Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

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

Veronika Šlachtová,[a] Nicolas Casaretto,[b] Lucie Brulíková,[a] Yvan Six*,[c]

[a] Department of Organic Chemistry, Faculty of Science, Palacký University Olomouc, 17. listopadu 12, 771 46, Olomouc, Czech Republic.

[b] Laboratoire de Chimie Moléculaire (LCM), UMR 9168 CNRS / École Polytechnique, Institut Polytechnique de Paris, 91128 Palaiseau Cedex, France.

[c] Laboratoire de Synthèse Organique (LSO), UMR 7652 CNRS / ENSTA /École Polytechnique, Institut Polytechnique de Paris, 91128 Palaiseau Cedex, France.

Experimental procedures and mechanistic proposals

I. 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) or Fluorochem (www.fluorochem.co.uk), and used as received, without purification.

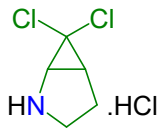
The temperatures mentioned are the temperatures of the cold baths or the oil baths used. The microwave-promoted experiments were run using a CEM Discover Microwave Synthesis System with the power, temperature and time parameters indicated; the reaction vessels were not flushed with an inert gas. All other reactions were carried out under nitrogen or argon.

Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (silica gel 60 F254). The plates were examined, after elution, under UV light and then developed using *p*-anisaldehyde or phosphomolybdic acid (PMA) stains. 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.

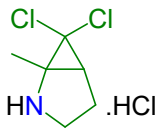
NMR spectra were recorded with an AVANCE 400 Bruker spectrometer (^{1}H at 400.2 MHz, ^{13}C at 100.6 MHz), a JEOL ECA400II spectrometer (^{1}H at 399.8 MHz, ^{13}C at 100.5 MHz) or a JEOL ECX-500SS spectrometer (^{1}H at 500.2 MHz, ^{13}C at 125.8 MHz), in $CDCl_3$ or DMSO-d_6, at ambient temperature (~21 °C).

II. Preparation of the bicyclic cyclopropyl ammonium salts 1

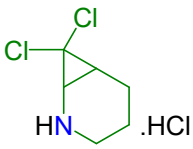
The synthesis of the cyclopropyl ammonium hydrochloride salts **1a-e**, used in this study and shown below, was already described in detail in an earlier article.[1]



1a



1b



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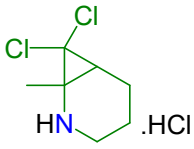
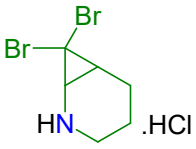


1d



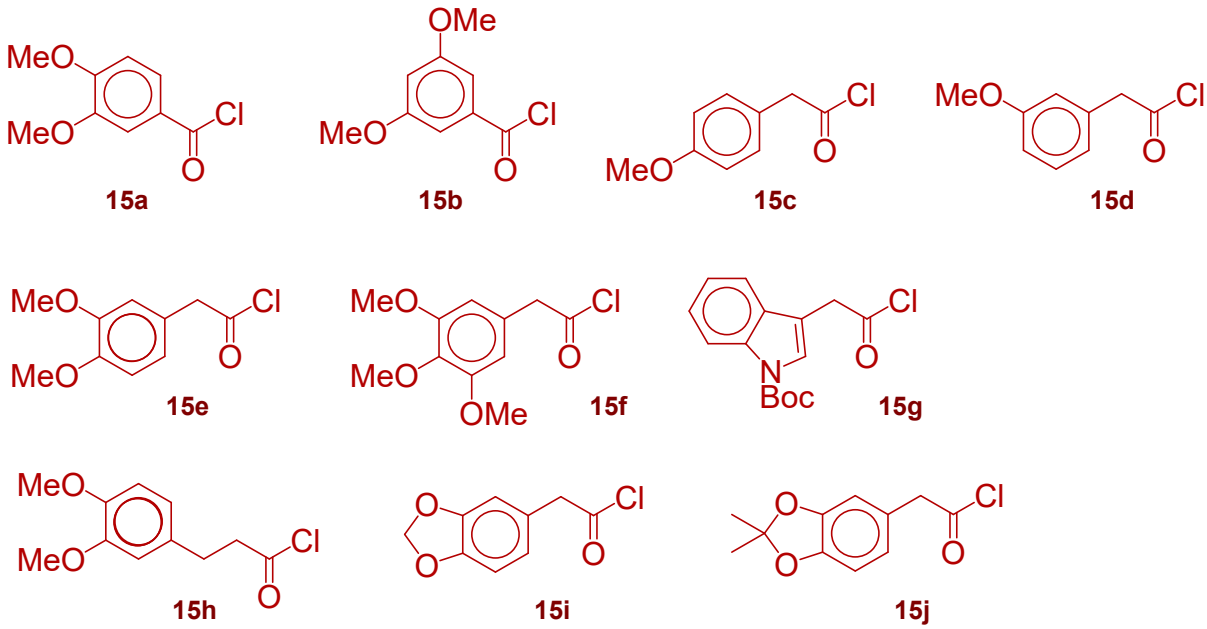
1e

[1]– C. Chen, P. Kattanguru, O. A. Tomashenko, R. Karpowicz, G. Siemiaszko, A. Bhattacharya, V. Calasans, Y. Six, *Org. Biomol. Chem.* **2017**, *15*, 5364–5372.

III. Synthesis of the acyl chlorides 15

The known acyl chlorides **15a**,[2] **15b**,[3] **15c**,[4] **15d**,[5] **15e**,[6] **15f**,[7] **15h**,[8] and **15i**[9] were prepared from the corresponding carboxylic acids as reported in the literature: either by stirring with a few equivalents of thionyl chloride at reflux,[2,4,10,11,12,13,14] or by reaction with oxalyl chloride in CH_2Cl_2 at room temperature.[15,16]

The unprecedented acyl chlorides **15g** and **15j** were prepared as described further below.



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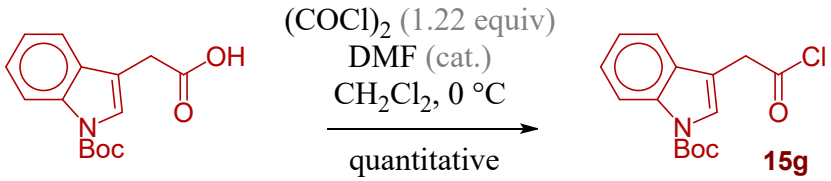
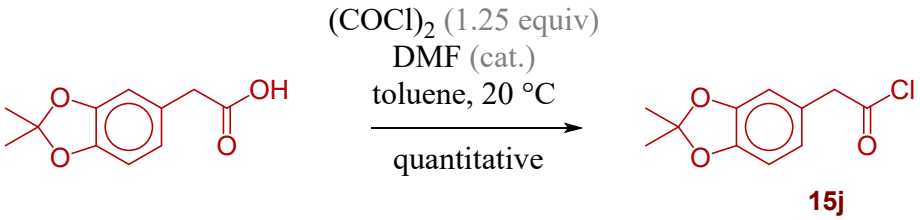
tert-Butyl 3-(2-chloro-2-oxo-ethyl)indole-1-carboxylate **15g**



DMF (4 drops) was added, at 0 °C, to a solution of 2-(1-*tert*-butoxycarbonylindol-3-yl)acetic acid[17] (1.00 equiv, 1.59 mmol, 437 mg) and oxalyl chloride (1.22 equiv, 1.95 mmol, 165 µL) in dry CH_2Cl_2 (16 mL). After 2 h of stirring at 0 °C, the volatile components were removed under reduced pressure to afford pure acyl chloride **15g** (622 mg, quantitative yield).

2-(2,2-Dimethyl-1,3-benzodioxol-5-yl)acetyl chloride **15j**



DMF (3 drops) was added to a solution of 2-(2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)acetic acid (1.00 equiv, 3.32 mmol, 691 mg)[18] and oxalyl chloride (1.25 equiv, 4.15 mmol, 356 µL) in dry toluene (10.5 mL). The mixture was stirred at 20 °C for 4 h. The volatile components were then removed under reduced pressure to afford pure acyl chloride **15j** as an orange oil (775 mg, quantitative yield).

17– 2-(1-*Tert*-butoxycarbonylindol-3-yl)acetic acid was prepared in three steps from indol-3-ylacetic acid, as described in the literature: S. Knör, A. V. Khrenov, B. Laufer, E. L. Saenko, C. A. E. Hauser, H. Kessler, *J. Med. Chem.* **2007**, *50*, 4329–4339 (supporting information).

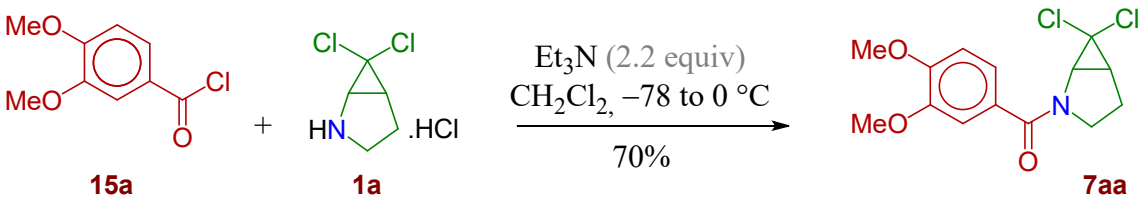
18– 2-(2,2-Dimethylbenzo[d][1,3]dioxol-5-yl)acetic acid was prepared in three steps from 3,4-dihydroxyphenylacetic acid, as described in the literature: B. Geiseler, L. Fruk, *J. Mater. Chem.* **2012**, *22*, 735–741; and references cited therein.

IV. Synthesis of the amide and thioamide substrates

General procedure A: Schotten-Baumann conditions.
1 M NaOH aqueous solution (2.0 mL per mmol of **1**) was added to a solution of acyl chloride **15** (1.40 equiv) and cyclopropylamine hydrochloride **1** (1.00 equiv) in CH_2Cl_2 (1.5 mL per mmol of **1**). After 15 min of vigorous stirring, the mixture was diluted with CH_2Cl_2 (10 mL per mmol of **1**) and H_2O (10 mL per mmol of **1**) was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL per mmol of **1**). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

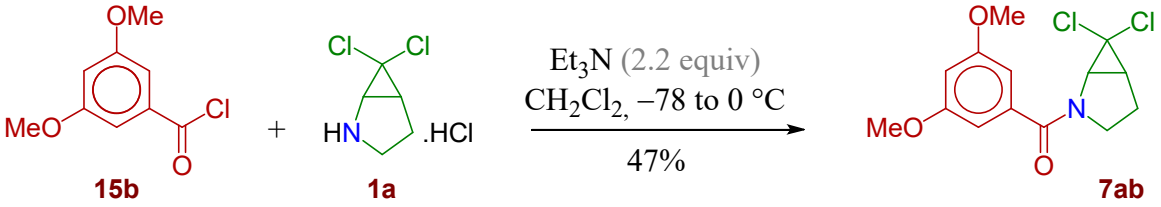
General procedure B: Acylation conducted at low temperature using Et_3N as the base.
Et_3N (1.20−2.20 equiv) was added dropwise, at −78 °C, to a solution of acyl chloride **15** (1.20−1.25 equiv) and cyclopropylamine hydrochloride **1** (1.00 equiv) in CH_2Cl_2 (1.5 mL per mmol of **1**). The mixture was allowed to warm to 0 °C while stirring was continued for 1 to 2 h. The resulting mixture was then diluted with CH_2Cl_2 (10 mL per mmol of **1**) and H_2O (10 mL per mmol of **1**) was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL per mmol of **1**). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-(3,4-dimethoxyphenyl)methanone **7aa** (Table 1)



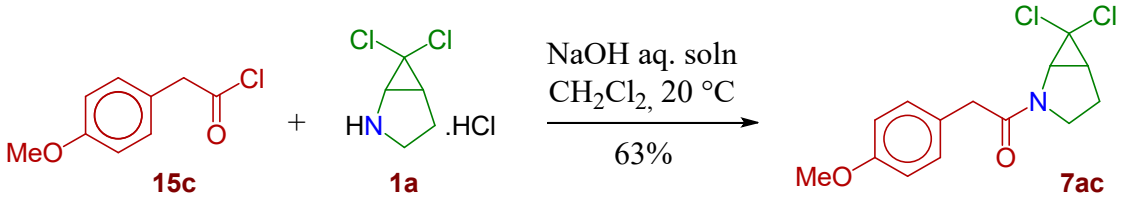
General procedure B was applied with Et_3N (2.20 equiv, 3.90 mmol, 543 µL), acyl chloride **15a** (1.10 equiv, 1.95 mmol, 391 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 1.77 mmol, 334 mg). Purification of the crude product (508 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 30 to 80%) gave pure amide **7aa** (395 mg, 1.25 mmol, 70%).

(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-(3,5-dimethoxyphenyl)methanone **7ab** (Table 1)



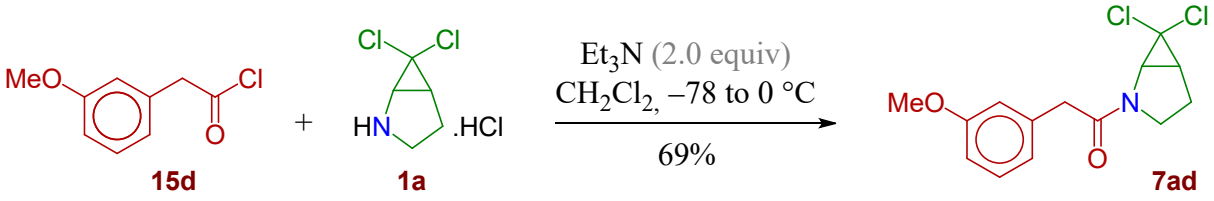
General procedure B was applied with Et_3N (2.20 equiv, 2.37 mmol, 331 µL), acyl chloride **15b** (1.20 equiv, 1.19 mmol, 239 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 1.08 mmol, 204 mg). Purification of the crude product (orange oil, 314 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 70%) gave pure amide **7ab** (161 mg, 509 µmol, 47%).

1-(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-2-(4-methoxyphenyl)ethanone **7ac** (Table 1)



General procedure A was applied with acyl chloride **15c** (1.40 equiv, 1.21 mmol, 224 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 865 µmol, 163 mg). Purification of the crude product by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure amide **7ac** (163 mg, 543 µmol, 63%).

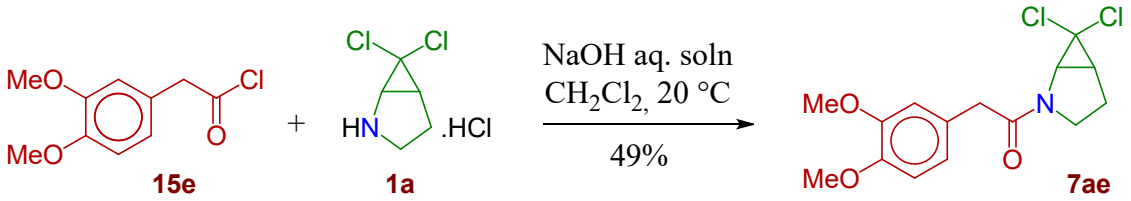
1-(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-2-(3-methoxyphenyl)ethanone **7ad** (Table 1)



General procedure B was applied with Et_3N (2.00 equiv, 3.96 mmol, 552 µL), acyl chloride **15d** (1.25 equiv, 1.47 mmol, 457 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 1.98 mmol, 373 mg). Purification of the crude product (orange oil, 515 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 60%) gave pure amide **7ad** (410 mg, 1.37 mmol, 69%).

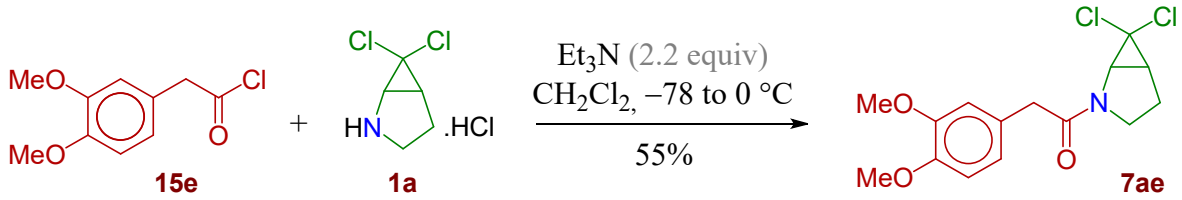
1-(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-2-(3,4-dimethoxyphenyl)ethanone **7ae** (Table 1)

■ Run 1: Procedure A.



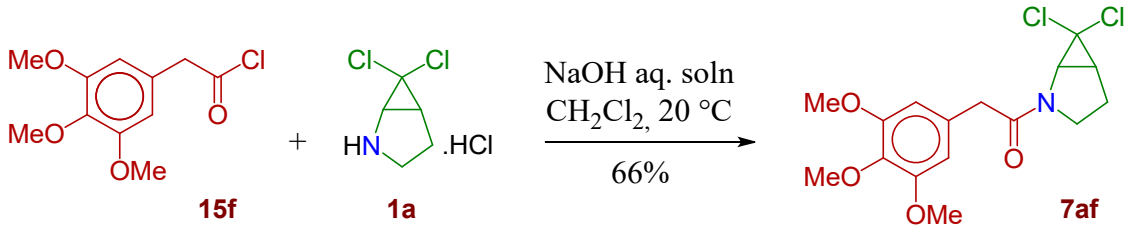
General procedure A was applied with acyl chloride **15e** (1.40 equiv, 1.21 mmol, 260 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 865 µmol, 163 mg). Purification of the crude product (brown oil) by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure amide **7ae** (141 mg, 427 µmol, 49%).

■ Run 2: Procedure B.



General procedure B was applied with Et_3N (2.20 equiv, 2.87 mmol, 399 µL), acyl chloride **15e** (1.10 equiv, 1.43 mmol, 307 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 1.30 mmol, 245 mg). Purification of the crude product by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure amide **7ae** (238 mg, 721 µmol, 55%).

1-(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-2-(3,4,5-trimethoxyphenyl)ethanone **7af** (Table 1)



General procedure A was applied with acyl chloride **15f** (1.40 equiv, 1.06 mmol, 260 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 759 µmol, 143 mg). Purification of the crude product (orange oil, 219 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure amide **7af** (181 mg, 502 µmol, 66%).

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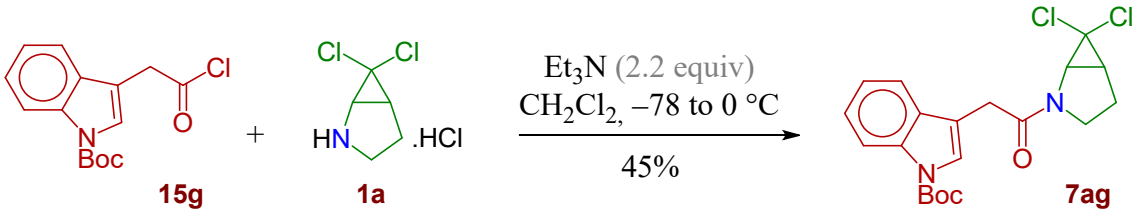
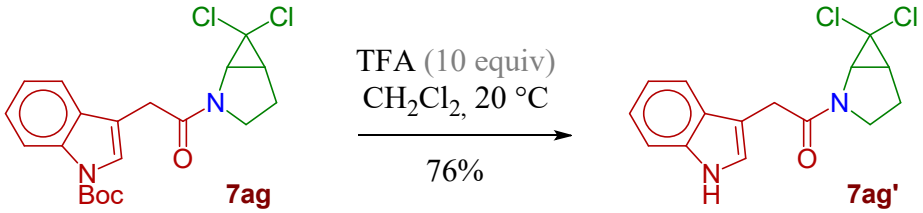
tert-Butyl 2-(2-(6,6-dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1*H*-indole-1-carboxylate **7ag** (Table 1)



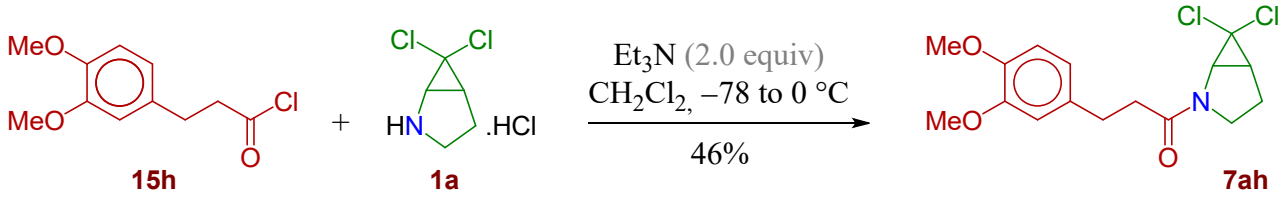
General procedure B was applied with Et_3N (2.20 equiv, 1.56 mmol, 217 µL), acyl chloride **15g** (1.10 equiv, 782 µmol, 230 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 711 µmol, 134 mg). Purification of the crude product (orange oil, 217 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 60%) gave pure amide **7ag** (132 mg, 322 µmol, 45%).

2-(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-2-(1*H*-indole-3-yl)ethan-1-one **7ag′** (Table 1)



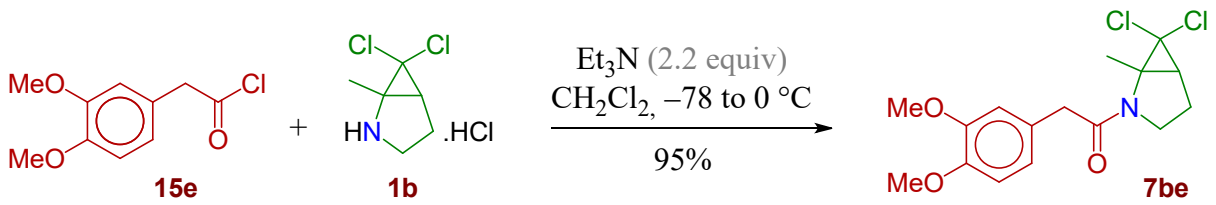
TFA (10.0 equiv, 1.78 mmol, 136 µL) was added dropwise to a stirred solution of *N*-Boc-protected indole derivative **7ag** (1.00 equiv, 178 µmol, 73.0 mg) in CH_2Cl_2 (2.0 mL). After 5 h of stirring, the mixture was diluted with CH_2Cl_2 (20 mL), and then washed successively with 1 M NaOH aq. solution (2 × 20 mL) and H_2O (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford fairly pure amide **7ag′** (41.9 mg, 136 µmol, 76%).

1-(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-3-(3,4-dimethoxyphenyl)propan-1-one **7ah** (Table 1)



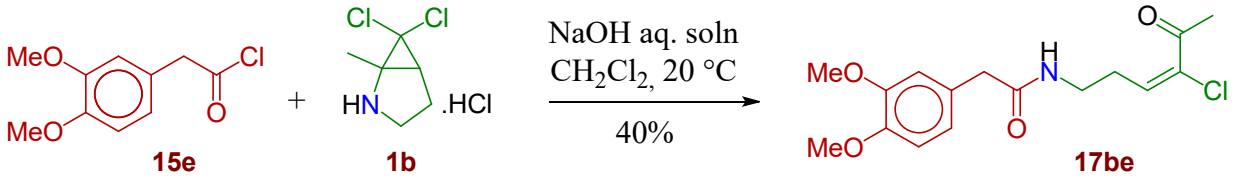
General procedure B was applied with Et_3N (2.00 equiv, 3.96 mmol, 552 µL), acyl chloride **15h** (1.25 equiv, 2.47 mmol, 565 mg) and cyclopropylamine hydrochloride **1a** (1.00 equiv, 1.98 mmol, 373 mg). Purification of the crude product (orange oil, 617 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 60%) gave pure amide **7ah** (315 mg, 915 µmol, 46%).

1-(6,6-Dichloro-1-methyl-2-azabicyclo[3.1.0]hexan-2-yl)-
2-(3,4-dimethoxyphenyl)ethanone **7be** (Table 1)



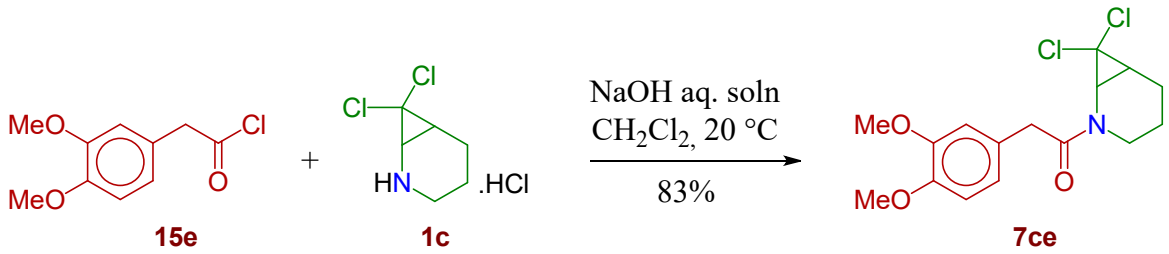
General procedure B was applied with Et_3N (2.20 equiv, 2.09 mmol, 291 µL), acyl chloride **15e** (1.10 equiv, 1.04 mmol, 224 mg) and cyclopropylamine hydrochloride **1b** (1.00 equiv, 948 µmol, 192 mg). Purification of the crude product (orange oil, 370 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 80%) gave pure amide **7be** (309 mg, 898 µmol, 95%).

N-[(*E*)-4-Chloro-5-oxo-hex-3-enyl]-2-(3,4-dimethoxyphenyl)acetamide **17be** (Scheme 5)



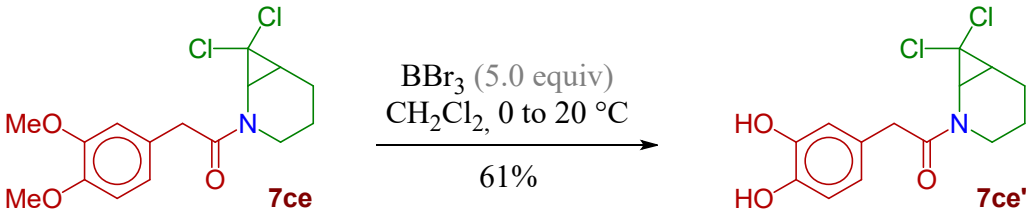
General procedure A was applied with acyl chloride **15e** (1.40 equiv, 740 µmol, 159 mg) and cyclopropylamine hydrochloride **1b** (1.00 equiv, 528 µmol, 107 mg). Purification of the crude product by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 100%) gave pure amide **17be** (69.0 mg, 212 µmol, 40%).

1-(7,7-Dichloro-2-azabicyclo[4.1.0]heptan-2-yl)-2-(3,4-dimethoxyphenyl)ethanone **7ce** (Table 1)



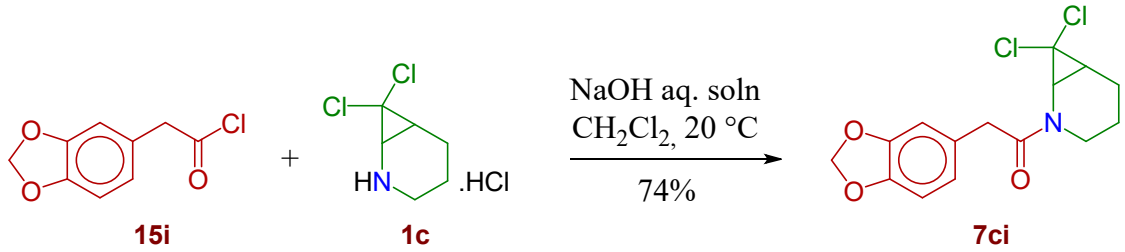
General procedure A was applied with acyl chloride **15e** (1.40 equiv, 857 µmol, 184 mg) and cyclopropylamine hydrochloride **1c** (1.00 equiv, 612 µmol, 124 mg). Purification of the crude product (brown oil, 209 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 50 to 75%) gave pure amide **7ce** (174 mg, 505 µmol, 83%).

1-(7,7-Dichloro-2-azabicyclo[4.1.0]heptan-2-yl)-2-(3,4-dihydroxyphenyl)ethanone **7ce'** (Table 1)



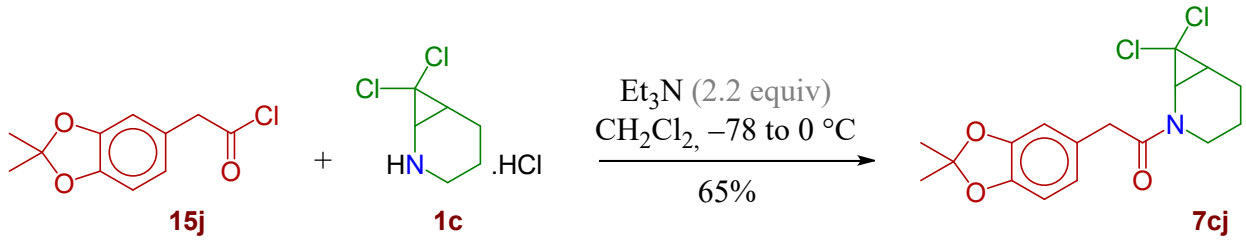
Boron tribromide (1.0 M in hexanes, 5.00 equiv, 988 µmol, 988 µL) was added dropwise, at 0 °C, to a solution of amide **7ce** (1.00 equiv, 198 µmol, 68.0 mg) in dry CH_2Cl_2 (2.0 mL). After 2 h of stirring at 20 °C, 0.5 M HCl aqueous solution (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown oil (52.0 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 50 to 100%) gave pure dihydroxy-substituted compound **7ce'** (37.8 mg, 120 µmol, 61%).

2-(1,3-Benzodioxol-5-yl)-1-(7,7-dichloro-2-azabicyclo[4.1.0]heptan-2-yl)ethanone **7ci** (Table 1)



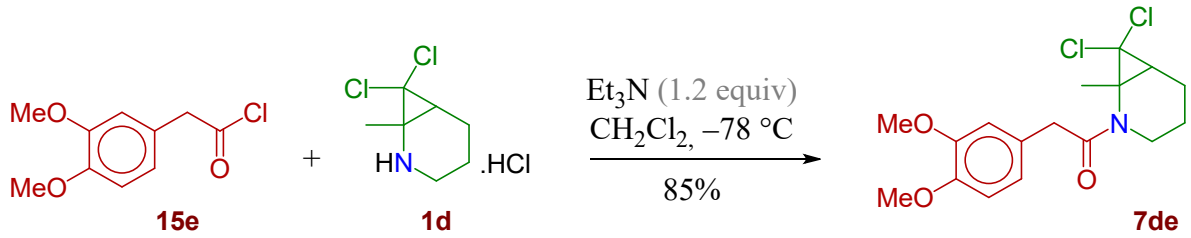
General procedure A was applied with acyl chloride **15i** (1.40 equiv, 1.27 mmol, 253 mg) and cyclopropylamine hydrochloride **1c** (1.00 equiv, 908 µmol, 184 mg). Purification of the crude product (brown oil, 299 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 10 to 40%) gave pure amide **7ci** (220 mg, 671 µmol, 74%).

1-(7,7-Dichloro-2-azabicyclo[4.1.0]heptan-2-yl)-2-(2,2-dimethyl-1,3-benzodioxol-5-yl)ethanone **7cj** (Table 1)



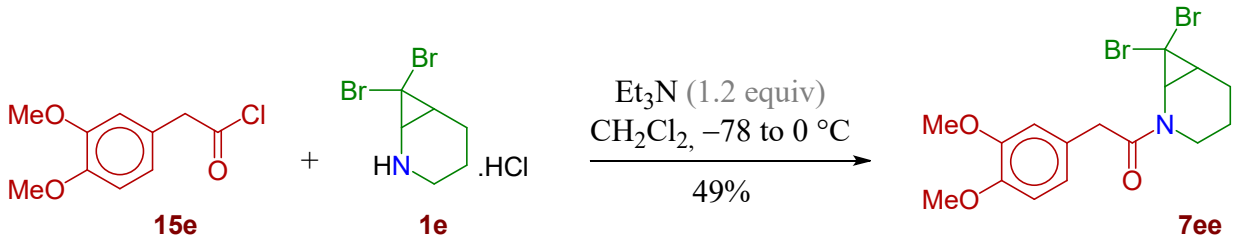
General procedure B was applied with Et_3N (2.20 equiv, 2.56 mmol, 358 µL), acyl chloride **15j** (1.10 equiv, 1.28 mmol, 291 mg) and cyclopropylamine hydrochloride **1c** (1.00 equiv, 1.17 mmol, 236 mg). Purification of the crude product (orange oil, 378 mg) by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 60%) gave pure amide **7cj** (273 mg, 766 µmol, 65%).

1-(7,7-Dichloro-1-methyl-2-azabicyclo[4.1.0]heptan-2-yl)-2-(3,4-dimethoxyphenyl)ethanone **7de** (Table 1)



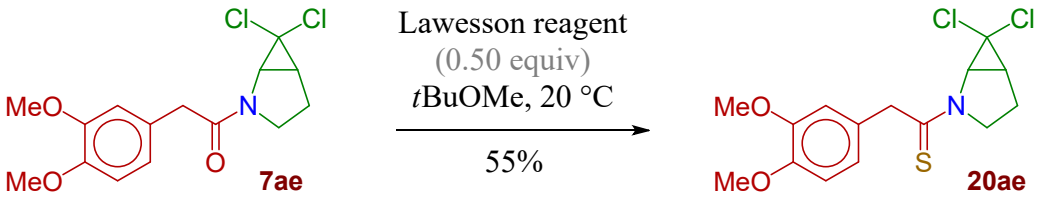
General procedure B was applied with Et_3N (1.20 equiv, 1.47 mmol, 205 µL), acyl chloride **15e** (1.20 equiv, 1.47 mmol, 184 mg) and cyclopropylamine hydrochloride **1d** (1.00 equiv, 1.22 mmol, 265 mg). Purification of the crude product by flash column chromatography (EtOAc/petroleum ether, gradient from 10 to 80%) gave pure amide **7de** (371 mg, 1.04 mmol, 85%).

1-(7,7-Dibromo-2-azabicyclo[4.1.0]heptan-2-yl)-2-(3,4-dimethoxyphenyl)ethanone **7ee** (Table 1)



General procedure B was applied with Et_3N (1.20 equiv, 1.12 mmol, 155 µL), acyl chloride **15e** (1.20 equiv, 1.12 mmol, 239 mg) and cyclopropylamine hydrochloride **1e** (1.00 equiv, 927 µmol, 270 mg). Purification of the crude product by flash column chromatography (EtOAc/petroleum ether, gradient from 10 to 80%) gave pure amide **7ee** (198 mg, 457 µmol, 49%).

1-(6,6-Dichloro-2-azabicyclo[3.1.0]hexan-2-yl)-2-(3,4-dimethoxyphenyl)ethane-1-thione **20ae**



Lawesson reagent (50.0% equiv, 151 µmol, 61.2 mg) was added to a solution of amide **7ae** (1.00 equiv, 303 µmol, 100 mg) in *t*BuOMe (1.2 mL) at 20 °C. After 19 h of stirring at 20 °C, more Lawesson reagent (50.0% equiv) was introduced, and then again (50.0% equiv) after 46 h. After a further 66 h of stirring, the solvent was removed under reduced pressure to afford an orange amorphous solid (270 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 10 to 40 %) afforded pure thioamide **20ae** (58.0 mg, 168 µmol, 55%).

V. Cyclopropane ring-opening/cyclisation sequence

General procedure C:
First step in MeCN 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).
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 °C for 20−60 min. After cooling, saturated $NaHCO_3$ aqueous solution (typically 40 mL per mmol of **7**) was added and the mixture was extracted with EtOAc (typically 3 × 25 mL per mmol of **7**). The combined organic phases were dried over $MgSO_4$, 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 °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 ^1H 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 $NaHCO_3$ aqueous solution (20 mL) was added and the mixture was extracted with EtOAc (3 × 10−15 mL). The combined organic phases were dried over $MgSO_4$, 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 $NaHCO_3$ aqueous solution (40 mL per mmol of **7**) was added and the mixture was extracted with EtOAc (3 × 30 mL per mmol of **7**). The combined organic phases were dried over $MgSO_4$, 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 $AgBF_4$; second step in toluene at 90 °C, with 0.50 equiv of TfOH

(conditions suitable for azabicyclo[4.1.0]heptane substrates).

$AgBF_4$ (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 $CHCl_3$, 3 × 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 $NaHCO_3$ aqueous solution (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 $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was then purified by flash column chromatography on silica gel.

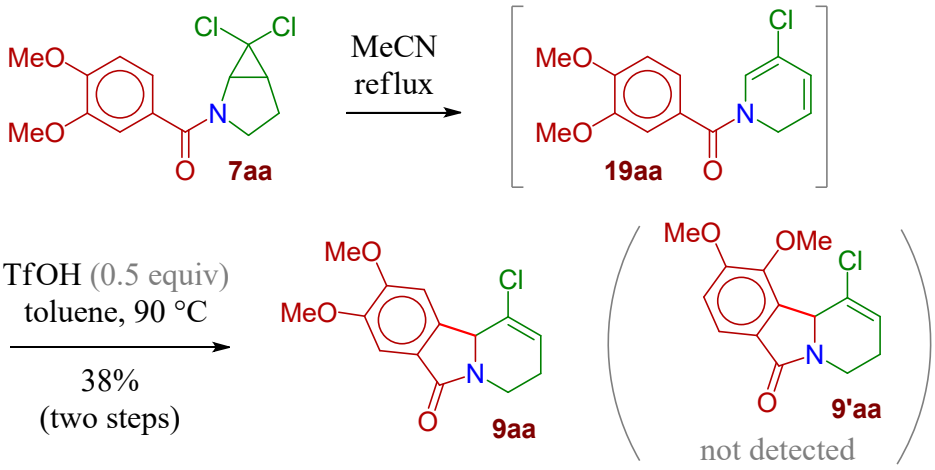
General procedure G:

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).

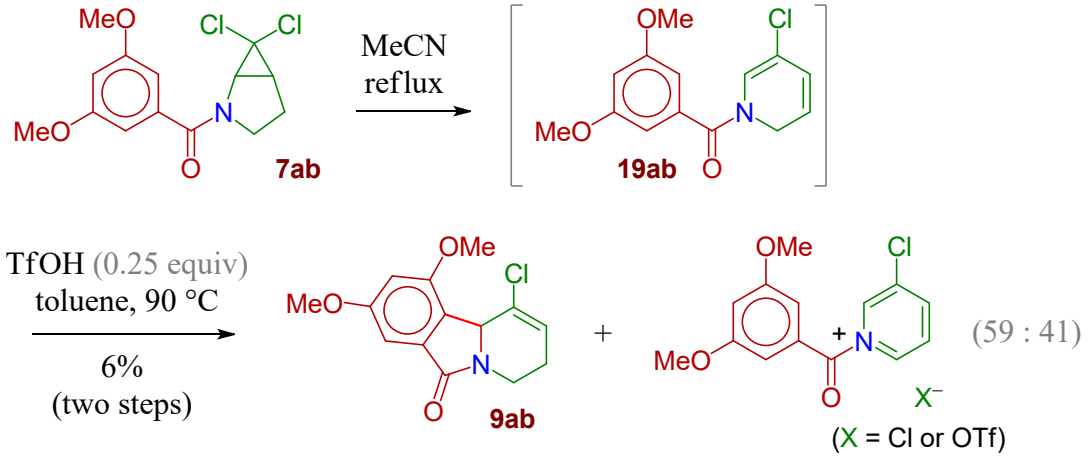
A solution of amide **7** (1.00 equiv) in PhCl (typically 6.0−8.0 mL per mmol of **7**) was heated at reflux for 3−5 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was concentrated under reduced pressure to afford the dihydropyridine intermediate **19**. This 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 $NaHCO_3$ 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 $MgSO_4$, 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** (Table 2)



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 ^{1}H NMR spectroscopy revealed the presence of the expected cyclised product **9aa**. The 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).

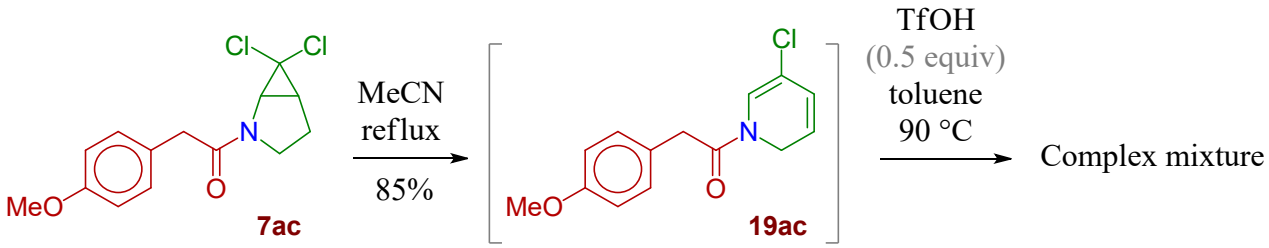
(5-Chloropyridin-1(2*H*)-yl)-2-(3,5-dimethoxyphenyl)methanone **19ab** and 1-chloro-8,10-dimethoxy-3,10b-dihydropyrido[2,1-a]isoindol-6(4*H*)-one **9ab** (Table 2)



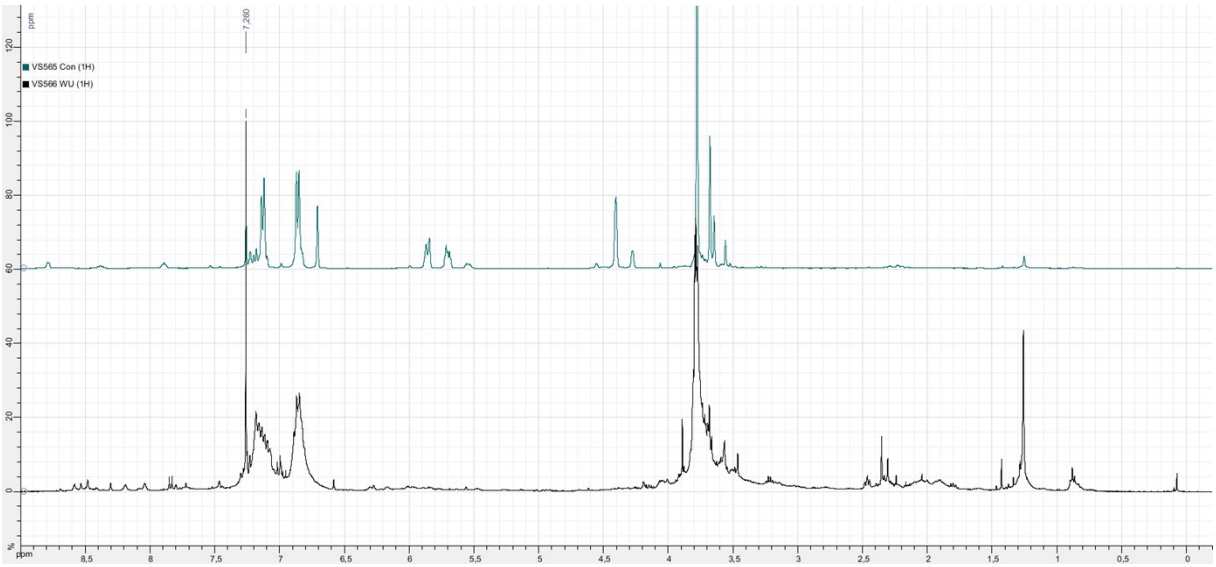
General procedure C was applied to **7ab** (1.00 equiv, 509 µmol, 161 mg). After the first step in MeCN (5.0 mL), fairly pure dihydropyridine derivative **19ab** was obtained as a yellow oil (133 mg). In the second step (toluene, 5.0 mL), 0.250 equiv of trifluoromethanesulfonic acid was employed (119 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 $AcNH_4$ solution / MeCN, gradient formed from 40 to 70%).

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** (Table 2)



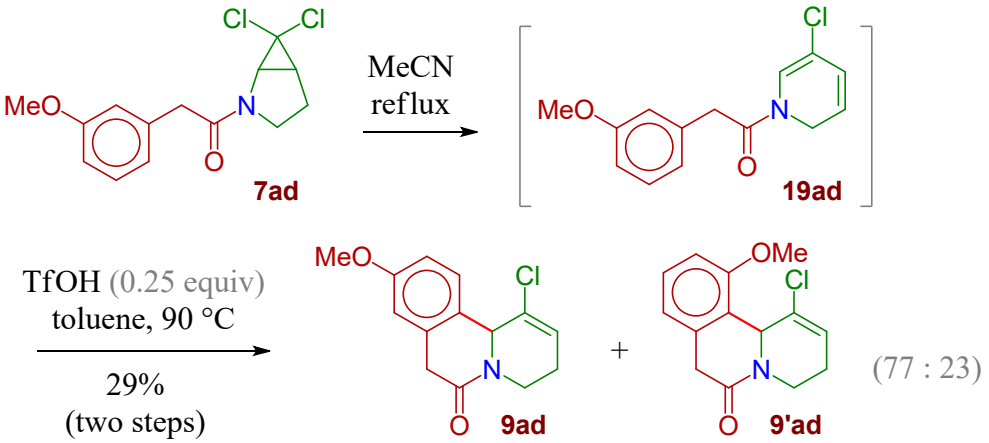
General procedure C was applied to **7ac** (1.00 equiv, 543 µmol, 163 mg). After the first step in MeCN (4.0 mL), fairly pure dihydropyridine derivative **19ac** was obtained as a orange oil (121 mg). In the second step (toluene, 3.0 mL), heating was maintained for 30 min. Analysis of the crude product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



^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz),
compared with the spectrum of the intermediate **19ac** (in green).

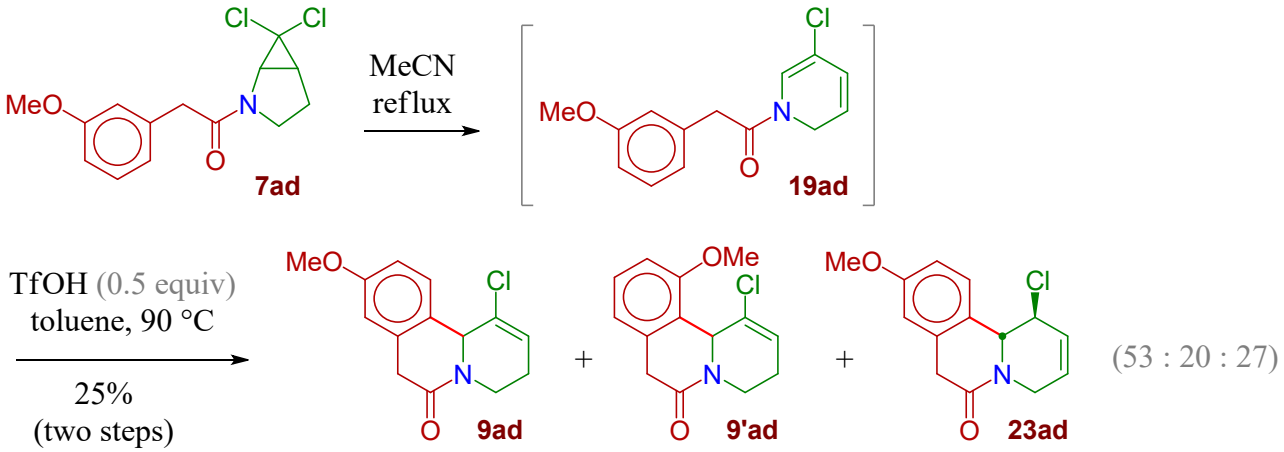
1-(5-Chloropyridin-1(2*H*)-yl)-2-(3-methoxyphenyl)ethan-1-one **19ad**, 1-chloro-9-methoxy-3,4,7,11b-tetrahydro-6*H*-pyrido[2,1-a]isoquinolin-6-one **9ad** and 1-chloro-9-methoxy-1,4,7,11b-tetrahydro-6*H*-pyrido[2,1-a]isoquinolin-6-one **23ad**

■ Run 1: conditions C, with 0.25 equiv of TfOH (Table 2).



General procedure C was applied to **7ad** (1.00 equiv, 683 µmol, 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 µmol, 13.7 µL) and heating was maintained for 40 min. Analysis of the crude product (orange oil, 100 mg) by ^{1}H NMR spectroscopy showed that it contained a 77:23 mixture of **9ad** and the 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 µmol, 7% over two steps) and **9ad** (39.0 mg, 148 µmol, 22% over two steps).

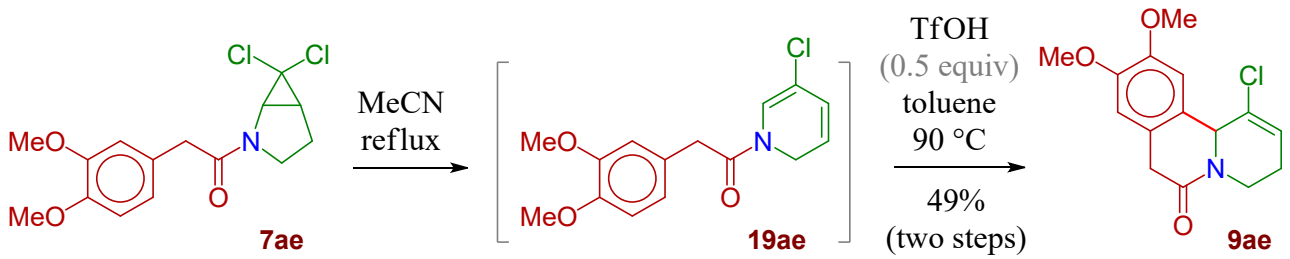
■ Run 2: conditions C (Scheme 8, top).



General procedure C was applied to **7ad** (1.00 equiv, 683 µmol, 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}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 µmol, 6% over two steps) and a 59:41 mixture of benzoquinolizidine isomers **9ad** and **23ad** (33.0 mg, 125 µmol, 19% over two steps).

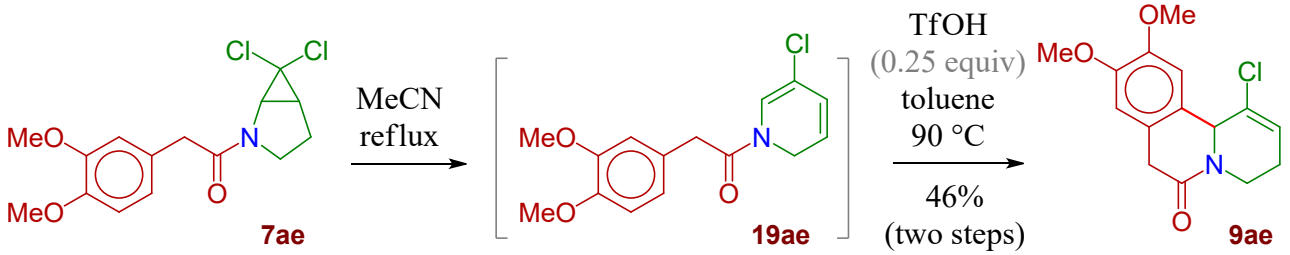
1-(5-Chloropyridin-1(2*H*)-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one **19ae** and 1-chloro-9,10-dimethoxy-3,4,7,11b-tetrahydro-6*H*-pyrido[2,1-a]isoquinolin-6-one **9ae**

■ Run 1: conditions C (Table 2).



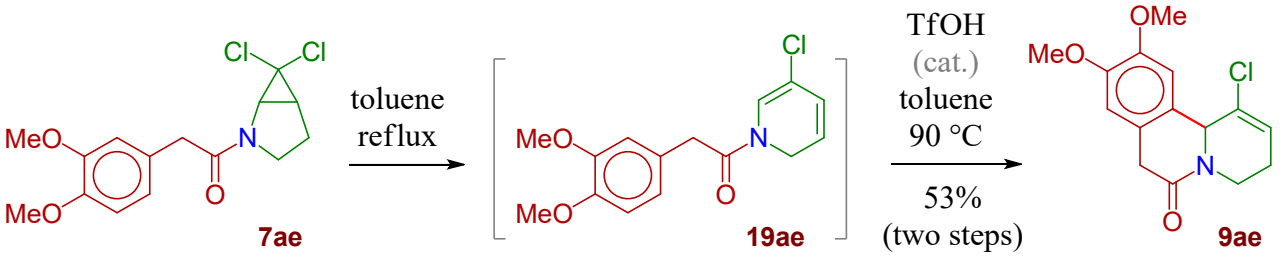
General procedure C was applied to **7ae** (1.00 equiv, 427 µmol, 141 mg). After the first step in MeCN (3.0 mL), fairly pure dihydropyridine derivative **19ae** was obtained as an orange oil (100 mg). In the second step (toluene, 3.0 mL), heating was maintained for 40 min. Analysis of the crude product (orange oil, 84.0 mg) by ^{1}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 µmol, 49% over the two steps).

■ Run 2: conditions C, with 0.25 equiv of TfOH.



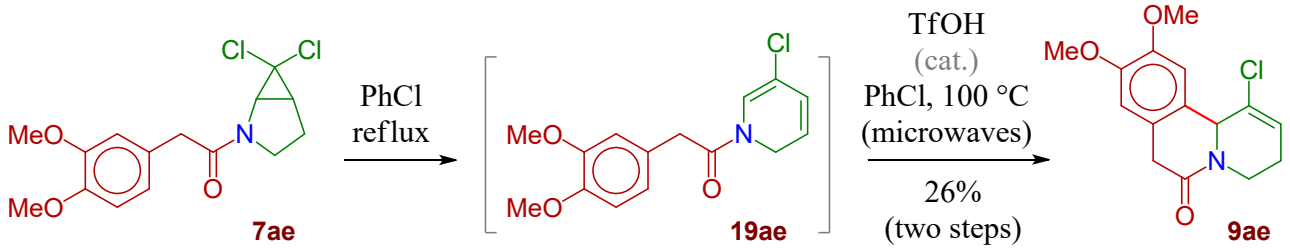
General procedure C was applied to **7ae**(1.00 equiv, 721 µmol, 238 mg). After the first step in MeCN (6.0 mL), fairly pure dihydropyridine derivative **19ae** was obtained (201 mg). In the second step, carried out with 81.8 mg of this intermediate product in toluene (3.0 mL), heating was maintained for 30 min. Analysis of the crude product (138 mg) by ^{1}H NMR spectroscopy showed that it contained a 92:08 mixture of **9ae** and **23ae**. The regioisomer **9′ae** was not detected. Purification by flash column chromatography (EtOAc/petroleum ether, gradient from 40 to 80%) gave pure benzoquinolizidine **9ae** (49.1 mg, 167 µmol, 46% over the two steps).

■ Run 3: conditions D (Table 2).



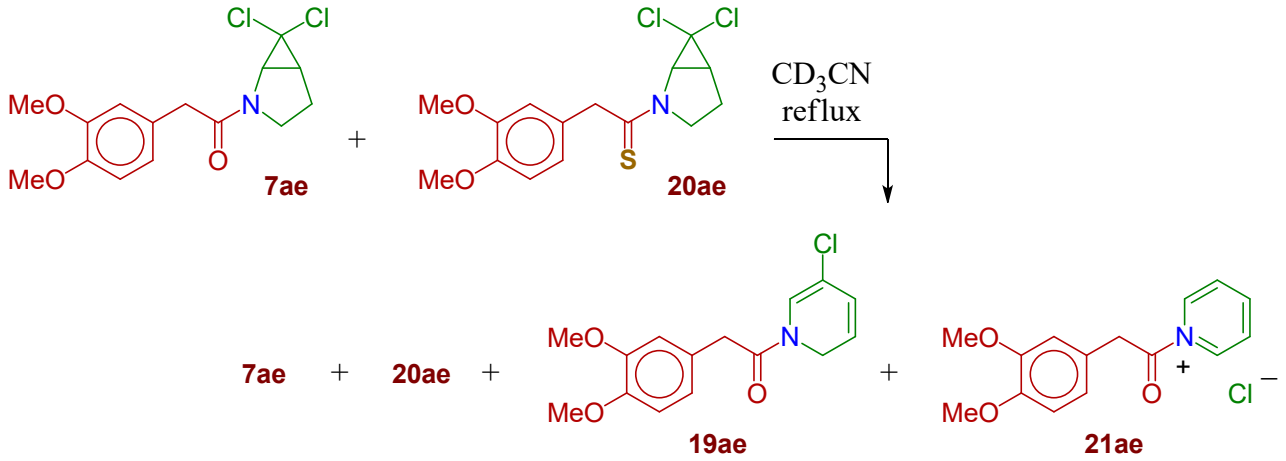
General procedure D was applied to **7ae** (1.00 equiv, 121 µmol, 40.0 mg), with 4.0 mL of toluene. For the first step, analysis by ^{1}H NMR spectroscopy of a sample, taken after 3 h of reaction, showed it contained fairly pure dihydropyridine derivative **19ae**. For the second step, one drop of TfOH 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 µmol, 53% over the two steps).

■ Run 4: both steps performed in chlorobenzene.



A solution of amide **7ae** (1.00 equiv, 121 µmol, 40.0 mg) in PhCl (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 **19ae** as an orange oil (30.0 mg). This crude product was then dissolved in PhCl again (0.50 mL). Trifluoromethanesulfonic acid (1 drop) was added and the mixture was heated with a microwave synthesis reactor (250 W, 100 °C, 30 min). After cooling, saturated $NaHCO_3$ aqueous solution (20 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford an orange oil (20.0 mg). Analysis by ^{1}H NMR spectroscopy did not reveal the presence of the other possible regioisomer **9'ae**. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 50 to 100%) gave pure benzoquinolizidine **9ae** (9.0 mg, 31 µmol, 26% over the two steps).

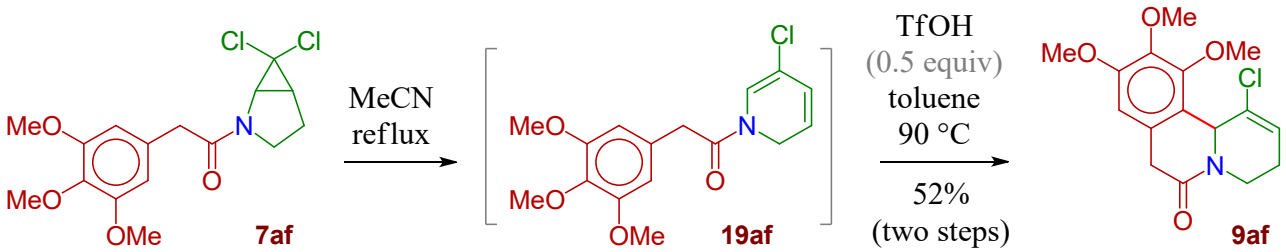
Competitive ring-opening experiment performed from an equimolar mixture of amide **7ae** and thioamide **20ae**. Formation of 1-(5-chloropyridin-1(2*H*)-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one **19ae** and a new compound tentatively identified as the acylpyridium salt **21ae** (Scheme 7)



	7ae	:	**20ae**	:	**19ae**	:	**21ae**
$t = 0$	48	:	52	:	0	:	0
$t = 30$ min	0	:	52	:	33	:	15
$t = 60$ min	0	:	52	:	27	:	21
$t = 120$ min	0	:	52	:	15	:	33

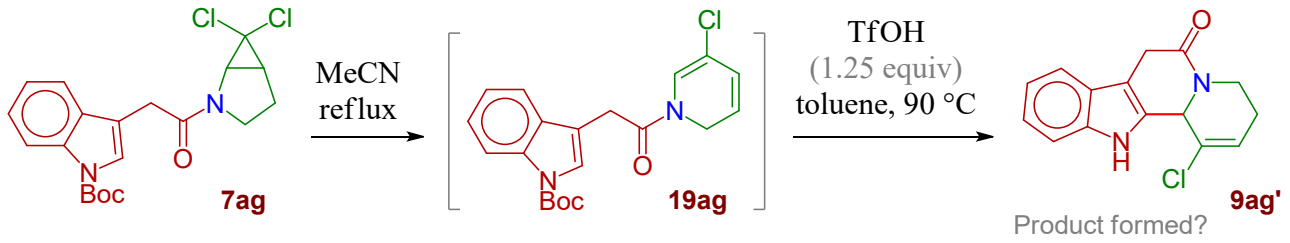
A solution of amide **7ae** (1.00 equiv, 15.1 µmol, 5.0 mg) and thioamide **20ae** (1.00 equiv, 14.4 µmol, 5.0 mg) in CD_3CN (0.50 mL) was heated at reflux in a closed NMR tube for 30 min. The reaction mixture was analysed by ^1H and ^{13}C NMR spectroscopy and found to contain a mixture of starting **20ae**, dihydropyridine derivative **19aea** 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 $^1H/^{13}C$ 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).

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



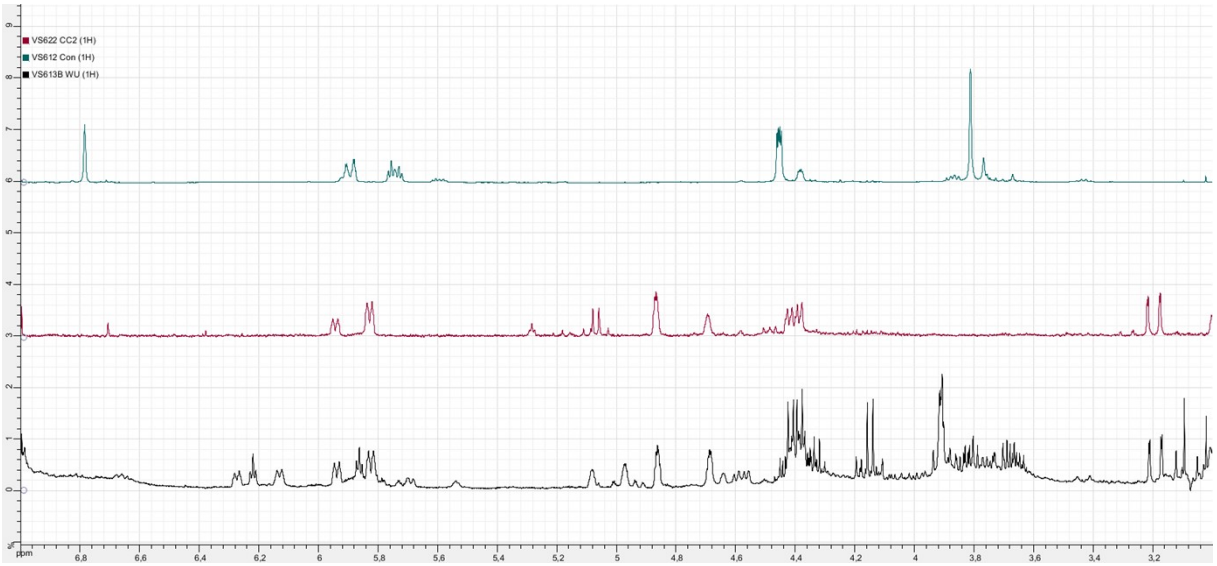
General procedure C was applied to **7af** (1.00 equiv, 502 µmol, 181 mg). After the first step in MeCN (4.0 mL), fairly pure dihydropyridine derivative **19af** was obtained as an orange oil (139 mg). In the second step (toluene, 3.0 mL), heating was maintained for 1 h. Purification of the crude product (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 µmol, 52% over the two steps).

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



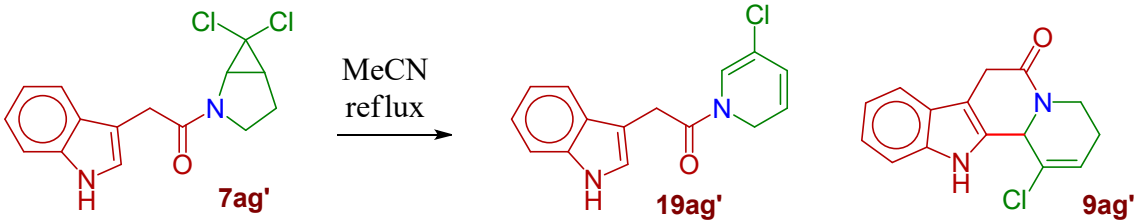
A solution of amide **7ag** (1.00 equiv, 259 µmol, 106 mg) in MeCN (4.0 mL) was heated at reflux for 1 h, with a gentle flow of nitrogen at the top of the condenser. After cooling, the solution was concentrated under reduced pressure to afford fairly pure dihydropyridine derivative **19ag** as a yellow oil (97.4 mg).

Trifluoromethanesulfonic acid (1.25 equiv, 164 µmol, 14.5 µL) was added to a solution of **19ag** (1.00 equiv, 131 µmol, 48.7 mg) in dry toluene (1.0 mL) and the mixture was heated at 90 °C for 30 min. After cooling, saturated $NaHCO_3$ aqueous solution (20 mL) was added and the mixture was extracted with EtOAc (3 × 7.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product (light brown oil, 29.2 mg). Analysis by ^{1}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.



^{1}H NMR spectrum of the crude product ($CDCl_3$, 400 MHz), compared with the spectrum of the intermediate **19ag** (top, in green) and with the spectrum of a partially purified sample of **9ag′**, produced from **7ag′** (middle, in red). Note the perfect correspondence of the signals at 3.20, 4.87 and 5.83 ppm.

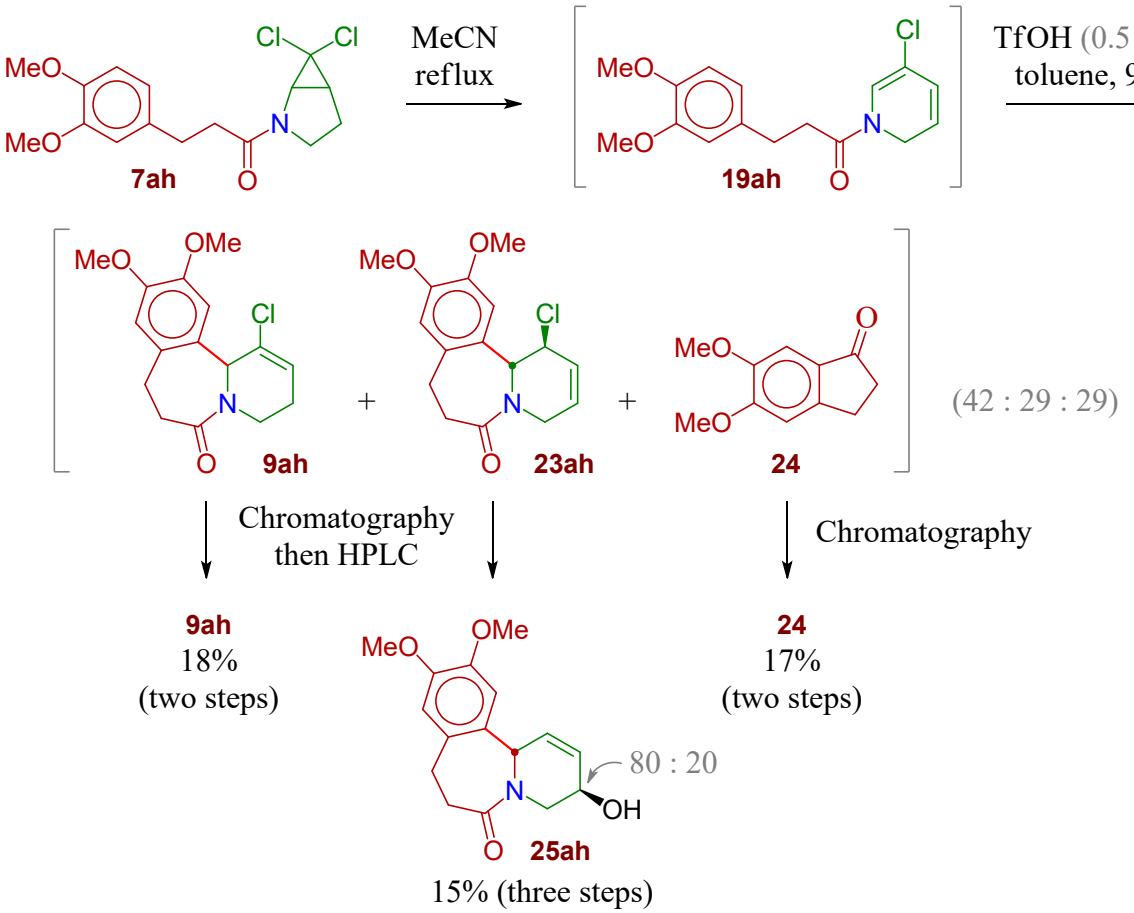
Attempted transformation of **7ag′** into 1-(5-chloro-2*H*-pyridin-1-yl)-2-(1*H*-indol-3-yl)ethanone **19ag′**; possible synthesis of 1-chloro-4,7,12,12b-tetrahydro-3*H*-indolo[2,3-a]quinolizin-6-one **9ag′** (Table 2)



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 ^{1}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′**.

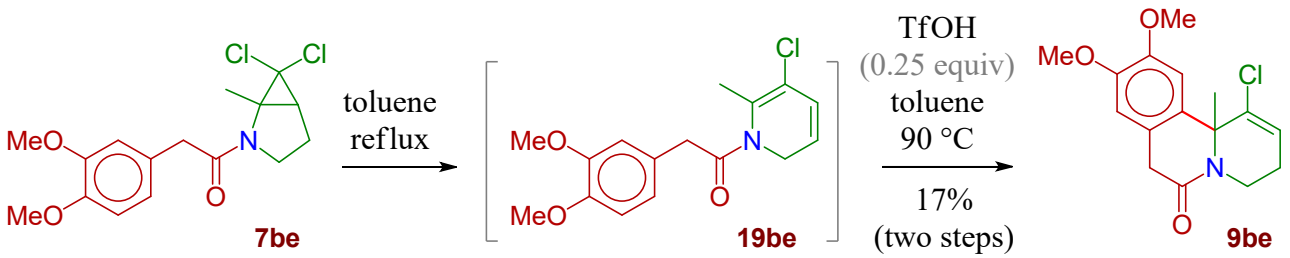
1-(5-Chloropyridin-1(2*H*)-yl)-3-(3,4-dimethoxyphenyl)propan-1-one **19ah** and 1-chloro-10,11-dimethoxy-4,7,8,12b-tetrahydro-3*H*-pyrido[2,1-a][2]benzazepin-6-one **9ah** (Table 2). 1-Chloro-10,11-dimethoxy-4,7,8,12b-tetrahydro-1*H*-pyrido[2,1-a][2]benzazepin-6-one **23ah** and 1-hydroxy-10,11-dimethoxy-1,7,8,12b-tetrahydrobenzo[c]pyrido[1,2-a]azepin-6(4*H*)-on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



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 ^{1}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_4OAc 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).

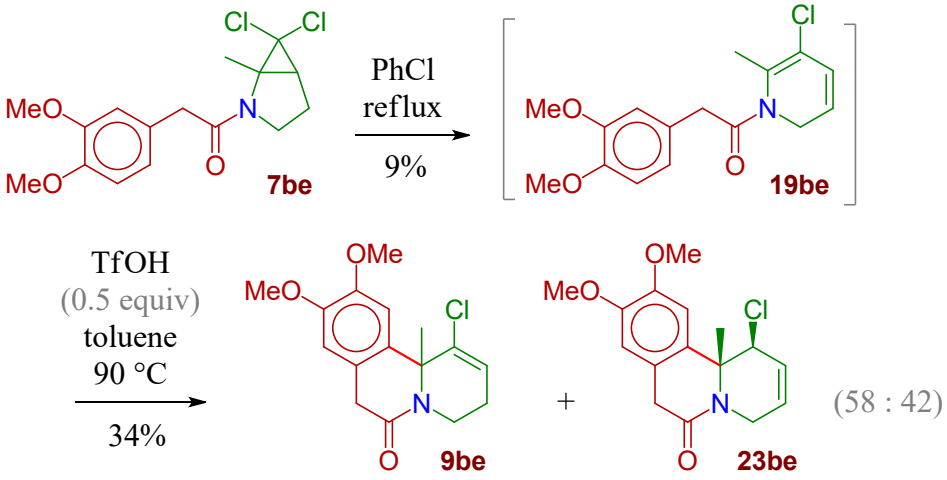
1-(5-Chloro-6-methylpyridin-1(2*H*)-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one **19be**
and 1-chloro-9,10-dimethoxy-11b-methyl-3,4,7,11b-
tetrahydro-6*H*-pyrido[2,1-a]isoquinolin-6-one **9be**

■ Run 1: conditions D (Table 2).



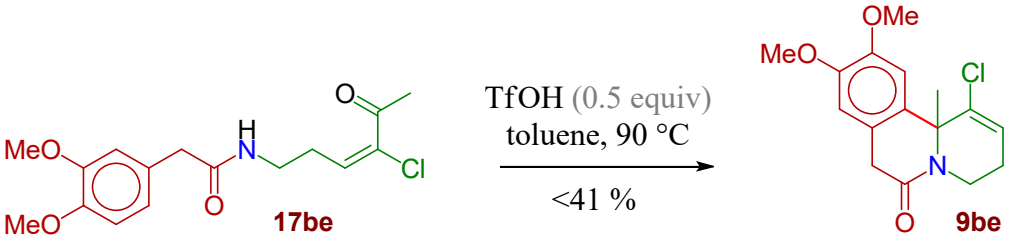
General procedure D was applied to **7be** (1.00 equiv, 188 µmol, 64.7 mg), with 3.0 mL of toluene. For the first step, analysis by ^{1}H NMR spectroscopy of a sample, taken after 8 h of reaction, showed it contained an unidentified compound and a 32:68 mixture of **19be** and starting **7be**. For the second step, 0.250 equiv of TfOH (38.7 µmol, 3–4 µL) was used and the mixture was heated at 90 °C for 25 min. 38.7 µmol, 3.4 µL). Analysis of the crude product (orange oil, 79.0 mg) by ^{1}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 µmol, 37%) and pure benzoquinolizidine **9be** (9.9 mg, 32.2 µmol, 17% over two steps).

■ Run 2: conditions G, with isolation of the intermediate **17eb**.

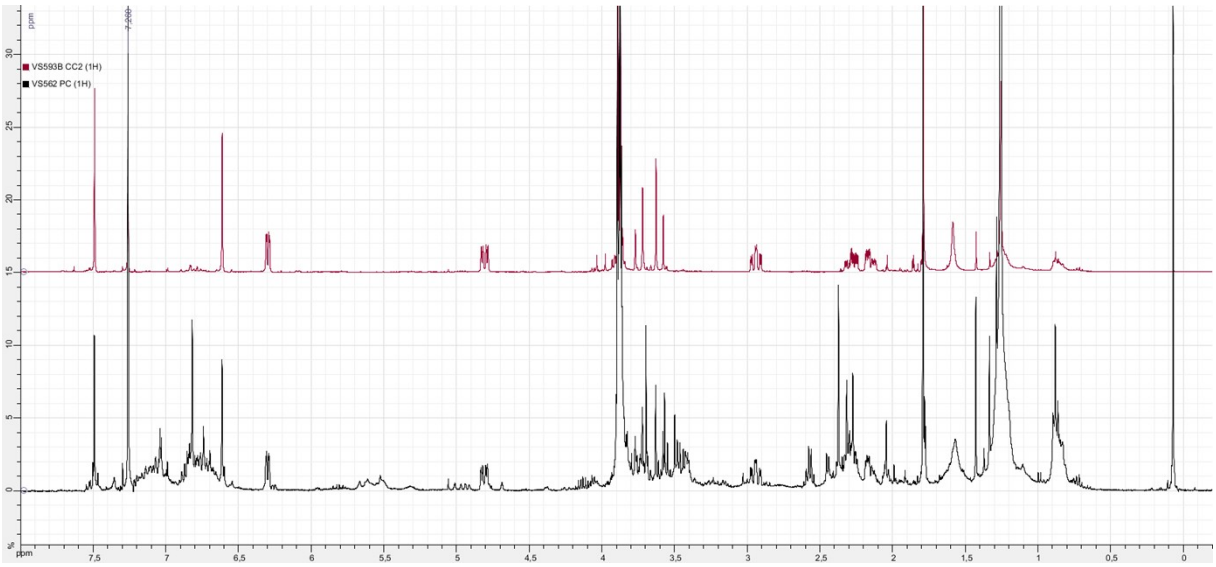


General procedure G was applied to **7be** (1.00 equiv, 683 µmol, 235 mg). For the first step, reflux in PhCl (5.0 mL) was maintained for 5 h. Analysis of the concentrated residue (brown oil, 108 mg) by ^{1}H NMR spectroscopy showed the full conversion of **7be**. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 40 to 70%) gave pure dihydropyridine derivative **19be** as a yellow oil (18.2 mg, 59.1 µmol, 9%). The second step was performed with this purified material, in 0.50 mL of toluene and with 0.500 equiv of TfOH (29.2 µmol, 2.6 µL). Analysis of the crude product (orange oil, 16.5 mg) by ^{1}H NMR spectroscopy revealed the presence of benzoquinolizidines **9be** and **23be** as the main components, in 58:42 ratio. The other possible regioisomer **9'be** was not detected. Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 40 to 60%) gave a 53:47 mixture of **9be** and **23be**, as a colourless oil [6.2 mg, corresponding to 10.3 µmol (17%) and 9.2 µmol (16%) of **9be** and **23be** respectively].

1-Chloro-9,10-dimethoxy-11b-methyl-3,4,7,11b-tetrahydro-6*H*-pyrido[2,1-a]isoquinolin-6-one **9be** from the secondary amide **17be**

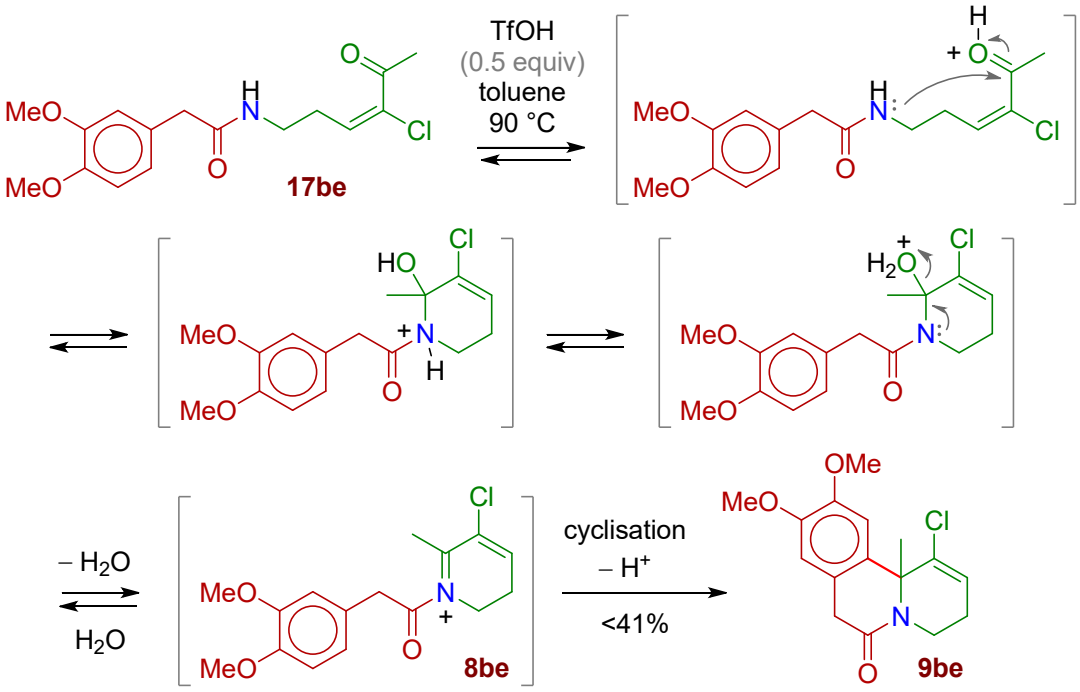


Trifluoromethanesulfonic acid (0.500 equiv, 63.5 µmol, 5.6 µL) was added to a solution of amide **17be** (1.00 equiv, 127 µmol, 41.4 mg) in dry toluene (1.2 mL) and the mixture was heated at 90 °C for 2 h. After cooling, saturated $NaHCO_3$ aqueous solution (10 mL) was added and the mixture was extracted with EtOAc (3 × 7.0 mL). The combined organic phases were dried over $MgSO_4$, 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 µmol, < 41%).

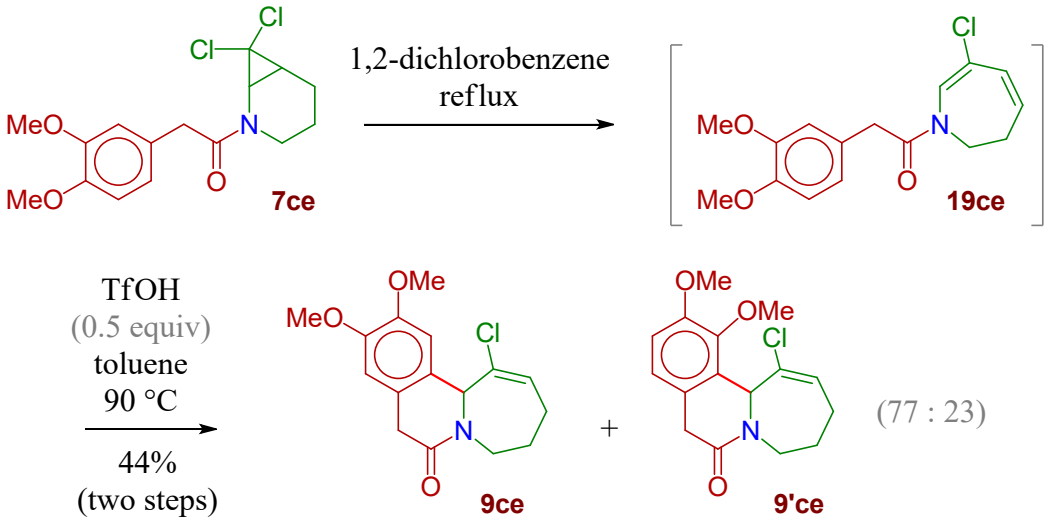


^{1}H NMR spectrum of the compound obtained after purification ($CDCl_3$, 400 MHz), compared with the spectrum of an authentic sample of **9be** (in red).

■ Proposed mechanism:



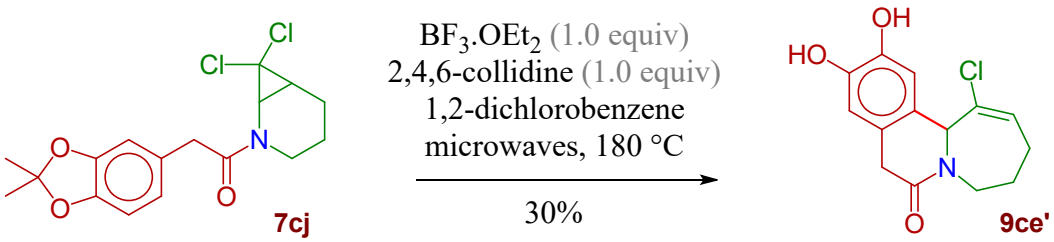
1-(6-Chloro-2,3-dihydro-1*H*-azepin-1-yl)-2-(3,4-dimethoxyphenyl)ethan-1-one **19ce** and 1-chloro-10,11-dimethoxy-4,5,8,12b-tetrahydroazepino[2,1-a]isoquinolin-7(3*H*)-one **9ce** (Table 2)



General procedure E was applied to **7ce** (1.00 equiv, 505 µmol, 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}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 µmol, 44% over the two steps). The isomer **9′ce** was not isolated.

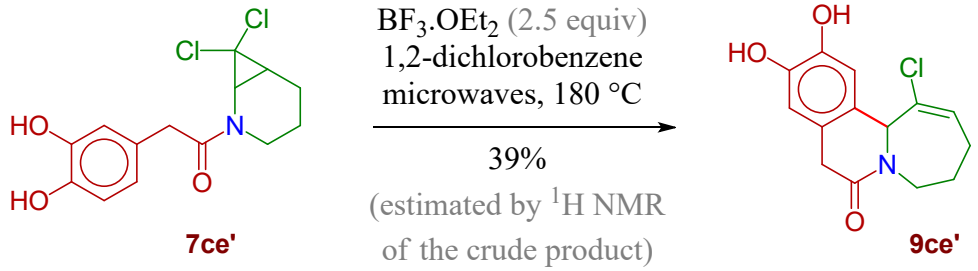
1-Chloro-10,11-dihydroxy-4,5,8,12b-tetrahydroazepino[2,1-a]isoquinolin-7(3*H*)-one **9ce′**

■ Run 1: from the amide **7cj**, in the presence of 1 equiv of $BF_3.OEt_2$ and collidine (Scheme 6).



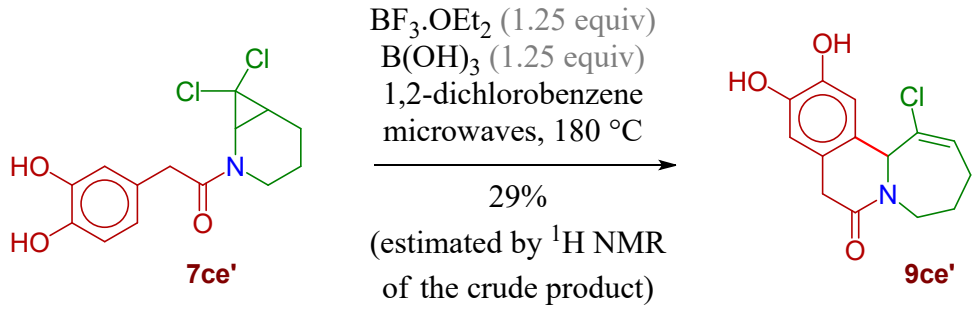
$BF_3.OEt_2$ (1.00 equiv, 200 µmol, 24.7 µL) and 2,4,6-collidine (1.00 equiv, 200 µmol, 26.4 µL) were added, at 20 °C, to a solution of amide **7cj** (1.00 equiv, 200 µmol, 71.2 mg) in 1,2-dichlorobenzene (1.6 mL). The mixture was heated at 180 °C for 15 min (microwave reactor, power 250 W). After cooling, H_2O (5.0 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5.0 mL). The combined organic phases were dried over Na_2SO_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 / CH_2Cl_2, gradient from 0 to 10%) gave pure tetrahydroazepinoisoquinoline **9ce′** (16.6 mg, 59.3 µmol, 30%).

■ Run 2: from the amide **7ce′**, in the presence of 2.5 equiv of $BF_3.OEt_2$ (Table 2).



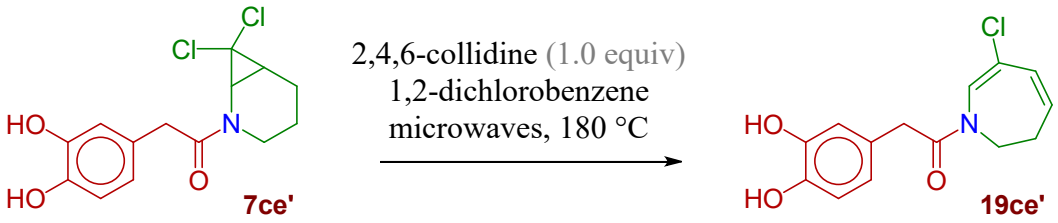
$BF_3.OEt_2$ (2.50 equiv, 395 µmol, 48.8 µL) was added, at 20 °C, to a solution of amide **7ce′** (1.00 equiv, 158 µmol, 50.0 mg) in 1,2-dichlorobenzene (1.0 mL). The mixture was heated at 180 °C for 2 × 30 min (microwave reactor, power 250 W). After cooling, 1.0 M HCl aqueous solution (5.0 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown amorphous solid (35.5 mg). Analysis by ^{1}H NMR spectroscopy showed that this crude product contained a 51:49 mixture of tetrahydroazepinoisoquinoline **9ce′** and unreacted amide **7ce′**, corresponding to 60.8 µmol (39%) and 58.5 µmol (37%) respectively.

■ Run 3: from the amide **7ce′**, in the presence of 2.5 equiv of $BF_3.OEt_2$/boric acid mixture.



Boric acid (1.25 equiv, 198 µmol, 12.2 mg) and $BF_3.OEt_2$ (1.25 equiv, 198 µmol, 24.4 µL) were added, at 20 °C, to a solution of amide **7ce′** (1.00 equiv, 158 µmol, 50.0 mg) in 1,2-dichlorobenzene (1.0 mL). The mixture was heated at 180 °C for 2 × 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 CH_2Cl_2 (3 × 5.0 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown amorphous solid (25.0 mg). Analysis by ^{1}H NMR spectroscopy showed that this crude product contained a 54:46 mixture of tetrahydroazepinoisoquinoline **9ce′** and unreacted amide **7ce′**, corresponding to 45.5 µmol (29%) and 38.8 µmol (25%) respectively.

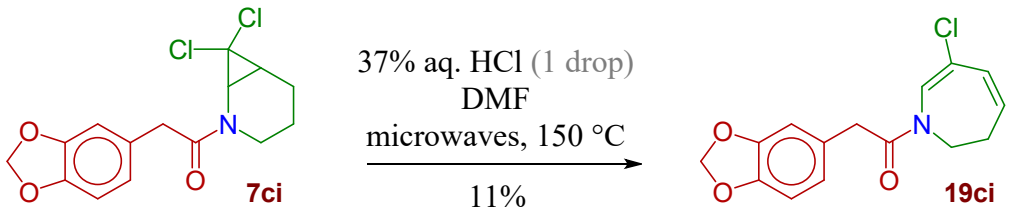
1-(6-Chloro-2,3-dihydro-1*H*-azepin-1-yl)-2-(3,4-dihydroxyphenyl)ethan-1-one **19ce′**



A solution of amide **7ce′** (1.00 eq, 22.8 µmol, 7.2 mg) and 2,4,6-collidine (1.00 eq, 22.8 µmol, 3.0 µL) in 1,2-dichlorobenzene (1.0 mL) was heated at 180 °C for 15 min (microwave reactor, power 250 W). After cooling, 1.0 M HCl aqueous solution (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in EtOAc (0.50 mL), filtered through a pad of silica gel, rinsed with EtOAc (3 × 6.0 mL) and concentrated under reduced pressure to afford reasonably pure **19ce′** (14 mg).

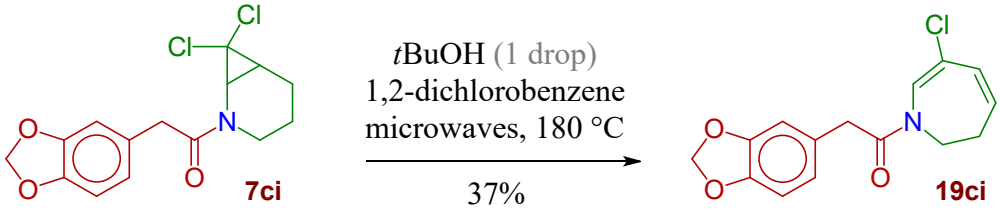
2-(1,3-Benzodioxol-5-yl)-1-(6-chloro-2,3-dihydroazepin-1-yl)ethenone **19ci**

■ Run 1: in DMF at 150 °C, in the presence of HCl.



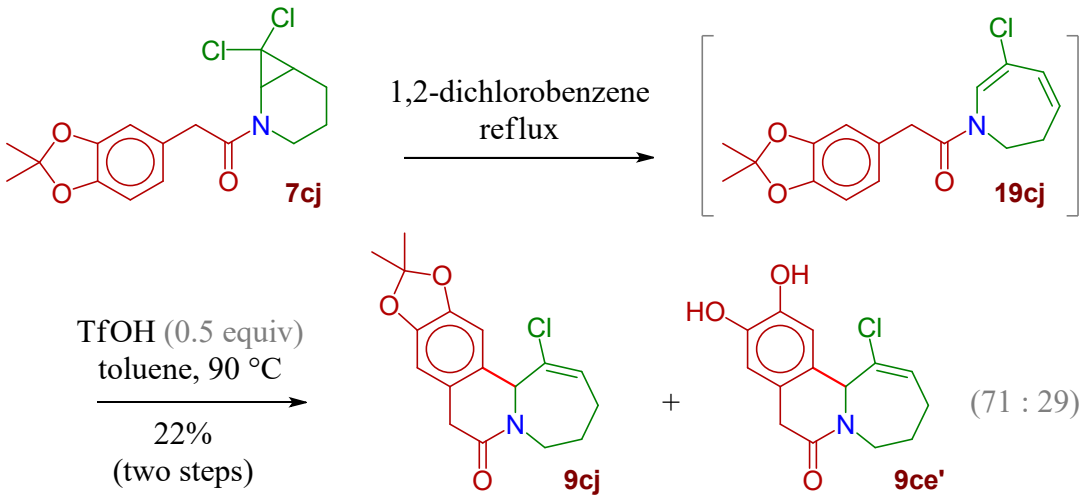
37% HCl aqueous solution (1 drop) was added, at 20 °C, to a solution of amide **7ci** (1.00 equiv, 64.6 µmol, 21.2 mg) in DMF (1.0 mL). The mixture was heated at 150 °C for 40 min (microwave reactor, power 250 W). After cooling, H_2O (15 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford an orange oil (46.0 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 5 to 50%) afforded pure ring-expanded compound **19ci** (2.0 mg, 6.9 µmol, 11%) and starting amide **7ci** (11.0 mg, 33.5 µmol, 52%).

■ Run 2: in 1,2-dichlorobenzene at 180 °C.



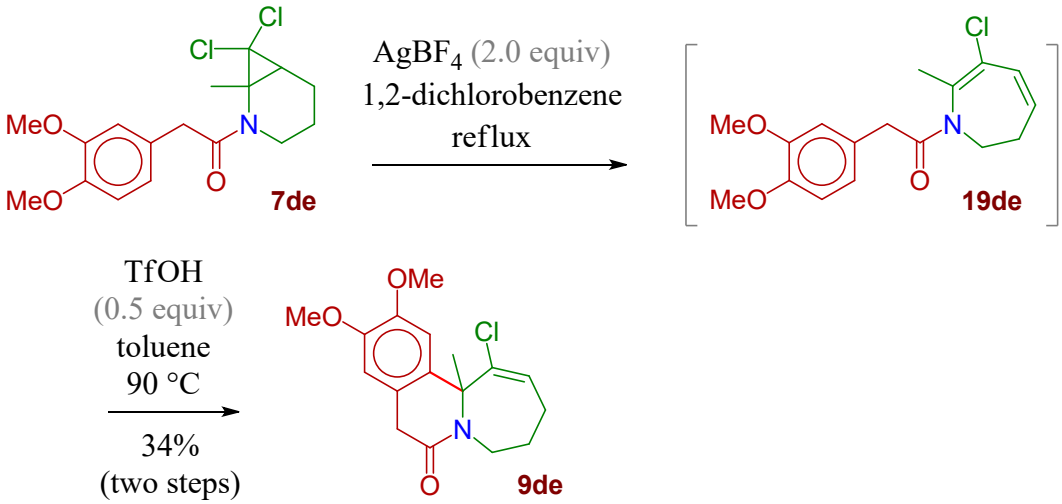
Tert-butanol (1 drop) was added, at 20 °C, to a solution of amide **7ci** (1.00 equiv, 64.6 µmol, 21.2 mg) in 1,2-dichlorobenzene (1.0 mL). The mixture was heated at 180 °C for 30 min (microwave reactor, power 250 W). After cooling, H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford an orange liquid (271 mg). Purification by flash column chromatography on silica gel (EtOAc / petroleum ether, gradient from 5 to 50%) gave pure **19ci** (7.0 mg, 24 µmol, 37%) and starting amide **7ci** (4.0 mg, 12 µmol, 19%).

1-(6-Chloro-2,3-dihydro-1*H*-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(3*H*)-one **9cj** (Table 2)



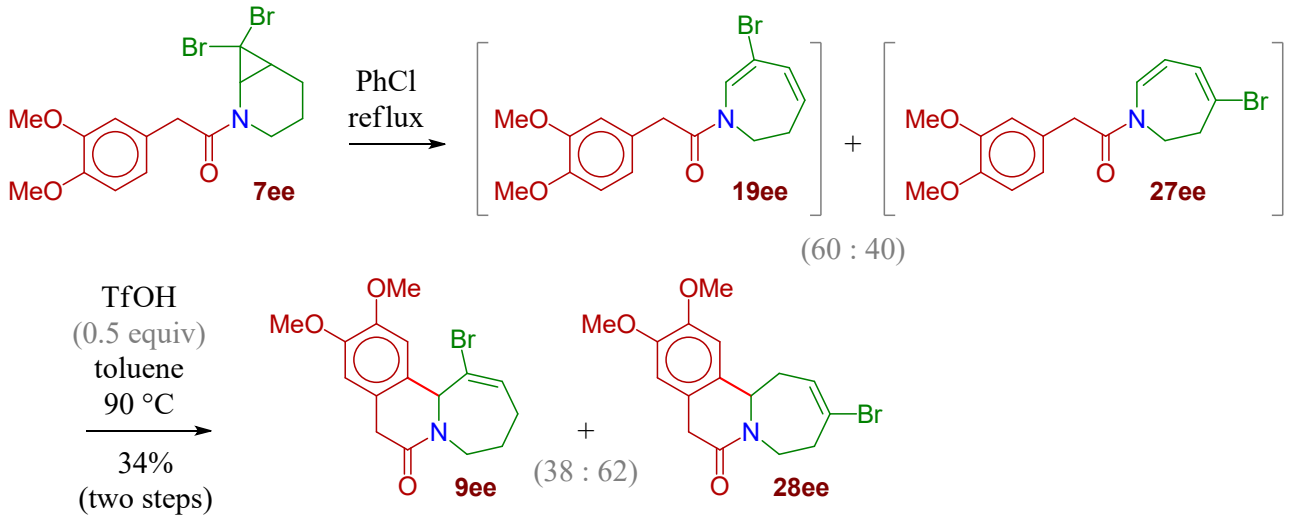
General procedure E was applied to **7cj** (1.00 equiv, 500 µmol, 178 mg). After the first step, conducted in refluxing 1,2-dichlorobenzene (2.0 mL) for 8 h, fairly pure dihydroazepine derivative **19cj** was obtained as a brown oil (102 mg). In the second step (toluene, 5.0 mL), heating was maintained for 30 min. Analysis of the crude product (orange oil, 77.5 mg) by ^{1}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 µmol, 16% over two steps) and **9ce′** (9.0 mg, 32.2 µmol, 6% over two steps).

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(3*H*)-one **9de** (Table 2)



General procedure F was applied to **7de** (1.00 equiv, 681 µmol, 244 mg). After the first step in 1,2-dichlorobenzene (6.0 mL), analysis of the concentrated residue (brown oil, 239 mg) by ^{1}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 µmol of **19de/9de**, 1.00 equiv) was dissolved in dry toluene (4.0 mL). Trifluoromethanesulfonic acid (0.546 equiv, 263 µmol, 23.3 µL) was added and the mixture was heated at 90 °C for 1 h. After cooling, saturated $NaHCO_3$ aqueous solution (20 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford an orange oil (118 mg). Analysis by ^{1}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 µmol, 34% over the two steps). Further purification was achieved by semipreparative HPLC (C18 reverse-phase column, 10 mM aqueous $AcNH_4$/MeCN, gradient formed from 40 to 70 %) to afford pure **9de** (36 mg, 112 µmol, 23% over the two steps).

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** (Table 2 and Scheme 11)



General procedure G was applied to **7ee** (1.00 equiv, 543 µmol, 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}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}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 µmol, 34% over the two steps). Further separation by semipreparative HPLC (C18 reverse-phase column, gradient formed from 40 to 70 % of 10 mM aqueous NH_4OAc and MeCN) afforded pure tetrahydroazepinoisoquinolines **9ee** (16.0 mg, 45.0 µmol, 8% over the two steps) and **28ee** (23.0 mg, 65.0 µmol, 12% over the two steps).

■ Proposed mechanism for the formation of **27ee**: