 $cm^{-1}$.

**1.3.3. 8,8-Cyclopentyl-1-aza-7-oxa-4-oxobicyclo[3.2.1]-octane (3c) and 7,7-cyclopentyl-1-aza-8-oxa-4-oxobicyclo-[3.2.1]octane (4c).** Cyclopentanone oxime (**1c**) and bis-(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 20 h. Subsequent work up afforded the crude product as a brown gum, comprising a 1:1 mixture of **3c** and **4c**. Flash chromatography, eluting with 3:1 v/v diethyl ether–ethyl acetate afforded **3c** (0.15 g, 42%) and **4c** (0.16 g, 43%).

Compound **3c**. Obtained as colourless needles from diethyl ether, mp 59–60°C. Found C, 66.35; H, 8.4; N, 7.65; $C_{10}H_{15}NO_2$ requires C, 66.25; H, 8.35; N, 7.75%; $\delta_H$ (300 MHz) 4.19 (d, 1H, *J*=8.1 Hz, H6), 4.01 (dd, 1H, *J*=8.1, 5.2 Hz, H6′), 3.59 (dd, 1H, *J*=14.8, 9.9 Hz, H2′), 3.24 (ddd, 1H, *J*=14.9, 10.0, 6.9 Hz, H2), 2.87 (d, 1H, *J*=5.2 Hz, H5), 2.62 (dt, 1H, *J*=16.8, 10.0 Hz, H3), 2.20 (dd, 1H, *J*=16.4, 6.9 Hz, H3′), 2.05–1.95 (m, 1H, cyclopentyl-H) and 1.86–1.55 (m, 7H, 7×cyclopentyl-H); *m/z* (%), 181 ($M^+$, 37), 127 (7), 112 (9), 99 (100), 83 (57), 67 (42), 55 (85) and 41 (42); $\nu$ (C=O) 1715 $cm^{-1}$.

Compound **4c**. Obtained as a colourless oil. Found, C, 66.2; H, 8.5; N, 7.45; $C_{10}H_{15}NO_2$ requires C, 66.25; H, 8.35; N, 7.75%; $\delta_H$ (300 MHz) 4.40 (d, 1H, *J*=8.7 Hz, H5), 3.68 (ddd, 1H, *J*=14.7, 10.8, 6.2 Hz, H2′), 3.46 (dd, 1H, *J*=14.7, 8.2 Hz, H2), 2.59–2.47 (m, 2H, H3 and H6′), 2.28 (dd, 1H, *J*=16.8, 6.2 Hz, H3′) and 2.06–1.60 (m, 9H, H6 and 8×cyclopentyl-H); *m/z* (%) 181 ($M^+$, 55), 110 (12), 99 (100), 83 (37), 67 (68), 55 (84) and 41 (55); $\nu$ (C=O) 1725 $cm^{-1}$.

**1.3.4. 8,8-Cyclohexyl-1-aza-7-oxa-4-oxobicyclo[3.2.1]-octane (3d) and 7,7-cyclohexyl-1-aza-8-oxa-4-oxobicyclo-[3.2.1]octane (4d).** Cyclohexanone oxime (**1d**) and bis-(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 20 h. The crude product was obtained as a brown gum, comprising a 1:4 mixture of **3d** and **4d**. Flash chromatography, eluting with diethyl ether, afforded **3d** (0.054 g, 13%) and **4d** (0.21 g, 54%).

Compound **3d**. Obtained as a colourless oil. Found C, 67.7; H, 8.55; N, 6.85; $C_{11}H_{17}NO_2$ requires C, 67.65; H, 8.8; N, 7.15%; $\delta_H$ (300 MHz) 4.12 (d, 1H, *J*=8.1 Hz, H6), 4.06 (dd, 1H, *J*=8.1, 5.2 Hz, H6′), 3.61 (dd, 1H, *J*=15.0, 10.1 Hz, H2′), 3.27 (ddd, 1H, *J*=15.0, 9.6, 6.9 Hz, H2), 2.99 (d, 1H, *J*=5.2 Hz, H5), 2.65 (dt, 1H, *J*=16.8, 9.6 Hz, H3′), 2.24 (dd, 1H, *J*=16.8, 6.9 Hz, H3) and 1.82–1.42 (m, 10H, 10×cyclohexyl-H); *m/z* (%) 196 (M+1, 7), 195 ($M^+$, 49), 178 (15), 138 (7), 124 (16), 113 (100), 83 (45), 67 (25), 55 (42) and 41 (29); $\nu$ (C=O) 1710 $cm^{-1}$.

Compound **4d**. Obtained as colourless needles from hexane, mp 84–86°C. Found C, 67.35; H, 9.0; N, 7.1; $C_{11}H_{17}NO_2$ requires C, 67.65; H, 8.8; N, 7.15%; $\delta_H$ (300 MHz) 4.36 (d, 1H, *J*=8.3 Hz, H5), 3.70 (ddd, 1H, *J*=14.8, 10.6, 6.4 Hz, H2′), 3.52 (dd, 1H, *J*=14.8, 8.7 Hz, H2), 2.55–2.41 (m, 2H, H3 and H6′), 2.28 (dd, 1H, *J*=16.9, 6.2 Hz, H3′) and 1.79–1.33 (m, 11H, H6 and 10×cyclohexyl-H); *m/z* (%) 196 (M+1, 10), 195 ($M^+$, 69), 178 (14), 152 (6), 138 (7), 124 (18), 113 (100), 81 (74), 55 (69) and 41 (51); $\nu$ (C=O) 1730 $cm^{-1}$.

**1.3.5. 8,8-Cycloheptyl-1-aza-7-oxa-4-oxobicyclo[3.2.1]-octane (3e) and 7,7-cycloheptyl-1-aza-8-oxa-4-oxobicyclo-[3.2.1]octane (4e).** Cyclohexanone oxime (**1d**) and bis-(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in toluene at reflux for 16 h. Subsequent work up afforded the crude product as a brown gum, comprising a 1:2 mixture of **3e** and **4e**. Flash chromatography, eluting with 4:1 v/v diethyl ether, afforded **3e** (0.11 g, 26%) and **4e** (0.24 g, 57%).

Compound **3e**. Obtained as a colourless oil. Found, C, 68.55; H, 9.4; N, 6.45; $C_{12}H_{19}NO_2$ requires C, 68.85; H, 9.15; N, 6.7%; $\delta_H$ (300 MHz) 4.12 (d, 1H, *J*=8.1 Hz, H6), 4.02 (dd, 1H, *J*=8.1, 5.3 Hz, H6′), 3.60 (dd, 1H, *J*=15.0, 10.1 Hz, H2′), 3.26 (ddd, 1H, *J*=15.0, 9.6, 7.0 Hz, H2), 2.89 (d, 1H, *J*=5.3 Hz, H5), 2.61 (dt, 1H, *J*=17.1, 9.6 Hz, H3′), 2.24–2.07 (m, 2H, H3 and cycloheptyl-H) and 1.81–1.37 (m, 11H, 11×cycloheptyl-H); *m/z* (%) 209 ($M^+$, 43), 192 (33), 181 (9), 138 (24), 127 (43), 95 (55), 83 (46), 55 (100) and 41 (59); $\nu$ (C=O) 1715 $cm^{-1}$.

Compound **4e**. Obtained as colourless needles from cyclohexane, mp 91–95°C. Found C, 68.7; H, 9.4; N, 6.7; $C_{12}H_{19}NO_2$ requires C, 68.85; H, 9.15; N, 6.7%; $\delta_H$ (300 MHz) 4.35 (d, 1H, *J*=8.7 Hz, H5), 3.70 (ddd, 1H, *J*=15.0, 10.7, 6.4 Hz, H2′), 3.53 (dd, 1H, *J*=15.0, 8.2 Hz, H2), 2.55–2.41 (m, 2H, H3 and H6′), 2.27 (dd, 1H, *J*=17.2, 6.4 Hz, H3′), 2.13–2.08 (m, 1H, cycloheptyl-H) and 1.92–1.46 (m, 12H, H6 and 11×cyclohepty-H); *m/z* (%) 209 ($M^+$, 20), 192 (13), 149 (18), 127 (27), 95 (47), 83 (39), 67 (47), 55 (93) and 41 (100); $\nu$ (C=O) 1730 $cm^{-1}$.

**1.3.6. 8,8-(4′-Tetrahydropyranyl)-1-aza-7-oxa-4-oxobicyclo[3.2.1]octane (3f) and 7,7-(4′-tetrahydropyranyl)-1-aza-8-oxa-4-oxobicyclo[3.2.1]octane (4f).** Tetrahydropyran-4-one oxime (**1f**) and bis(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 20 h. Subsequent work up afforded the crude product as a brown gum, comprising a 1:7 mixture of **3f** and **4f**. Flash chromatography, eluting with 2:1 v/v diethyl ether–ethyl acetate, afforded **3f** (0.029 g, 7%) and **4f** (0.19 g, 48%).

Compound **3f**. Obtained as colourless platelets from toluene, mp 77–80°C. Found C, 60.9; H, 7.7; N, 7.05; $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.65; N, 7.1%; $\delta_H$ (300 MHz) 4.18 (d, 1H, *J*=8.3 Hz, H6), 4.07 (dd, 1H, *J*=8.3, 5.4 Hz, H6′), 3.97 (ddd, 1H, *J*=11.4, 7.4, 3.6 Hz, tetrahydropyranyl-H), 3.81–3.62 (m, 4H, *J*=15.4, 9.6, 7.0 Hz, H2′ and 3×tetrahydropyranyl-H), 3.24 (ddd, 1H, *J*=7.0, 9.6, 15.4 Hz, H2), 2.89 (d, 1H, *J*=5.4 Hz, H5), 2.75–2.62 (m, 1H, H3′), 2.25 (dd, 1H, *J*=16.9, 7.0 Hz, H3), 1.86 (ddd, 1H, *J*=10.5, 7.0, 3.6 Hz, tetrahydropyranyl-H) and 1.73–1.60 (m, 3H, 3×tetrahydropyranyl-H); *m/z* (%) 197 ($M^+$, 25); 180 (23); 139 (22); 125 (21); 115 (31), 98 (58), 83 (69), 55 (100) and 41 (81); $\nu$ (C=O) 1715 $cm^{-1}$.

Compound **4f**. Obtained as colourless needles from toluene, mp 89–91°C. Found C, 61.15; H, 7.8; N, 6.8; $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.65; N, 7.1%; $\delta_H$ (300 MHz) 4.40 (d, 1H, $J$=8.6 Hz, H5), 3.94 (ddd, 1H, $J$=11.7, 6.2, 3.6 Hz, tetrahydropyranyl-H), 3.89–3.82 (m, 1H, tetrahydropyranyl-H), 3.73 (ddd, 1H, $J$=14.9, 10.8, 6.4 Hz, H2′), 3.64–3.58 (m, 2H, 2×tetrahydropyranyl-H), 3.50 (dd, 1H, $J$=14.9, 8.4 Hz, H2), 2.56–2.42 (m, 2H, H3 and H6′), 2.30 (dd, 1H, $J$=17.1, 6.4 Hz, H3′), 1.97–1.85 (m, 4H, H6 and 3×tetrahydropyranyl-H) and 1.72–1.67 (m, 1H, tetrahydropyranyl-H); *m/z* (%) 197 ($M^+$, 10), 180 (4), 139 (9), 125 (99), 97 (49), 83 (66), 69 (61), 55 (89) and 4 (100); $\nu$ (C=O) 1735 $cm^{-1}$.

**1.3.7. 7,7-(*N*-Methyl-4′-piperidyl)-1-aza-8-oxa-4-oxobicyclo[3.2.1]octane (4g).** *N*-Methyl-4-piperidyl oxime (**1g**) and bis(2-chloroethyl) ketone were reacted according to the general procedure (Model 1) in acetonitrile at reflux for 48 h. Subsequent work up afforded the crude product as a brown gum, comprising a 1:15 mixture of **3g** and **4g**. Flash chromatography, eluting with 95:3:2 v/v ethyl acetate–methanol–triethylamine afforded **4g** (0.14 g, 65%) as a colourless oil. Found C, 62.55; H, 8.8; N, 12.9; $C_{11}H_{18}N_2O_2$ requires C, 62.85; H, 8.65; N, 13.3%; $\delta_H$ (300 MHz) 4.39 (d, 1H, $J$=8.3 Hz, H5), 3.72 (ddd, 1H, $J$=14.8, 10.6, 6.3 Hz, H2′), 3.51 (dd, 1H, $J$=14.8, 8.6 Hz, H2), 2.71–2.21 (m, 10H, H6′, H3, H3′, N–$CH_3$ and 4×piperidyl-H) and 2.05–1.68 (m, 5H, H6 and 4×piperidyl-H); *m/z* (%) 210 ($M^+$, 1), 193 (3), 165 (7), 139 (55), 110 (100), 96 (41), 70 (77) and 24 (66); $\nu$ (C=O) 1725 $cm^{-1}$.

**1.3.8. 7,7-(*N*-Benzyl-4′-piperidyl)-1-aza-8-oxa-4-oxobicyclo[3.2.1]octane (4h).** *N*-Benzyl-4-piperidyl oxime (**1h**) and bis(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 48 h. Subsequent work up afforded the crude product as a brown gum, comprising a 1:10 mixture of **3h** and **4h**. Flash chromatography, eluting with 95:3:2 v/v ethyl acetate–methanol–triethylamine afforded **4h** (0.20 g, 77%) as a colourless oil. Found C, 68.95; H, 7.45; N, 9.55; $C_{17}H_{22}N_2O_2$ requires C, 71.3; H, 7.75; N, 9.8%; $\delta_H$ (300 MHz) 7.23 (m, 5H, 5×Ph-H), 4.38 (d, 1H, $J$=8.6 Hz, H5), 3.72 (ddd, 1H, $J$=15.1, 10.8, 6.3 Hz, H2′), 3.52–3.45 (m, 3H, 2×PhC*H*H and H2), 2.77 (m, 7H, H6′, H3′, H3 and 4×piperidyl-H) and 2.00–1.65 (m, 5H, H6 and 4×piperidyl-H); *m/z* (%) 287 (M+1, 1), 286 ($M^+$, 1), 269 (1), 241 (3), 215 (43), 186 (40), 146 (14), 91 (100), 65 (18) and 42 (26); $\nu$ (C=O) 1735 $cm^{-1}$.

**1.3.9. 7,7-(*N*-Acetyl-4′-piperidyl)-1-aza-8-oxa-4-oxobicyclo[3.2.1]octane (4i).** *N*-Acetyl-4-piperidyl oxime (**1i**) and bis(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 48 h. Subsequent work up afforded the crude product as a brown gum, comprising a 1:7 mixture of **3i** and **4i**. Flash chromatography, eluting with 95:3:2 v/v ethyl acetate–methanol–triethylamine afforded **4i** (0.16 g, 66%) as a colourless oil. Found C, 60.8; H, 7.75; N, 11.55; $C_{12}H_{18}N_2O_3$ requires C 60.5; H, 7.6; N, 11.75%; $\delta_H$ (300 MHz) 4.41 (d, 1H, $J$=8.5 Hz, H5), 3.85–3.62 (m, 3H, 2×piperidyl-H and H2′), 3.54–3.41 (m, 3H, H2 and 2×piperidyl-H), 2.52–2.41 (m, 2H, H3 and H6′), 2.34 (dd, 1H, $J$=16.9, 6.3 Hz, H3′), 2.12 (s, 3H, $COCH_3$) and 1.95–1.61 (m, 5H, H6 and 4×piperidyl-H); *m/z* (%) 238 ($M^+$, 4), 221 (4), 195 (12), 166 (45), 124 (67), 96 (78), 82 (60), 56 (52) and 43 (100); $\nu$ (C=O) 1720 and 1625 $cm^{-1}$.

**1.3.10. 7,7-Di-(2′-pyridyl)-1-aza-8-oxa-4-oxobicyclo-[3.2.1]octane (4j).** Di-2-pyridyl oxime (**1j**) and bis-(2-chloroethyl) ketone were reacted according to the general procedure (Mode 1) in acetonitrile at reflux for 20 h. Subsequent work up afforded the crude product as a brown gum, comprising of **4j** only. Flash chromatography, eluting with diethyl ether afforded **4j** (0.13 g, 46%) as a colourless oil. Found C, 68.45; H, 5.35; N, 14.65; $C_{16}H_{15}N_3O_2$ requires C, 68.3; H, 5.35; N, 14.95%; $\delta_H$ (400 MHz) 8.58 (d, 1H, $J$=4.9 Hz, pyridyl-H), 8.45 (d, 1H, $J$=4.8 Hz, pyridyl-H), 8.12 (d, 1H, $J$=8.0 Hz, pyridyl-H), 7.71 (dt, 1H, $J$=7.8, 1.8 Hz, pyridyl-H), 7.54 (dt, 1H, $J$=7.8, 1.8 Hz, pyridyl-H), 7.19 (dd, 1H, $J$=7.5, 4.9 Hz, pyridyl-H), 7.10 (dd, 1H, $J$=7.5, 4.9 Hz, pyridyl-H), 6.90 (d, 1H, $J$=7.9 Hz, pyridyl-H), 4.49 (d, 1H, $J$=8.7 Hz, H5), 4.19 (dd, 1H, $J$=13.8, 2.1 Hz, H6), 3.68 (m, 1H, H2′), 3.36 (dd, 1H, $J$=13.8, 8.7 Hz), 2.85–2.73 (m, 2H, H2 and H3) and 2.10–2.04 (m, 1H, H3′); *m/z* (%) 283 (M+2, 1), 282 (M+1, 4), 281 ($M^+$, 1), 264 (7), 252 (16), 195 (31), 183 (100), 147 (28), 104 (26), 78 (60) and 51 (34); $\nu$ (C=O) 1735 $cm^{-1}$.

### 1.4. General procedure for reductive cleavage of type-3 isoxazolidinones

A suspension of zinc dust (<10 μm) (1.32 g, 0.2 mol) in aqueous acetic acid (9 mL, 80% v/v) was stirred at 65°C for 20 min and then allowed to cool to room temperature. The acetic acid solution was decanted off and the zinc reground using a pestle and mortar. A fresh portion of aqueous acetic acid (9 mL, 80% v/v) was added and the mixture was stirred and cooled to 0–5°C. A solution of isoxazolidinone (1.0 mmol) in aqueous acetic acid (1 mL, 80% v/v) was added dropwise to the stirred suspension over 15 min and reaction progress monitored by TLC. On complete conversion, the mixture was filtered, diluted with water (50 mL), adjusted to pH 8 by the addition of sodium bicarbonate and saturated with sodium chloride. The mixture was filtered and the filtrate extracted with 1:3 v/v isopropanol–dichloromethane (3×100 mL). The extracts were combined, concentrated in vacuo, dichloromethane (50 mL) added to the residue and the resulting solution dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography, eluting with 10:1 v/v ethyl acetate–methanol.

**1.4.1. 2,2-Cyclopentyl-3-methyl-4-piperidone (5c).** Isoxazolidinone **3c** was reacted with zinc dust and acetic acid according to the general procedure at 65°C for 3 h. The product was obtained as a colourless oil (0.10 g, 61%). Found, C, 72.05; H, 10.4; N, 8.1; $C_{10}H_{17}NO$ requires C, 71.8; H, 10.25; N, 8.35%; $\delta_H$ (300 MHz) 3.19 (ddd, 1H, $J$=13.2, 6.3, 5.1 Hz, NC*H*H), 3.08 (ddd, 1H, $J$=13.2, 8.5, 5.2 Hz, NCH*H*), 2.49 (q, 1H, $J$=6.8 Hz, C(O)CH), 2.45–2.28 (m, 2H, 2×C(O)C*H*H), 1.98 (bs, 1H, NH), 1.98–1.53 (m, 8H, 8×cyclopentyl-H) and 1.06 (d, 3H, $J$=6.8 Hz, $CH_3$); *m/z* (%) 167 ($M^+$, 42), 148 (22), 138 (42), 125 (25), 110 (99), 67 (29), 55 (61) and 42 (43); $\nu$ (NH) 3250 and (C=O) 1705 $cm^{-1}$.

**1.4.2. 2,2-Dimethyl-3-hydroxylmethyl-4-piperidone (6a).** Isoxazolidinone **3a** was reacted with zinc dust and acetic acid according to the general procedure at 0–5°C for 1.5 h. The product was obtained as a colourless oil (0.075 g, 48%). HRMS Found 157.1098; $C_8H_{15}NO_2$ requires 157.1103; $\delta_H$ (300 MHz) 3.96 (dd, 1H, *J*=11.4, 7.8 Hz, C*H*HOH), 3.62 (dd, 1H, *J*=11.4, 3.0 Hz, CH*H*OH), 3.27–3.12 (m, 2H, 2×NC*H*H), 2.62 (bs, 2H, NH and OH), 2.47–2.37 (m, 3H, 2×C(O)C*H*H and C(O)CH), 1.25 (s, 3H, $CH_3$) and 1.06 (s, 3H, $CH_3$); *m/z* (%) 158 (M+1, 4), 157 ($M^+$, 23), 140 (65), 124 (12), 112 (59), 84 (56), 70 (100), 55 (61) and 42 (57); $\nu$ (OH) 3400, (NH) 3270 and (C=O) 1700 $cm^{-1}$.

**1.4.3. 2,2-Cyclopentyl-3-hydroxymethyl-4-piperidone (6c).** Isoxazolidinone **3c** was reacted with zinc dust and acetic acid according to the general procedure at 0–5°C for 70 min. The product was obtained as a colourless oil (0.18 g, 98%). HRMS found 183.1259; $C_{10}H_{17}NO_2$ requires 183.1259; $\delta_H$ (300 MHz) 4.03 (dd, 1H, *J*=11.3, 6.2 Hz, C*H*HOH), 3.66 (dd, 1H, *J*=11.3, 2.6 Hz, CH*H*OH), 3.14–3.09 (m, 2H, 2×NC*H*H), 2.68–2.56 (m, 3H, NH, OH and C(O)CH), 2.43–2.33 (m, 2H, 2×C(O)C*H*H) and 1.62–1.59 (m, 8H, 8×cyclopentyl-H); *m/z* (%) 183 ($M^+$, 9), 165 (20), 46 (37), 124 (30), 110 (75), 96 (51), 83 (39), 55 (100) and 41 (36); $\nu$ (OH) 3280 $cm^{-1}$; $\nu$ (NH) 3150 $cm^{-1}$ and $\nu$ (C=O) 1700 $cm^{-1}$.

**1.4.4. 2,2-(4′-Tetrahydropyranyl)-3-hydroxymethyl-4-piperidone (6f).** Isoxazolidinone **3f** was reacted with zinc dust and acetic acid according to the general procedure at 0–5°C for 3 h. The product was obtained as a colourless oil (0.17 g, 86%). HRMS found 199.1206; $C_{10}H_{17}NO_3$ requires 199.1208; $\delta_H$ (300 MHz) 4.05 (dd, 1H, *J*=11.4, 6.6 Hz, C*H*HOH), 3.83–3.61 (m, 5H, CH*H*OH and 4×tetrahydropyranyl-H), 3.27–3.06 (m, 2H, 2×NC*H*H), 2.66–2.57 (m, 1H, C(O)C*H*H), 2.45–2.37 (m, 4H, 2×C(O)C*H*H, NH and OH), 1.92–1.83 (m, 1H, tetrahydropyranyl-H), 1.76–1.67 (m, 1H, tetrahydropyranyl-H) and 1.57 (m, 2H, 2×tetrahydropyranyl-H); *m/z* (%) 199 ($M^+$, 26), 198 (11), 182 (46), 149 (36), 126 (90), 111 (85), 96 (52), 82 (54), 69 (49) and 55 (100); $\nu$ (OH) 3360, (NH) 3210 and (C=O) 1700 $cm^{-1}$.

**1.4.5. 2,2-Cyclohexylperhydroazepin-5-one (7) and 2,2-cyclohexylperhydroazepin-4-one (8).** A solution of **4d** (0.20 g, 1.0 mmol) in aqueous acetic acid (1 mL, 80% v/v) was added dropwise to a stirred suspension of zinc dust (1.32 g, 0.20 mol) in aqueous acetic acid (9 mL, 80% v/v) at 65°C. After 4 h at 65°C, the reaction mixture was filtered, diluted with water (50 mL), adjusted to pH 8 by the addition of sodium bicarbonate and saturated with sodium chloride. The mixture was filtered and the filtrate extracted with 1:3 v/v isopropanol–dichloromethane (3×100 mL). The extracts were combined and concentrated in vacuo. Dichloromethane (50 mL) was added to the residue and the resulting solution dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue comprised a 1:1 mixture of **7** and **8**. Flash chromatography, eluting with 97:3 v/v ethyl acetate–methanol afforded **7** (0.054 g, 30%) and **8** (0.051 g, 28%).

Compound **7**. Colourless oil. Found, C, 73.2; H, 10.4; N, 7.5; $C_{11}H_{19}NO$ requires C, 72.9; H, 10.55; N, 7.75%; $\delta_H$ (300 MHz) 2.97 (t, 2H, *J*=5.9 Hz, 2×NC*H*H), 2.57 (t, 2H, *J*=5.9 Hz, 2×C(O)$CH_2$), 2.45 (m, 2H, C(O)$CH_2$), 2.13 (bs, 1H, NH), 1.74–1.70 (m, 2H, 2×C(O)$CH_2$C*H*H) and 1.53–1.34 (m, 10H, 10×cyclohexyl-H); *m/z* (%) 182 (M+1, 5), 181 ($M^+$, 35), 138 (100), 125 (48), 110 (40), 97 (24), 82 (27), 69 (16) and 55 (24); $\nu$ (NH) 3190 $cm^{-1}$ and $\nu$ (C=O) 1705 $cm^{-1}$.

Compound **8**. Colourless oil. Found, C, 73.15; H, 10.9; N, 7.45; $C_{11}H_{19}NO$ requires C, 72.9; H, 10.55; N, 7.75%; $\delta_H$ (300 MHz) 2.96 (t, 2H, *J*=5.7 Hz, 2×NC*H*H), 2.64 (s, 2H, 2×C(O)$CH_2$), 2.42 (t, 2H, *J*=5.7 Hz, C(O)$CH_2$), 2.17 (bs, 1H, NH), 1.92–1.84 (m, 2H, 2×NC$H_2$C$H_2$) and 1.58–1.39 (m, 10H, 10×cyclohexyl-H); *m/z* (%) 182 (M+1, 9), 181 ($M^+$, 35), 163 (7), 152 (5), 138 (100), 125 (57), 110 (50), 97 (37), 82 (42) and 54 (32); $\nu$ (NH) 3300 and (C=O) 1705 $cm^{-1}$.

**1.4.6. 2,2-Cyclohexyl-4-hydroxy-5,5-[2′-(1,3-dithianyl)]-perhydroazepinone (9).** Boron trifluoride diethyl etherate (0.28 g, 2.0 mmol) was added to a stirred solution of isoxazolidinone **4d** (0.20 g, 1.0 mmol) and propane-1,3-dithiol (0.16 g, 1.5 mmol) in dry dichloromethane (10 mL) at 0°C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature. After 72 h the reaction mixture was poured into aqueous 0.2 M sodium bicarbonate solution (10 mL) and the mixture extracted with dichloromethane (3×30 mL). Work up afforded a pale yellow oil that was purified by flash chromatography, eluting with 2:1 v/v diethyl ether–petroleum ether to afford 4,4-[2′-(1,3-dithianyl)]-7,7-cyclohexyl-1-aza-8-oxabicyclo-[3.2.1]octane as colourless plates (0.22 g, 71%), mp 100–102°C. Found C, 58.8; H, 8.0; N, 4.8; S, 22.55; $C_{14}H_{23}NOS_2$ requires C, 58.9; H, 8.1; N, 4.9; S, 22.45%; $\delta_H$ (400 MHz) 4.45 (d, 1H, *J*=7.5 Hz, H5), 3.69 (ddd, 1H, *J*=14.9, 12.1, 5.4 Hz, H2′), 2.95 (dd, 1H, *J*=14.9, 5.4 Hz, H2), 2.90–2.65 (m, 4H, 4×SC*H*H), 2.20–2.09 (m, 2H, H6′ and H6), 1.98–1.84 (m, 4H, 2×S$CH_2$C$H_2$, H3′ and H3), 1.76–1.31 (m, 10H, 10×cyclohexyl-H); *m/z* (%) 286 (M+1, 1), 285 ($M^+$, 1), 269 (1), 253 (3), 173 (100), 132 (71), 110 (94), 81 (38), 71 (36), 55 (47) and 41 (97).

A solution of 4,4-[2′-(1,3-dithianyl)]-7,7-cyclohexyl-1-aza-8-oxabicyclo[3.2.1]octane in aqueous acetic acid (2 mL, 80% v/v) was added dropwise to a stirred suspension of zinc dust (1.32 g, 0.2 mol) in aqueous acetic acid (8 mL, 80% w/v) at 50°C. After 5 h the reaction mixture was filtered, diluted with water (50 mL), adjusted to pH 8 by the addition of sodium bicarbonate and saturated with sodium chloride. The mixture was filtered and the filtrate extracted with 1:3 v/v isopropanol–dichloromethane (3×100 mL). The extracts were combined and concentrated in vacuo. Dichloromethane (50 mL) was added to the residue and the resulting solution dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography, eluting with 97:3 v/v ethyl acetate–methanol to afford **9** (0.26 g, 91%) as an amorphous colourless powder, mp 141–144°C. HRMS found 287.1377; $C_{14}H_{25}NOS_2$ requires 287.1378; $\delta_H$ (300 MHz) 4.16 (dd, 1H, *J*=5.5, 3.1 Hz, C*H*OH), 3.03–2.72 (m, 6H, 2×NC*H*H and 4×SC*H*H), 2.32–1.91 (m, 6H, 2×$CH_2$C*H*H, 2×NC$CH_2$C*H*H, NH and OH) and 1.66–1.35 (m, 12H, 2×CH(OH)C*H*H and 10×cyclohexyl-H); *m/z* (%) 288

(M+1, 5), 287 ($M^+$, 27), 254 (12), 244 (69), 226 (14), 124 (32), 111 (100), 71 (30), 55 (41) and 41 (70).

### 1.5. General procedure for $NaBH_3CN$ mediated reduction

Sodium cyanoborohydride (0.38 g, 6.0 mmol) was added to a stirred solution of isoxazolidine (1.0 mmol) in methanol (10 mL) at room temperature. A few drops of methyl orange were added followed by sufficient 2N HCl–methanol to induce a red colour. On completion, the reaction mixture was concentrated in vacuo and the residue was dissolved in water (10 mL). The resulting solution was adjusted to pH 8 by the addition of sodium bicarbonate, saturated with sodium chloride, filtered and the filtrate extracted with dichloromethane (3×20 mL). The combined organic extracts were concentrated in vacuo and the residue purified by flash chromatography.

**1.5.1. *anti*-8,8-Cyclopentyl-1-aza-7-oxa-4-hydroxybicyclo-[3.2.1]octane (*anti*-11c).** Isoxazolidinone **3c** was reacted with sodium cyanoborohydride over 2 h according to the general procedure. Subsequent work up afforded the crude product as a colourless crystalline solid, comprising of *anti*-**11c** only. Flash chromatography, eluting with ethyl acetate afforded the product (0.016 g, 88%) as colourless prisms from toluene, mp 138–140°C. Found C, 65.45; H, 9.25; N, 7.4; $C_{10}H_{17}NO_2$ requires C, 65.55; H, 9.35; N, 7.65%; $\delta_H$ (300 MHz) 4.11 (t, 1H, $J$=4.8 Hz, H4), 3.83 (m, 2H, H6 and H6′), 3.28 (ddd, 1H, $J$=14.7, 12.0, 5.7 Hz, H2), 3.14 (dd, 1H, $J$=14.7, 7.3 Hz, H2′), 2.41–2.31 (m, 2H, H5 and cyclopentyl-H), 2.20–2.03 (m, 2H, H3′ and cyclopentyl-H), 1.95–1.57 (m, 6H, 5×cyclopentyl-H and OH), 1.39–1.28 (m, 2H, H3 and cyclopentyl-H); *m/z* (%) 183 ($M^+$, 20), 166 (9), 136 (7), 110 (18), 96 (100), 67 (43), 55 (33) and 41 (34).

**1.5.2. *anti*-8,8-Cyclohexyl-1-aza-7-oxa-4-hydroxybicyclo-[3.2.1]octane (*anti*-11d).** Isoxazolidinone **3d** was reacted with sodium cyanoborohydride over 3 h according to the general procedure. Subsequent work up afforded the crude product as a colourless crystalline solid which comprised a 7:1 mixture of *anti*-**11d** and *syn*-**11d**. Flash chromatography, eluting with 4:1 v/v ethyl acetate–diethyl ether, afforded *anti*-**11d** (0.076 g, 39%) as colourless prisms from toluene, mp 129–131°C. Found C, 66.8; H, 9.6; N, 7.25; $C_{11}H_{19}NO_2$ requires C, 66.95, H, 9.7; N, 7.1%; $\delta_H$ (300 MHz) 4.14 (dd, 1H, $J$=6.1, 4.0 Hz, H4), 3.93 (dd, 1H, $J$=7.3, 5.7 Hz, H6′), 3.77 (d, 1H, $J$=7.3 Hz, H6), 3.33 (ddd, 1H, $J$=14.8, 11.6, 6.4 Hz, H2′), 3.15 (dd, 1H, $J$=14.8, 8.1 Hz, H2), 2.51 (t, 1H, $J$=4.6 Hz, H5), 2.31–2.16 (m, 2H, H3′ and cyclohexyl-H) and 1.98–1.38 (m, 11H, H3, 9×cyclohexyl-H and OH); *m/z* (%) 197 ($M^+$, 10), 180 (6), 150 (4), 124 (13), 110 (100), 81 (24), 67 (23), 55 (22) and 41 (26).

**1.5.3. *anti*-8,8-(4′-Tetrahydropyranyl)-1-aza-7-oxa-4-hydroxybicyclo[3.2.1]octane (*anti*-11f).** Isoxazolidinone **3f** was reacted with sodium cyanoborohydride over 3 h according to the general procedure. Subsequent work up afforded the crude product as an amorphous colourless solid, comprising of a 15:1 mixture of *anti*-**11f** and *syn*-**11f**. Flash chromatography, eluting with ethyl acetate, afforded the *anti*-**11f** (0.024 g, 12%) as colourless rods, mp 145–147°C and a mixed fraction (0.10 g, 50%).

*anti*-**11f**. Found C, 59.95; H, 8.4; N, 6.85; $C_{10}H_{17}NO_3$ requires C, 60.3; H, 8.6; N, 7.05%; $\delta_H$ (300 MHz) 4.15 (t, 1H, $J$=4.9 Hz, H4), 3.99–3.62 (m, 6H, H6, H6′ and 4×tetrahydropyranyl-H), 3.34–3.15 (m, 2H, H2′ and H2), 2.58 (t, 1H, $J$=4.6 Hz, H5), 2.47–2.38 (m, 1H, tetrahydropyranyl-H), 2.29–2.16 (m, 2H, H3′ and tetrahydropyranyl-H), 1.90 (bs, 1H, OH), 1.68–1.56 (m, 2H, 2×tetrahydropyranyl-H) and 1.41 (dd, 1H, $J$=15.6, 5.9 Hz, H3); *m/z* (%) 199 ($M^+$, 15), 182 (12), 152 (7), 126 (18), 112 (100), 84 (37), 67 (24), 55 (31) and 41 (41).

**1.5.4. *anti*-7,7-Cyclohexyl-1-aza-8-oxa-4-hydroxybicyclo-[3.2.1]octane (*anti*-12d) and *syn*-7,7-cyclohexyl-1-aza-8-oxa-4-hydroxybicyclo[3.2.1]octane (*syn*-12d).** Sodium borohydride (0.15 g, 4.0 mmol) was added to a stirred solution of **4d** (0.20 g, 1.0 mmol) in dry isopropanol (10 mL) at room temperature. After 5 h the reaction mixture was concentrated in vacuo and the residue was dissolved in water (10 mL). The resulting solution was adjusted to pH 8 by the addition of sodium bicarbonate, saturated with sodium chloride, filtered and the filtrate extracted with dichloromethane (3×20 mL). The combined organic extracts were concentrated in vacuo to afford a colourless crystalline solid comprising a 3:1 mixture of *anti*-**12d** and *syn*-**12d**. Purification by flash chromatography afforded *anti*-**12d** (0.13 g, 67%) and *syn*-**12d** (0.043 g, 22%).

*anti*-**12d**. Obtained as colourless plates from cyclohexane, mp 133–136°C. Found C, 67.15; H, 9.75; N, 6.95; $C_{11}H_{19}NO_2$ requires C, 66.95; H, 9.7; N, 7.1%; $\delta_H$ (400 MHz) 4.29 (dd, 1H, $J$=7.9, 3.9 Hz, H5), 3.99 (ddd, 1H, $J$=10.2, 6.2, 4.0 Hz, C*H*OH), 3.28 (ddd, 1H, $J$=15.0, 12.7, 5.0 Hz, H2′), 3.12 (dd, 1H, $J$=14.9, 6.4 Hz, H2), 2.02 (dd, 1H, $J$=12.6, 7.9 Hz, H6′), 1.85 (d, 1H, $J$=12.6 Hz, H6) and 1.82–1.25 (m, 13H, H3, H3′, OH and 10×cyclohexyl-H); *m/z* (%) 197 ($M^+$, 11), 180 (6), 124 (14), 110 (100), 95 (8), 81 (32), 67 (21), 55 (33) and 41 (50).

*syn*-**12d**. Obtained as colourless plates from toluene, mp 101–104°C. Found C, 67.1; H, 9.5; N, 6.85; $C_{11}H_{19}NO_2$ requires C, 66.95; H, 9.7; N, 7.1%; $\delta_H$ (400 MHz) 4.27 (m, 1H, H5), 3.71–3.60 (m, 2H, H2′ and H4), 2.96 (dd, 1H, $J$=15.3, 6.5 Hz, H2), 2.67 (bs, 1H, OH), 2.21 (dd, 1H, $J$=12.5, 8.2 Hz, H6′), 2.01–1.89 (m, 1H, H3′) and 1.78–1.29 (m, 12H, H3, H6 and 10×cyclohexyl-H); *m/z* (%) 197 ($M^+$, 16), 180 (9), 124 (16), 110 (100), 96 (5), 81 (33), 67 (19), 55 (25) and 41 (32).

**1.5.5. *anti*-7,7-Cycloheptyl-1-aza-8-oxa-4-hydroxybicyclo-[3.2.1]octane (*anti*-12e).** Isoxazolidinone **4e** was reacted with sodium cyanoborohydride over 3 h according to the general procedure. Subsequent work up afforded the crude product as a colourless crystalline solid, comprising a 9:1 mixture of *anti*-**12e** and *syn*-**12e**. Flash chromatography, eluting with 3:1 v/v ethyl acetate–diethyl ether afforded the *anti*-**12e** (0.10 g, 47%) as colourless prisms, mp 93–96°C and a mixed fraction (0.057 g, 27%).

*anti*-**12e**. Found C, 68.1; H, 9.75; N, 6.55; $C_{12}H_{21}NO_2$ requires, C, 68.2; H, 10.0; N, 6.65%; $\delta_H$ (300 MHz) 4.29 (m,

1H, H5), 4.02–3.95 (m, 1H, H4), 3.29 (ddd, 1H, $J$=15.0, 12.7, 4.9 Hz, H2′), 3.13 (dd, 1H, $J$=15.0, 6.3 Hz, H2) and 2.17–1.37 (m, 17H, H3′, H3, H6′, H6′, 12×cyclopentyl-H and OH); $m/z$ (%) 211 ($M^+$, 14), 194 (14), 138 (21), 124 (100), 95 (30), 67 (31), 55 (33) and 41 (49).

**1.5.6. *anti*-7,7-(4′-Tetrahydropyranyl)-1-aza-8-oxa-4-hydroxybicyclo[3.2.1]octane (*anti*-12f).** Isoxazolidinone **4f** was reacted with sodium cyanoborohydride over 4 h according to the general procedure. Subsequent work up afforded the crude product as a colourless crystalline solid, comprising a 12:1 mixture of *anti*-**12f** and *syn*-**12f**. Flash chromatography, eluting with ethyl acetate afforded *anti*-**12f** (0.042 g, 21%) as colourless plates, mp 115–118°C and a mixed fraction (0.074 g, 37%).

*anti*-**12f**. Found C, 65.45; H, 9.25; N, 7.4; $C_{10}H_{17}NO_3$ requires C, 65.55; H, 9.25; N, 7.65%; $\delta_H$ (300 MHz) 4.33 (m, 1H, H5), 4.02 (m, 1H, C*H*OH), 3.92 (ddd, 1H, $J$=9.7, 5.9, 3.8 Hz, tetrahydropyran-H), 3.86–3.79 (m, 1H, tetrahydropyran-H), 3.63–3.55 (m, 2H, 2×tetrahydropyran-H), 3.33 (ddd, 1H, $J$=15.3, 13.2, 5.2 Hz, H2′), 3.09 (dd, 1H, $J$=15.3, 6.2 Hz, H2), 2.18–2.06 (m, 2H, H3′ and H6′), 1.96 (d, 1H, $J$=12.6 Hz, H6), 1.90–1.75 (m, 4H, 3×tetrahydropyranyl-H and OH), 1.67–1.60 (m, 1H, tetrahydropyranyl-H) and 1.42 (ddt, 1H, $J$=13.1, 10.3, 6.2 Hz, H3); $m/z$ (%) 200 (M+1, 5), 199 ($M^+$, 18), 182 (11), 156 (15), 126 (24), 112 (100), 98 (33), 82 (39), 55 (40) and 41 (72).

### 1.6. Single crystal X-ray diffraction analysis of 3c, *anti*-11c and *anti*-12d

Crystallographic data for **3c** were measured on a Stoe STADI4 diffractometer using $\omega-\theta$ scans and Cu Kα radiation ($\lambda$=1.54184 Å) and for **11c** and **12d** were measured on a Nonius KappaCCD area-detector diffractometer using a mixture of area detector $\omega$- and $\theta$-scans and Mo– Kα radiation ($\lambda$=0.71073 Å). All three structures were solved by direct methods using SHELXS-86[23] and were refined by full-matrix least-squares (based on $F2$) using SHELXL-97.[24] All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals $wR2$ and $R1$, given below, are defined as $wR2=(\sum[w(F_o^2-F_c^2)^2]/\sum[wF_o^2]^2)^{1/2}$ and $R1=\sum||F_o|-|F_c||/\sum|F_o|$.

*Crystal data for* **3c**. $C_{10}H_{15}NO_2$, 0.42×0.26×0.15 mm$^3$, $M$=181.23, monoclinic, space group $P21$, $a$=6.4979(2), $b$=10.2025(4), $c$=14.5685(13) Å, $\beta$=99.987(4)°, $U$=951.18(10) Å$^3$, $Z$=4, $D_c$=1.27 g cm$^{-3}$, $\mu$=0.711 mm$^{-1}$, $F(000)$=392, $T$=293 K.

Data collection. $3.08<\theta<64.48°$; 2804 unique data were collected [$R_{int}$=0.047]; 2757 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=236, goodness of fit, $s$=1.071; $wR2$=0.1120, $R1$=0.0422.

*Crystal data for* **11c**. $C_{10}H_{17}NO_2$: $M$=183.25, monoclinic, space group $P21/n$, $a$=6.3034(2), $b$=18.2420(5), $c$=8.1740(2) Å, $\beta$=101.3760(18)°, $U$=921.44(4) Å$^3$, $Z$=4, $D_c$=1.32 g cm$^{-3}$, $\mu$=0.091 mm$^{-1}$, $F(000)$=400, $T$=190 K.

Data collection. $2.50<\theta<30.0°$; 2456 unique data were collected [$R_{int}$=0.016]; 2161 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=120, goodness of fit, $s$=1.069; $wR2$=0.1258, $R1$=0.0453.

*Crystal data for* **12d**. $C_{11}H_{19}NO_2$: $M$=197.27, monoclinic, space group $P21/n$, $a$=8.5701(2), $b$=11.6422(3), $c$=10.9446(2) Å, $\beta$=111.9290(16)°, $U$=1012.99(4) Å$^3$, $Z$=4, $D_c$=1.29 g cm$^{-3}$, $\mu$=0.088 mm$^{-1}$, $F(000)$=432, $T$=190 K.

Data collection. $2.50<\theta<30.0°$; 1977 unique data were collected [$R_{int}$=0.012]; 1835 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=129, goodness of fit, $s$=1.066; $wR2$=0.0932, $R1$=0.0353.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC182398, 182399 and 182400. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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