# Synthesis of New Azocine Derivatives and Their Functionalization by Nucleophilic Addition to Their Iminium Salts

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A route to the eight-membered nitrogen heterocycles **20a**,**b** is described starting from the 3-alkyl-*N*-benzylpyridinium salts **14a**,**b**. These azocine derivatives were converted into their respective iminium salts **11** by treatment with methanesulfonic acid. A study concerning the regioselectivity of nucleophilic additions to these salts is presented. Nucleophiles like hydride or Grignard reagents react selectively in the 2-position to give adducts such as **22** and **23**, while azide and phenylthiolate attack the 6-position to give **24** and **25**, respectively.


## Introduction

Azocine derivatives are an important and diverse class of compounds that are found in a range of natural and nonnatural products. These eight-membered nitrogen heterocycles are present in complex structures of many natural substances such apparicine (**1**),[1] magallanesine (**2**),[2] and manzamine A (**3**),[3] an important antitumoral marine alkaloid (Figure 1). Among the nonnatural products, the more commonly found azocines are substituted and fully or partly reduced. These compounds have found application as therapeutic agents in view of their various biological properties, for example as antimalarials, antitussives, nasal decongestants, antihypertensives, and analgesics.[4] Another large and much-studied class of compounds containing the azocine ring is synthetic benzofuroazocines (**4**), which, due their structure close to that of hypnoanalgesics, possess important activity in the central nervous system (CNS).[5] Finally, these monocyclic medium rings have also found use as synthetic intermediates, for example, in the synthesis of the pyrrolizidine ring system,[6] and they constitute important medium-size cycles in conformational studies.

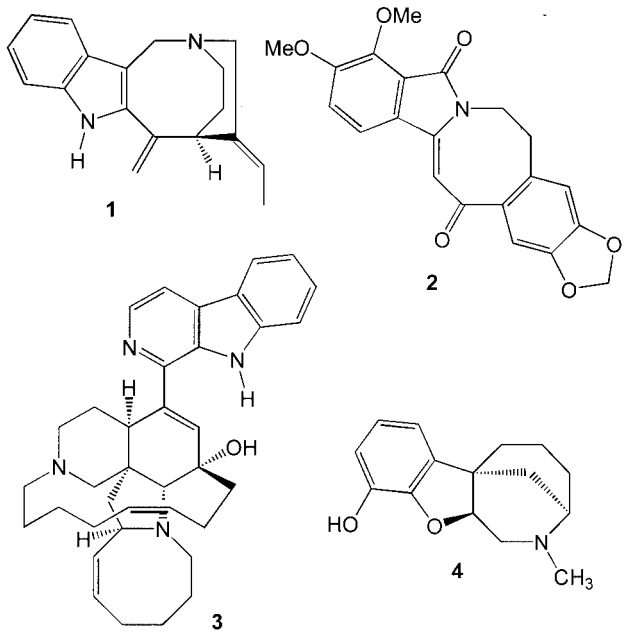


Figure 1. Substances containing the azocine ring.

In spite of its importance, the azocine ring system is generally difficult to obtain,[4] especially in its highly functionalized form, and relatively few methods are available for its preparation. The conventional cyclization methods remain very specific and usually fail, with few exceptions. Thus, there are few examples of the preparation of azocines by cyclization from an alicyclic chain by intramolecular nucleophilic substitution.[7] Other methods used are the fragmentation of a fused 5/5-ring system,[8] and, more commonly, the [2+2] cycloaddition reaction between an unsaturated

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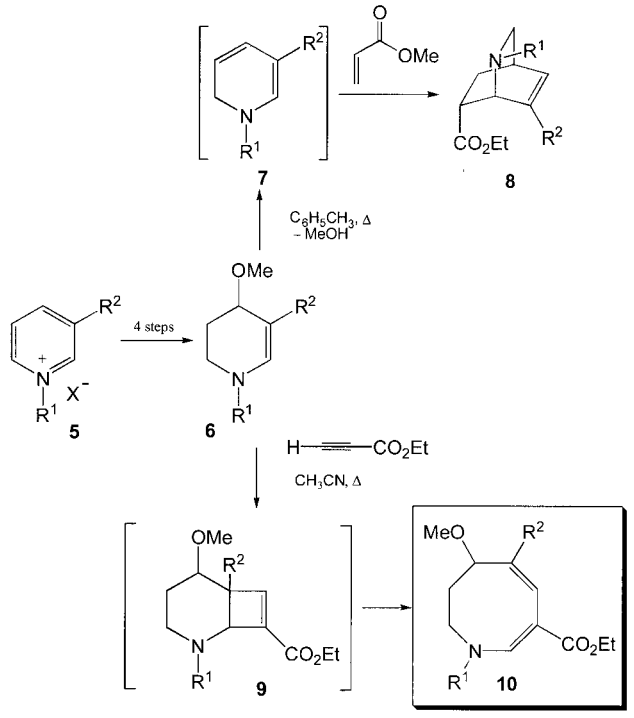
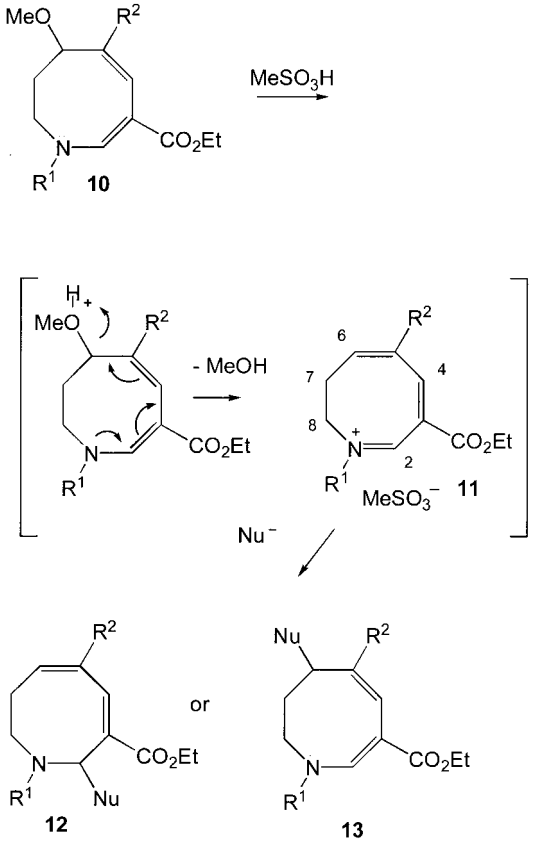
six-membered ring (generally an enamine) and an acetylene derivative by photochemical or thermal cycloaddition.[9,10] Considering the high potential of azocine rings, it seems useful to develop general methodologies to build and functionalize these heterocycles. For example, the synthesis of an eight-membered iminoalditol was described recently.[11]

We recently reported[12] an access to functionalized azocine derivatives starting from the pyridinium salts **5** via 1,4,5,6-tetrahydropyridines **6** (Scheme 1; $R^1$ = alkyl or benzyl, $R^2$ = alkyl). These 1,4,5,6-tetrahydropyridines are good precursors of 1,6-dihydropyridines of type **7**, which could react with common dienophiles to produce isoquinuclidine derivatives **8**.[13] Alternatively, these 1,4,5,6-tetrahydropyridines can also react with acetylene derivatives through a [2+2] cycloaddition, which affords azocines **10**[14] by electrocyclic opening of the cyclobutene intermediate **9**.




Scheme 1. Synthesis of isoquinuclidine and azocine derivatives from pyridinium salts.

In this paper we describe details of the synthesis of new azocines derivatives using this strategy. The azocines thus obtained can be converted into the corresponding iminium salt (**11**) by treatment with one equivalent of acid, which results in loss of methanol. The study of nucleophilic addition to these new iminium salts to give substituted azocine derivatives of type **12** or **13** is also reported (Scheme 2).




Scheme 2. Nucleophilic additions to azocine iminium rings.

## Results and Discussion

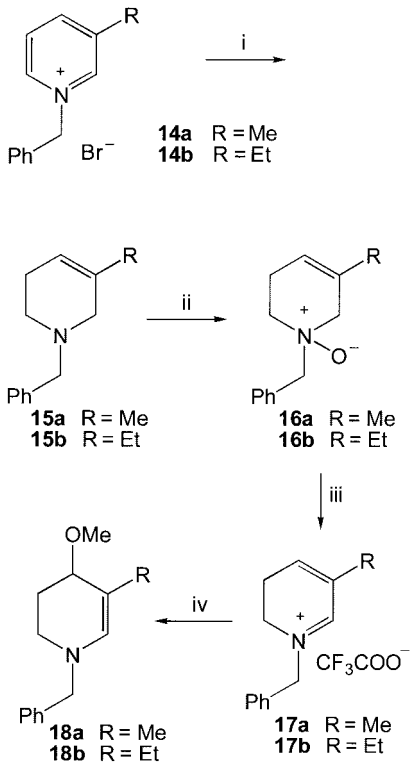
### Preparation of 1,4,5,6-Tetrahydropyridines

The preparation of 1,4,5,6-tetrahydropyridines is outlined in Scheme 3. Thus, the 3-alkyl-1,2,5,6-tetrahydropyridines **15a**,**b** were initially obtained from 3-alkylpyridinium salts **14a**,**b** following well-established procedures.[15] These tetrahydropyridines were obtained with yields of between 61 and 63% and were subsequently oxidized with *meta*-chloroperbenzoic acid (1.2 to 1.5 equivalents) at 0 °C to avoid the possible epoxidation of the double bond. The *N*-oxide derivatives **16a**,**b** were characterized and then converted into their respective dihydropyridinium salts **18a**,**b** in a Polonovsky–Potier reaction[16] with trifluoroacetic anhydride (1.5 to 2 equivalents) to afford the intermediate salts **17a** and **17b**. These salts are very unstable and cannot be purified. After removal of solvent and unreacted trifluoroacetic anhydride they were immediately treated with sodium methoxide (5 to 7 equivalents). The methoxide anion bound to the 4-position of the dihydropyridinium salts to give **18a** (from **16a**) and **18b** (from **16b**). The structures of **18a**,**b** were confirmed by $^1$H NMR spectroscopy. The spectra display singlets for the hydrogens of methoxy group at $\delta$ = 3.35 ppm, and a multiplet for the allylic hydrogen H-4 at approximately $\delta$ = 3.50 ppm, for both products. The olefinic proton H-2 appears at $\delta$ = 5.93 ppm as a large singlet.

### Preparation of 1,6,7,8- and 1,2,7,8-Tetrahydroazocines

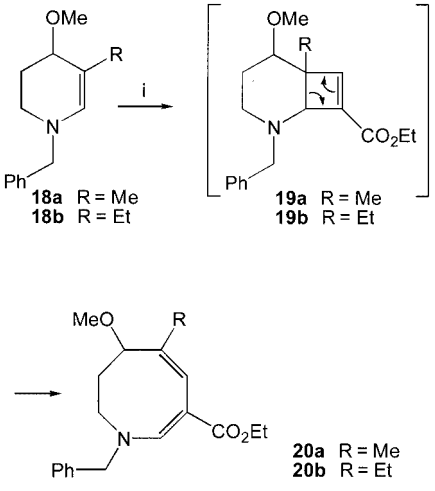
After isolation, the tetrahydropyridines **18a**,**b** were warmed under acetonitrile reflux for two hours in the presence of ethyl propiolate. In this step, the [2+2] cycloaddition reaction occurs to produce the cyclobutene intermediates




Scheme 3. Reaction conditions: (i) $NaBH_4$, MeOH/$H_2O$ (9:1), reflux; (ii) *m*-CPBA, $CH_2Cl_2$, 0 °C; (iii) $(CF_3CO)_2O$, $CH_2Cl_2$; (iv) MeONa, MeOH/$CH_2Cl_2$ (1:1).

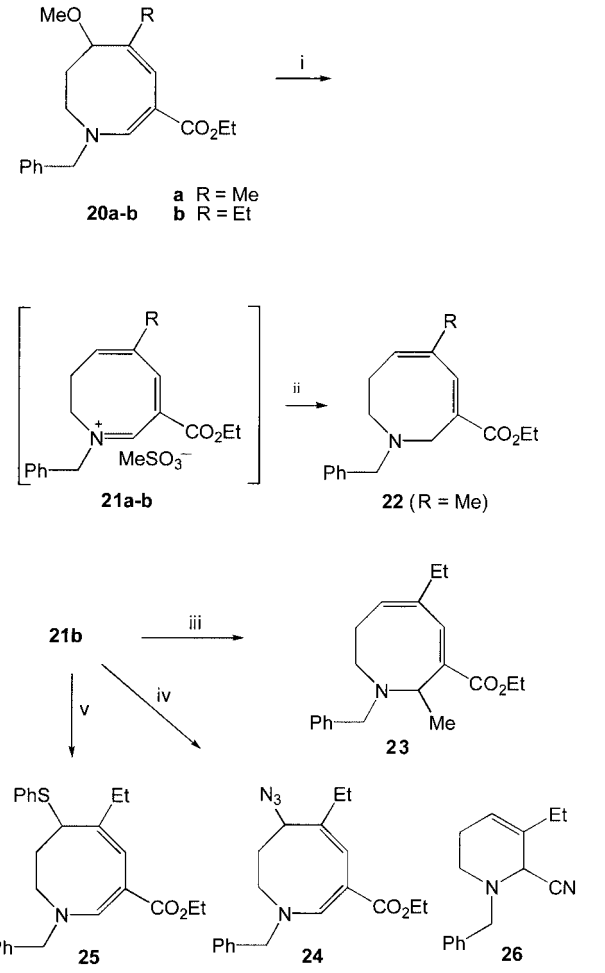
(**19a**,**b**). Due to the reaction conditions and to the cyclobutene instability, subsequent electrocyclic ring opening forms the tetrahydroazocine rings **20a**,**b** (Scheme 4).




Scheme 4. Reaction conditions: (i) ethyl propiolate, $CH_3CN$, reflux, 2 h.

The yields of these reactions are good, varying from 57 to 94%, despite the instability of the dihydropyridines and the cyclobutene intermediates. It is interesting to note that the use of toluene as a solvent gave very low cycloaddition yields. NMR analysis confirmed the structures of the tetrahydroazocines **20a**,**b**.

The azocines **20** form iminium salts **21a**,**b** cleanly and instantaneouslywhen treated with methanesulfonic acid. The reaction can be carried out in an NMR tube and the resulting $^1H$ NMR spectrum shows formation of a single product with new characteristic olefinic signals corresponding to H-6 ($\delta$ = 6.02 ppm), H-4 ($\delta$ = 7.55 ppm), and H-2 ($\delta$ = 9.09 ppm). The crude iminium salts **21a**,**b** were immediately treated with different nucleophiles to produce new azocine derivatives (Scheme 5).




Scheme 5. Reaction conditions: (i) $MeSO_3H$, $CH_2Cl_2$; (ii) $NaBH_4$, MeOH/$CH_2Cl_2$; (iii) MeMgBr, THF; (iv) $NaN_3$, $CH_2Cl_2$, DMF; (v) PhSNa, $CH_2Cl_2$/$H_2O$.

Treatment of iminium salt **21a** with sodium borohydride gave the reduced compound **22**, and, as expected for such a hard nucleophile, the addition occurred in the 2-position. The structure of **22** was deduced by $^1H$ NMR spectroscopy, which revealed mainly the signal change of hydrogen H-2 to $\delta$ = 3.45 ppm in the reduced product (two hydrogens).

Subsequent reactions were performed with tetrahydroazocine **20b**, which was initially converted into the corresponding iminium salt **21b** and subsequently treated with methylmagnesium bromide; 1,2,7,8-tetrahydroazocine (**23**) was obtained in 49% yield. Also, the regioisomer resulting

from the addition of the methyl group to the 2-position was obtained preferentially, as confirmed by $^1$H NMR spectroscopy. The products of attack at other positions (4 or 6) were not observed.

When we used softer nucleophiles like azide and phenylthiolate, the addition occurred in the 6-position of the iminium salt in a conjugated manner. Thus, sodium azide reacts with the iminium salt **21b** to give 1,6,7,8-tetrahydroazocine (**24**) in 55% yield. Tetrahydroazocine **25** was the product of the reaction between iminium salt **21b** and sodium phenylthiolate in 68% yield. No other addition products were isolated in these cases.

In the study of the addition of cyanide to iminium salt **21b**, the only isolated product was tetrahydropyridine **26**. It is likely that a retro-cycloaddition occurred, even at low temperature and pH about 4.0 (mild reaction conditions). Attempts to add iodide (sodium iodide) and sodium ethyl acetoacetate enolate to iminium salt **21b** yielded a complex mixture of compounds.

## Conclusions

Tetrahydroazocines **20** have been synthesized, in good yields, by an easy five-step method starting from pyridinium salts **5**. These tetrahydroazocines were converted into iminium salts that could be treated with nucleophiles to give new tetrahydroazocines like **22**, **23**, **24**, and **25** in moderate yields. It is evident from these studies that the addition to the iminium salts **21a**,**b** exhibits nucleophile-dependent regiospecificity. For example, very soft nucleophiles such as azide and thiophenolate bind to the softest of the three iminium electrophilic centers (position 6), whereas harder nucleophiles such as hydride and Grignard reagent attack the hardest center (position 2). No attack in position 4 was observed in any case. Attempts to introduce cyano, iodide, and enolates did not give the expected products. Further studies to extend this approach to other azocines, including chiral derivatives,[17] are currently in progress in our laboratories.

## Experimental Section

**1-Benzyl-3-methyl-1,2,5,6-tetrahydropyridine (15a):** sodium borohydride (4.00 g, 105.73 mmol) was added slowly to a solution of 1-benzyl-3-methylpyridinium bromide (**14a**; 11.07 g, 41.91 mmol) in methanol/water (9:1; 100 mL). The reaction mixture was stirred for 16 h at room temperature. The solvent was distilled under reduced pressure, the residue was solubilized with water, and extracted with ethyl acetate (5×50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give an orange liquid. The crude product was purified by column chromatography on alumina [ethyl acetate/heptane (0:100 to 2:98), 0.5% to 0.5% by volume of 200 mL]. Pure **15a** was obtained as a yellow liquid (4.80 g, 25.65 mmol, 61%). $^1$H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.62 (s, 3 H, $CH_3$), 2.11 [m, 2 H, C(5)–H], 2.49 [t, $^3J$ = 5.7 Hz, 2 H, C(6)-H], 2.84 [m, 2 H, C(2)-H], 3.58 (s, 2 H, C$H_2$Ph), 5.48 [m, 1 H, C(4)-H], 7.20–7.40 (m, 5 H, Ph) ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta$ = 21.09 ($CH_3$), 26.10 [C(5)], 49.57 [C(6)], 57.11 [C(2)], 62.94 ($CH_2$Ph), 119.56 [C(4)], 127.04, 128.26, 129.23, (5 C Ph), 132.39 [C(3)], 138.52 ($C_{quat}$ Ph) ppm. MS (EI): *m*/*z* (%) = 187 (58) [M$^+$], 172 (32), 91 (100). MS (CI) (isobutane): *m*/*z* (%) = 188 (100) [MH]$^+$.

**1-Benzyl-3-ethyl-1,2,5,6-tetrahydropyridine(15b):** Following the procedure outlined for the preparation of **15a**, the salt 1-benzyl-3-ethylpyridinium bromide (9.52 g, 34.24 mmol) was treated with sodium borohydride (3.20 g, 85.61 mmol). Pure **15b** was obtained as a pale-orange liquid (4.33 g, 21.53 mmol, 63%). $^1$H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.98 [t, $^3J$ = 7.5 Hz, 3 H, $CH_3$ (Et)], 1.91 [qd, $^3J$ = 1.3, 7.5 Hz, 2 H, $CH_2$ (Et)], 2.11 [m, 2 H, C(5)-H], 2.48 [t, $^3J$ = 5.8 Hz, 2 H, C(6)-H], 2.86 [m, 2 H, C(2)-H], 3.56 (s, 2 H, $CH_2$Ph), 5.46 [m, 1 H, C(4)-H], 7.20–7.40 (m, 5 H, Ph) ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta$ = 12.05 [$CH_3$ (Et)], 25.90 [C(5)], 27.84 [$CH_2$ (Et)], 49.73 [C(6)], 55.96 [C(2)], 62.91 [$CH_2$Ph], 117.54 [C(4)], 126.92, 128.15, 129.10, (5 C Ph), 137.73 [C(3)], 138.45 ($C_{quat}$ Ph) ppm. MS (EI): *m*/*z* (%) = 201 (26) [M$^+$], 186 (16), 172 (40), 91 (100).

**1-Benzyl-3-methyl-1,2,5,6-tetrahydropyridine *N*-Oxide(16a):** The tetrahydropyridine **15a** (4.80 g, 25.67 mmol) was dissolved in anhydrous dichloromethane (30 mL). The solution was cooled to 0 °C, and *meta*-chloroperbenzoic acid (6.64 g, 38.50 mmol) was added slowly. Stirring was continued for 15 min at room temperature. The mixture was quickly filtered through a short column of alumina [methanol/dichloromethane (0:100, 2.5:97.5, 5:95), 100 mL of each], and the *N*-oxide solution was concentrated under reduced pressure at room temperature. The *N*-oxide **16a** was obtained as a brown oil (4.67 g, 22.97 mmol, 92%) that was immediately used for the next reactions. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.68 (s, 3 H, $CH_3$), 2.32 [m, 1 H, C(5)-H], 2.68 [m, 1 H, C(5)-H], 3.38 [t, $^3J$ = 6.2 Hz, 2 H, C(6)-H], 3.55 [dl, $^3J$ = 16.0 Hz, 1 H, C(2)-H], 3.83 [d, $^3J$ = 16.0 Hz, 1 H, C(2)-H], 4.46 (d, $^3J$ = 12.4 Hz, 1 H, $CH_2$Ph), 4.52 (d, $^3J$ = 12.4 Hz, 1 H, $CH_2$Ph), 5.60 [m, 1 H, C(4)-H], 7.38–7.60 (m, 5 H, Ph) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 20.48 ($CH_3$), 23.02 [C(5)], 61.09 [C(6)], 67.24 [C(2)], 72.19 ($CH_2$Ph), 118.60 [C(4)], 128.04 [C(3) or $C_{quat}$ Ph], 128.40, 129.41, (3 C Ph), 130.13 [C(3) or $C_{quat}$ Ph], 132.38 (2 C Ph) ppm. MS (FAB+): *m*/*z* (%) = 204 (100) [MH]$^+$, 186 (10). MS (CI) (isobutane): *m*/*z* (%) = 204 (4) [MH]$^+$, 202 (5), 188 (100).

**1-Benzyl-3-ethyl-1,2,5,6-tetrahydropyridine *N*-Oxide(16b):** Following the procedure outlined for the preparation of **16a**, the tetrahydropyridine **15b** (3.48 g, 17.30 mmol) was treated with *meta*-chloroperbenzoic acid (3.58 g, 20.70 mmol). The *N*-oxide **16b** was obtained as a brown oil (3.68 g, 16.93 mmol, 98%) which was immediately used for the next reaction. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.02 [t, $^3J$ = 7.4 Hz, 3 H, $CH_3$ (Et)], 1.97 [q, $^3J$ = 7.4 Hz, 2 H, $CH_2$ (Et)], 2.31 [m, 1 H, C(5)–H], 2.70 [m, 1 H, C(5)–H], 3.28 [m, 2 H, C(6)–H], 3.54 [dl, $^3J$ = 16.0 Hz, 1 H, C(2)–H], 3.72 [d, $^3J$ = 16.0 Hz, 1 H, C(2)–H], 4.36 (s, 2 H, $CH_2$Ph), 5.60 [m, 1 H, C(4)–H], 7.35–7.65 (m, 5 H, Ph) ppm. $^{13}$C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta$ = 11.60 [$CH_3$ (Et)], 23.29 [C(5)], 27.38 [$CH_2$ (Et)], 61.65 [C(6)], 67.07 [C(2)], 71.78 ($CH_2$Ph), 116.59 [C(4)], 128.48, 129.51, (3 C Ph), 130.35 [C(3) or $C_{quat}$ Ph], 132.51 (2 C Ph), 133.89 [$C_{quat}$ Ph or C(3)] ppm. MS (FAB+): *m*/*z* (%) = 218 (83) [M$^+$], 200 (13), 91 (100).

**1-Benzyl-4-methoxy-3-methyl-1,4,5,6-tetrahydropyridine (18a):** The *N*-oxide **16a** (2.10 g, 10.38 mmol) was dissolved in anhydrous methylene chloride (20 mL) and the solution was cooled to 0 °C. Trifluoroacetic anhydride (3.00 mL, 20.76 mmol) was added slowly and the mixture was stirred at 0 °C for 20 min. After distillation of solvent and excess trifluoroacetic anhydride under reduced pressure, the residue was dissolved in anhydrous dichloromethane (15 mL). This solution was added slowly to a sodium methoxide

solution [prepared by addition of 1.20 g (51.90 mmol) of sodium to 25 mL of methanol] at 0 °C and the reaction was stirred for 30 min at room temperature. The reaction mixture was poured into an ethyl acetate/pentane (2:8) mixture with water and the aqueous layer was extracted with ethyl acetate/pentane (2:8; 5 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure at room temperature. The tetrahydropyridine **18a** was obtained without purification as an orange liquid (1.64 g, 7.55 mmol, 73%) which was immediately used for the next reaction. $^1$H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.63 [m, 1 H, C(5)-H], 1.72 (d, $^3J$ = 0.7 Hz, 3 H, $CH_3$), 1.99 (dddd, $^3J$ = 2.7, 2.8, 3.0, 14.0 Hz, 1 H, C(5)-H], 2.72 [m, 2 H, C(6)-H], 3.35 (s, 3 H, $OCH_3$), 3.47 [m, 1 H, C(4)-H], 3.89 [d, $^3J$ = 14.4 Hz, 1 H, $CH_2$Ph), 3.99 (d, $^3J$ = 14.4 Hz, 1 H, $CH_2$Ph), 5.93 [s, 1 H, C(2)-H], 7.20–7.36 (m, 5 H, Ph) ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta$ = 18.73 ($CH_3$), 26.72 [C(5)], 42.38 [C(6)], 55.87 ($OCH_3$), 59.46 ($CH_2$Ph), 74.74 [C(4)], 104.37 [C(3)], 127.06, 128.08, 128.21 (5 C Ph), 135.03 [C(2)], 138.48 ($C_{quat}$ Ph) ppm. MS (EI): *m*/*z* (%) = 217 (25) [M$^+$], 186 (100), 91 (82). HRMS: *m*/*z* = 217.1461 (calcd. for $C_{14}H_{19}NO$, *m*/*z* = 217.1467).

**1-Benzyl-3-ethyl-4-methoxy-1,4,5,6-tetrahydropyridine (18b):** Following the procedure outlined for preparation of **18a**, the *N*-oxide **16b** (1.02 g, 4.72 mmol) was treated with trifluoroacetic anhydride (1.00 mL, 7.08 mmol) at 0 °C. The intermediate trifluoroacetate obtained (**17b**) was treated with a sodium methoxide solution [0.76 g (33 mmol) of sodium and 20 mL of methanol]. The tetrahydropyridine **18b** was obtained as an orange liquid (849 mg, 3.67 mmol, 78%). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.01 [t, $^3J$ = 7.4 Hz, 3 H, $CH_3$ (Et)], 1.59 [m, 1 H, C(5)-H], 2.01 [dq, $^3J$ = 2.9, 14.0 Hz, 1 H, C(5)-H], 2.09 (q, $^3J$ = 7.4 Hz, 2 H, $CH_2$ (Et)], 2.74 [m, 2 H, C(6)-H], 3.34 (s, 3 H, $OCH_3$), 3.56 [m, 1 H, C(4)-H], 3.92 (d, $^3J$ = 14.4 Hz, 1 H, $CH_2$Ph), 4.02 (d, $^3J$ = 14.4 Hz, 1 H, $CH_2$Ph), 5.92 [s, 1 H, C(2)-H], 7.20–7.40 (m, 5 H, Ph) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.47 [$CH_3$ (Et)], 25.44, 26.27 [C(5) and $CH_2$ (Et)], 42.05 [C(6)], 55.38 ($OCH_3$), 59.32 ($CH_2$Ph), 72.74 [C(4)], 110.27 [C(3)], 126.91, 127.91, 128.16 (5 C Ph), 134.13 [C(2)], 138.32 ($C_{quat}$ Ph) ppm. MS (EI): *m*/*z* (%) = 231 (35) [M$^+$], 200 (100), 91 (100). HRMS: *m*/*z* = 231.1619 (calcd. for $C_{15}H_{21}NO$, *m*/*z* = 231.1623).

**Ethyl 1-Benzyl-6-methoxy-5-methyl-1,6,7,8-tetrahydroazocine-3-carboxylate (20a):** Ethyl propiolate (0.56 mL, 5.51 mmol) was added to a solution of tetrahydropyridine **18a** (598 mg, 2.78 mmol) in acetonitrile (20 mL). This solution was maintained under reflux for 2 h. After solvent distillation under reduced pressure, the residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 5:95). The tetrahydroazocine **20a** was obtained as a pale-yellow solid, which was subsequently recrystallized from diethyl ether/heptane to give white crystals (827 mg, 2.62 mmol, 94%, m.p. 111–113 °C). IR (KBr): 1680 ($\nu_{C=O}$) cm$^{-1}$. $^1$H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.03 [m, 1 H, C(7)-H], 1.29 [t, $^3J$ = 7.1 Hz, 3 H, $CH_3$ (EtO)], 1.57 [tt, $^3J$ = 5.0, 12.6 Hz, 1 H, C(7)-H], 1.64 (d, $^3J$ = 1.6 Hz, 3 H, $CH_3$), 2.85 [m, 1 H, C(8)-H], 3.24 (s, 3 H, $CH_3O$), 3.60 [m, 1 H, C(8)-H], 4.00–4.40 [m, 3 H, C(6)-H and $CH_2$Ph], 4.20 [q, $^3J$ = 7.1 Hz, 2 H, $CH_2$ (EtO)], 6.28 [m, 1 H, C(4)-H], 7.23–7.40 (m, 5 H, Ph), 7.61 [s, 1 H, C(2)-H] ppm. $^{13}$C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta$ = 14.74 [$CH_3$ (EtO)], 16.82 ($CH_3$), 21.12 [C(7)], 44.98 [C(8)], 57.07 ($CH_3O$), 59.82 ($CH_2$Ph), 61.51 [$CH_2$ (EtO)], 79.21 [C(6)], 95.26 [C(3)], 122.39 [C(4)], 127.78, 128.18, 128.93 (5 C Ph), 131.33 [C(5)], 136.61 ($C_{quat}$ Ph), 148.99 [C(2)], 169.88 (COOEt) ppm. MS (EI): *m*/*z* (%) = 315 (100) [M$^+$], 300 (9), 284 (80), 270 (25), 242 (28), 224 (30), 91 (100). HRMS: *m*/*z* = 315.1842 (calcd. for $C_{19}H_{25}NO_3$, *m*/*z* = 315.1835). $C_{19}H_{25}NO_3$: calcd. C 72.37, H 8.33, N 4.31; found C 72.35, H 7.99, N 4.44.

**Ethyl 1-Benzyl-5-ethyl-6-methoxy-1,6,7,8-tetrahydroazocine-3-carboxylate (20b):** Following the procedure outlined for preparation of **20a**, the tetrahydropyridine **18b** (395 mg, 1.71 mmol) was treated with ethyl propiolate (0.92 mL, 9.10 mmol) to give the tetrahydroazocine **20b** as white crystals (321 mg, 0.97 mmol, 57%, m.p. 116–118 °C). IR (KBr): 1680 ($\nu_{C=O}$) cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.05 [m, 1 H, C(7)-H], 1.07 [t, $^3J$ = 7.4 Hz, 3 H, $CH_3$ (Et)], 1.29 [t, $^3J$ = 7.1 Hz, 3 H, $CH_3$ (EtO)], 1.62 [m, 1 H, C(7)-H], 2.03 [m, 2 H, $CH_2$ (Et)], 2.85 [m, 1 H, C(8)-H], 3.23 (s, 3 H, $CH_3O$), 3.62 [m, 1 H, C(8)-H], 4.06–4.39 [m, 5 H, C(6)-H, $CH_2$ (EtO) and $CH_2$Ph), 6.27 [m, 1 H, C(4)-H], 7.24–7.37 (m, 5 H, Ph), 7.63 [s, 1 H, C(2)-H] ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$, 25 °C): $\delta$ = 12.50 [$CH_3$ (Et)], 14.78 [$CH_3$ (EtO)], 22.21, 22.52 [C(8) and $CH_2$ (Et)], 45.02 [C(8)], 57.33 ($CH_3O$), 59.87 ($CH_2$Ph), 61.57 ($CH_2$ (EtO)], 79.73 [C(6)], 95.38 [C(3)], 120.73 [C(4)], 127.83, 128.23, 128.99 (5 C Ph), 135.93, 136.74 [C(8) and $C_{quat}$ Ph], 148.93 [C(2)], 170.03 (COOEt) ppm. $C_{20}H_{24}NO_3$ (329.20): calcd. C 72.98, H 8.32, N 4.22; found C 72.92, H 8.26, N 4.25.

**1-Benzyl-3-ethoxycarbonyl-5-ethyl-7,8-dihydroazocinium Methanesulfonate (21b):** Methanesulfonic acid (40 µL, 0.60 mmol) was added to a solution of tetrahydroazocine **20b** (50 mg, 0.15 mmol) in deuterochloroform (0.4 mL) and the mixture was stirred for about 10 min. The formation of iminium salt **21b** was confirmed by thin-layer chromatography and $^1$H NMR spectroscopy. $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.05 [t, $^3J$ = 7.5 Hz, 3 H, $CH_3$ (Et)], 1.37 [t, $^3J$ = 7.1 Hz, 3 H, $CH_3$ (EtO)], 2.23 [q, $^3J$ = 7.5 Hz, 2 H, $CH_2$ (Et)], 2.83 [m, 2 H, C(7)-H], 4.19 [t, $^3J$ = 5.7 Hz, 2 H, C(8)-H], 4.35 [q, $^3J$ = 7.1 Hz, 2 H, $CH_2$ (EtO)], 5.26 (m, 2 H, $CH_2$Ph), 6.02 [m,1 H, C(6)–H], 7.49 (m, 5 H, Ph), 7.55 [s, 1 H, C(4)–H], 9.09 [s, 1 H, C(2)-H] ppm.

**Ethyl 1-Benzyl-5-methyl-1,2,7,8-tetrahydroazocine-3-carboxylate (22):** Methanesulfonic acid (176 µL, 2.66 mmol) was added to a solution of tetrahydroazocine **20a** (184 mg, 0.58 mmol) in dichloromethane (12 mL) and the mixture was stirred at room temperature for 15 min. After formation of iminium salt **21a** (confirmed by thin-layer chromatography), a suspension of sodium borohydride (55 mg, 1.46 mmol) in methanol (20 mL) was added. The mixture was stirred for 20 h, when thin layer chromatography (ethyl acetate/hexane 2:8) showed the completion of the reaction. The mixture was extracted with ethyl acetate/water (5 × 15 mL of ethyl acetate). The organic layers were combined and dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 5:95). After removal of solvent, the product **22** was obtained as a yellow oil (44 mg, 0.15 mmol, 26%). IR (KBr): 1720 ($\nu_{C=O}$) cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.28 [t, $^3J$ = 7.1 Hz, 3 H, $CH_3$ (EtO)], 1.83 (s, 3 H, $CH_3$), 2.22 [m, 2 H, C(7)–H], 2.50 [m, 2 H, C(8)-H], 3.45 [m, 2 H, C(2)-H], 3.73 (s, 2 H, $CH_2$Ph), 4.20 [q, $^3J$ = 7.1 Hz, 2 H, $CH_2$ (EtO)], 5.64 [m, 1 H, C(6)–H], 7.12 [s, 1 H, C(4)-H], 7.21–7.32 (m, 5 H, Ph) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$, 25 °C): $\delta$ = 14.25 [$CH_3$ (EtO)], 22.46 ($CH_3$), 27.87 [C(7)], 46.54 [C(8)], 49.18 [C(2)], 60.71 [$CH_2$ (EtO)], 61.28 [$CH_2$Ph], 126.89, 128.11, 129.10 (5 C Ph), 130.04 [C(6)], 129.96, 133.33, 139.31 [C(3), C(5) and $C_{quat}$ Ph), 140.96 [C(4)], 167.74 (COOEt) ppm. HRMS (EI): *m*/*z* = 285.1726 (calcd. for $C_{18}H_{23}NO_2$: 285.1729).

**Ethyl 1-Benzyl-5-ethyl-2-methyl-1,2,7,8-tetrahydroazocine-3-carboxylate (23):** The iminium salt **21b** was prepared by the procedure outlined above from the tetrahydroazocine **20b** (102 mg, 0.31 mmol) and methanesulfonic acid (82 µL, 1.24 mmol). After

formation of the iminium salt the solvent was distilled off under reduced pressure and the residue was dissolved in anhydrous tetrahydrofuran (7 mL). The solution was cooled to –25 °C (nitrogen atmosphere) and then a methylmagnesium bromide solution (3.0 M in diethyl ether; 0.72 mL, 2.16 mmol) was added. The reaction mixture was stirred at –20 °C for 30 min and then at room temperature for the same time. The reaction was stopped by the addition of ammonium chloride solution 10% (15 mL) and the mixture was extracted with diethyl ether (5 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated to give an oil that was purified by column chromatography on silica gel eluting with ethyl acetate/hexane (5:95). The pure product **23** was obtained as a light-yellow oil (47 mg, 0.15 mmol, 49%). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.05 [t, $^3J$ = 7.5 Hz, 3 H, $CH_3$ (Et)], 1.28 [t, $^3J$ = 7.2 Hz, 3 H, $CH_3$ (EtO)], 1.34 (d, $^3J$ = 7.2 Hz, 3 H, $CH_3$), 2.04 [m, 2 H, C(7)–H], 2.19 [q, $^3J$ = 7.5 Hz, 2 H, $CH_2$ (Et)], 2.52 [m, 1 H, C(8)-H], 2.68 [m, 1 H, C(8)–H], 3.54 (d, $^3J$ = 13.6 Hz, 1 H, $CH_2$Ph), 3.81 (m, 1 H, $CH_2$Ph), 4.19 [q, $^3J$ = 7.2 Hz, C(2)-H and $CH_2$ (EtO)], 5.60 [t, $^3J$ = 7.9 Hz, 1 H, C(6)-H], 7.07 [s, 1 H, C(4)-H], 7.23–7.31 (m, 5 H, Ph) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.61 [$CH_3$ (Et)], 14.40 [$CH_3$ (EtO)], 16.45 ($CH_3$), 25.03 [C(7)], 29.91 [$CH_2$ (Et)], 44.90 [C(8)], 55.03 [C(2) and $CH_2$Ph], 60.85 [$CH_2$ (EtO)], 126.77, 127.89, 128.26, 128.78 [C(6) and 5 C Ph], 132.95, 139.46, 140.82 [C(3), [C(5) and $C_{quat}$ Ph), 138.88 [C(4)], 168.55 (COOEt) ppm. HRMS (EI): *m*/*z* = 313.2045 (calcd. for $C_{20}H_{27}NO_2$: 313.2042).

**Ethyl 6-Azido-1-benzyl-5-ethyl-1,6,7,8-tetrahydroazocine-3-carboxylate (24):** The iminium salt **21b** was prepared by the procedure outlined above from the tetrahydroazocine **20b** (65 mg, 0.20 mmol) and methanesulfonic acid (54 μL, 0.83 mmol). After formation of the iminium salt sodium azide (139 mg, 2.01 mmol) and dimethylformamide (10 drops) were added at room temperature and the reaction mixture was stirred for 3 h. After this period, water (20 mL) was added and the mixture was basified with 10% sodium carbonate solution and extracted with chloroform (4 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. After purification by column chromatography on silica gel (ethyl acetate/hexane, 5:95), the tetrahydroazocine **24** (37 mg, 0.11 mmol, 55%) was obtained as a yellow oil. $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.07 [t, $^3J$ = 7.4 Hz, 3 H, $CH_3$ (Et)], 1.08 [m, 1 H, C(7)-H], 1.29 [t, $^3J$ = 7.1 Hz, 3 H, $CH_3$ (EtO)], 1.51 [m, 1 H, C(7)-H], 2.05 [m, 2 H, $CH_2$ (Et)], 2.88 [m, 1 H, C(8)–H], 3.68 [m, 1 H, C(8)-H], 4.17 [m, 2 H, $CH_2$ (EtO)], 4.31 (s, 2 H, $CH_2$Ph), 4.49 [dd, $^3J$ = 5.2, 12.0 Hz, 1 H, C(6)-H], 6.24 [s, 1 H, C(4)-H], 7.24–7.43 (m, 5 H, Ph), 7.68 [s, 1 H, C(2)-H] ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$, 25 °C): $\delta$ = 12.62 [$CH_3$ (Et)], 14.80 [$CH_3$ (EtO)], 24.21, 29.91 [C(7) and $CH_2$ (Et)], 45.20 [C(8)], 60.11 and 62.09 [$CH_2$ (EtO) and $CH_2$Ph], 62.04 [C(6)], 95.38 [C(3)], 121.05 [C(4)], 127.91, 128.53, 129.18 (5 C Ph), 133.43, 136.47 [C(5) and $C_{quat}$ Ph], 149.24 [C(2)], 169.75 (COOEt) ppm. $C_{19}H_{24}N_4O_2$ (340.19): calcd. C 67.40, H 7.46, N 16.08; found C 67.04, H 7.11, N 16.46.

**Ethyl 1-Benzyl-5-ethyl-2-methyl-6-phenylthio-1,6,7,8-tetrahydroazocine-3-carboxylate (25):** The iminium salt **21b** was prepared by the procedure outlined above from the tetrahydroazocine **20b** (84 mg, 0.25 mmol), chloroform (5 mL), and methanesulfonic acid (66 μL, 1.02 mmol). After formation of the iminium salt the mixture was cooled to 0 °C and a solution of sodium phenylthiolate [prepared by mixing of 0.16 mL (1.60 mmol) of thiophenol and 1.6 mL of 1 M sodium hydroxide solution] was added quickly. The two-phase system was stirred vigorously at room temperature for 1 h, after which a 10% sodium carbonate solution (5 mL) was added. The organic layer was separated and the aqueous phase washed with three additional portions (15 mL) of dichloromethane. The combined organic layers were washed with 1 M sodium hydroxide solution (15 mL), and then water (20 mL). The organic solution was dried with anhydrous sodium sulfate and concentrated to give the crude product **25**. This product was purified by column chromatography on silica gel (ethyl acetate/hexane, 5:95), and recrystallized from diethyl ether/pentane to give the tetrahydroazocine **25** as white crystals (71 mg, 0.17 mmol, 68%, m.p. 63–66 °C). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.04 [t, $^3J$ = 7.4 Hz, 3 H, $CH_3$ (Et)], 1.20 [m, 1 H, C(7)-H], 1.30 [t, $^3J$ = 7.1 Hz, 3 H, $CH_3$ (EtO)], 1.66 [m, 1 H, C(7)-H], 2.15 [m, 2 H, $CH_2$ (Et)], 2.84 [m, 1 H, C(8)-H], 3.87 [m, 1 H, C(8)-H], 4.19 [m, 3 H, $CH_2$ (EtO) and 1 × $CH_2$Ph], 4.39 [m, 2 H, C(6)-H and 1 × $CH_2$Ph], 6.28 [s, 1 H, C(4)-H], 7.08–7.32 (m, 10 H, Ph), 7.70 [s, 1 H, C(2)-H] ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$, 25 °C): $\delta$ = 12.72 [$CH_3$ (Et)], 14.91 [$CH_3$ (EtO)], 22.60 [C(7)], 25.31 [$CH_2$ (Et)], 45.35 [C(8)], 46.78 [C(6)], 59.89 [$CH_2$ (EtO)], 61.59 ($CH_2$Ar), 95.40 [C(3)], 121.90 [C(4)], 125.38, 127.69, 127.83, 128.28, 128.96, 129.05 (10 C Ph), 134.04, 136.55, 137.50 [C(5) and 2 $C_{quat}$ Ph], 149.52 [C(2)], 169.98 (COOEt) ppm. $C_{25}H_{29}NO_2S$ (407.19): calcd. 73.45, H 6.83, N 3.36; found C 73.67, H 7.17, N 3.44.

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