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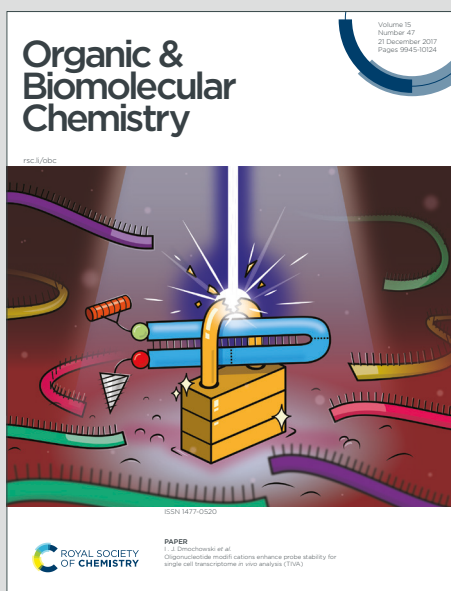
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# Bicyclic *N*-Dihalocyclopropylamide Derivatives as Precursors of Nitrogen-Containing Fused Polycyclic Systems.

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Veronika Šlachťová,<sup>a</sup> Nicolas Casaretto,<sup>b</sup> Lucie Brulíková,<sup>a</sup> Yvan Six\*.<sup>c</sup>

- <sup>a</sup> Department of Organic Chemistry, Faculty of Science, Palacký University Olomouc, 17. listopadu 12, 771 46, Olomouc, Czech Republic.
- <sup>b</sup> Laboratoire de Chimie Moléculaire (LCM), UMR 9168 CNRS / École Polytechnique, Institut Polytechnique de Paris, 91128 Palaiseau Cedex, France.
- <sup>c</sup> Laboratoire de Synthèse Organique (LSO), UMR 7652 CNRS / ENSTA / École Polytechnique, Institut Polytechnique de Paris, 91128 Palaiseau Cedex, France.

## Abstract

Examples of carbon-carbon bond-forming cyclisation reactions, involving allyl cations generated by the thermal ring-opening of halocyclopropanes, have been scarcely reported. In this contribution, we are describing the results of a study conducted with *N*-dihalocyclopropylamide substrates, designed as precursors of cyclic iminium intermediates that were aimed at participating in intramolecular reactions with electron-rich aromatic groups. Competitive side-reactions were identified, and access to the desired polycyclic products was carefully evaluated. The results were found to be strongly dependent on the substitution pattern of the nucleophilic aromatic moieties, as well as on the sizes of the rings of the target products. In spite of the rather moderate yields generally obtained, this approach represents a particularly short and inexpensive route to various interesting nitrogen-containing polycyclic systems, namely benzoindolizidine, benzoquinolizidine, piperidinobenzoazepane and azepanoisoquinoline compounds.

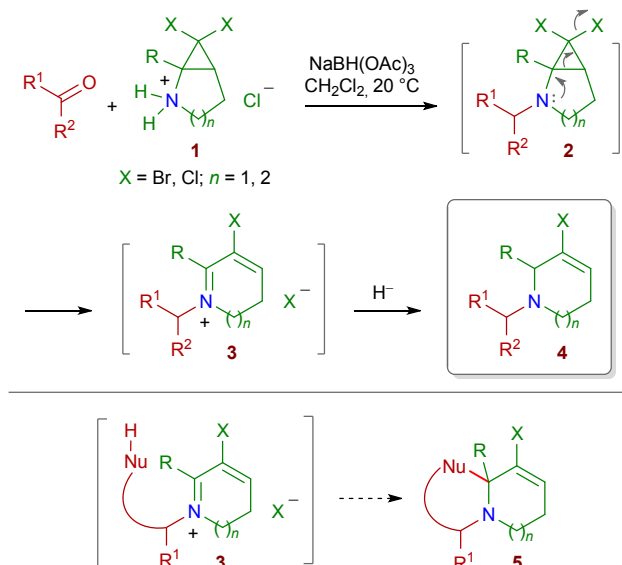
Keywords: halocyclopropanes; allyl cations; iminium ions; aromatic electrophilic substitution; nitrogen heterocycles

## Introduction

Cyclopropanes substituted with a leaving group (Cl, Br, OTs...) may undergo a thermal transformation that can be assimilated to an electrocyclic ring-opening reaction, with the simultaneous departure of the leaving group.<sup>1</sup> This provides a general way to generate allyl cations. In particular, a number of applications have been developed using *gem*-dihalocyclopropanes,<sup>2</sup> among which very few involve carbon-carbon bond-making processes.<sup>3</sup>

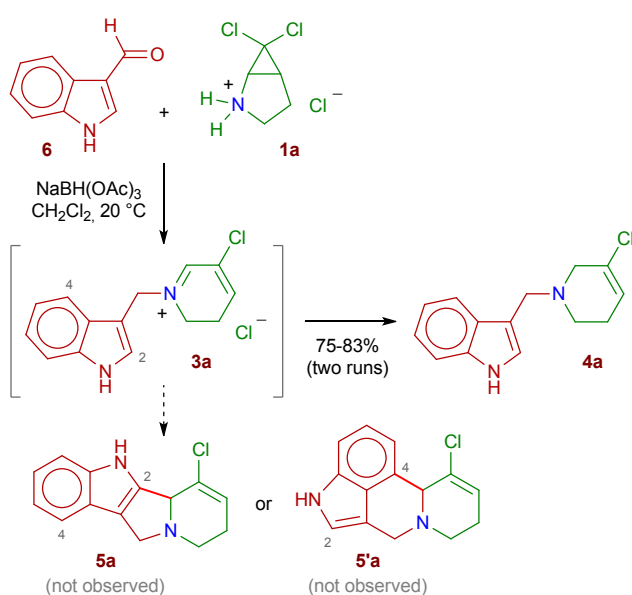
A few years ago, we reported a large rate acceleration in the case of bicyclic amine substrates **2**. Indeed, these molecules, generated by reductive amination of aldehydes or ketones with amino-2-halocyclopropanes hydrochloride salts **1**, undergo spontaneous ring-opening at room temperature. The resulting iminium species **3** are then trapped by the hydride reagent used in excess, to give

functionalised azepane or piperidine derivatives **4** (Scheme 1).<sup>4</sup> We next considered the possibility of getting the transient cationic intermediate **3** to react with other nucleophiles already attached to the molecule, in order to obtain interesting bicyclic nitrogen-containing systems **5** (Scheme 1, bottom).



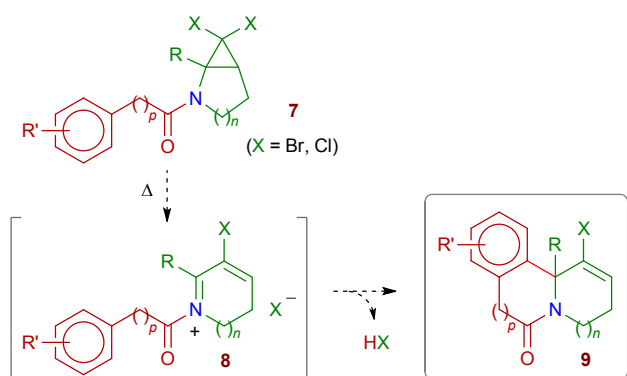
**Scheme 1.** Previous work: reductive amination/cyclopropane ring-opening/iminium reduction sequence.

This idea was probed with indole-3-carboxaldehyde **6** and the hydrochloride salt **1a**. However, possible cyclisation at position 2 or 4 of the indole ring was not observed. Instead of the desired products **5a** or **5'a**, the tertiary amine **4a** was obtained in good yield, showing that reduction of the iminium intermediate **3a** by the hydride reagent was a faster competitive process (Scheme 2).<sup>4</sup>



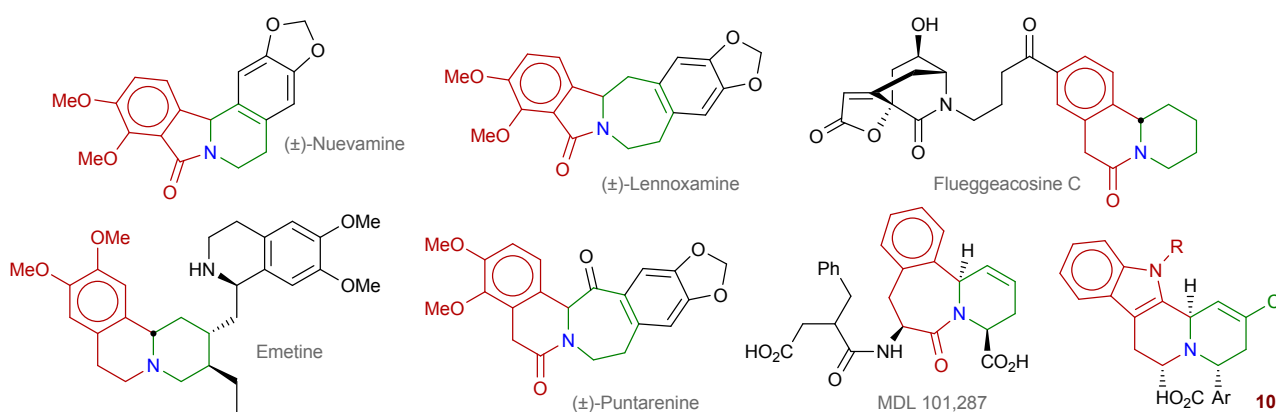
**Scheme 2.** Attempted synthesis of the cyclised products **5a** and **5'a** from aldehyde **6** and the aminocyclopropane hydrochloride **1a**.

Generating the cyclic iminium intermediate in the absence of any hydride reagent and, more generally, under conditions that would not interfere with the cyclisation process, was thus a more promising approach. With this respect, stable carboxylic amide precursors **7** were judged more suitable substrates than transient, unstable amines of type **2**. The ring-opening could be triggered by heating, and it was hoped that the intermediate iminium species **8** would then undergo cyclisation to produce various lactams **9** (Scheme 3).



**Scheme 3.** Planned transformation of aminodihalocyclopropanes **7** into polycyclic systems **9**.

The type of skeletons thus targeted is of special interest, as it is found in the structures of plant natural products and other biologically active molecules. Selected examples are displayed in **Figure 1**. Nuevamine and lennoxamine were isolated from a South American shrub, *Berberis Darwinii*.<sup>5</sup> The former exercises a protective effect against oxidative damage.<sup>6</sup> Flueggeacosine C, a recently isolated compound, can induce neuronal differentiation.<sup>7</sup> The alkaloid emetine, was introduced over a century ago for the treatment of amoebic dysentery, in spite of its emetic properties.<sup>8</sup> Its activity against various viruses has prompted its evaluation in the treatment of Covid-19.<sup>9</sup> Puntarenine, isolated from the yellowroot *Xanthorrhiza simplicissima*, displays moderate activity against pathogenic fungi.<sup>10</sup> MDL 101,287 is a synthetic enkephalinase inhibitor, patented by the Merrell Dow Pharmaceuticals company.<sup>11</sup> Finally, compounds having the general structure **10**, inspired from alkaloids such as yohimbine, were shown to be potent inhibitors of MptpB, a virulence factor of *Mycobacterium tuberculosis*.<sup>12</sup>



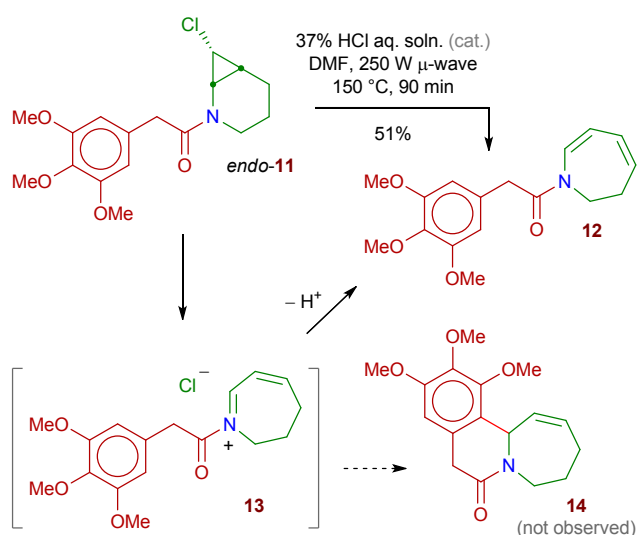
**Figure 1.** Selected examples of natural products and biologically active compounds having the targeted polycyclic systems in their structures.

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## Results and discussion

### Early results

In our previous work, a single attempt at performing a cyclopropane ring-opening/intramolecular aromatic electrophilic substitution sequence was carried out with the monochloro substrate *endo*-**11**, fitted with an electron-rich trimethoxyphenyl group. After heating at 150 °C with microwaves in DMF, in the presence of a drop of concentrated HCl aqueous solution, the dihydroazepine derivative **12** had been obtained in 51% yield (**Scheme 4**). The other diastereoisomer *exo*-**11** had been left unreacted under the same conditions, which is consistent with the Woodward-Hoffmann-DePuy rule.<sup>1a</sup> The production of **12** can readily be interpreted as the result of the loss of a proton from the iminium intermediate **13**,<sup>13</sup> rather than the desired cyclisation to the tricyclic system **14**.



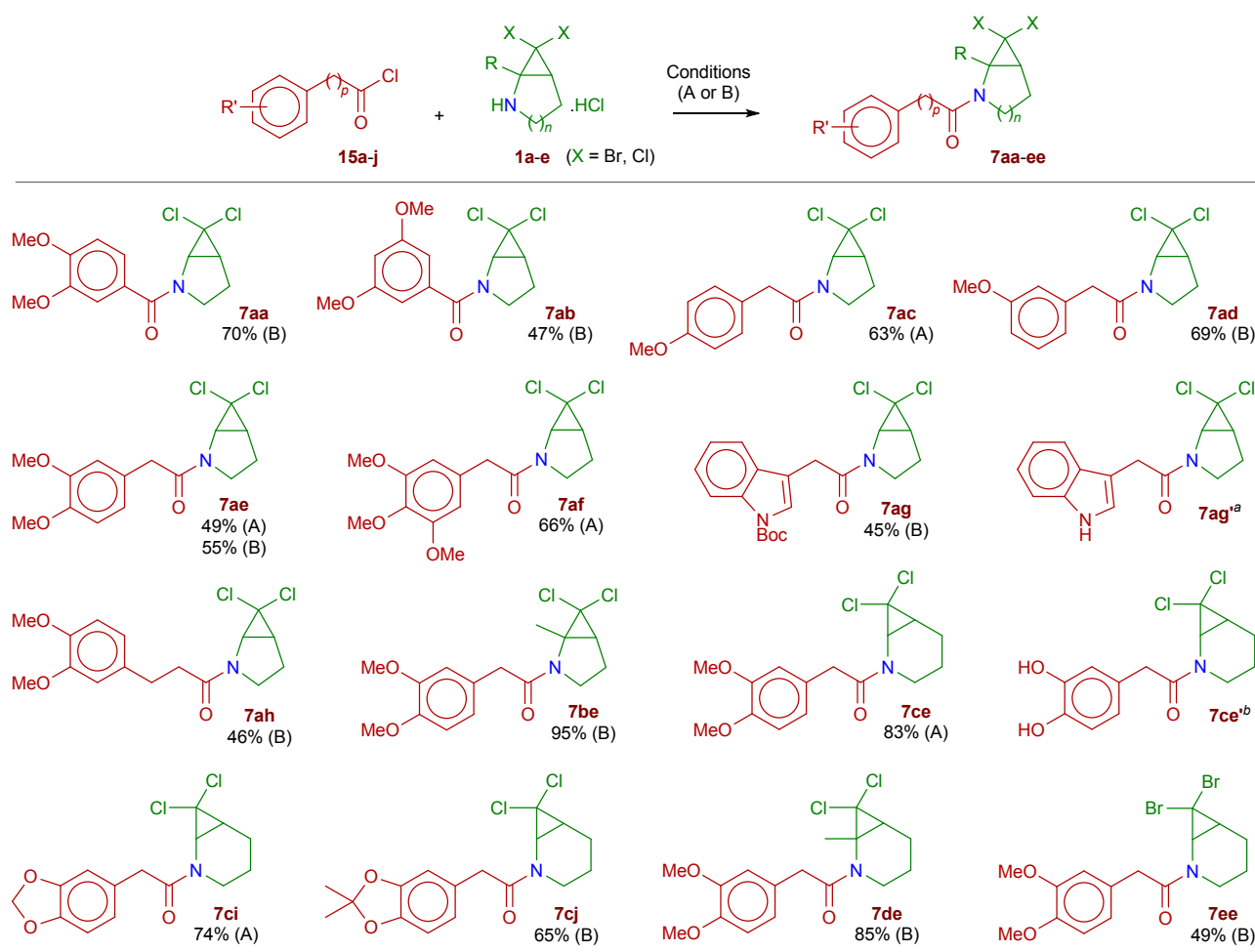
**Scheme 4.** Ring-expansion of the chlorocyclopropane compound *endo*-**11**.

Undeterred by this little encouraging preliminary result, we decided to focus on dihalocyclopropane substrates, to investigate alternative conditions that might favour their cyclisation, and to examine the influence of the chain length, ring size and substitution pattern.

### Synthesis of the substrates

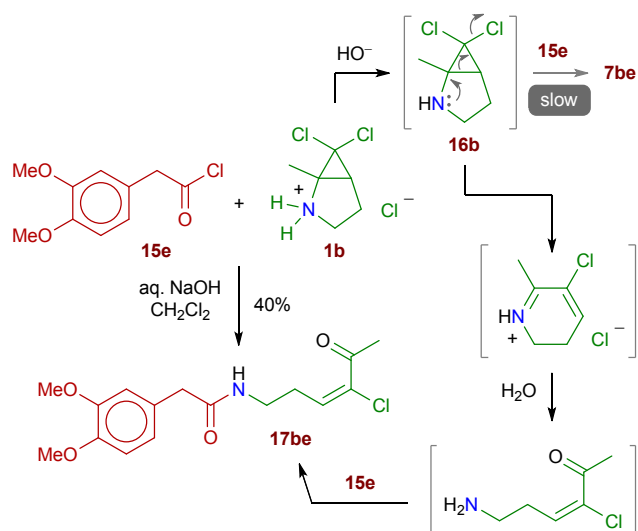
To this end, a range of *N*-(2,2-dihalocyclopropyl)amides **7aa-ee** were prepared, with diversely substituted aromatic rings, different spacers between the latter and the carbonyl group and various fused bicyclic cyclopropane systems, with or without a methyl group at the ring junction (**Table 1**). These molecules were typically made by reaction of the requisite acyl chlorides **15** with the aminocyclopropane hydrochloride salts **1**, the synthesis of which has already been described.<sup>4</sup> Two

sets of conditions were applied, either classic Schotten-Baumann type conditions involving a biphasic reaction medium, composed of a sodium hydroxide aqueous solution and dichloromethane (conditions A), or the use of triethylamine as the base, in dichloromethane, at low temperature (conditions B). In general, moderate to good yields were obtained using either method. However, some syntheses, like the preparation of **7be**, could be achieved under conditions B only. This can be imputed to the diminished nucleophilicity of the unstable amine intermediate **16b**, caused by the presence of the angular methyl group. This is evidenced by the outcome of an attempted synthesis of **7be** under conditions A, which resulted in the formation of the secondary amide **17be** (Scheme 5, top). This result can be explained by the competitive ring-opening of **16b**, followed by (reversible) hydrolysis to the primary amine **18b**, which is then rapidly trapped by the acyl chloride **15e** (Scheme 5, bottom). Under conditions B, competitive ring-opening may occur as well but it is plausible that the much lower temperature can minimise it. As for the free indole and the bis-hydroxyl-substituted substrates **7ag'** and **7ce'**, they were prepared by cleavage of the Boc group of **7ag** and demethylation of **7ce**, respectively.



**Table 1.** Synthesis of the substrates **7aa-ee**. Conditions A: 1 M NaOH aqueous solution, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 15 minutes. Conditions B: Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 to 0 °C, 2 h.

<sup>a</sup> Synthesised by cleavage of the Boc group of **7ag** (TFA, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 76%). <sup>b</sup> Synthesised by demethylation of **7ce** (BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 20 °C, 61%).

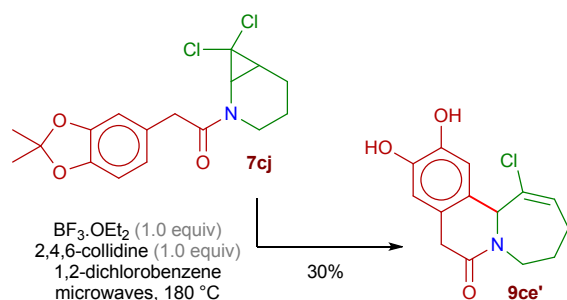


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**Scheme 5.** Formation of the undesired secondary amide **17be**, starting from the acyl chloride **15e** and the cyclopropylammonium salt **1b**.

#### Investigation of the cyclisation reactions

With the desired set of substrates being synthesised, the projected cyclisation process could be explored. Various conditions were investigated, with some limited success.<sup>14</sup> For instance, heating the acetal-protected catechol substrate **7cj** with microwaves in the presence of trifluoroborane etherate and 2,4,6-collidine, introduced as a base intended to trap the HCl produced, directly provided the deprotected cyclised product **9ce'**, albeit in rather low 30% yield (**Scheme 6**). An analogous result was achieved starting from the unprotected catechol derivative **7ce'**.<sup>14</sup>



**Scheme 6.** Direct transformation of the 2,2-dichloroaminocyclopropane **7cj** into the tetrahydroazepinoisoquinoline **9ce'**.

These early results seemed promising enough, but suffered from a lack of generality and were associated with reproducibility problems. Moreover, this first series of experiments displayed a strong tendency to produce cyclic *N*-dienylamide derivatives **19**, rather than the desired cyclised molecules. These compounds **19** arose from deprotonation of the iminium intermediates **8**, just as had happened in the case of the iminium species **13**, and the ultimate isolation of **12** (**Scheme 4**).<sup>4,13</sup> Nonetheless, it was reasoned that the iminium species **8** could be regenerated by treatment with a strong acid, and



that under such conditions, cyclisation could eventually be forced to proceed. Such a two-step sequence was thus put under scrutiny (**Table 2**).

For the first, ring-expanding step, heating the azabicyclo[3.1.0]hexane systems **7aa-be** in acetonitrile (b.p. 82 °C) at reflux for 1 h was found to be suitable, except for the methyl-substituted substrate **7be**, for which essentially no conversion was observed. In refluxing toluene (b.p. 111 °C), the reaction of **7be** remained incomplete after 8 h and it took 5 h in refluxing chlorobenzene (b.p. 132 °C) to achieve full conversion. The ring-expansion of the higher homologues **7ce-ee** having a fused six-membered ring required higher temperature as well. This can be explained by the reduced ring strain of the azabicyclo[4.1.0]heptane bicyclic system. The reactions of these substrates were thus typically performed in refluxing 1,2-dichlorobenzene (b.p. 180 °C). An exception was the dibromocyclopropane substrate **7ee** which, as expected, was easier to open than the dichloro analogue **7ce**. Its transformation could thus be performed at comparatively lower temperature, in refluxing chlorobenzene (see **Scheme 10**), although no significant conversion was observed in refluxing acetonitrile. Again, and conversely, the substrate **7de** fitted with an angular methyl group and chlorine atoms was found to be more reluctant towards ring-opening. Its reaction required the use of silver trifluoroborate, which promoted the departure of a chloride ion.

Overall, the ring-expanding process afforded the expected cyclic *N*-dienylamide intermediates **19aa-ee** in all cases. These compounds were observed by NMR but were typically not isolated and engaged directly in the second step. The only exception was the reaction of the free indole derivative **7ag'**, which upon heating in acetonitrile led to an unidentified product, not obtained in pure form, which could be the cyclised compound **9ag'**, thus produced directly. This transformation will be the subject of further investigations in the near future.

From the *N*-dienylamide intermediates **19**, the subsequent cyclisation step was typically performed in toluene at 90 °C, in the presence of 0.5 equivalent of trifluoromethanesulfonic acid. The reactions proceeded in low to moderate yields but the expected nitrogen-containing polycyclic systems **9** could generally be obtained (**Table 2**). Interestingly, in the case of the azabicyclo[3.1.0]hexane substrates, both steps, cyclopropane ring-cleavage and intramolecular electrophilic aromatic substitution, can be performed in the same solvent, toluene, following a more practical one-pot procedure. This is demonstrated by the transformation of **7ae**, which gave **9ae** in slightly improved yield (53%, conditions D), as compared with the original two-step method (49%, conditions C). Under these one-pot conditions, one should note that the first step is markedly slower, in spite of the higher refluxing temperature of toluene. This is not surprising: indeed, this transformation produces conjugated iminium and halide ions from a neutral molecule; the more polar solvent acetonitrile is expected to provide better stabilisation of the developing charges of the transition state.

The following additional comments can be made. First and as expected, substrates having the most electron-rich aromatic rings display a tendency to give better results. This can be seen, for instance, by comparing the transformations of **7ad**, **7ae** and **7af**. Indeed, the 3,4,5-trimethoxyphenyl-substituted substrate **7af** led to the production of the cyclised compound **9af** in 52% yield while, under otherwise identical conditions, the 3,4-dimethoxyphenyl- and 3-methoxyphenyl-substituted substrates **7ae** and **7ad** gave the corresponding products in 49% and 29% yields (**Table 2**). This is also consistent with the poor result obtained with the 4-methoxyphenyl-substituted substrate **7ac**, for which the +M effect of the methoxy substituent does not activate the right positions.

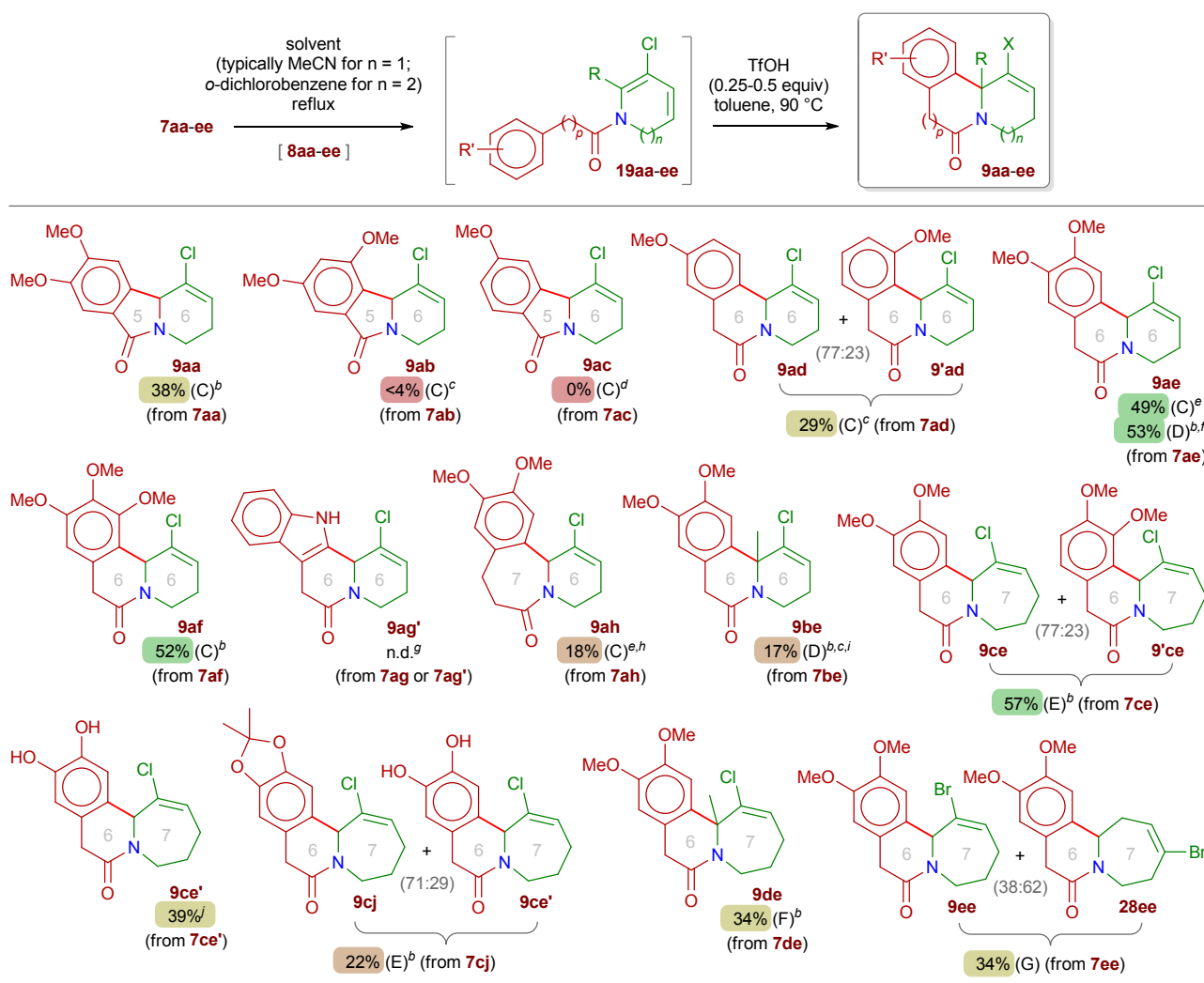
Nevertheless, steric factors proved to be important as well. For instance, while the cyclisation of **7aa** proceeded reasonably well, the synthesis of **9ab** was inefficient (<4% yield), in spite of an

electronically ideal 3,5-dimethoxyl substitution pattern. Indeed, in this molecule, both possible cyclisation sites are sterically hindered by the presence of substituents at the *ortho* positions.

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Considering the size of the ring that is being closed, the ease of the intramolecular electrophilic aromatic substitution follows the trend  $6 > 5 > 7$ . The formation of the isoindolinone **9aa** is less efficient (38% yield) than that of the homologue **9ae** (49% under the same conditions). For **9aa**, outside its somewhat higher ring strain, a possible explanation could reside in the bond angles connecting those atoms of the iminium intermediate **8aa**, which belong to the ring being formed. These angles, all close to  $120^\circ$ , are not ideal for the formation of a five-membered ring. As for the closure of the seven-membered ring starting from **7ah**, the results clearly show that it is even more difficult (18% of product **9ah**, entry 6; 33% combined yield with the by-product **25ah**; see Scheme 8). This is consistent with the reputation of seven-membered rings to be comparatively challenging to make.<sup>15</sup>

More generally, it must be mentioned that the formation of by-products was observed in several cases, which can account for the unsatisfactory yields sometimes recorded, at least in part (see the next subsection for detail). Other reaction conditions were investigated, with no improvement of the results. They are detailed in the supporting information.

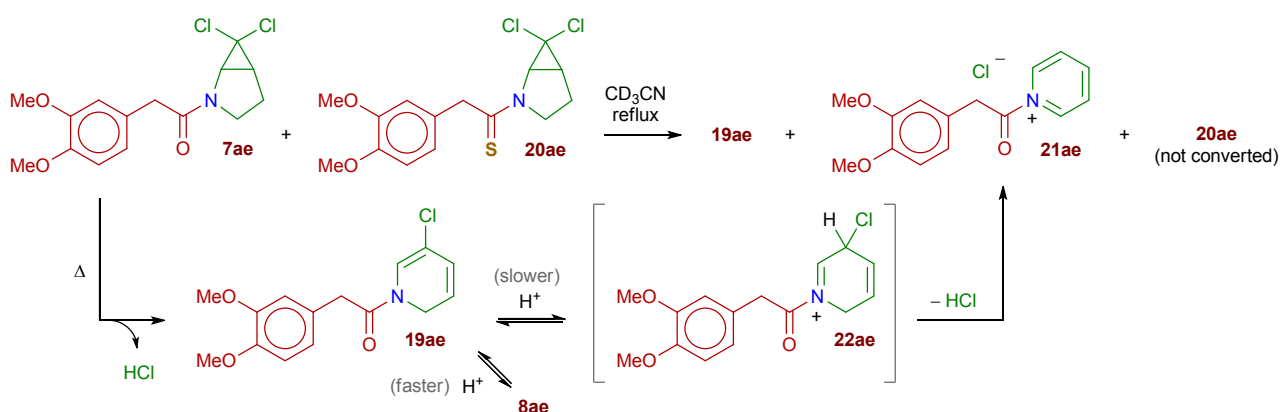


**Table 2.** Synthesis of the cyclised products **9** via the cyclopropane-ring cleavage intermediates **19**.

<sup>a</sup> Conditions C: MeCN, reflux (first step); TfOH (0.5 equiv), toluene, 90 °C (second step). Conditions D: toluene, reflux (first step); TfOH (0.5 equiv), toluene, 90 °C (second step). Conditions E: 1,2-dichlorobenzene, reflux (first step); TfOH (0.5 equiv), toluene, 90 °C (second step). Conditions F: AgBF<sub>4</sub> (2.0 equiv), 1,2-dichlorobenzene, reflux. (first step); TfOH (0.5 equiv), toluene, 90 °C (second step). <sup>b</sup> No other regioisomer **9'** or **23** was detected. <sup>c</sup> 0.25 equiv of TfOH was used. <sup>d</sup> A complex mixture of unidentified products was obtained. <sup>e</sup> Minor amounts of isomer **23** were observed. <sup>f</sup> One drop of TfOH was used. <sup>g</sup> This product was not obtained in sufficiently pure form to confirm its structure with absolute certainty and to determine the yield. <sup>h</sup> Other products were formed as well. See **Scheme 8** and corresponding text. <sup>i</sup> Some starting cyclopropane **7be** was recovered (37%). <sup>j</sup> Other conditions were applied: BF<sub>3</sub>.OEt<sub>2</sub> (2.5 equiv), 1,2-dichlorobenzene, 180 °C (microwaves). The yield was estimated by NMR.

In a complementary experiment, the possibility that secondary amides such as **17be** could also be suitable precursors for the cyclised products was probed. A trial in which **17be** was submitted to the typical reaction conditions resulted in the production of **9be**, together with several by-products. The yield remained low (<41%) and **9be** could not be obtained with satisfactory purity. This Pictet-Spengler-like route was thus not judged as a practical alternative to the reaction of the cyclopropane **7be**.

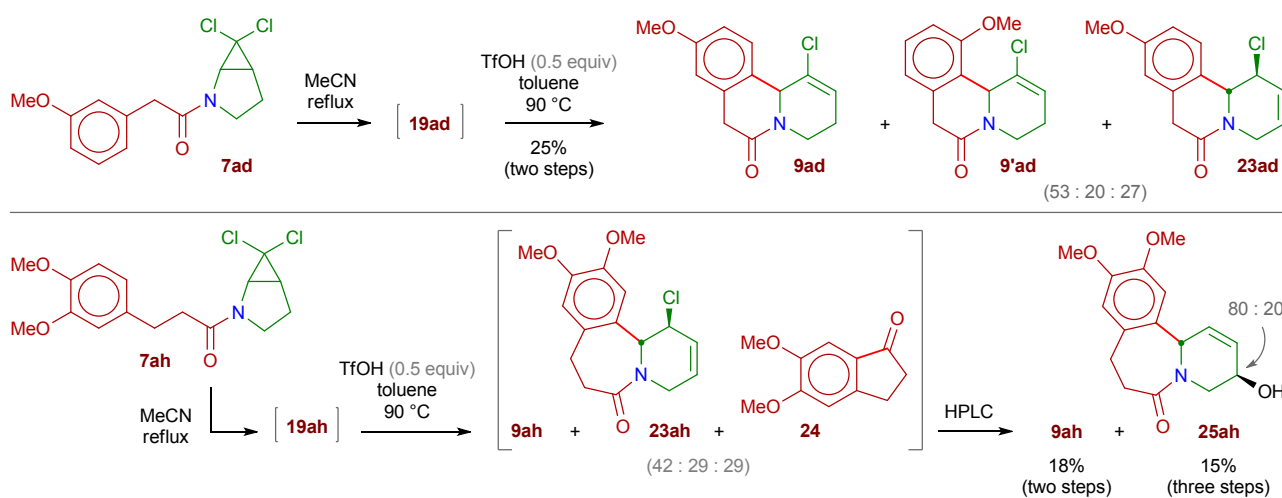
The question of the use of thioamide precursors, rather than the amide precursors **7**, was examined as well. The thioamide **20ae** was thus prepared from the corresponding amide **7ae**, using Lawesson's reagent, and a competition experiment with **7ae** and **20ae** was run in an NMR tube (**Scheme 7**). While **7ae** was entirely converted after 30 minutes of reflux in acetonitrile-*d*<sub>3</sub>, the thioamide **20ae** remained unscathed. The transformation of **7ae** into the dihydropyridine derivative **19ae** was observed as expected. The latter was found to slowly undergo conversion into a new compound, the <sup>1</sup>H NMR signals of which are consistent with the *N*-acylpyridinium structure **21ae**. In contrast to the other reactions, which had been performed with a gentle flow of nitrogen, this experiment was conducted in a closed NMR tube. The HCl produced was not allowed to escape and a plausible mechanism for the formation of **21ae** involves reversible protonation of **19ae** at the carbon atom bearing the chlorine substituent, generating the iminium species **22ae**. Dehydrochlorination of this intermediate would then irreversibly produce **21ae**.



**Scheme 7.** Competition experiment performed from an equimolar mixture of amide **7ae** and thioamide **20ae**; proposed mechanism for the generation of the *N*-acylpyridinium salt **21ae**.

### Non-typical reaction outcomes

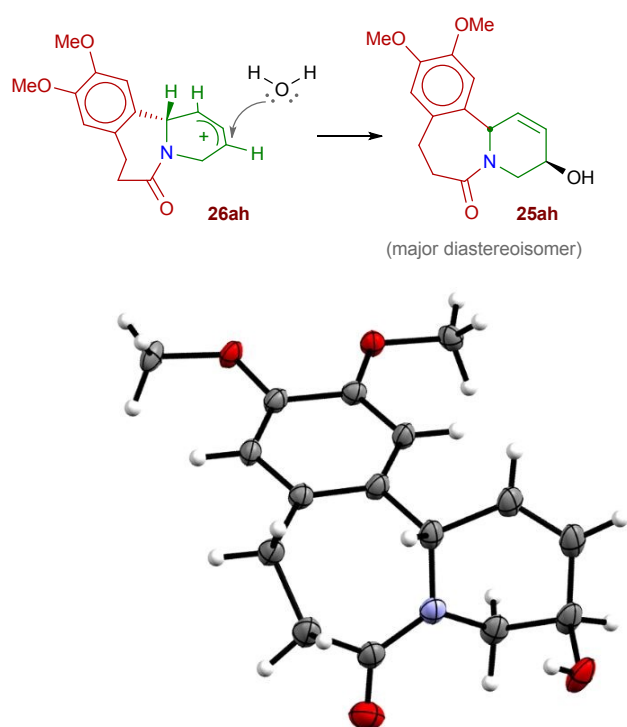
The challenge raised by the synthesis of the desired polycyclic heterocycles, already highlighted by the possibility of the side formation of *N*-acylpyridinium species such as **21ae**, is further illustrated in some cases, by the production of other unexpected compounds. For instance, various amounts of cyclised molecules **23**, having the C=C double bond located at a different position, were identified starting from **7ad**, **7ae**, **7ah** and **7be**. Two examples are presented in **Scheme 8**. The relative configuration of the chiral centres of **23ad** is assigned as shown, on the basis of the high value (10.0 Hz) of the  $^3J$  coupling constant between the ring junction proton and the proton located at the  $\alpha$  position relative to the chlorine atom, consistent with a dihedral angle close to  $180^\circ$ . Starting from **7ah**, significant amounts of the by-product **23ah**, analogous to **23ad**, were detected as well. The relative configuration of **23ah** is tentatively assigned by comparison with **23ad**. The marginal production of the indanone compound **24** is also worthy of note. It is readily explained by an intramolecular Friedel-Crafts-type acylation reaction. Interestingly, purification of the crude product by flash chromatography followed by HPLC eventually led to the isolation of the alcohol diastereoisomers **25ah**. A pure sample of the major diastereoisomer was obtained by recrystallisation from MeOH containing a few drops of  $\text{CHCl}_3$ . Its structure and relative configuration were confirmed by X-ray crystallography (**Scheme 9**).<sup>16</sup> A plausible explanation for the formation of **25ah** is an  $\text{S}_{\text{N}}1'$  substitution reaction taking place at the allylic chloride subunit of **23ah**, under the conditions of the HPLC purification. Water being present in the mobile phase, it could play the role of the nucleophile. The regio- and diastereo-selectivity observed can be explained by preferential attack of the allyl cation intermediate **26ah** at the least hindered site, approaching from the least hindered top face (**Scheme 9**, top).<sup>17</sup>



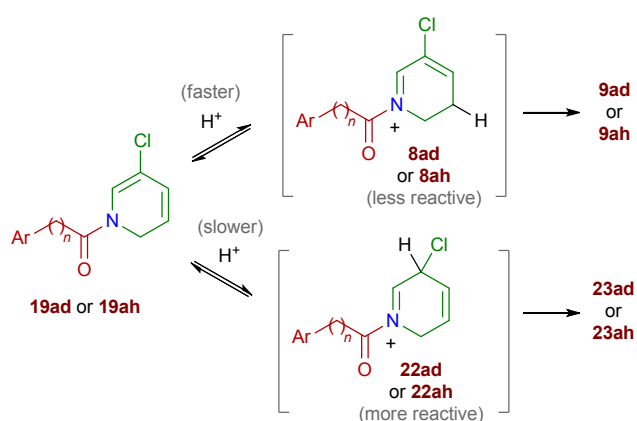
**Scheme 8.** Competitive formation of allylic chloride by-products **23ad** and **23ah**, and transformation of the latter into alcohol diastereoisomers **25ah**.

As for the competitive formation of cyclised by-products of type **23**, it may arise from alternative protonation at the most hindered site of **19** (e.g. **19ad** or **19ah**, **Scheme 10**). The resulting iminium intermediate **22ad** or **22ah** could then undergo cyclisation, with the electron-rich aromatic group attacking at the face opposite to the chlorine substituent, to produce **23ad** or **23ah**, with the diastereoselectivity observed. The outcome of the reaction would be determined by the Curtin-Hammett principle: on the one hand, formation of the iminium intermediates **8ad** or **8ah** would be faster than the generation of its regioisomers **22ad** or **22ah**; on the other hand, **8ad** and **8ah** are

conjugated and are expected to be less reactive than **22ad** or **22ah**. Accordingly, in difficult cyclisation reactions, such as the seven-membered ring-closure producing **9ah**, the alternative pathway leading to **23ah** becomes increasingly significant.



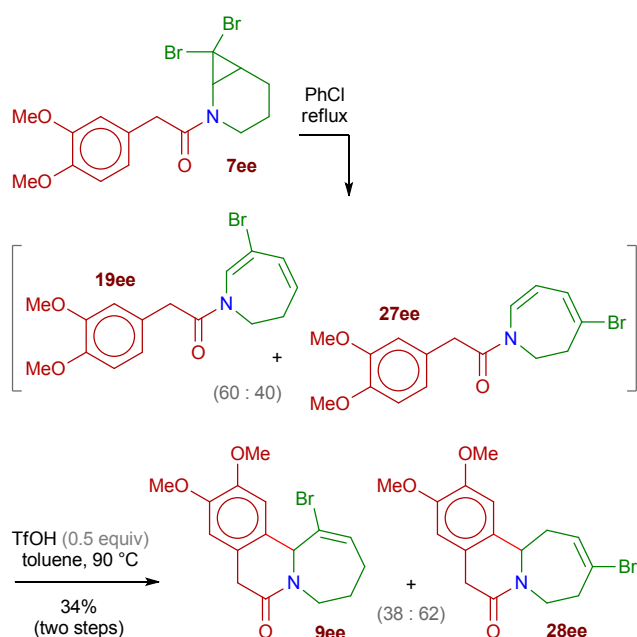
**Scheme 9.** Regio- and diastereo-selective trapping of the allyl cation intermediate **26ah** by water, and X-ray structure of the major diastereoisomer of alcohol **25ah**. Ellipsoids are drawn at the 50% probability level.



**Scheme 10.** Competitive pathways leading either to the cyclised products **9** or **23**.

Another rather surprising competitive process was observed starting from the dibromo substrate **7ee**. Indeed, along with the expected cyclised product **9ee**, an isomer **28ee** was observed (**Scheme 11**). This product had both the bromine atom and the C=C double bond located at a different position of the seven-membered ring. Analysis of the mixture obtained after the first step revealed the presence, in comparatively large amounts, of **27ee**, a regioisomer of the expected intermediate **19ee** and an

obvious precursor of **28ee**. To account for its presence, an isomerisation of **19ee** is proposed, by a game of protonation/deprotonation/bromide elimination and addition elementary steps, which are detailed in the supporting information.



**Scheme 11.** Cyclopropane ring-opening and cyclisation, performed from the dibromo substrate **7ee**.

### Analysis

The often low or moderate yields obtained in the cyclisation reactions can be attributed, in large part, to selectivity problems with the elementary step of the protonation of the *N*-dienylamide intermediates **19**. Indeed, this protonation can take place at various positions. Although these competitive events are reversible, our results indicate that the positively charged species thus produced can lead to undesired products:

- Protonation at the oxygen atom of the carbonyl group can trigger subsequent attack by a nucleophile, with eventual loss of the nitrogen-containing heterocycle. This may proceed in an intramolecular fashion, as evidenced by the formation of indanone **24** (**Scheme 8**), or intermolecularly. In the latter case, the nucleophile could be either the starting material or the product(s), which would result in high molecular weight oligomeric products.
- Protonation at the nitrogen atom would lead to another type of amidium species, which could follow similar unwanted pathways.
- Protonation at the site bearing the halogen atom generates iminium intermediates **22**, which can eventually lead to pyridinium salts **21** or regioisomers **23** or **28**.
- Only protonation at the remote  $\delta$  position of the dienyl system produces the iminium intermediates **8**, which are the precursors of the desired polycyclic products **9**.

### Conclusions

In summary, bicyclic *N*-dihalocyclopropylamide derivatives, fitted with a remote electron-rich aromatic group, can participate in a cyclopropane ring-opening / intramolecular electrophilic aromatic substitution sequence. This provides an expedient access to various functionalised polycyclic systems that include two fused rings having a nitrogen atom at the ring junction.

Nevertheless, these transformations proved to be challenging, for several reasons:

The cyclopropane ring-opening step requires heating to overcome its activation energy. The latter depends both on the nature of the bicyclic system and on the nature of the halide substituents. The more strained azabicyclo[3.1.0]hexane substrates are easier to open than the azabicyclo[4.1.0]heptane compounds and, as expected, the dibromocyclopropane derivatives open more readily than their dichlorocyclopropane counterparts.

The ring-opened cyclic iminium species are strongly acidic. For the cyclisation reactions, triflic acid is used to regenerate them by protonation of the cyclic *N*-dienylamide intermediates. Out of several possible protonation sites, only one can lead to the desired products. Heating is required as well, to favour access to the suitable rotamer of the amide group for cyclisation, and to reach the transition state. The formation of 5-, 6- and 7-membered rings can thus be achieved, with variable results.

Due to these troublesome aspects and the possibility of competitive unwanted pathways, some of which were disclosed experimentally, yields seldom exceeded 50%. This limitation is to be balanced with the interesting structures of the products, as well as the small number of steps and the low cost of their synthesis.

## Experimental part

### *General information*

When used as solvents for reactions, dichloromethane and toluene were purified using a MB SPS-800 solvent purification system (MBRAUN). Petroleum ether (40–60 °C fraction) was distilled at 450 mbar before use. Other solvents and commercial reagents were purchased from Sigma-Aldrich ([www.sigmaaldrich.com](http://www.sigmaaldrich.com)) or Fluorochem ([www.fluorochem.co.uk](http://www.fluorochem.co.uk)), and used as received, without purification. The procedures for the syntheses of the amide substrates **7aa-ee**, as well as the corresponding characterisation data, can be found in the supporting information.

The temperatures mentioned are the temperatures of the oil baths used. The microwave-promoted experiments were run using a CEM Discover Microwave Synthesis System with the power, 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.

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. The LC-MS analyses were carried out on a UHPLC-MS system (Waters, Santa Clara, USA). This system consists of an Acquity UHPLC chromatograph with a photodiode array detector and a single quadrupole mass spectrometer and uses a XSelect C18 column (dimensions 1.8 μm, 2.1 × 50 mm at 30 °C and a flow rate of 600 μL/min). The mobile phase was (A) 10 mM ammonium acetate in HPLC-grade water and (B) HPLC-grade acetonitrile. A gradient was formed from 10% A to 80% B over 2.5 min; kept for 1.5 min. The column was re-equilibrated with a 10% solution of B for 1 min. The ESI source operated at a discharge current of 5 μA, vaporiser temperature of 350 °C and capillary temperature of 200 °C.

Melting points were determined using a Büchi B-545, a Stuart SMP30 or a Stuart SMP40 apparatus. Infrared spectra were recorded with a Nicolet Avatar 370 FT-IR spectrometer (data processed with OMNIC 9.8.372) or a Perkin-Elmer Spectrum Two FT-IR spectrometer. NMR spectra were recorded with an AVANCE 400 Bruker spectrometer ( $^1\text{H}$  at 400.2 MHz,  $^{13}\text{C}$  at 100.6 MHz), a JEOL ECA400II spectrometer ( $^1\text{H}$  at 399.8 MHz,  $^{13}\text{C}$  at 100.5 MHz) or a JEOL ECX-500SS spectrometer ( $^1\text{H}$  at 500.2 MHz,  $^{13}\text{C}$  at 125.8 MHz), in  $\text{CDCl}_3$  or  $\text{DMSO-}d_6$ , at ambient temperature ( $\sim 21^\circ\text{C}$ ). Chemical shifts  $\delta$  are given in parts per million (ppm). They are either referenced to the peak of tetramethylsilane, defined at  $\delta = 0.00$  for  $^1\text{H}$  and  $^{13}\text{C}$  NMR, or to the solvent peak [in  $\text{CDCl}_3$ :  $\delta = 7.26$  (residual  $\text{CHCl}_3$ ) for  $^1\text{H}$  NMR and  $\delta = 77.0$  for  $^{13}\text{C}$  NMR; in  $\text{DMSO-}d_6$ :  $\delta = 2.50$  for  $^1\text{H}$  NMR and  $\delta = 39.51$  for  $^{13}\text{C}$  NMR]. Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Coupling constants  $J$  are given in Hz and are rounded to the closest multiple of 0.5. HRMS analysis was performed with LC-MS and an Orbitrap high-resolution mass spectrometer (Dionex, Ultimate 3000, Thermo Exactive plus, MA, USA) operating in positive full scan mode in the range of 80-1200  $m/z$ . The settings for electrospray ionisation were as follows:  $150^\circ\text{C}$  oven temperature and 3.6 kV source voltage. The acquired data were internally calibrated with phthalate as a contaminant in methanol ( $m/z$  297.15909). Samples were diluted to a final concentration of 0.1 mg/mL in a solution of water and acetonitrile (50:50, v/v). The samples were injected into the mass spectrometer following HPLC separation on a Kinetex C18 column (2.6  $\mu\text{m}$ , 100  $\text{\AA}$ ,  $50 \times 3.0$  mm) using an isocratic mobile phase of 0.01M MeCN/ammonium acetate (80/20) at a flow rate of 0.3 mL/min. Alternatively, HRMS experiments were performed using a tims-TOF mass spectrometer (Bruker) in the *Laboratoire de Chimie Moléculaire* (Ecole polytechnique, CNRS, Institut Polytechnique de Paris, Palaiseau, France). The electrospray source was used in positive mode. Samples were prepared in acetonitrile with 0.1% of formic acid, introduced at a 5  $\mu\text{L}/\text{min}$  flow rate into the interface of the instrument. Capillary and end plate voltages were set at 4.5 kV and 0.7 kV. Nitrogen was used as the nebulizer and drying gas at 2.5 bar and 3 L/min, respectively, with a drying temperature of  $180^\circ\text{C}$ . Tuning mix (Agilent) was used for calibration. The elemental compositions of all ions were determined with the instrument software Data Analysis; the precision of mass measurement was less than 3 ppm.

### General procedure C:

**First step in MeCN at reflux; second step in toluene at  $90^\circ\text{C}$ , in the presence of 0.50 equiv of TfOH (conditions suitable for azabicyclo[3.1.0]hexane substrates).**

A solution of amide **7** (1.00 equiv) in MeCN (typically 7.0–8.0 mL per mmol of **7**) was heated at reflux for 1 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was concentrated under reduced pressure to afford the dihydropyridine intermediate **19**. This crude product was then dissolved in dry toluene (typically, same volume as MeCN in the first step). Trifluoromethanesulfonic acid (0.500 equiv) was added and the mixture was heated at  $90^\circ\text{C}$  for 20–60 min. After cooling, saturated  $\text{NaHCO}_3$  aqueous solution (typically 40 mL per mmol of **7**) was added and the mixture was extracted with EtOAc (typically  $3 \times 25$  mL per mmol of **7**). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

### General procedure D:

**Both steps performed in toluene (reflux, then  $90^\circ\text{C}$  in the presence of 0.25 equiv of TfOH) (conditions suitable for azabicyclo[3.1.0]hexane substrates).**



A solution of amide **7** (1.00 equiv) in toluene (typically 15–35 mL per mmol of **7**) was heated at reflux for 3–8 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, a sample was taken from the solution and analysed by  $^1\text{H}$  NMR spectroscopy to check the conversion of the starting material and the formation of the dihydropyridine intermediate **19**. Trifluoromethanesulfonic acid (0.250 equiv) was added and the mixture was heated at 90 °C for 25–180 min. After cooling, saturated  $\text{NaHCO}_3$  aqueous solution (20 mL) was added and the mixture was extracted with EtOAc ( $3 \times 10$ –15 mL). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

#### General procedure E:

**First step in 1,2-dichlorobenzene at reflux; second step in toluene at 90 °C, in the presence of 0.50 equiv of TfOH (conditions suitable for azabicyclo[4.1.0]heptane substrates).**

A solution of amide **7** (1.00 equiv) in 1,2-dichlorobenzene (typically 4.0–8.0 mL per mmol of **7**) was heated at reflux for 2–8 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was concentrated under reduced pressure to afford the dihydroazepine intermediate **19**. This crude product was then dissolved in dry toluene (typically, 8.0–10 mL per mmol of **7**). Trifluoromethanesulfonic acid (0.500 equiv) was added and the mixture was heated at 90 °C for 30 to 120 min. After cooling, saturated  $\text{NaHCO}_3$  aqueous solution (40 mL per mmol of **7**) was added and the mixture was extracted with EtOAc ( $3 \times 30$  mL per mmol of **7**). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

#### General procedure F:

**First step in 1,2-dichlorobenzene at reflux, in the presence of  $\text{AgBF}_4$ ; second step in toluene at 90 °C, with 0.50 equiv of TfOH (conditions suitable for azabicyclo[4.1.0]heptane substrates).**

$\text{AgBF}_4$  (2.00 equiv) was added to a solution of amide **7** (1.00 equiv) in 1,2-dichlorobenzene (9.0 mL per mmol of **7**) and the resulting mixture was heated at reflux for 4 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was filtered through a pad of celite (rinsing with  $\text{CHCl}_3$ ,  $3 \times 9.0$  mL per mmol of **7**) and concentrated under reduced pressure to afford the dihydroazepine intermediate **19**. This crude product was then dissolved in dry toluene (9.0 mL per mmol of **7**). Trifluoromethanesulfonic acid (0.500 equiv) was added and the mixture was heated at 90 °C for 1 h. After cooling, saturated  $\text{NaHCO}_3$  aqueous solution (40 mL per mmol of **7**) was added and the mixture was extracted with EtOAc (typically  $3 \times 30$  mL per mmol of **7**). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

#### General procedure G:

**First step in PhCl at reflux; second step in toluene at 90 °C, in the presence of 0.50 equiv of TfOH (conditions suitable for azabicyclo[3.1.0]hexane substrates, used in “difficult” cases).**

A solution of amide **7** (1.00 equiv) in PhCl (typically 6.0–8.0 mL per mmol of **7**) was heated at reflux for 3–5 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was concentrated under reduced pressure to afford the dihydropyridine intermediate **19**. This crude product was then dissolved in dry toluene (typically, same volume as MeCN in the first step). Trifluoromethanesulfonic acid (0.500 equiv) was added and the mixture was heated at 90 °C for

30 min. After cooling, saturated NaHCO<sub>3</sub> aqueous solution (typically 40 mL per mmol of **7**) was added and the mixture was extracted with EtOAc (typically 3 × 30 mL per mmol of **7**). The combined organic phases were 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.

**(5-Chloro-2*H*-pyridin-1-yl)-(3,4-dimethoxyphenyl)methanone 19aa and 1-chloro-8,9-dimethoxy-4,10b-dihydro-3*H*-pyrido[1,2-*b*]isoindol-6-one 9aa**

**General procedure C** was applied to **7aa** (1.00 equiv, 75.9 μmol, 24.0 mg). After the first step in MeCN (2.0 mL), fairly pure dihydropyridine derivative **19aa** was obtained as a yellow oil (20.0 mg). In the second step (toluene, 3.0 mL), heating was maintained for 20 min. Analysis of the crude product (orange oil, 14.0 mg) by <sup>1</sup>H NMR spectroscopy revealed the presence of the expected cyclised product **9aa**. The other possible regioisomer **9'aa** was not detected. Purification by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) afforded pure benzoindolizidine **9aa** (8.0 mg, 28.6 μmol, 38% over two steps).

**19aa**: Orange oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 3.89 (3 H, s), 3.92 (3 H, s), 4.47 (2 H, dd, *J* 4.0, 2.0), 5.75 (1 H, dtd, *J* 10.0, 4.0, 1.0), 5.95 (1 H, dtd, *J* 10.0, 2.0, 1.5), 6.67 (1 H, br s), 6.88 (1 H, br d, *J* 8.0), 7.08 (1 H, d, *J* 2.0), 7.10 (1 H, br dd, *J* 8.0, 2.0).

**9aa**: Colourless oil. IR (neat): ν 3398 (w), 2931 (w), 1677 (s, C=O), 1601 (m), 1497 (s), 1397 (m), 1302 (s), 1268 (s), 1220 (s), 1018 (m), 867 (w), 734 (s) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 2.19 (1 H, dddd, *J* 17.5, 6.5, 4.5, 2.0, 1.0), 2.44 (1 H, dddd, *J* 17.5, 11.5, 6.0, 4.0, 2.0), 3.16 (1 H, ddd, *J* 13.5, 11.5, 4.5), 3.94 (3 H, s), 3.98 (3 H, s), 4.51 (1 H, ddd, *J* 13.5, 6.0, 1.0), 5.05 (1 H, dt, *J* 4.0, 2.0), 5.98 (1 H, dt, *J* 6.5, 2.0), 7.32 (1 H, s), 7.39 (1 H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz): δ 26.9, 36.8, 56.26, 56.32, 60.3, 105.2, 107.0, 124.7, 124.9, 129.0, 135.6, 150.4, 152.5, 168.6. HRMS *m/z* (ES<sup>+</sup>) 280.0733 (MH<sup>+</sup> C<sub>14</sub>H<sub>15</sub><sup>35</sup>ClNO<sub>3</sub><sup>+</sup> requires 280.0735), 282.0703 (MH<sup>+</sup> C<sub>14</sub>H<sub>15</sub><sup>37</sup>ClNO<sub>3</sub><sup>+</sup> requires 282.0705).

**(5-Chloropyridin-1(2*H*)-yl)-2-(3,5-dimethoxyphenyl)methanone 19ab and 1-chloro-8,10-dimethoxy-3,10b-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one 9ab**

**General procedure C** was applied to **7ab** (1.00 equiv, 509 μmol, 161 mg). After the first step in MeCN (5.0 mL), fairly pure dihydropyridine derivative **19ab** was obtained as a yellow oil (133 mg). In the second step (toluene, 5.0 mL), 0.250 equiv of trifluoromethanesulfonic acid was employed (119 μmol, 10.5 μL) and heating was maintained for 45 min. Purification of the crude product (orange oil, 110 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 80%) afforded a 59:41 mixture of benzoindolizidine **9ba** and a by-product tentatively identified as (3-chloropyridin-1-ium-1-yl)-(3,5-dimethoxyphenyl)methanone chloride (or triflate), with some contaminants (9.1 mg, 18.3 μmol and 12.7 μmol respectively, *i.e.* 4% and 2% respectively). A clean 57:43 mixture of both compounds (3.2 mg) was obtained by semipreparative HPLC (C18 reverse-phase column; 10 mM aqueous AcNH<sub>4</sub> solution / MeCN, gradient formed from 40 to 70%).

**19ab**: Yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 3.81 (6 H, s), 4.51 (2 H, br s), 5.76 (1 H, br d, *J* 10.0), 5.94 (1 H, dtd, *J* 10.0, 2.0, 1.5), 6.55 (1 H, t, *J* 2.5), 6.56 (1 H, br s), 6.59 (2 H, d, *J* 2.5).

**9ab**: Orange oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 2.17 (1 H, dddd, *J* 17.5, 6.0, 4.5, 2.0, 1.0), 2.50 (1 H, dddd, *J* 17.5, 11.5, 6.5, 3.5, 2.5), 3.15 (1 H, ddd, *J* 13.5, 11.5, 4.5), 3.86 (3 H, s), 3.87 (3 H, s), 4.48 (1 H, ddd, *J* 13.5, 6.5, 1.0), 5.22 (1 H, dt, *J* 3.5, 2.0), 5.94 (1 H, ddd, *J* 6.0, 2.5, 2.0), 6.64 (1 H, d, *J* 2.0), 6.95 (1 H, d, *J* 2.0). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz): δ 26.5, 37.3, 55.5, 55.9, 60.2, 98.3, 103.5, 123.1, 125.5, 130.3, 135.1, 156.7, 162.4, 168.4. HRMS *m/z* (ES<sup>+</sup>) 280.0735 (MH<sup>+</sup> C<sub>14</sub>H<sub>15</sub><sup>35</sup>ClNO<sub>3</sub><sup>+</sup> requires 280.0735).

**1-(5-Chloropyridin-1(2*H*)-yl)-2-(4-methoxyphenyl)ethan-1-one **19ac** and attempted synthesis of 1-chloro-10-methoxy-3,4,7,11b-tetrahydro-6*H*-pyrido[2,1-*a*]isoquinolin-6-one **9ac****

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**General procedure C** was applied to **7ac** (1.00 equiv, 543  $\mu\text{mol}$ , 163 mg). After the first step in MeCN (4.0 mL), fairly pure dihydropyridine derivative **19ac** was obtained as a orange oil (121 mg). In the second step (toluene, 3.0 mL), heating was maintained for 30 min. Analysis of the crude product (60.0 mg) by  $^1\text{H}$  NMR spectroscopy revealed that it contained a complex mixture of compounds, and no expected product **9ac**.

**19ac**: Orange oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), 80 : 20 mixture of two rotamers. Major rotamer:  $\delta$  3.68 (2 H, br s), 3.78 (3 H, s), 4.41 (2 H, dd,  $J$  4.0, 1.5), 5.70 (1 H, dt,  $J$  10.0, 4.0), 5.86 (1 H, dt,  $J$  10.0, 1.5), 6.71 (1 H, s), 6.86 (2 H, br d,  $J$  8.0), 7.13 (2 H, br d,  $J$  8.0). Minor rotamer, characteristic signals:  $\delta$  4.28 (2 H, dd,  $J$  4.0, 1.5), 5.54 (1 H, dt,  $J$  10.0, 4.0).

**1-(5-Chloropyridin-1(2*H*)-yl)-2-(3-methoxyphenyl)ethan-1-one **19ad**, 1-chloro-9-methoxy-3,4,7,11b-tetrahydro-6*H*-pyrido[2,1-*a*]isoquinolin-6-one **9ad** and 1-chloro-9-methoxy-1,4,7,11b-tetrahydro-6*H*-pyrido[2,1-*a*]isoquinolin-6-one **23ad****

Conditions C, with 0.25 equiv of TfOH: **general procedure C** was applied to **7ad** (1.00 equiv, 683  $\mu\text{mol}$ , 205 mg). After the first step in MeCN (5.0 mL), fairly pure dihydropyridine derivative **19ad** was obtained as an orange oil (163 mg). In the second step (toluene, 5.0 mL), 0.250 equiv of trifluoromethanesulfonic acid was employed (155  $\mu\text{mol}$ , 13.7  $\mu\text{L}$ ) and heating was maintained for 40 min. Analysis of the crude product (orange oil, 100 mg) by  $^1\text{H}$  NMR spectroscopy showed that it contained a 77:23 mixture of **9ad** and its regioisomer **9'ad**. Purification by flash column chromatography on silica gel (EtOAc/petroleum ether, gradient from 30 to 100%) gave pure benzoquinolizidines **9'ad** (12.0 mg, 45.5  $\mu\text{mol}$ , 7% over two steps) and **9ad** (39.0 mg, 148  $\mu\text{mol}$ , 22% over two steps).

Conditions C: **general procedure C** was applied to **7ad** (1.00 equiv, 683  $\mu\text{mol}$ , 205 mg). After the first step in MeCN (5.0 mL), fairly pure dihydropyridine derivative **19ad** was obtained as an orange oil (172 mg). In the second step (toluene, 5.0 mL), heating was maintained for 30 min. Analysis of the crude product (orange oil, 137 mg) by  $^1\text{H}$  NMR spectroscopy showed that it contained a 53:20:27 mixture of **9ad**, **9'ad** and **23ad**. Purification by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 60%) gave pure benzoquinolizidine **23ad** (10.0 mg, 38.0  $\mu\text{mol}$ , 6% over two steps) and a 59:41 mixture of benzoquinolizidine isomers **9ad** and **23ad** (33.0 mg, 125  $\mu\text{mol}$ , 19% over two steps).

**19ad**: Orange oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), 80 : 20 mixture of two rotamers. Major rotamer:  $\delta$  3.73 (2 H, br s), 3.79 (3 H, br s), 4.43 (2 H, dd,  $J$  4.0, 2.0), 5.72 (1 H, dtd,  $J$  10.0, 4.0, 0.5), 5.87 (1 H, dtd,  $J$  10.0, 2.0, 1.5), 6.70 (1 H, dd,  $J$  1.5, 0.5), 6.76–6.84 (3 H, m), 7.25 (1 H, dd,  $J$  8.5, 7.5). Minor rotamer, characteristic signals:  $\delta$  3.70 (2 H, s), 3.79 (3 H, br s), 4.28 (2 H, dd,  $J$  4.0, 2.0), 5.55 (1 H, dtd,  $J$  10.0, 4.0, 0.5), 5.88 (1 H, dtd,  $J$  10.0, 2.0, 1.5).

**9ad**: Orange oil. IR (neat):  $\nu$  2922 (w), 1645 (s, C=O), 1611 (m), 1421 (m), 1248 (s), 1173 (w), 1031 (s), 956 (m), 839 (w), 801 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.19 (1 H, dddd,  $J$  17.5, 6.5, 4.0, 2.0, 1.5), 2.46 (1 H, dddd,  $J$  17.5, 11.5, 6.0, 3.5, 2.0), 2.96 (1 H, ddd,  $J$  13.0, 11.5, 4.0), 3.61 (2 H, AB system,  $\delta_A$  3.59,  $\delta_B$  3.63,  $J_{AB}$  19.0), 3.81 (3 H, s), 4.61 (1 H, dddd,  $J$  13.0, 6.0, 1.5, 1.0), 5.18 (1 H, dtd,  $J$  3.5, 2.0, 1.0), 6.19 (1 H, dt,  $J$  6.5, 2.0), 6.71 (1 H, d,  $J$  2.5), 6.81 (1 H, dd,  $J$  8.5, 2.5), 7.34 (1 H, d,  $J$  8.5).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.1, 38.1, 40.4, 55.3, 60.6, 112.0, 112.2, 124.0, 126.7, 128.4, 130.0, 134.3, 159.5, 170.0. HRMS  $m/z$  ( $\text{ES}^+$ ) 264.0786 ( $\text{MH}^+$   $\text{C}_{14}\text{H}_{15}^{35}\text{ClNO}_2^+$  requires 264.0786), 266.0753 ( $\text{MH}^+$   $\text{C}_{14}\text{H}_{15}^{37}\text{ClNO}_2^+$  requires 266.0756).

**9'ad**: Yellow crystals. M.p. 162.0–167.0 °C (EtOAc). IR (neat):  $\nu$  2900 (w), 1662 (s, C=O), 1600 (m), 1477 (m), 1425 (w), 1265 (s), 1104 (w), 792 (w), 737 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.16 (1 H, dddd,  $J$  18.0, 5.5, 4.5, 3.0, 0.5), 2.72 (1 H, dddd,  $J$  18.0, 12.0, 7.0, 3.5, 3.0), 3.09 (1 H, ddd,  $J$  13.0, 12.0, 5.5), 3.62 (2 H, AB system,  $\delta_A$  3.60,  $\delta_B$  3.64,  $J_{AB}$  20.5), 3.88 (3 H, s), 4.71 (1 H, ddd,  $J$  13.0, 7.0, 0.5), 5.74 (1 H, ddd,  $J$  3.5, 3.0, 2.5), 5.94 (1 H, ddd,  $J$  4.5, 3.0, 2.5), 6.76 (1 H, br d,  $J$  7.5), 6.81 (1 H, br d,  $J$  8.5), 7.29 (1 H, dd,  $J$  8.5, 7.5).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.4, 36.5, 42.4, 55.4, 56.9, 108.4, 119.1, 119.4, 125.2, 129.6, 131.5, 133.4, 156.7, 170.6 (C6). HRMS  $m/z$  ( $\text{ES}^+$ ) 264.0788 ( $\text{MH}^+$   $\text{C}_{14}\text{H}_{15}^{35}\text{ClNO}_2^+$  requires 264.0786), 266.0757 ( $\text{MH}^+$   $\text{C}_{14}\text{H}_{15}^{37}\text{ClNO}_2^+$  requires 266.0756).

**23ad**: Orange oil. IR (neat):  $\nu$  2920 (w), 1651 (m, C=O), 1635 (m), 1513 (m), 1456 (m), 1252 (m), 1027 (m), 944 (w), 824 (m), 726 (s)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  3.52 (1 H, dddd,  $J$  18.0, 3.5, 2.5, 1.5), 3.65 (2 H, AB system,  $\delta_A$  3.64,  $\delta_B$  3.66,  $J_{AB}$  20.0), 3.82 (3 H, s), 4.41 (1 H, dddt,  $J$  10.0, 3.5, 2.0, 1.5), 4.54 (1 H, d,  $J$  10.0), 5.12 (1 H, dddd,  $J$  18.0, 4.0, 2.0, 1.5), 5.89 (1 H, ddt,  $J$  10.0, 2.5, 1.5), 5.94 (1 H, ddt,  $J$  10.0, 4.0, 1.5), 6.68 (1 H, d,  $J$  2.5), 6.83 (1 H, dd,  $J$  8.5, 2.5), 7.44 (1 H, d,  $J$  8.5).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz):  $\delta$  36.5, 42.3, 55.3, 58.0, 63.2, 112.25, 112.32, 122.1, 128.0, 129, 130.3, 132.8, 159.8, 167.5. HRMS  $m/z$  ( $\text{ES}^+$ ) 264.0787 ( $\text{MH}^+$   $\text{C}_{14}\text{H}_{15}^{35}\text{ClNO}_2^+$  requires 264.0786), 286.0606 ( $\text{MNa}^+$   $\text{C}_{14}\text{H}_{14}^{35}\text{ClNNO}_2^+$  requires 286.0605).

**1-(5-Chloropyridin-1(2H)-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one 19ae, 1-chloro-9,10-dimethoxy-3,4,7,11b-tetrahydro-6H-pyrido[2,1-a]isoquinolin-6-one 9ae and 1-chloro-9,10-dimethoxy-1,4,7,11b-tetrahydro-6H-pyrido[2,1-a]isoquinolin-6-one 23ae**

Conditions C: **general procedure C** was applied to **7ae** (1.00 equiv, 427  $\mu\text{mol}$ , 141 mg). After the first step in MeCN (3.0 mL), fairly pure dihydropyridine derivative **19ae** was obtained as an orange oil (100 mg). In the second step (toluene, 3.0 mL), heating was maintained for 40 min. Analysis of the crude product (orange oil, 84.0 mg) by  $^1\text{H}$  NMR spectroscopy showed that it contained a 89:11 mixture of **9ae** and **23ae**. The regioisomer **9'ae** was not detected. Purification by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure benzoquinolizidine **9ae** (61.0 mg, 208  $\mu\text{mol}$ , 49% over the two steps).

Conditions D: **general procedure D** was applied to **7ae** (1.00 equiv, 121  $\mu\text{mol}$ , 40.0 mg), with 4.0 mL of toluene. For the first step, analysis by  $^1\text{H}$  NMR spectroscopy of a sample, taken after 3 h of reaction, showed it contained fairly pure dihydropyridine derivative **19ae**. For the second step, one drop of TfOH was used and the mixture was heated at 90 °C for 3 h. Purification of the crude product by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) afforded pure benzoquinolizidine **9ae** (19.0 mg, 64.7  $\mu\text{mol}$ , 53% over the two steps).

**19ae**: Orange oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), 80 : 20 mixture of two rotamers. Major rotamer:  $\delta$  3.70 (2 H, s), 3.87 (6 H, br s), 4.42 (2 H, dd,  $J$  4.0, 2.0), 5.73 (1 H, dtd,  $J$  10.0, 4.0, 1.0), 5.87 (1 H, dtd,  $J$  10.0, 2.0, 1.5), 6.74 (1 H, dd,  $J$  1.5, 1.0), 6.72–6.86 (3 H, m). Minor rotamer, characteristic signals:  $\delta$  4.31 (2 H, dd,  $J$  4.0, 2.0), 5.57 (1 H, br dt,  $J$  10.0, 4.0), 5.89 (1 H, dtd,  $J$  10.0, 2.0, 1.5).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz), 80 : 20 mixture of two rotamers. Major rotamer:  $\delta$  39.8, 41.8, 55.8, 55.8, 111.3, 111.8, 114.4, 120.9, 122.5, 122.7, 124.4, 125.9, 148.1, 149.1, 169.0.

**9ae**: Yellow oil. IR (neat):  $\nu$  2934 (w), 1656 (s, C=O), 1515 (s), 1459 (m), 1319 (m), 1257 (s), 1232 (m), 1120 (m), 1017 (m), 763 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.19 (1 H, dddd,  $J$  17.5, 6.5, 4.5, 2.0, 1.5), 2.51 (1 H, dddd,  $J$  17.5, 12.0, 6.0, 3.0, 2.0), 2.96 (1 H, ddd,  $J$  13.0, 12.0, 4.5), 3.57 (2 H, AB system,  $\delta_A$  3.55,  $\delta_B$  3.60,  $J_{AB}$  19.5), 3.88 (3 H, s), 3.89 (3 H, s), 4.64 (1 H, br dd,  $J$  13.0, 6.0), 5.18 (1 H, br s), 6.16 (1 H, dt,  $J$  6.5, 2.0), 6.64 (1 H, s), 6.94 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.2, 37.0, 40.7, 56.0, 56.2, 61.1, 109.9, 111.3, 123.1, 124.8, 126.7, 130.1, 147.2, 149.1, 170.2.

HRMS  $m/z$  (ES<sup>+</sup>) 294.0893 (MH<sup>+</sup> C<sub>15</sub>H<sub>17</sub><sup>35</sup>CINO<sub>3</sub><sup>+</sup> requires 294.0891), 296.0865 (MH<sup>+</sup> C<sub>15</sub>H<sub>17</sub><sup>37</sup>CINO<sub>3</sub><sup>+</sup> requires 296.0862).

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**23ae:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), characteristic signals:  $\delta$  4.42 (1 H, dddt,  $J$  10.0, 3.5, 2.5, 1.5), 4.52 (1 H, d,  $J$  10.0), 5.14 (1 H, dddd,  $J$  18.5, 4.0, 2.5, 1.5), 5.89 (1 H, ddt,  $J$  10.0, 2.5, 1.5), 5.95 (1 H, ddt,  $J$  10.0, 4.0, 1.5).

**Competitive ring-opening experiment performed from an equimolar mixture of amide 7ae and thioamide 20ae. Formation of 1-(5-chloropyridin-1(2H)-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one 19ae and a new compound tentatively identified as the acylpyridium salt 21ae**

A solution of amide **7ae** (1.00 equiv, 15.1  $\mu$ mol, 5.0 mg) and thioamide **20ae** (1.00 equiv, 14.4  $\mu$ mol, 5.0 mg) in CD<sub>3</sub>CN (0.50 mL) was heated at reflux in a closed NMR tube for 30 min. The reaction mixture was analysed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and found to contain a mixture of starting **20ae**, dihydropyridine derivative **19ae** and a new compound believed to be the acylpyridium salt dihydropyridine derivative **21ae**, in a ratio of 52 : 33 : 15. **7ae** had been entirely consumed. Heating at reflux was continued for an additional 30 min and then for 1 h. The reaction was monitored by <sup>1</sup>H/<sup>13</sup>C NMR spectroscopy and the ratio was determined to have changed to 52 : 27 : 21 (reaction time 1 h) and 52 : 15 : 33 (reaction time 2 h).

**21ae:** <sup>1</sup>H NMR (CD<sub>3</sub>CN, 400 MHz), characteristic signals:  $\delta$  3.53 (2 H, s), 8.00 (2 H, br dd,  $J$  8.0, 6.5), 8.56 (1 H, tt,  $J$  8.0, 1.5), 8.70 (2 H, br dd,  $J$  6.5, 1.5).

**1-(5-Chloropyridin-1(2H)-yl)-2-(3,4,5-trimethoxyphenyl)ethan-1-one 19af and 1-chloro-9,10,11-trimethoxy-3,4,7,11b-tetrahydro-6H-pyrido[2,1-a]isoquinolin-6-one 9af**

**General procedure C** was applied to **7af** (1.00 equiv, 502  $\mu$ mol, 181 mg). After the first step in MeCN (4.0 mL), fairly pure dihydropyridine derivative **19af** was obtained as an orange oil (139 mg). In the second step (toluene, 3.0 mL), heating was maintained for 1 h. Purification of the crude product (orange oil, 98.0 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure benzoquinolizidine **9af** (84.0 mg, 259  $\mu$ mol, 52% over the two steps).

**19af:** Orange oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), 80 : 20 mixture of two rotamers. Major rotamer:  $\delta$  3.68 (2 H, s), 3.82 (3 H, s), 3.83 (6 H, s), 4.42 (2 H, dd,  $J$  4.0, 2.0), 5.73 (1 H, dtd,  $J$  10.0, 4.0, 0.5), 5.88 (1 H, dtd,  $J$  10.0, 2.0, 1.5), 6.44 (2 H, s), 6.74 (1 H, dd,  $J$  1.5, 0.5). Minor rotamer, characteristic signals:  $\delta$  4.31 (2 H, dd,  $J$  4.0, 2.0), 5.58 (1 H, br dt,  $J$  10.0, 4.0).

**9af:** Yellow oil. IR (neat):  $\nu$  2935 (w), 1644 (s, C=O), 1491 (s), 1456 (s), 1376 (m), 1238 (s), 1212 (s), 978 (s), 836 (m), 749 (s), 732 (s) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  2.14 (1 H, dddd,  $J$  18.0, 5.5, 5.0, 3.0, 0.5), 2.72 (1 H, dddd,  $J$  18.0, 11.5, 7.0, 3.5, 3.0), 3.08 (1 H, ddd,  $J$  13.0, 11.5, 5.5), 3.55 (2 H, AB part of an ABXY system,  $\delta_A$  3.51,  $\delta_B$  3.58,  $J_{AB}$  20.0,  $J_{AX}$  0.0,  $J_{AY}$  0.0,  $J_{BX}$  1.5,  $J_{BY}$  1.0), 3.84 (3 H, s), 3.86 (3 H, s), 4.03 (3 H, s), 4.69 (1 H, br dd,  $J$  13.0, 7.0), 5.59 (1 H, ddd,  $J$  3.5, 3.0, 2.5), 5.93 (1 H, ddd,  $J$  5.0, 3.0, 2.5), 6.39 (1 H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.6 MHz):  $\delta$  25.3, 36.7, 42.6, 56.0, 57.3, 60.7, 60.9, 105.0, 115.9, 125.1, 127.6, 131.6, 139.8, 151.1, 154.2, 170.8. HRMS  $m/z$  (ES<sup>+</sup>) 324.0997 (MH<sup>+</sup> C<sub>16</sub>H<sub>19</sub><sup>35</sup>CINO<sub>4</sub><sup>+</sup> requires 324.0997), 346.0815 (MNa<sup>+</sup> C<sub>16</sub>H<sub>18</sub><sup>35</sup>CINNaO<sub>4</sub><sup>+</sup> requires 346.0817).

**tert-Butyl 2-(2-(5-Chloropyridin-1(2H)-yl)-2-oxoethyl)-1H-indole-1-carboxylate 19ag and possible synthesis of 1-chloro-4,7,12,12b-tetrahydro-3H-indolo[2,3-a]quinolizin-6-one 9ag'**

A solution of amide **7ag** (1.00 equiv, 259  $\mu$ mol, 106 mg) in MeCN (4.0 mL) was heated at reflux for 1 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was concentrated under reduced pressure to afford fairly pure dihydropyridine derivative **19ag** as a yellow oil (97.4 mg). Trifluoromethanesulfonic acid (1.25 equiv, 164  $\mu$ mol, 14.5  $\mu$ L) was added to a solution of **19ag** (1.00 equiv, 131  $\mu$ mol, 48.7 mg) in dry toluene (1.0 mL) and the mixture was heated at 90

°C for 30 min. After cooling, saturated NaHCO<sub>3</sub> aqueous solution (20 mL) was added and the mixture was extracted with EtOAc (3 × 7.0 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the crude product (light brown oil, 29.2 mg). Analysis by <sup>1</sup>H NMR spectroscopy confirmed the full conversion of **19ag** and the presence of a compound, the signals of which could be consistent with the cyclised product structure **9ag'**. However, we were not able to obtain this molecule in pure form by flash chromatography and, for this reason, it remains to be identified with certainty.

Alternative attempted synthesis from the unprotected indole derivative **7ag'**: a solution of amide **7ag'** (1.00 equiv, 136 μmol, 41.9 mg) in MeCN (2.0 mL) was heated at reflux for 1 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was concentrated under reduced pressure to afford the crude product (21.0 mg). Analysis by <sup>1</sup>H NMR spectroscopy revealed that it contained a major compound, the signals of which did not correspond to the expected structure **19ag'** but were identical to those of the molecule observed in the reaction of **19ag**, which is tentatively assigned the structure **9ag'**. When this compound was submitted to the usual subsequent cyclisation reaction conditions (0.25 equiv trifluoromethanesulfonic acid, toluene, 90 °C, 30 min.), no further transformation was observed, which provides additional support for its identification as **9ag'**.

**19ag**: Colourless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), 80 : 20 mixture of two rotamers. Major rotamer: δ 1.66 (9 H, s), 3.81 (2 H, s), 4.45 (2 H, dd, *J* 4.0, 2.0), 5.74 (1 H, dtd, *J* 10.0, 4.0, 0.5), 5.89 (1 H, dtd, *J* 10.0, 2.0, 1.0), 6.78 (1 H, dd, *J* 1.0, 0.5), 7.25 (1 H, td, *J* 7.5, 1.0), 7.33 (1 H, ddd, *J* 8.0, 7.5, 1.0), 7.51 (1 H, br s), 7.52 (1 H, br d, *J* 7.5), 8.14 (1 H, br d, *J* 8.0). Minor rotamer, characteristic signals: δ 3.77 (2 H, s, H7), 4.38 (2 H, dd, *J* 4.0, 2.0), 5.59 (1 H, br dt, *J* 10.0, 4.0).

**9ag'**: Orange oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 2.25–2.34 (1 H, m), 2.29 (1 H, d, *J* 16.5), 2.40–2.51 (1 H, m), 2.91–3.02 (1 H, m), 3.20 (1 H, dd, *J* 16.5, 1.5), 4.40 (1 H, br dd, *J* 13.0, 6.0), 4.87 (1 H, ddd, *J* 3.0, 2.0, 1.5), 5.83 (1 H, dt, *J* 6.5, 2.0), 7.19–7.47 (3 H, m), 7.67 (1 H, br d, *J* 7.5), 8.24 (1 H, br s, NH).

**1-(5-Chloropyridin-1(2*H*)-yl)-3-(3,4-dimethoxyphenyl)propan-1-one 19ah, 1-chloro-10,11-dimethoxy-4,7,8,12b-tetrahydro-3*H*-pyrido[2,1-*a*][2]benzazepin-6-one 9ah, 1-chloro-10,11-dimethoxy-4,7,8,12b-tetrahydro-1*H*-pyrido[2,1-*a*][2]benzazepin-6-one 23ah, 5,6-dimethoxyindan-1-one 24 and 1-hydroxy-10,11-dimethoxy-1,7,8,12b-tetrahydrobenzo[*c*]pyrido[1,2-*a*]azepin-6(4*H*)-one distereoisomers 25ah**

**General procedure C** was applied to **7ah** (1.00 equiv, 683 μmol, 235 mg). After the first step in MeCN (5.0 mL), relatively pure dihydropyridine derivative **19ah** was obtained as a brown oil (206 mg). In the second step (toluene, 5.0 mL), heating was maintained for 30 min. Analysis of the crude product (orange oil, 183 mg) by <sup>1</sup>H NMR spectroscopy showed that it contained a 42:29:29 mixture of expected compound **9ah**, isomer **23ah** and indanone **24**. The regioisomer **9'ah** was not detected. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 30 to 70%) afforded indanone **24** (22 mg, 114 μmol, 17% over two steps) and a mixture of products (101 mg). The latter was further purified by semipreparative HPLC (C18 reverse-phase column, gradient formed from 30 to 60 % of 10 mM aqueous NH<sub>4</sub>OAc and MeCN) to give pure **9ah** (38 mg, 123 μmol, 18% over two steps) and a 80:20 diastereomeric mixture of alcohols **25ah** (29 mg, 100 μmol, 15% over two steps).

**19ah**: Orange oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz), 81 : 19 mixture of two rotamers. Major rotamer: δ 2.66 (2 H, t, *J* 7.5), 2.93 (2 H, t, *J* 7.5), 3.85 (3 H, s), 3.87 (3 H, br s), 4.40 (2 H, dd, *J* 4.0, 2.0), 5.70 (1 H, dtd, *J* 10.0, 4.0, 1.0), 5.86 (1 H, dtd, *J* 10.0, 2.0, 1.5), 6.58 (1 H, dd, *J* 1.5, 1.0), 6.71–6.86 (3 H,

m). Minor rotamer, characteristic signals:  $\delta$  4.25 (2 H, dd,  $J$  4.0, 2.0), 5.55 (1 H, dtd,  $J$  10.0, 4.0, 1.0), 5.89 (1 H, dtd,  $J$  10.0, 2.0, 1.5).

**9ah**: Colourless oil. IR (neat):  $\nu$  2895 (w), 1624 (s, C=O), 1516 (s), 1463 (w), 1253 (s), 1210 (m), 1107 (m), 1051 (m), 870 (m), 809 (m), 774 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.26 (1 H, dddt,  $J$  17.5, 6.0, 4.0, 1.5), 2.39 (1 H, dddt,  $J$  17.5, 11.5, 5.5, 2.5), 2.53 (1 H, ddd,  $J$  13.0, 11.5, 4.0), 2.73 (1 H, m), 3.02 (1 H, m), 3.25–3.37 (2 H, m), 3.84 (3 H, s), 3.86 (3 H, s), 4.36 (1 H, br dd,  $J$  13.0, 6.0), 5.62 (1 H, br s), 6.37 (1 H, dt,  $J$  5.5, 1.5), 6.65 (1 H, s), 6.74 (1 H, s).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.7, 27.5, 33.5, 33.9, 56.0, 56.2, 58.5, 110.5, 114.0, 127.0, 127.8, 128.2, 129.6, 146.6, 148.8, 171.2. HRMS  $m/z$  ( $\text{ES}^+$ ) 308.1041 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{35}\text{ClNO}_3^+$  requires 308.1048), 310.1009 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{37}\text{ClNO}_3^+$  requires 310.1018).

**23ah** (not obtained in pure form):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), characteristic signals:  $\delta$  3.91 (3 H, s), 3.97 (3 H, s), 4.25–4.51 (1 H, br s), 4.92–5.08 (2 H, br s), 6.01 (1 H, ddd,  $J$  10.0, 3.5, 2.5), 6.07 (1 H, br d,  $J$  10.0), 6.64 (1 H, s), 6.90 (1 H, s).

**24**:<sup>18</sup> Yellow foam.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.66 (2 H, distorted t,  $J$  5.5), 3.04 (2 H, distorted t,  $J$  5.5), 3.89 (3 H, s), 3.95 (3 H, s), 6.88 (1 H, s), 7.16 (1 H, s).

**25ah**, 80 : 20 mixture of the ( $3R^*$ ,  $12bS^*$ ) and ( $3R^*$ ,  $12bR^*$ ) diastereoisomers : White amorphous solid. IR (neat):  $\nu$  3139 (w), 2933 (w), 1600 (s, C=O), 1518 (s), 1447 (m), 1341 (m), 1194 (m), 1072 (s), 1021 (m), 778 (m)  $\text{cm}^{-1}$ . HRMS  $m/z$  ( $\text{ES}^+$ ) 272.1281 ( $[\text{M}-\text{OH}]^+$   $\text{C}_{16}\text{H}_{18}\text{NO}_3^+$  requires 272.1282), 290.1386 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{20}\text{NO}_4^+$  requires 290.1387), 312.1203 ( $\text{MNa}^+$   $\text{C}_{16}\text{H}_{19}\text{NNaO}_4^+$  requires 312.1207), 601.2520 ( $\text{M}_2\text{Na}^+$   $\text{C}_{32}\text{H}_{38}\text{N}_2\text{NaO}_8^+$  requires 601.2521).

( $3R^*$ ,  $12bS^*$ )-**25ah** (major diastereoisomer, purified by crystallisation from MeOH containing a few drops of  $\text{CHCl}_3$ ): White crystals. M.p. 225.0–228.0 °C (MeOH).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  2.43 (1 H, ddd,  $J$  14.0, 8.0, 3.5), 2.47 (1 H, dd,  $J$  13.5, 3.0), 2.91 (1 H, ddd,  $J$  17.0, 10.5, 8.0), 3.20 (1 H, ddd,  $J$  17.0, 9.0, 3.5), 3.33 (1 H, br s, OH), 3.43 (1 H, ddd,  $J$  14.0, 10.5, 9.0), 3.69 (3 H, s), 3.72 (3 H, s), 4.05 (1 H, ddd,  $J$  5.0, 3.0, 2.0), 4.14 (1 H, ddd,  $J$  13.5, 2.0, 1.0), 5.75 (1 H, dd,  $J$  4.0, 2.0), 6.09 (1 H, dd,  $J$  10.0, 4.0), 6.22 (1 H, dddd,  $J$  10.0, 5.0, 2.0, 1.0), 6.60 (1 H, s), 6.79 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 125.8 MHz):  $\delta$  27.1, 33.4, 42.1, 52.1, 55.5, 55.7, 60.7, 110.7, 114.5, 126.9, 129.6, 129.6, 129.8, 146.0, 148.1, 171.6.

( $3R^*$ ,  $12bR^*$ )-**25ah** (minor diastereoisomer, not obtained in pure form):  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz), characteristic signals:  $\delta$  2.02 (1 H, dd,  $J$  12.0, 10.0), 3.72 (3 H, s), 4.04 (1 H, m), 4.32 (1 H, ddd,  $J$  12.0, 6.0, 1.0), 5.67 (1 H, dt,  $J$  3.0, 2.5), 5.99 (1 H, dd,  $J$  10.5, 3.5, 2.0), 6.10 (1 H, m), 6.69 (1 H, s), 6.79 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100.6 MHz), characteristic signals:  $\delta$  27.0, 32.8, 40.9, 52.1, 55.5, 55.8, 62.7, 111.0, 114.4, 124.7, 130.0, 146.0, 148.2, 171.0.

A suitable crystal of the major alcohol diastereoisomer ( $3R^*$ ,  $12bS^*$ )-**25ah** was selected and mounted on a Bruker APEX-II CCD diffractometer. The crystal was kept at 150 K during data collection. Using OLEX2,<sup>19</sup> the structure was solved with the SHELXT structure solution program,<sup>20</sup> using Intrinsic Phasing, and refined with the SHELXL refinement package,<sup>21</sup> using Least Squares minimisation. Further detail is provided in the Supporting information.<sup>16</sup>

### 1-(5-Chloro-6-methylpyridin-1(2H)-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one **19be** and 1-chloro-9,10-dimethoxy-11b-methyl-3,4,7,11b-tetrahydro-6H-pyrido [2,1-a]isoquinolin-6-one **9be**

Conditions D: **general procedure D** was applied to **7be** (1.00 equiv, 188  $\mu\text{mol}$ , 64.7 mg), with 3.0 mL of toluene. For the first step, analysis by  $^1\text{H}$  NMR spectroscopy of a sample, taken after 8 h of reaction, showed it contained an unidentified compound and a 32:68 mixture of **19be** and starting

**7be**. For the second step, 0.250 equiv of TfOH (38.7  $\mu\text{mol}$ , 3–4  $\mu\text{L}$ ) was used and the mixture was heated at 90  $^{\circ}\text{C}$  for 25 min. 38.7  $\mu\text{mol}$ , 3.4  $\mu\text{L}$ ). Analysis of the crude product (orange oil, 79.0 mg) by  $^1\text{H}$  NMR spectroscopy did not reveal the presence of the other possible regioisomer **9'be**. Purification by flash column chromatography (EtOAc / petroleum ether, gradient from 30 to 100%) gave pure unreacted **7be** (24.0 mg, 69.7  $\mu\text{mol}$ , 37%) and pure benzoquinolizidine **9be** (9.9 mg, 32.2  $\mu\text{mol}$ , 17% over two steps).

Alternative synthesis from the secondary amide **17be**: trifluoromethanesulfonic acid (0.500 equiv, 63.5  $\mu\text{mol}$ , 5.6  $\mu\text{L}$ ) was added to a solution of amide **17be** (1.00 equiv, 127  $\mu\text{mol}$ , 41.4 mg) in dry toluene (1.2 mL) and the mixture was heated at 90  $^{\circ}\text{C}$  for 2 h. After cooling, saturated  $\text{NaHCO}_3$  aqueous solution (10 mL) was added and the mixture was extracted with EtOAc (3  $\times$  7.0 mL). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford a yellow oil (28.0 mg). Flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 50 to 100%) afforded a mixture containing imperfectly purified **9be** (16.0 mg, < 52.0  $\mu\text{mol}$ , < 41%).

**19be**: Yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.27 (3 H, s), 3.69 (2 H, s), 3.856 (3 H, s), 3.859 (3 H, s), 4.16 (2 H, br s), 5.76 (1 H, br s), 5.95 (1 H, br d,  $J$  9.5), 6.77 (1 H, d,  $J$  2.0), 6.78 (2 H, AB part of an ABX system,  $\delta_A$  6.75,  $\delta_B$  6.81,  $J_{AB}$  8.0,  $J_{AX}$  2.0,  $J_{BX}$  0.0).

**9be**: Colourless oil. IR (neat):  $\nu$  2923 (w), 1646 (s, C=O), 1514 (s), 1397 (m), 1257 (s), 1229 (m), 854 (w), 791 (w), 770 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.79 (3 H, s), 2.15 (1 H, dddd,  $J$  17.0, 7.5, 3.5, 1.5), 2.28 (1 H, dddd,  $J$  17.0, 11.5, 5.0, 2.5), 2.94 (1 H, ddd,  $J$  13.0, 11.5, 3.5), 3.67 (2 H, AB system,  $\delta_A$  3.61,  $\delta_B$  3.74,  $J_{AB}$  20.0), 3.87 (3 H, s), 3.89 (3 H, s), 4.81 (1 H, br dd,  $J$  13.0, 5.0), 6.30 (1 H, dd,  $J$  7.5, 2.5), 6.61 (1 H, s), 7.49 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.8, 26.3, 36.6, 37.5, 55.9, 56.1, 63.9, 109.9, 110.4, 123.9, 128.8, 129.6, 134.5, 147.1, 148.6, 169.7. HRMS  $m/z$  ( $\text{ES}^+$ ) 308.1050 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{35}\text{ClNO}_3^+$  requires 308.1048), 310.1018 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{37}\text{ClNO}_3^+$  requires 310.1018).

### 1-(6-Chloro-2,3-dihydro-1H-azepin-1-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one **19ce** and 1-chloro-10,11-dimethoxy-4,5,8,12b-tetrahydroazepino[2,1-a]isoquinolin-7(3H)-one **9ce**

**General procedure E** was applied to **7ce** (1.00 equiv, 505  $\mu\text{mol}$ , 174 mg). After the first step conducted in refluxing 1,2-dichlorobenzene (4.0 mL) for 2 h, fairly pure dihydroazepine derivative **19ce** was obtained as a brown oil (138 mg). In the second step (toluene, 4.0 mL), heating was maintained for 2 h. Analysis of the crude product (orange oil, 128 mg) by  $^1\text{H}$  NMR spectroscopy showed that it contained a 64:19:17 mixture of **9ce**, **9'ce** and starting **7ce** (**9ce/9'ce** ratio 77:23). Purification by flash column chromatography on silica gel (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure tetrahydroazepinoisoquinoline **9ce** (68.0 mg, 221  $\mu\text{mol}$ , 44% over the two steps). The isomer **9'ce** was not isolated.

**19ce**: Colourless oil. IR (neat):  $\nu$  2936 (w), 1668 (s, C=O), 1597 (m), 1515 (s), 1419 (w), 1388 (m), 1261 (s), 1237 (s), 1149 (m), 1027 (m), 963 (w), 790 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.52 (2 H, td,  $J$  5.0, 3.0), 3.68–3.74 (4 H, m), 3.87 (6 H, br s), 5.91–5.99 (2 H, m), 6.76–6.79 (2 H, m), 6.83 (1 H, d,  $J$  8.5), 6.90 (1 H, br s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  32.5, 41.4, 42.7, 55.85, 55.87, 111.3, 111.9, 119.3, 121.1, 126.1, 126.6, 127.6, 134.2, 148.1, 149.1, 169.2. HRMS  $m/z$  ( $\text{ES}^+$ ) 308.1048 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{35}\text{ClNO}_3^+$  requires 308.1048), 310.1022 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{37}\text{ClNO}_3^+$  requires 310.1018).

**9ce**: Orange oil. IR (neat):  $\nu$  2934 (w), 1646 (s, C=O), 1516 (s), 1456 (m), 1415 (w), 1264 (s), 1230 (m), 1165 (w), 1118 (m), 1033 (s), 762 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.82–1.99 (2 H, m),



2.24–2.31 (2 H, m), 2.98 (1 H, dt,  $J$  13.5, 6.5), 3.54 (2 H, AB system,  $\delta_A$  3.47,  $\delta_B$  3.60,  $J_{AB}$  18.5), 3.869 (3 H, s), 3.873 (3 H, s), 4.72 (1 H, dt,  $J$  13.5, 6.5), 5.26 (1 H, br s), 6.14 (1 H, td,  $J$  6.5, 2.0), 6.64 (1 H, s), 6.76 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.4, 25.5, 37.4, 46.2, 56.0, 56.1, 64.0, 109.9, 110.9, 125.1, 125.1, 130.9, 133.8, 147.4, 149.0, 169.7. HRMS  $m/z$  ( $\text{ES}^+$ ) 308.1048 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{35}\text{ClNO}_3^+$  requires 308.1048), 310.1022 ( $\text{MH}^+$   $\text{C}_{16}\text{H}_{19}^{37}\text{ClNO}_3^+$  requires 310.1018).

**9'ce**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), characteristic signals:  $\delta$  3.23 (1 H, dt,  $J$  13.5, 4.5), 5.99 (1 H, ddd,  $J$  7.0, 5.0, 1.5).

### 1-Chloro-10,11-dihydroxy-4,5,8,12b-tetrahydroazepino[2,1-a]isoquinolin-7(3H)-one **9ce'**

$\text{BF}_3 \cdot \text{OEt}_2$  (1.00 equiv, 200  $\mu\text{mol}$ , 24.7  $\mu\text{L}$ ) and 2,4,6-collidine (1.00 equiv, 200  $\mu\text{mol}$ , 26.4  $\mu\text{L}$ ) were added, at 20  $^\circ\text{C}$ , to a solution of amide **7cj** (1.00 equiv, 200  $\mu\text{mol}$ , 71.2 mg) in 1,2-dichlorobenzene (1.6 mL). The mixture was heated at 180  $^\circ\text{C}$  for 15 min (microwave reactor, power 250 W). After cooling,  $\text{H}_2\text{O}$  (5.0 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5.0$  mL). The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford a brown amorphous solid (49.8 mg). Purification by flash column chromatography on silica gel (acidified with a small amount of AcOH, MeOH /  $\text{CH}_2\text{Cl}_2$ , gradient from 0 to 10%) gave pure tetrahydroazepinoisoquinoline **9ce'** (16.6 mg, 59.3  $\mu\text{mol}$ , 30%).

Alternative synthesis from the amide **7ce'**:  $\text{BF}_3 \cdot \text{OEt}_2$  (2.50 equiv, 395  $\mu\text{mol}$ , 48.8  $\mu\text{L}$ ) was added, at 20  $^\circ\text{C}$ , to a solution of amide **7ce'** (1.00 equiv, 158  $\mu\text{mol}$ , 50.0 mg) in 1,2-dichlorobenzene (1.0 mL). The mixture was heated at 180  $^\circ\text{C}$  for  $2 \times 30$  min (microwave reactor, power 250 W). After cooling, 1.0 M HCl aqueous solution (5.0 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5.0$  mL). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford a brown amorphous solid (35.5 mg). Analysis by  $^1\text{H}$  NMR spectroscopy showed that this crude product contained a 51:49 mixture of tetrahydroazepinoisoquinoline **9ce'** and unreacted amide **7ce'**, corresponding to 60.8  $\mu\text{mol}$  (39%) and 58.5  $\mu\text{mol}$  (37%) respectively.

**9ce'**: White crystals. M.p. 203.0–207.0  $^\circ\text{C}$  ( $\text{CHCl}_3$ ). IR (neat):  $\nu$  3449 (w), 2936 (w), 1632 (s, C=O), 1523 (w), 1445 (m), 1285 (m), 1064 (s), 877 (w), 859 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.87–1.97 (2 H, m), 2.23–2.33 (2 H, m), 3.02 (1 H, dt,  $J$  13.5, 6.0), 3.45 (2 H, AB system,  $\delta_A$  3.36,  $\delta_B$  3.54,  $J_{AB}$  18.0), 4.71 (1 H, dt,  $J$  13.5, 6.5), 5.21 (1 H, s), 6.15 (1 H, td,  $J$  6.5, 2.0), 6.58 (1 H, s), 6.81 (1 H, s).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  1.68 (1 H, m), 1.83 (1 H, m), 2.11 (1 H, dddq,  $J$  15.5, 8.0, 6.5, 2.0), 2.33 (1 H, dddd,  $J$  15.5, 9.0, 7.5, 2.0), 3.00 (1 H, ddd,  $J$  13.5, 7.0, 5.0), 3.29 (2 H, AB system,  $\delta_A$  3.26,  $\delta_B$  3.33,  $J_{AB}$  18.5), 4.42 (1 H, dt,  $J$  13.5, 6.0), 5.51 (1 H, br s), 6.13 (1 H, td,  $J$  6.5, 2.0), 6.57 (1 H, s), 6.69 (1 H, s), 8.88 (1 H, s, OH), 8.94 (1 H, s, OH).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100.6 MHz):  $\delta$  24.9, 25.0, 36.7, 45.1, 62.1, 113.8, 114.9, 123.3, 124.3, 130.6, 134.2, 143.3, 145.0, 169.1. HRMS  $m/z$  ( $\text{ES}^+$ ) 280.0733 ( $\text{MH}^+$   $\text{C}_{14}\text{H}_{15}^{35}\text{ClNO}_3^+$  requires 280.0735), 282.0703 ( $\text{MH}^+$   $\text{C}_{14}\text{H}_{15}^{37}\text{ClNO}_3^+$  requires 282.0705).

### 1-(6-Chloro-2,3-dihydro-1H-azepin-1-yl)-2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethan-1-one **19cj** and 1-chloro-11,11-dimethyl-4,5,8,13b-tetrahydroazepino[2,1-a][1,3]dioxolo[4,5-g]isoquinolin-7(3H)-one **9cj**

**General procedure E** was applied to **7cj** (1.00 equiv, 500  $\mu\text{mol}$ , 178 mg). After the first step, conducted in refluxing 1,2-dichlorobenzene (2.0 mL) for 8 h, fairly pure dihydroazepine derivative **19cj** was obtained as a brown oil (102 mg). In the second step (toluene, 5.0 mL), heating was maintained for 30 min. Analysis of the crude product (orange oil, 77.5 mg) by  $^1\text{H}$  NMR spectroscopy showed that it contained a 71:29 mixture of **9cj** and deprotected product **9ce'**. Purification by flash column chromatography on silica gel (acidified with a few drops of AcOH, EtOAc/petroleum ether,

gradient from 50 to 90%) gave pure tetrahydroazepinoisoquinolines **9cj** (26.0 mg, 81.3  $\mu\text{mol}$ , 16% over two steps) and **9ce'** (9.0 mg, 32.2  $\mu\text{mol}$ , 6% over two steps).

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**19cj**: Orange oil. IR (neat):  $\nu$  2934 (w), 1668 (m, C=O), 1496 (s), 1377 (w), 1254 (s), 1235 (m), 981 (m), 836 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.66 (6 H, s), 2.52 (2 H, td,  $J$  5.0, 2.5), 3.67 (2 H, s), 3.71 (2 H, t,  $J$  5.0), 5.92–6.00 (2 H, m), 6.637 (1 H, d,  $J$  1.5), 6.642 (2 H, AB part of an ABX system,  $\delta_A$  6.62,  $\delta_B$  6.67,  $J_{AB}$  8.0,  $J_{AX}$  1.5,  $J_{BX}$  0.0), 6.88 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.8, 32.5, 41.4, 42.8, 108.2, 109.1, 118.0, 119.3, 121.5, 126.6, 126.6, 127.5, 134.2, 146.6, 147.8, 169.2. HRMS  $m/z$  ( $\text{ES}^+$ ) 320.1048 ( $\text{MH}^+$   $\text{C}_{17}\text{H}_{19}^{35}\text{ClNO}_3^+$  requires 320.1048), 322.1015 ( $\text{MH}^+$   $\text{C}_{17}\text{H}_{19}^{37}\text{ClNO}_3^+$  requires 322.1018).

**9cj**: Yellow oil. IR (neat):  $\nu$  2990 (w), 2935 (w), 1644 (s, C=O), 1523 (w), 1491 (s), 1376 (m), 1238 (s), 1212 (s), 978 (s), 870 (w), 786 (m), 732 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.65 (3 H, s), 1.70 (3 H, s), 1.82–1.99 (2 H, m), 2.21–2.33 (2 H, m), 2.97 (1 H, ddd,  $J$  14.0, 6.5, 6.0), 3.50 (2 H, AB system,  $\delta_A$  3.44,  $\delta_B$  3.56,  $J_{AB}$  18.5), 4.70 (1 H, ddd,  $J$  14.0, 6.5, 6.0), 5.19 (1 H, br s), 6.14 (1 H, td,  $J$  6.5, 2.0), 6.53 (1 H, s), 6.64 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz):  $\delta$  25.4, 25.5, 25.8, 25.8, 37.9, 46.0, 64.1, 107.1, 107.8, 118.4, 125.73, 125.74, 130.9, 133.6, 146.0, 147.5, 169.9. HRMS  $m/z$  ( $\text{ES}^+$ ) 320.1046 ( $\text{MH}^+$   $\text{C}_{17}\text{H}_{19}^{35}\text{ClNO}_3^+$  requires 320.1048), 322.1015 ( $\text{MH}^+$   $\text{C}_{17}\text{H}_{19}^{37}\text{ClNO}_3^+$  requires 322.1018).

### 1-(6-Chloro-7-methyl-2,3-dihydroazepin-1-yl)-2-(3,4-dimethoxyphenyl)ethanone **19de** and 1-chloro-10,11-dimethoxy-12b-methyl-4,5,8,12b-tetrahydroazepino[2,1-a]isoquinolin-7(3H)-one **9de**

**General procedure F** was applied to **7de** (1.00 equiv, 681  $\mu\text{mol}$ , 244 mg). After the first step in 1,2-dichlorobenzene (6.0 mL), analysis of the concentrated residue (brown oil, 239 mg) by  $^1\text{H}$  NMR spectroscopy was uneasy, presumably because of possible complexation of the organic components with silver salts. It suggested that the crude material contained some minor amounts of remaining **7de** and, as the major components, a 50:50 mixture of dihydroazepine derivative **19de** and tetrahydroazepinoisoquinoline **9de**. For the second step, part of this crude mixture (169 mg, 1.00 equiv, assumed 482  $\mu\text{mol}$  of **19de/9de**, 1.00 equiv) was dissolved in dry toluene (4.0 mL). Trifluoromethanesulfonic acid (0.546 equiv, 263  $\mu\text{mol}$ , 23.3  $\mu\text{L}$ ) was added and the mixture was heated at 90  $^\circ\text{C}$  for 1 h. After cooling, saturated  $\text{NaHCO}_3$  aqueous solution (20 mL) was added and the mixture was extracted with EtOAc (3  $\times$  15 mL). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford an orange oil (118 mg). Analysis by  $^1\text{H}$  NMR spectroscopy did not reveal the presence of the other possible regioisomer **9'de**. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 40 to 75%) gave nearly pure **9de** (52.0 mg, 162  $\mu\text{mol}$ , 34% over the two steps). Further purification was achieved by semipreparative HPLC (C18 reverse-phase column, 10 mM aqueous  $\text{AcNH}_4/\text{MeCN}$ , gradient formed from 40 to 70 %) to afford pure **9de** (36 mg, 112  $\mu\text{mol}$ , 23% over the two steps).

**9de**: Orange oil. IR (neat):  $\nu$  2936 (w), 1654 (s, C=O), 1516 (s), 1407 (m), 1284 (s), 1259 (m), 1232 (m), 1144 (w), 1058 (w), 735 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.66 (1 H, m), 1.81 (3 H, s), 1.91–2.13 (1 H, m), 3.18 (1 H, ddd,  $J$  14.0, 7.5, 7.0), 3.62 (2 H, br s), 3.87 (3 H, s), 3.88 (3 H, s), 4.56 (1 H, ddd,  $J$  14.0, 7.0, 4.5), 6.11 (1 H, dd,  $J$  9.5, 6.0), 6.59 (1 H, s), 7.12 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz):  $\delta$  22.9, 24.1, 26.3, 37.2, 39.8, 55.9, 56.1, 68.1, 109.0, 109.8, 123.5, 129.1, 130.2, 135.6, 147.7, 148.9, 169.7. HRMS  $m/z$  ( $\text{ES}^+$ ) 322.1201 ( $\text{MH}^+$   $\text{C}_{17}\text{H}_{21}^{35}\text{ClNO}_3^+$  requires 322.1204), 324.1169 ( $\text{MH}^+$   $\text{C}_{17}\text{H}_{21}^{37}\text{ClNO}_3^+$  requires 324.1175).

**1-(6-Bromo-2,3-dihydro-1*H*-azepin-1-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one 19ee, 1-(4-bromo-2,3-dihydroazepin-1-yl)-2-(3,4-dimethoxyphenyl)ethenone 27ee, 1-bromo-10,11-dimethoxy-4,5,8,12b-tetrahydroazepino[2,1-*a*]isoquinolin-7(3*H*)-one 9ee and 3-bromo-10,11-dimethoxy-4,5,8,12b-tetrahydro-1*H*-azepino[2,1-*a*]isoquinolin-7-one 28ee**

**General procedure G** was applied to **7ee** (1.00 equiv, 543  $\mu\text{mol}$ , 198 mg). For the first step, reflux in PhCl (3.5 mL) was maintained for 3 h. Analysis of the concentrated residue (brown oil, 122 mg) by  $^1\text{H}$  NMR spectroscopy showed that it contained a fairly pure 60:40 mixture of dihydroazepine derivatives **19ee** and **27ee**. After the second step, performed in 0.5 mL of toluene, analysis of the crude product (orange oil, 102 mg) by  $^1\text{H}$  NMR spectroscopy showed that it contained a 38:62 mixture of **9ee** and isomer **28ee**. Purification by flash column chromatography on silica gel (EtOAc/petroleum ether, gradient from 40 to 75%) afforded a 36:64 mixture of **9ee** and **28ee** (66.0 mg, 187  $\mu\text{mol}$ , 34% over the two steps). Further separation by semipreparative HPLC (C18 reverse-phase column, gradient formed from 40 to 70 % of 10 mM aqueous  $\text{NH}_4\text{OAc}$  and MeCN) afforded pure tetrahydroazepinoisoquinolines **9ee** (16.0 mg, 45.0  $\mu\text{mol}$ , 8% over the two steps) and **28ee** (23.0 mg, 65.0  $\mu\text{mol}$ , 12% over the two steps).

**19ee**: Brown oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.51 (2 H, qd,  $J$  5.0, 2.0), 3.68–3.77 (4 H, m), 3.87 (6 H, br s), 5.85 (1 H, dt,  $J$  12.0, 5.0), 6.08 (1 H, dtd,  $J$  12.0, 2.0, 1.0), 6.73–6.85 (3 H, m), 7.05 (1 H, br s).

**27ee**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz), 74 : 26 mixture of two rotamers. Major rotamer, characteristic signals:  $\delta$  2.94 (2 H, t,  $J$  5.0), 5.09 (1 H, dd,  $J$  9.0, 8.0), 6.30 (1 H, br d,  $J$  8.0), 6.65 (1 H, br d,  $J$  9.0). Minor rotamer, characteristic signals:  $\delta$  5.27 (1 H, dd,  $J$  9.0, 8.0), 6.62 (1 H, br d,  $J$  9.0).

**9ee**: Yellow oil. IR (neat):  $\nu$  2930 (w), 1722 (m), 1662 (m, C=O), 1445 (m), 1242 (s), 1114 (m), 1026 (m), 741 (w), 694 (w)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.87–1.95 (2 H, m), 2.26–2.33 (2 H, m), 2.99 (1 H, dt,  $J$  13.5, 6.5), 3.56 (2 H, AB system,  $\delta_A$  3.48,  $\delta_B$  3.63,  $J_{AB}$  18.5), 3.886 (3 H, s), 3.892 (3 H, s), 4.75 (1 H, dt,  $J$  13.5, 6.0), 5.28 (1 H, dt,  $J$  2.0, 1.5), 6.44 (1 H, td,  $J$  6.5, 2.0), 6.65 (1 H, s), 6.76 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz):  $\delta$  25.2, 27.4, 37.6, 46.4, 56.0, 56.2, 64.5, 109.8, 111.0, 125.1, 125.2, 126.6, 135.6, 147.4, 149.1, 169.8. HRMS  $m/z$  ( $\text{ES}^+$ ) 353.0544 ( $\text{MH}^+ \text{C}_{16}\text{H}_{19}^{79}\text{BrNO}_3^+$  requires 352.0543), 354.0522 ( $\text{MH}^+ \text{C}_{16}\text{H}_{19}^{81}\text{BrNO}_3^+$  requires 354.0522).

**28ee**: Orange oil. IR (neat):  $\nu$  2933 (w), 1636 (m, C=O), 1513 (m), 1450 (w), 1251 (s), 1116 (s), 1013 (w), 760 (m), 728 (m)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.37 (1 H, dddd,  $J$  17.0, 10.5, 3.5, 2.5), 2.44 (1 H, dddd,  $J$  17.0, 8.0, 3.0, 1.0), 2.80 (1 H, ddd,  $J$  17.5, 4.0, 2.5), 2.95 (1 H, ddd,  $J$  13.5, 11.5, 2.5), 3.18 (1 H, ddddd,  $J$  17.5, 11.5, 4.0, 3.0, 2.5, 1.0), 3.58 (2 H, AB system,  $\delta_A$  3.54,  $\delta_B$  3.61,  $J_{AB}$  20.0), 3.868 (3 H, s), 3.869 (3 H, s), 4.51 (1 H, dd,  $J$  10.5, 3.0), 4.55 (1 H, dt,  $J$  13.5, 4.0), 6.26 (1 H, ddd,  $J$  8.0, 3.5, 3.0), 6.61 (1 H, s), 6.63 (1 H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz):  $\delta$  36.2, 39.6, 40.9, 45.7, 56.0, 56.2, 62.6, 108.5, 110.3, 123.2, 125.2, 127.0, 129.5, 148.1, 148.8, 168.1. HRMS  $m/z$  ( $\text{ES}^+$ ) 353.0543 ( $\text{MH}^+ \text{C}_{16}\text{H}_{19}^{79}\text{BrNO}_3^+$  requires 352.0543), 354.0522 ( $\text{MH}^+ \text{C}_{16}\text{H}_{19}^{81}\text{BrNO}_3^+$  requires 354.0522).

## Supporting information

Full experimental details: procedures, compound characterisation data and NMR spectra.

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- <sup>16</sup> CCDC-2246661 contains the supplementary crystallographic data for this publication. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- <sup>17</sup> As pointed out by a referee, an alternative *syn* S<sub>N</sub>2' mechanism could be considered as well. Recent calculations, performed with sterically unbiased allylic chloride derivatives CH<sub>2</sub>=CHCH<sub>2</sub>Cl, suggest a general tendency in favour of the S<sub>N</sub>2 pathway over the S<sub>N</sub>2' and, in the case of the latter, a marked preference for *anti* selectivity: T. Hansen, P. Vermeeren, L. de Jong, F. M. Bickelhaupt, T. A. Hamlin. S<sub>N</sub>2 versus S<sub>N</sub>2' Competition. *J. Org. Chem.* **2022**, *87*, 8892–8901. However, in this particular case, the same steric factors invoked earlier could indeed retard these processes sufficiently to allow a *syn* S<sub>N</sub>2' mechanism to operate.
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