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## Synthesis of functionalised azepanes and piperidines from bicyclic halogenated aminocyclopropane derivatives†

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A series of 6,6-dihalo-2-azabicyclo[3.1.0]hexane and 7,7-dihalo-2-azabicyclo[4.1.0]heptane compounds were prepared by the reaction of dihalocarbene species with *N*-Boc-2,3-dihydro-1*H*-pyrroles or -1,2,3,4-tetrahydropyridines. Monochloro substrates were synthesised as well, using a chlorine-to-lithium exchange reaction. The behaviour of several aldehydes and ketones under reductive amination conditions with deprotected halogenated secondary cyclopropylamines was investigated, showing that this transformation typically triggers cyclopropane ring cleavage to give access to interesting nitrogen-containing ring-expanded products.

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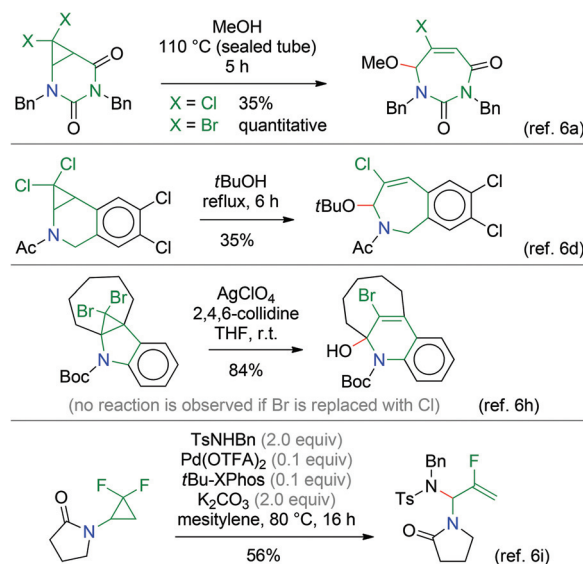
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### Introduction

Our long-standing interest in fused bicyclic aminocyclopropanes has led us to develop several transformations of these compounds for the preparation of nitrogen-containing polycyclic systems.<sup>1</sup> All these methods involve cyclopropane substrates in which the amino group is the only activating substituent.<sup>2</sup> We recently decided to turn our attention to 2,2-dihalo-substituted aminocyclopropane derivatives. Indeed, the presence of a *gem*-dihalocyclopropane substructure offers extended opportunities for subsequent transformations.<sup>3</sup> Of special interest is the thermal ring-opening of halocyclopropanes, proceeding with concomitant departure of a halide ion, to generate allyl cation species.<sup>3,4</sup> Starting from fused bicyclic systems, ring-enlarged products can thus be obtained. Many examples can be found in the literature,<sup>3</sup> some of which served in the syntheses of natural products.<sup>5</sup>

Nevertheless, reports involving nitrogen-substituted *gem*-dihalocyclopropane compounds are comparatively scarce.<sup>5e,6</sup> Typically, the starting materials are stable amide, carbamate or

urea derivatives, *i.e.* with the lone pair of the nitrogen atom being delocalised into a carbonyl group. These ring-opening reactions (Scheme 1) require heating and/or activation by silver salts (or a Pd catalyst as in the bottom example) and are often low-yielding. Interestingly, sporadic reports show that amines can be more reactive (Scheme 2),<sup>7</sup> which can be rationalised by



**Scheme 1** Selected literature examples of cyclopropane ring-opening reactions of nitrogen-substituted *gem*-dihalocyclopropane derivatives, with departure of a halide ion.

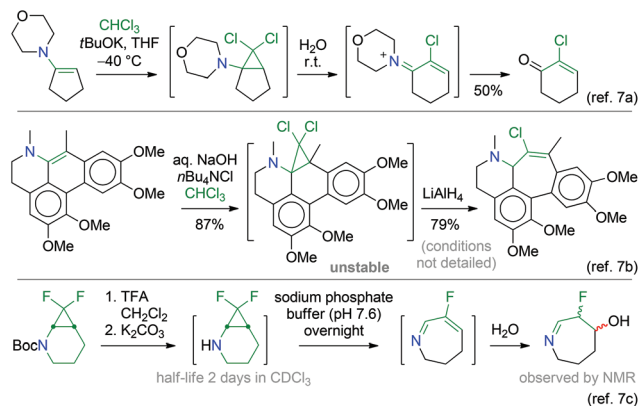
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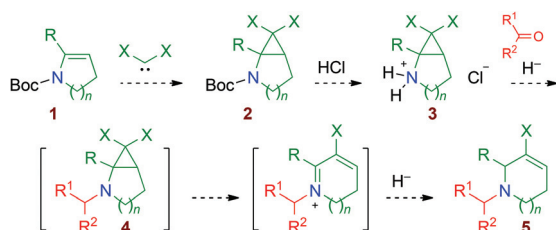


**Scheme 2** Reported ring-expansion reactions of 2,2-dihalogenated aminocyclopropanes.

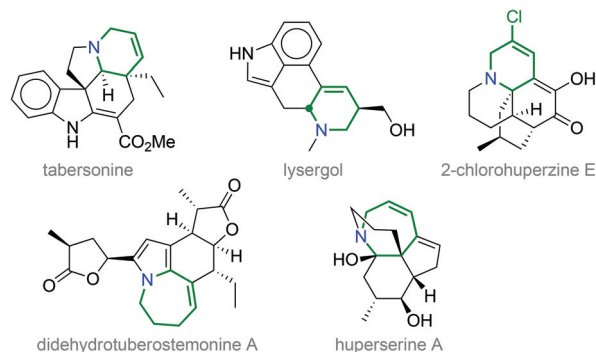
a much more efficient stabilisation of the developing positive charge during the ring-opening process leading to the allyl cation intermediate.

On the basis of these observations, we thought that a fairly general approach could be designed to prepare functionalised halogen-substituted 1,2,3,6-tetrahydropyridine and 2,3,4,7-tetrahydro-1*H*-azepine derivatives **5** (Scheme 3,  $n = 1$  or 2). Starting from *N*-Boc-protected cyclic enamine derivatives **1**, a dihalocyclopropanation reaction would produce stable *N*-Boc-bicyclic secondary cyclopropylamines **2**. After the removal of the Boc group, reductive amination of aldehydes or ketones would generate thermally unstable dihalogenated aminocyclopropanes **4**. This transformation would thus not only introduce functionality but also trigger the ring-expansion process.

Eventually, the corresponding allyl cation adducts would be reduced by the hydride reagent, affording the desired ring-enlarged products **5** (Scheme 3). It is worth noting that 1,2,3,6-tetrahydropyridines and 2,3,4,7-tetrahydro-1*H*-azepines are important heterocycles, which are present as substructures of many natural products: e.g. vinca alkaloids such as tabersonine, vindoline, vinblastine and vincristine;<sup>8</sup> ergot alkaloids such as lysergol and ergotamine;<sup>9</sup> pleurostylin,<sup>10</sup> didehydrotuberostemonine A,<sup>11</sup> huperserines A, B and C;<sup>12</sup> and curindolizine.<sup>13</sup> Moreover, 2-chlorohuperzine E is an interesting example of a 5-chloro-1,2,3,6-tetrahydropyridine isolated from a plant extract (Fig. 1).<sup>14</sup>



**Scheme 3** Strategy for the production of functionalised ring-enlarged cyclic amines **5** from dihalogenated bicyclic aminocyclopropanes **2**.



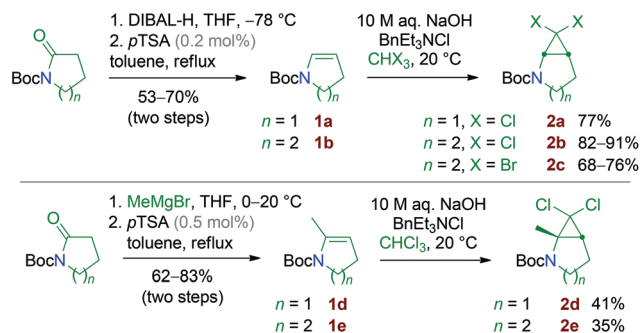
**Fig. 1** Examples of natural product structures containing 1,2,3,6-tetrahydropyridine and 2,3,4,7-tetrahydro-1*H*-azepine subunits.

## Results and discussion

### Synthesis of the substrates

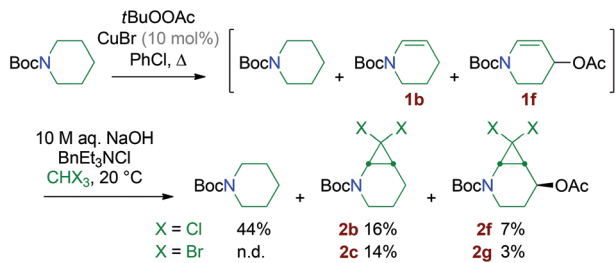
In practice, two routes were investigated for the synthesis of the dihalocyclopropane substrates **2**: the first one involved functional group transformation from lactams: installation of the Boc group, nucleophilic addition of a hydride or a methyl carbanion onto the carbonyl group and elimination of water.<sup>15</sup> Finally, the cyclic *N*-Boc enamines **1** thus obtained were reacted with dihalocarbene species generated from chloroform or bromoform, using the phase-transfer catalysis method developed by M. Małosza (Scheme 4).<sup>16</sup> The second route consisted of applying a Kharasch–Sosnovsky reaction onto *N*-Boc-piperidine (Scheme 5). This approach was much lower yielding but practical and low cost, since the unreacted starting material could be recycled after the cyclopropanation step.

Small amounts of the more complex cyclopropanes **2f** and **2g** were also isolated, resulting from cyclopropanation of the by-product **1f** formed by oxidation of the *N*-Boc-enamine **1b**. Application of the same method to *N*-Boc-pyrrolidine gave poor results in our hands. The stable *N*-Boc protected aminocyclopropane substrates **2a–f** were then readily converted into secondary amine hydrochlorides by treatment with HCl (Scheme 6). In the process, the acetate group of **2f** was hydrolysed into an alcohol function.

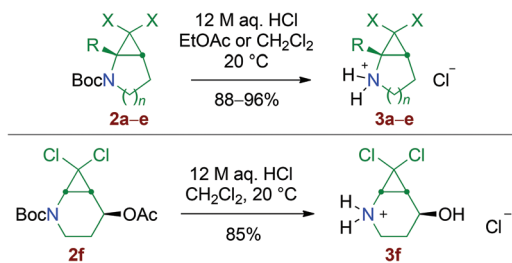


**Scheme 4** Synthesis of the dihalocyclopropane substrates **2a–e** from lactams.





**Scheme 5** Synthesis of **2b–c** and **2f–g** using the Kharasch–Sosnovsky reaction.



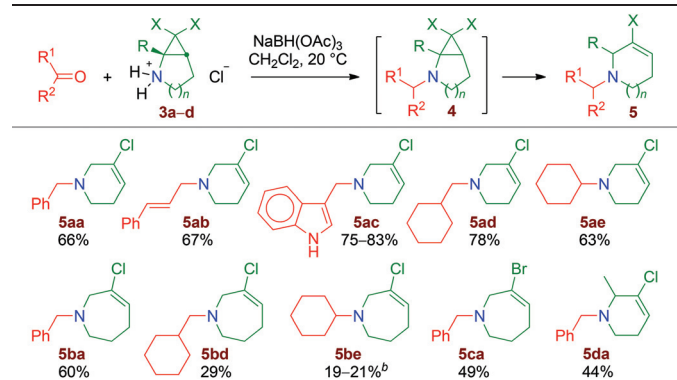
**Scheme 6** Preparation of secondary amine hydrochloride salts **3a–f**.

### Reductive amination – ring enlargement

When a set of aldehydes and ketones were reacted with 2,2-dihalogenated aminocyclopropane salts **3a–e** in the presence of  $\text{NaBH}(\text{OAc})_3$ , the reductive amination products **4** were initially formed, as evidenced by NMR after 30–60 minutes of reaction.<sup>‡</sup> However, from **3a–d**, these were gradually transformed into ring-enlarged products **5**, as anticipated (Table 1).§ In particular, the 6,6-dichloro-2-azabicyclo[3.1.0]hexane **3a** gives the chloroazacyclohexenes **5aa–ae** in moderate to good yields. The presence of a methyl group in **3d** is tolerated and the product **5da** was isolated in 44% yield. Starting from the homologous 7,7-dihalo-2-azabicyclo[4.1.0]heptane substrates, yields were uniformly lower. This is due, at least in part, to competitive processes leading to by-products (*vide infra*). Interestingly, halogen-substituted tetrahydroazepine derivatives, with structures closely related to those of **5ba**, **5bd–be** and **5ca**, have been demonstrated to be cycloallene precursors that can be used as intermediates in the preparation of valuable polycyclic building blocks.<sup>17</sup> The salt **3f** containing a hydroxyl group proved to be unsuitable, affording, with benzaldehyde, the corresponding chloroazepine derivative in 6% yield only. Starting from the better substrate **3b**, poor results were also obtained when butyraldehyde and indole-3-carboxaldehyde were employed.<sup>‡</sup>

A much simpler version of the reaction involves the generation of secondary amines by deprotonation of the salts **3**

**Table 1** Transformation of 2,2-dihalogenated aminocyclopropane salts **3a–d** into ring-enlarged products **5**, under reductive amination conditions<sup>a</sup>

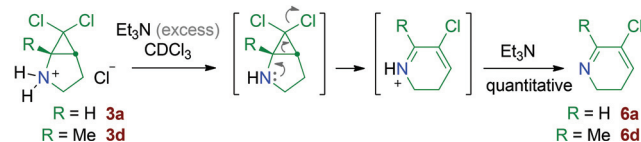


<sup>a</sup> Reactions typically run overnight using 1.0 equiv. of aldehyde or ketone, 1.0 equiv. of cyclopropylammonium salt and 2.4 equiv. of  $\text{NaBH}(\text{OAc})_3$ . <sup>b</sup> The major product of this reaction was 3-(chloromethylene)-1-cyclohexyl-piperidine **7be**.

with triethylamine. This was done on a few milligram scale in NMR tubes containing  $\text{CDCl}_3$  solutions of **3a** and **3d**. The rearrangement is fast under these conditions and the clean formation of the 5-chloro-2,3-dihydropyridines **6a** and **6d** is observed after 5 minutes at room temperature (Scheme 7).¶

Interestingly, starting from the methyl-substituted compound **3e** and under the reductive amination conditions applied for substrates **3a–d**, the reaction takes a different course. Indeed, 3-chloromethylenepiperidine derivatives **7ea** and **7eb** are isolated as single geometrical isomers (Scheme 8). A similar phenomenon is observed when **3b** is reacted with cyclohexanone, with the formation of **7be** as the major product.

The formation of compounds **7** can be explained by a 2,2-dichloro-1-aminocyclopropane-ring opening proceeding at the C1–C2 bond (Scheme 8, bottom).<sup>18</sup> Steric hindrance around the nitrogen atom appears to be a key factor for this process, as well as the size of the nitrogen-containing heterocycle. Indeed, starting from **3a** and **3d**, which are the lower homologues of **3b** and **3e**, selectivity is in favour of the ring-expanded molecules **5ae** and **5da** (Table 1). Nonetheless, careful analysis of the crude products of all the reductive amination experi-



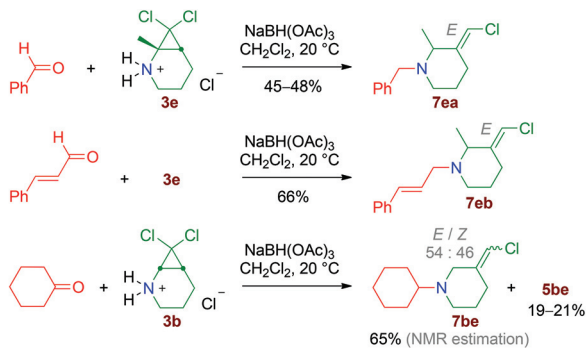
**Scheme 7** Simpler version of the reaction.

<sup>‡</sup> See the ESI† for details.

<sup>§</sup> The quality of the hydride reagent proved important. See the ESI† for a short study in the case of the reaction of benzaldehyde with **3b**.

<sup>¶</sup> Using  $\text{K}_2\text{CO}_3$  as the base, no reaction was observed after several hours, most certainly because of the very low solubility of this reagent in chloroform. With NaOH, complex mixtures of products were generated after 5 minutes.





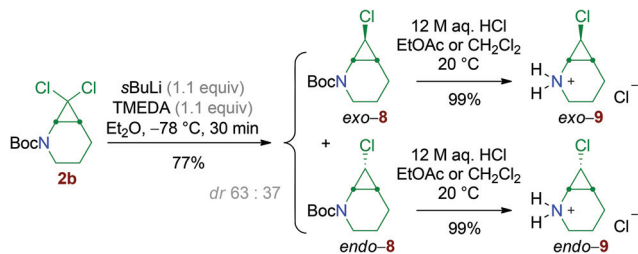
**Scheme 8** Formation of 3-chloromethylenepiperidine derivatives under reductive amination conditions performed with **3e**.

ments revealed, in several cases, the formation of minor amounts of compounds of type **7**, as well as of other by-products.<sup>‡</sup>

### Results with monochlorocyclopropane substrates

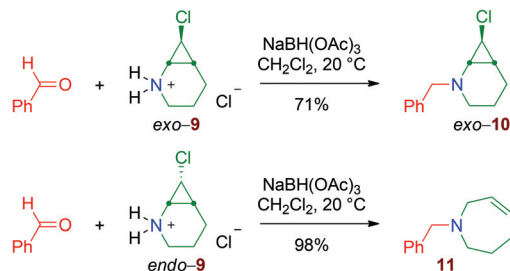
The reactivity of 2-monochloro aminocyclopropane derivatives was next investigated. The dichlorocyclopropane **2b** was transformed into the monochloro diastereoisomers **8** by chlorine-to-lithium exchange using *s*BuLi/TMEDA.<sup>||</sup> After separation by flash chromatography, these molecules were converted into the hydrochloride salts, *exo*- and *endo*-**9** (Scheme 9).

Application of reductive amination conditions with benzaldehyde proceeds with high chemoselectivity: while the *exo* compound gives the tertiary cyclopropylamine *exo*-**10**, *endo*-**9** is converted into the ring-expanded tetrahydroazepine **11** (Scheme 10), showing that the *endo* bicyclic aminocyclopropane *endo*-**10** is not stable and readily undergoes rearrangement, like the dihalo derivatives **4**. These divergent results are in agreement with the so-called Woodward–Hoffmann–DePuy rule.<sup>19,20</sup> Briefly, the reaction is thought to proceed by a mechanism where the departure of the halide ion and the two-electron electrocyclic cyclopropane-cleavage take place in a con-

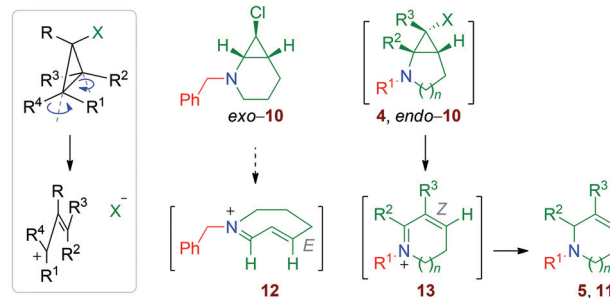


**Scheme 9** Preparation of monochloro diastereoisomers from **2b**.

<sup>||</sup> Without TMEDA, yields are significantly lower. Using *n*BuLi/TMEDA instead of *s*BuLi/TMEDA, no Cl–Li exchange is observed.



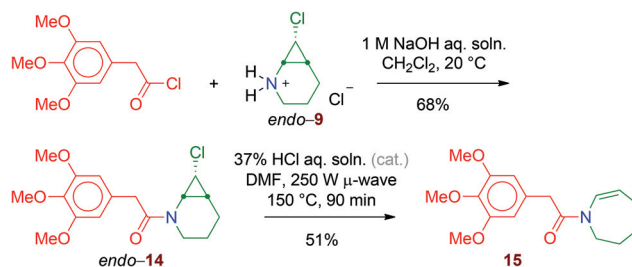
**Scheme 10** Transformation of *exo*- and *endo*-**9** under reductive amination conditions with benzaldehyde.



**Scheme 11** Stereochemical outcome of the transformation of halocyclopropanes into allyl cation species.

certed fashion. Moreover, the sense of the disrotatory ring-opening is dictated by the relative configurations of the cyclopropane carbon atoms, so that substituents that are *trans* to the leaving group move outward (Scheme 11, framed). While the substrates having a halogen substituent in the *endo* relative configuration, *i.e.* *endo*-**10** and all the dihalo substrates, can be transformed into cyclic cation intermediates **13**, *exo*-**10** cannot participate in such a process because the unacceptably strained *E* cation **12** would be produced (Scheme 11).

Finally, the successful transformation of *endo*-**9** into the amide *endo*-**14** demonstrates that the reaction of the acyl chloride is fast enough to trap the free secondary amine before it undergoes cyclopropane cleavage. Like the *N*-Boc derivative *endo*-**8**, *endo*-**14** is a stable compound that can be purified by flash chromatography. However, when heated under microwave conditions, it is transformed into the dihydroazepine



**Scheme 12** Acylation of *endo*-**9**; transformation into the dihydroazepine **15**.



derivative **15** (Scheme 12).\*\* In contrast, *exo*-**14**, prepared in the same way as *endo*-**14**, does not react, even in the presence of  $\text{AgBF}_4$ .†

## Conclusions

In summary, endocyclic amine systems fused with a dihalo-cyclopropane ring undergo cyclopropane cleavage to typically afford ring-expanded products. A minor competitive pathway, which can become predominant with some substrates, is the cleavage of the other cyclopropane bonds adjacent to this atom. Monochloro substrates can also participate in the ring-expansion process, provided that relative configuration of the chlorine substituent is *endo*. All these transformations readily take place at room temperature, after the amine function is created by a reductive amination reaction or by simple deprotonation of the corresponding hydrochloride salt. In contrast, amides or *N*-Boc carbamate substrates require activation (e.g. heating) for the ring-expansion to proceed, still on the condition that a halogen substituent is present with the *endo* relative configuration.

## Experimental

Selected experimental procedures and data are presented hereafter. Full details can be found in the ESI.†

*sec*-Butyllithium (1.3–1.4 M solution in cyclohexane) was purchased from Sigma-Aldrich or Alfa Aesar and titrated according to a literature method.<sup>21</sup> Diethyl ether, and dichloromethane were purified using a MB SPS-800 solvent purification system (MBRAUN). Other solvents and commercial reagents were used as received, without purification. Petroleum ether refers to the 40–60 °C fraction. The microwave-promoted experiments were run using a CEM Discover Microwave Synthesis System with the temperature and time parameters indicated; the reaction vessels were not flushed with an inert gas. All other reactions were carried out under nitrogen or argon. The temperatures mentioned are the temperatures of the cold baths or the oil baths used. Flash column chromatography was performed on VWR Chemicals or Merck silica gel 60 (40–63 μm). Concentration under reduced pressure was carried out using rotary evaporators at 40 °C. NMR spectra were recorded with AM 400 or AVANCE 400 Bruker spectrometers (<sup>1</sup>H at 400.2 MHz, <sup>13</sup>C at 100.6 MHz). Chemical shifts δ are given in ppm, referenced to the peak of tetramethylsilane, defined at δ = 0.00 (<sup>1</sup>H NMR), or the solvent peak of CDCl<sub>3</sub>, defined at δ = 77.0 (<sup>13</sup>C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, m = multiplet, and br = broad. Coupling constants

*J* are given in Hz and are rounded to the closest multiple of 0.5. Infrared spectra were recorded with a PerkinElmer 2000 or a PerkinElmer Spectrum Two FT-IR spectrometer. Melting points were determined using a Büchi 535 apparatus and were not corrected. Low-resolution mass spectra were recorded on a Hewlett-Packard Quad GC-MS engine spectrometer *via* direct injection. High-resolution mass spectrometry was performed on a JEOL GC-mate II spectrometer. Underlined *m/z* values indicate the base peaks.

### General procedure A: Cyclopropanation of *N*-Boc dihydropyrroles and *N*-Boc tetrahydropyridines with dichlorocarbene<sup>22</sup>

10 M NaOH aqueous solution (20 mL) was slowly added to a solution of *N*-Boc cyclic enamine substrate **1** (1.00 equiv., 3.50 mmol) and benzyltriethylammonium chloride (0.63 equiv., 2.20 mmol) in CHCl<sub>3</sub> (20 mL). After 90–180 min of vigorous stirring at 20 °C, the aqueous phase was removed. The organic layer was washed with H<sub>2</sub>O (20 mL) and brine (20 mL), then dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

**2a.** Pale yellow solid. M.p. 54.3–55.9 °C. IR (neat)  $\nu$  2978 (m), 2934 (w), 2904 (w), 1707 (s, C=O), 1478 (w), 1450 (w), 1393 (s), 1368 (m), 1356 (m), 1346 (m), 1288 (w), 1257 (m), 1173 (m), 1127 (m), 1052 (w), 877 (m), 860 (m) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), 63: 37 mixture of two rotamers. Major rotamer: δ 1.50 (9 H, s), 2.11–2.36 (3 H, m), 3.37–3.66 (2 H, m), 3.63 (1 H, d, *J* 7.0). Minor rotamer: δ 1.45 (9 H, s), 2.11–2.36 (3 H, m), 3.28 (1 H, td, *J* 10.5, 5.5), 3.37–3.66 (1 H, m), 3.82 (1 H, d, *J* 7.0). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz), 63: 37 mixture of two rotamers. Major rotamer: δ 24.4, 28.0, 35.9, 48.6, 48.8, 65.1, 80.2, 154.7. Minor rotamer: δ 25.2, 28.0, 34.6, 48.3, 49.0, 64.8, 80.1, 154.7. MS (EI): *m/z* 114, 116, 118, 132, 160, 162, 176, 178 ([M – *t*BuO]<sup>+</sup> with two <sup>35</sup>Cl), 180 ([M – *t*BuO]<sup>+</sup> with one <sup>35</sup>Cl and one <sup>37</sup>Cl), 195, 200, 201, 226, 251 (M<sup>+</sup> with two <sup>35</sup>Cl). HRMS (EI): *m/z* 251.0474 (M<sup>+</sup> C<sub>10</sub>H<sub>15</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>2</sub><sup>+</sup> requires 251.0475).

**2b.** Pale yellow oil. IR (neat)  $\nu$  2976 (m), 2935 (m), 2873 (w), 2361 (w), 2342 (w), 1710 (s, C=O), 1476 (w), 1455 (m), 1403 (s), 1392 (m), 1368 (s), 1354 (m), 1308 (m), 1257 (m), 1168 (s), 1137 (m), 1093 (w), 1024 (w), 839 (w), 824 (w), 772 (w) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), 85: 15 mixture of two rotamers. Major rotamer: δ 1.39–1.51 (1 H, m), 1.53 (9 H, s), 1.61–1.75 (2 H, m), 1.93–2.06 (2 H, m), 2.82 (1 H, ddd, *J* 12.5, 8.5, 3.5), 3.24 (1 H, d, *J* 9.0), 3.51 (1 H, ddd, *J* 12.5, 7.0, 4.0). Minor rotamer, characteristic signals: δ 1.50 (9 H, s), 3.02 (1 H, ddd, *J* 12.0, 7.5, 4.0), 3.27 (1 H, ddd, *J* 12.0, 9.5, 4.5), 3.33 (1 H, d, *J* 9.0). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz), 85: 15 mixture of two rotamers. Major rotamer: δ 17.1, 21.2, 28.3, 28.4, 40.0, 40.2, 63.4, 80.4, 156.0. Minor rotamer, characteristic signals: δ 17.0, 21.4, 39.7, 41.6. MS (EI): *m/z* 128, 130, 132, 135, 174, 192 ([M – *t*BuO]<sup>+</sup> with two <sup>35</sup>Cl), 194 ([M – *t*BuO]<sup>+</sup> with one <sup>35</sup>Cl and one <sup>37</sup>Cl), 209, 211, 232, 234. HRMS (EI): *m/z* 265.0627 (M<sup>+</sup> C<sub>11</sub>H<sub>17</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>2</sub><sup>+</sup> requires 265.0631).

**2c.** White solid. M.p. 46.8–48.0 °C. IR (neat)  $\nu$  2971 (m), 2933 (w), 2872 (w), 1704 (s, C=O), 1451 (w), 1400 (m), 1392 (m),

\*\*The production of **15** can be explained by the loss of a proton from the iminium intermediate **13**, which we were hoping would cyclise onto the electron-rich aromatic ring.



1366 (m), 1348 (m), 1315 (w), 1255 (w), 1161 (m), 1135 (m), 1015 (w), 755 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), **88**: 12 mixture of two rotamers. Major rotamer:  $\delta$  1.44 (1 H, m), 1.55 (9 H, s), 1.52–1.62 (1 H, m), 1.74 (1 H, m), 2.02–2.13 (2 H, m), 2.90 (1 H, ddd,  $J$  12.5, 8.0, 4.0), 3.29 (1 H, d,  $J$  9.0), 3.43 (1 H, ddd,  $J$  12.5, 8.0, 4.5). Minor rotamer, characteristic signals:  $\delta$  1.50 (9 H, s), 3.08 (1 H, ddd,  $J$  12.5, 6.5, 4.0), 3.22 (1 H, ddd,  $J$  12.5, 9.5, 4.0), 3.37 (1 H, d,  $J$  9.0).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz), **88**: 12 mixture of two rotamers. Major rotamer:  $\delta$  19.0, 21.1, 28.3, 29.4, 36.7, 40.2, 40.6, 80.4, 155.8. Minor rotamer, characteristic signals:  $\delta$  21.2, 28.3, 36.5, 40.1, 41.8, 80.3, 155.9. MS (EI):  $m/z$  94, 95, 119, 146, 174, 175, 176, 199, 218, 220, 255, 280 ( $[\text{M} - t\text{BuO}]^+$  with two  $^{79}\text{Br}$ ), 282 ( $[\text{M} - t\text{BuO}]^+$  with one  $^{79}\text{Br}$  and one  $^{81}\text{Br}$ ), 284 ( $[\text{M} - t\text{BuO}]^+$  with two  $^{81}\text{Br}$ ), 297, 299, 301, 353 ( $\text{M}^{++}$  with two  $^{79}\text{Br}$ ), 355 ( $\text{M}^{++}$  with one  $^{79}\text{Br}$  and one  $^{81}\text{Br}$ ), 357 ( $\text{M}^{++}$  with two  $^{81}\text{Br}$ ). HRMS (EI):  $m/z$  352.9629 ( $\text{M}^{++} \text{C}_{11}\text{H}_{17}^{79}\text{Br}_2\text{NO}_2^{++}$  requires 352.9621).

### Monochloro substrates *exo-8* and *endo-8*

*sec*-Butyllithium solution (0.91 M in cyclohexane, 1.10 equiv., 1.10 mmol, 1.21 mL) was added dropwise, at  $-78^\circ\text{C}$ , to a solution of *tert*-butyl 7,7-dichloro-2-azabicyclo[4.1.0]heptane-2-carboxylate **2b** (1.00 equiv., 1.00 mmol, 266 mg) and TMEDA (1.10 equiv., 1.10 mmol, 165  $\mu\text{L}$ ) in  $\text{Et}_2\text{O}$  (11 mL). After 15 minutes of stirring at  $-78^\circ\text{C}$ ,  $\text{H}_2\text{O}$  (20 mL) was added. The mixture was then extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford a pale yellow oil (237 mg). Purification by flash column chromatography on silica gel ( $\text{EtOAc}$ /petroleum ether, gradient from 2 to 10%) afforded pure *exo-8* (105 mg, 453  $\mu\text{mol}$ , 45%), a 75 : 25 mixture of the *endo* and *exo* diastereoisomers of **8** (64.7 mg, 279  $\mu\text{mol}$ , 28%) and pure *endo-8* (7.0 mg, 30  $\mu\text{mol}$ , 3%).

*exo-8*. Colourless oil. IR (neat)  $\nu$  2977 (m), 2934 (m), 2868 (w), 1702 (s, C=O), 1447 (w), 1418 (m), 1384 (m), 1366 (m), 1300 (w), 1269 (w), 1246 (w), 1164 (m), 1131 (m), 1035 (w), 1005 (w), 774 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), **79**: 21 mixture of two rotamers. Major rotamer:  $\delta$  1.12 (1 H, tddd,  $J$  13.0, 12.0, 4.5, 3.5), 1.50 (9 H, s), 1.57 (1 H, br ddd,  $J$  9.5, 6.0, 4.0), 1.61 (1 H, dddd,  $J$  13.0, 6.0, 3.5, 2.0), 1.72 (1 H, ddt,  $J$  13.5, 13.0, 6.0), 1.97 (1 H, br dd,  $J$  13.5, 4.5), 2.43 (1 H, ddd,  $J$  13.0, 12.0, 2.0), 2.65 (1 H, dd,  $J$  4.0, 1.5), 3.03 (1 H, dd,  $J$  9.5, 1.5), 3.76 (1 H, dt,  $J$  13.0, 3.5). Minor rotamer:  $\delta$  1.45–1.77 (4 H, m, H2, H3a), 1.46 (9 H, s), 1.97 (1 H, br d,  $J$  13.5), 2.56 (1 H, br t,  $J$  12.5), 2.71 (1 H, br d,  $J$  3.5), 3.15 (1 H, br d,  $J$  9.5), 3.59 (1 H, br d,  $J$  12.5).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz), **79**: 21 mixture of two rotamers. Major rotamer:  $\delta$  19.2, 22.4, 23.1, 28.4, 35.8, 37.5, 39.7, 80.0, 156.0. Minor rotamer:  $\delta$  19.2, 22.3, 22.8, 28.4, 35.1, 37.3, 41.3, 80.1, 156.0. MS (EI)  $m/z$  98, 110, 130, 140, 158 ( $[\text{M} - t\text{BuO}]^+$  with  $^{35}\text{Cl}$ ), 160 ( $[\text{M} - t\text{BuO}]^+$  with  $^{37}\text{Cl}$ ), 179, 196 ( $[\text{M} - \text{Cl}]^+$ ). HRMS  $m/z$  (EI) 158.0370 ( $[\text{M} - t\text{BuO}]^+ \text{C}_7\text{H}_9\text{ClNO}^+$  requires 158.0368).

*endo-8*. Colourless crystals. M.p. 62–64  $^\circ\text{C}$ . IR (neat)  $\nu$  2975 (m), 2933 (m), 2869 (w), 1700 (s, C=O), 1478 (w), 1454 (w), 1407 (m), 1391 (m), 1365 (m), 1309 (m), 1272 (w), 1256 (w), 1169 (m), 1137 (m), 1066 (w), 963 (w), 774 (m), 712 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR

( $\text{CDCl}_3$ , 400 MHz), **72**: 28 mixture of two rotamers. Major rotamer:  $\delta$  1.40–1.73 (4 H, m), 1.48 (9 H, s), 1.94 (1 H, m), 2.86 (1 H, ddd,  $J$  12.0, 8.5, 4.0), 2.89 (1 H, dd,  $J$  9.0, 5.5), 3.14 (1 H, dd,  $J$  8.0, 5.5), 3.53 (1 H, ddd,  $J$  12.0, 7.0, 4.5). Minor rotamer:  $\delta$  1.40–1.73 (4 H, m), 1.48 (9 H, s), 1.98 (1 H, m), 2.96 (1 H, dd,  $J$  9.0, 5.5), 3.06 (1 H, ddd,  $J$  12.5, 7.0, 4.0), 3.24 (1 H, dd,  $J$  8.0, 5.5), 3.26 (1 H, ddd,  $J$  12.5, 8.5, 4.0).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz), **72**: 28 mixture of two rotamers. Major rotamer:  $\delta$  15.1, 16.2, 22.3, 28.2, 29.5, 37.0, 40.7, 79.4, 156.3. Minor rotamer:  $\delta$  15.0, 15.9, 22.3, 28.2, 29.5, 36.7, 42.3, 79.6, 156.4. MS (EI)  $m/z$  96, 98, 99, 140, 141, 158 ( $[\text{M} - t\text{BuO}]^+$  with  $^{35}\text{Cl}$ ), 160 ( $[\text{M} - t\text{BuO}]^+$  with  $^{37}\text{Cl}$ ), 175, 196 ( $[\text{M} - \text{Cl}]^+$ ). HRMS  $m/z$  (EI) 196.1335 ( $[\text{M} - \text{Cl}]^+ \text{C}_{11}\text{H}_{18}\text{NO}_2^+$  requires 196.1333).

### Typical procedure for the preparation of the hydrochloride salts

12 M HCl aqueous solution (5.0 equiv., 18.8 mmol, 1.57 mL) was added dropwise to a vigorously stirred solution of **2b** (1.00 equiv., 3.76 mmol, 1.00 g) in  $\text{CH}_2\text{Cl}_2$  (8.0 mL). After 16 h of stirring at  $20^\circ\text{C}$ , the solution was concentrated under reduced pressure. The residue was washed with a small amount of  $\text{Et}_2\text{O}$  ( $2 \times 4.0$  mL) and dried under high vacuum to afford pure **3b** (724 mg, 3.58 mmol, 95%).

**3b**. White solid. M.p.  $136.5^\circ\text{C}$  (decomposition).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.69 (1 H, m), 1.83 (1 H, br s), 1.97 (1 H, br ddd,  $J$  13.5, 6.5, 5.5), 2.08–2.22 (2 H, m), 2.93 (1 H, br ddd,  $J$  12.5, 9.5, 3.0), 3.35 (1 H, br ddd,  $J$  12.5, 7.0, 3.0), 3.48 (1 H, br d,  $J$  9.5), 9.14 (1 H, br s, NH), 11.60 (1 H, br s, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  15.0, 16.5, 25.2, 36.6, 40.5, 59.3. MS (EI):  $m/z$  94, 102, 103, 104, 130, 131, 132, 164, 166 ( $[\text{M} - \text{Cl}]^+$  with two  $^{35}\text{Cl}$ ), 167.

### General procedure B: Reductive amination reactions of aldehydes and ketones with the cyclopropylammonium salts **3** or **9**

Sodium triacetoxyborohydride (2.40 equiv., 240  $\mu\text{mol}$ , 50.9 mg) was added at  $20^\circ\text{C}$  to a solution of aldehyde or ketone (1.00 equiv., 100  $\mu\text{mol}$ ) and cyclopropylammonium chloride **3** or **9** (1.00 equiv., 100  $\mu\text{mol}$ ) in dry  $\text{CH}_2\text{Cl}_2$  (1.0 mL). After 15 h of stirring at r.t., saturated  $\text{NaHCO}_3$  aqueous solution (15 mL) was added. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 15$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel (typically, a few drops of  $\text{Et}_3\text{N}$  were added to the eluents used).

**5aa**. Pale yellow oil. IR (neat)  $\nu$  3063 (w), 3029 (m), 2919 (s), 2803 (s), 2761 (m), 2724 (w), 1664 (m), 1495 (m), 1455 (m), 1368 (m), 1347 (m), 1149 (m), 1126 (s), 1045 (m), 962 (m), 844 (s), 835 (s), 738 (s)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.22 (2 H, tdt,  $J$  5.5, 4.0, 2.5), 2.58 (2 H, t,  $J$  5.5), 3.10 (2 H, td,  $J$  2.5, 1.5), 3.62 (2 H, s), 5.85 (1 H, tt,  $J$  4.0, 1.5), 7.24–7.38 (5 H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  26.2, 48.4, 57.3, 61.7, 122.5, 127.2, 128.3, 128.8, 129.0, 137.8. MS (EI):  $m/z$  116, 117, 118, 172, 207 ( $\text{M}^{++}$  with  $^{35}\text{Cl}$ ), 209 ( $\text{M}^{++}$  with  $^{35}\text{Cl}$ ). HRMS (EI):  $m/z$  207.0819 ( $\text{M}^{++} \text{C}_{12}\text{H}_{14}^{35}\text{ClN}^{++}$  requires 207.0810).



**5ae.** Pale yellow oil. IR (neat)  $\nu$  2929 (s), 2855 (m), 2802 (w), 2361 (w), 2343 (w), 1665 (w), 1450 (m), 1379 (w), 1138 (w), 987 (w), 958 (w), 839 (w), 772 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.18–1.30 (1 H, m), 1.24 (2 H, m), 1.25 (2 H, m), 1.64 (1 H, br d,  $J$  12.0), 1.81 (2 H, m), 1.89 (2 H, m), 2.22 (2 H, tdt,  $J$  5.5, 4.0, 2.5), 2.40 (1 H, m), 2.64 (2 H, t,  $J$  5.5), 3.23 (2 H, td,  $J$  2.5, 2.0), 5.84 (1 H, tt,  $J$  4.0, 2.0).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.8, 26.2, 26.7, 28.8, 44.9, 53.4, 62.7, 122.7, 129.2. MS (EI):  $m/z$  130, 132, 156, 158, 170, 199 ( $\text{M}^+$  with  $^{35}\text{Cl}$ ), 201 ( $\text{M}^+$  with  $^{37}\text{Cl}$ ). HRMS (EI):  $m/z$  199.1134 ( $\text{M}^+ \text{C}_{11}\text{H}_{18}^{35}\text{ClN}^+$  requires 199.1123).

**5ba.** Pale yellow oil. IR (neat)  $\nu$  3063 (w), 3029 (w), 2930 (s), 2839 (m), 2810 (m), 1642 (w), 1494 (m), 1453 (m), 1436 (m), 1361 (w), 1118 (m), 1028 (w), 1015 (w), 969 (w), 951 (w), 822 (w), 757 (m), 733 (s)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.70 (2 H, tt,  $J$  6.0, 5.5), 2.24 (2 H, dt,  $J$  6.5, 5.5, 1.0), 2.94 (2 H, t,  $J$  6.0), 3.56 (2 H, t,  $J$  1.0), 3.75 (2 H, s), 6.08 (1 H, t,  $J$  6.5), 7.26 (1 H, distorted tt,  $J$  7.0, 1.5), 7.29–7.38 (4 H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  24.2, 26.9, 56.5, 58.2, 60.2, 127.1, 128.3, 128.9, 129.6, 132.6, 138.7. MS (EI):  $m/z$  91 ( $\text{Bn}^+$ ), 92, 120, 121, 130, 186 ( $[\text{M} - \text{Cl}]^+$ ), 220, 221 ( $\text{M}^+$  with  $^{35}\text{Cl}$ ), 222, 223 ( $\text{M}^+$  with  $^{37}\text{Cl}$ ). HRMS (EI):  $m/z$  221.0977 ( $\text{M}^+ \text{C}_{13}\text{H}_{16}^{35}\text{ClN}^+$  requires 221.0966).

**5be.** Pale yellow oil. IR (neat)  $\nu$  2929 (s), 2855 (m), 2806 (w), 2361 (w), 2342 (w), 1698 (w), 1450 (w), 1260 (w), 1125 (w), 1018 (w), 963 (w), 772 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.04–1.32 (3 H, m), 1.61 (1 H, dm,  $J$  12.5), 1.67 (2 H, tt,  $J$  6.0, 5.5), 1.77 (2 H, dm,  $J$  12.0), 1.91 (2 H, br d,  $J$  11.5), 2.20 (2 H, dt,  $J$  6.0, 5.5), 2.56 (1 H, tt,  $J$  10.5, 3.0), 2.95 (2 H, t,  $J$  6.0), 3.57 (2 H, br s), 5.98 (1 H, br t,  $J$  6.0).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.2, 25.6, 26.2, 26.7, 29.7, 52.7, 58.0, 60.6, 129.2, 132.3. MS (EI):  $m/z$  112, 170, 171, 172, 213 ( $\text{M}^+$  with  $^{35}\text{Cl}$ ), 215 ( $\text{M}^+$  with  $^{37}\text{Cl}$ ). HRMS (EI):  $m/z$  213.1279 ( $\text{M}^+ \text{C}_{12}\text{H}_{20}^{35}\text{ClN}^+$  requires 213.1279).

**5ca.** Pale yellow oil. IR (neat)  $\nu$  3029 (w), 2928 (s), 2850 (m), 2811 (m), 2361 (w), 2342 (w), 1495 (w), 1454 (m), 1436 (w), 1362 (w), 1118 (m), 728 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.69 (2 H, quint,  $J$  5.5), 2.21 (2 H, dt,  $J$  6.5, 5.5), 2.95 (2 H, t,  $J$  5.5), 3.67 (2 H, s), 3.76 (2 H, s), 6.33 (1 H, t,  $J$  6.5), 7.22–7.40 (5 H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  24.1, 28.5, 56.4, 57.9, 62.1, 123.0, 127.1, 128.3, 128.9, 134.0, 138.8. MS (EI):  $m/z$  120, 121, 130, 186 ( $[\text{M} - \text{Br}]^+$ ), 265 ( $\text{M}^+$  with  $^{79}\text{Br}$ ), 267 ( $\text{M}^+$  with  $^{81}\text{Br}$ ). HRMS (EI):  $m/z$  265.0468 ( $\text{M}^+ \text{C}_{13}\text{H}_{16}^{79}\text{BrN}^+$  requires 265.0461).

**5da.** Pale yellow oil. IR (neat)  $\nu$  3028 (w), 2976 (m), 2935 (m), 2836 (m), 2809 (m), 2361 (w), 2342 (w), 1495 (w), 1453 (m), 1368 (m), 1120 (m), 970 (m), 801 (m), 734 (s)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.31 (3 H, d,  $J$  6.5), 1.99 (1 H, dddd,  $J$  17.0, 5.5, 5.0, 3.0), 2.34 (1 H, dddd,  $J$  17.0, 10.0, 3.0, 2.5), 2.62 (1 H, ddd,  $J$  13.0, 5.5, 2.5), 2.94 (1 H, ddd,  $J$  13.0, 10.0, 5.0), 3.17 (1 H, q,  $J$  6.5), 3.72 (2 H, AB system,  $\delta_A$  3.68,  $\delta_B$  3.77,  $J_{AB}$  13.5), 5.87 (1 H, t,  $J$  4.0), 7.22–7.39 (5 H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  16.6, 24.2, 42.1, 57.6, 58.3, 122.5, 127.0, 128.3, 128.7, 135.0, 139.0. MS (EI):  $m/z$  120, 206 ( $[\text{M} - \text{Me}]^+$  with  $^{35}\text{Cl}$ ), 207, 208 ( $[\text{M} - \text{Me}]^+$  with  $^{37}\text{Cl}$ ), 221 ( $\text{M}^+$  with  $^{35}\text{Cl}$ ). HRMS (EI):  $m/z$  221.0971 ( $\text{M}^+ \text{C}_{13}\text{H}_{16}^{35}\text{ClN}^+$  requires 221.0966).

**7ea.** Pale yellow oil. IR (neat)  $\nu$  3063 (w), 3028 (w), 2935 (s), 2854 (m), 2811 (m), 1731 (w), 1637 (w), 1494 (w), 1455 (m), 1366 (m), 1291 (m), 1125 (m), 1028 (m), 775 (m), 732 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.21 (3 H, d,  $J$  7.0), 1.55–1.74 (2 H, m), 2.19 (1 H, dddd,  $J$  14.0, 12.0, 5.5, 1.5), 2.61 (1 H, dt,  $J$  13.0, 3.5), 2.70 (1 H, dt,  $J$  14.0, 4.0), 2.89 (1 H, ddd,  $J$  13.0, 11.0, 3.5), 3.32 (1 H, qdd,  $J$  7.0, 1.5, 1.0), 3.63 (2 H, AB system,  $\delta_A$  3.62,  $\delta_B$  3.64,  $J_{AB}$  14.0), 5.87 (1 H, d,  $J$  1.0), 7.24 (1 H, br t,  $J$  7.0), 7.31 (2 H, br dd,  $J$  7.5, 7.0), 7.34 (2 H, br d,  $J$  7.5).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  14.3, 23.2, 23.5, 46.0, 57.4, 58.5, 110.9, 126.9, 128.3, 128.7, 139.0, 141.2. MS (EI):  $m/z$  117, 149, 220 ( $[\text{M} - \text{Me}]^+$  with  $^{35}\text{Cl}$ ), 221, 222 ( $[\text{M} - \text{Me}]^+$  with  $^{37}\text{Cl}$ ), 235 ( $\text{M}^+$  with  $^{35}\text{Cl}$ ). HRMS (EI):  $m/z$  235.1131 ( $\text{M}^+ \text{C}_{14}\text{H}_{18}^{35}\text{ClN}^+$  requires 235.1123).

**exo-10.** Colourless oil. IR (neat)  $\nu$  3029 (m), 2939 (s), 2859 (m), 2800 (m), 1494 (m), 1453 (s), 1349 (m), 1315 (m), 1247 (m), 1155 (m), 1061 (m), 1029 (m), 762 (s), 737 (s)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.28 (1 H, dddd,  $J$  13.0, 6.5, 5.5, 2.5), 1.35 (1 H, dddd,  $J$  9.5, 9.0, 3.5, 2.5), 1.42 (1 H, dddd,  $J$  13.0, 9.5, 9.0, 5.5, 3.0), 1.51 (1 H, dddd,  $J$  14.0, 9.0, 5.5, 2.5), 1.93 (1 H, ddt,  $J$  14.0, 9.0, 5.5), 2.02 (1 H, ddd,  $J$  11.5, 9.5, 2.5), 2.40 (1 H, dd,  $J$  9.5, 2.5), 2.42 (1 H, ddd,  $J$  11.5, 6.5, 3.0), 2.76 (1 H, dd,  $J$  3.5, 2.5), 3.69 (2 H, AB system,  $\delta_A$  3.65,  $\delta_B$  3.73,  $J_{AB}$  13.0), 7.19 (1 H, br t,  $J$  7.0), 7.23–7.32 (4 H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  20.6, 21.7, 22.3, 33.9, 44.4, 47.6, 61.4, 127.1, 128.2, 129.2, 138.0. MS (EI):  $m/z$  91 ( $\text{Bn}^+$ ), 92, 94, 95, 102, 186 ( $[\text{M} - \text{Cl}]^+$ ), 187, 220, 221 ( $\text{M}^+$  with  $^{35}\text{Cl}$ ), 222. HRMS (EI):  $m/z$  186.1273 ( $[\text{M} - \text{Cl}]^+ \text{C}_{13}\text{H}_{16}\text{N}^+$  requires 186.1278), 221.0989 ( $\text{M}^+ \text{C}_{13}\text{H}_{16}^{35}\text{ClN}^+$  requires 221.0966).

**11.** Colourless oil. IR (neat)  $\nu$  3023 (m), 2928 (s), 2837 (m), 2803 (m), 2760 (m), 1652 (w), 1495 (m), 1453 (m), 1354 (m), 1153 (m), 1115 (m), 1028 (w), 741 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.61 (2 H, distorted quint,  $J$  5.5), 2.18 (2 H, br qd,  $J$  5.5, 1.0), 2.80 (2 H, distorted t,  $J$  5.5), 3.10 (2 H, dd,  $J$  5.5, 1.0), 3.58 (2 H, s), 5.57 (1 H, dt,  $J$  11.0, 5.5, 1.0), 5.85 (1 H, dt,  $J$  11.0, 5.5, 1.0), 7.14–7.30 (5 H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.8, 28.2, 53.4, 58.1, 60.5, 126.8, 128.2, 128.9, 129.3, 133.5, 139.4. MS (EI):  $m/z$  91 ( $\text{Bn}^+$ ), 92, 96, 110, 120, 131, 172, 186, 187 ( $\text{M}^+$ ), 188. HRMS (EI):  $m/z$  187.1354 ( $\text{M}^+ \text{C}_{13}\text{H}_{17}\text{N}^+$  requires 187.1356).

#### Amide *endo*-14

1 M NaOH aqueous solution (10 mL) was added to a solution of 2-(3,4,5-trimethoxyphenyl)acetyl chloride (1.10 equiv., 274  $\mu\text{mol}$ , 67.0 mg) and *endo*-9 (1.00 equiv., 249  $\mu\text{mol}$ , 41.6 mg) in  $\text{CH}_2\text{Cl}_2$  (10 mL). After 2 h of stirring at 20  $^\circ\text{C}$ , the organic layer was separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  10 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford a thick pale yellow oil (74.0 mg). Purification by flash column chromatography on silica gel (EtOAc/petroleum ether, gradient from 30 to 100%) afforded pure *endo*-14 (57.6 mg, 218  $\mu\text{mol}$ , 68%).

**endo-14.** Thick pale yellow oil. IR (neat)  $\nu$  2996 (w), 2939 (m), 2871 (w), 2838 (w), 1651 (s, C=O), 1590 (m), 1508 (m), 1457 (m), 1424 (m), 1334 (m), 1240 (m), 1125 (s),



1008 (m), 789 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), 84:16 mixture of two rotamers. Major rotamer:  $\delta$  1.50–1.75 (4H, m), 2.02 (1H, m), 2.83 (1H, ddd,  $J$  13.0, 8.5, 3.5), 2.98 (1H, dd,  $J$  9.5, 5.0), 3.34 (1H, dd,  $J$  8.0, 5.0), 3.74 (2 H, AB system,  $\delta_{\text{A}}$  3.71,  $\delta_{\text{B}}$  3.77,  $J_{\text{AB}}$  15.0), 3.83 (3H, s), 3.85 (6H, s), 3.93 (1H, ddd,  $J$  13.0, 6.5, 4.0), 6.51 (2H, s). Minor rotamer, characteristic signals:  $\delta$  3.15 (1H, ddd,  $J$  12.0, 8.0, 4.0), 3.21 (1H, dd,  $J$  9.0, 6.0), 3.35 (1 H, m), 6.51 (2H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz), 84:16 mixture of two rotamers. Major rotamer:  $\delta$  16.2, 16.3, 21.8, 30.5, 37.2, 39.9, 40.9, 56.0, 60.7, 106.3, 130.5, 136.6, 153.0, 172.8. Minor rotamer:  $\delta$  14.7, 16.0, 22.6, 29.9, 36.4, 41.3, 43.8, 56.0, 60.7, 105.6, 130.3, 136.5, 153.1, 172.3. MS (EI):  $m/z$  96, 97, 181, 182, 208, 244, 246, 304 ( $[\text{M} - \text{Cl}]^+$ ), 339 ( $\text{M}^+$  with  $^{35}\text{Cl}$ ), 341 ( $\text{M}^+$  with  $^{37}\text{Cl}$ ). HRMS (EI):  $m/z$  339.1228 ( $\text{M}^+ \text{C}_{17}\text{H}_{22}^{35}\text{ClNO}_4^{++}$  requires 339.1232).

### Amide 15

37% HCl aqueous solution (1 drop) was added, at 20 °C, to a solution of *endo*-14 (1.00 equiv., 64.7  $\mu\text{mol}$ , 22.0 mg) in DMF (1.0 mL). The mixture was heated at 150 °C for 90 minutes in a microwave reactor (power 250 W). After cooling,  $\text{H}_2\text{O}$  (15 mL) was added and the mixture was extracted with EtOAc ( $3 \times 10$  mL). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford a sticky orange oil (14.0 mg). Purification by flash column chromatography on silica gel (EtOAc/petroleum ether, gradient from 5 to 50%) gave pure 15 (10.0 mg, 33.0  $\mu\text{mol}$ , 51%).

15. Pale yellow oil. IR (neat)  $\nu$  2996 (w), 2937 (w), 2838 (w), 1666 (m, C=O), 1634 (m), 1599 (m), 1591 (m), 1508 (m), 1461 (m), 1425 (m), 1332 (m), 1240 (m), 1126 (s), 1007 (w), 715 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.51 (2H, qd,  $J$  5.0, 1.5), 3.75 (2H, s), 3.77 (2H, t,  $J$  5.0), 3.83 (3H, s), 3.84 (6H, s), 5.30 (1H, dd,  $J$  9.0, 7.5), 5.86 (1H, ddt,  $J$  11.5, 7.5, 1.5), 5.98 (1H, dt,  $J$  11.5, 5.0), 6.45 (2H, s), 6.62 (1H, d,  $J$  9.0).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  32.6, 41.7, 42.2, 56.1, 60.8, 105.9, 111.1, 122.7, 129.2, 129.9, 133.6, 136.9, 153.3, 169.1. MS (EI):  $m/z$  95, 97, 109, 111, 121, 123, 125, 135, 147, 193, 208, 221, 303 ( $\text{M}^+$ ).

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