Synthetic Study of Matrine-Type Alkaloids: Stereoselective Construction of the AB Rings of the Quinolizidine Skeleton

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Abstract: A new method has been developed for the stereoselective construction of the AB rings of the quinolizidine skeleton of matrine-type alkaloids with a *cis-cis* stereochemistry. The key features of this method involve: (i) construction of the quinolizidine by reduction of an acylpyridinium cation; and (ii) late-stage introduction of methoxypyridine by sequential Stille coupling and diastereoselective hydrogenation reactions.

Key words: quinolizidines, stereoselective synthesis, alkaloids, matrine, pyridines

Matrine is representative of the alkaloids derived from *Sophora flavescens* Ait., and has been used for many years as a traditional Chinese medicine (KuShen).[1] The structure of matrine is characterized by a tetracyclic core consisting of two quinolizidine moieties and four contiguous stereogenic centers (Figure 1).[2] To date, over 30 matrine-type alkaloids have been reported, and these compounds typically only differ from each other in terms of their oxidation level and relative stereochemistry.[3] Alkaloids belonging to this structural class also exhibit a variety of biological properties, including antitumor,[4a,e] antiviral,[4b,c] and anti-inflammatory[4d] activities. Because of their interesting and diverse biological activities, these compounds have attracted considerable attention from medicinal chemists.

Although there are many congeners in this structural class, only four racemic total syntheses and three semisyntheses have been reported to date, including those of matrine,[6–8,9a] leontine,[6a] sophoramine,[9b] and isosophoramine.[9c,10] These syntheses revealed that stereoselective construction of the tetracyclic core of these compounds represents a significant synthetic challenge. Brown et al.[11] recently reported the synthesis of (+)-allomatrine, whereby the tetracyclic core was elegantly constructed in a diastereoselective manner by using an imino-aldol reaction and *N*-acyliminium cyclization. However, methods for the stereoselective synthesis of tetracyclic cores with a *cis-cis* configuration, such as those found in sophoramine and matrine, remain scarce. We recently reported a procedure for the synthesis of quinolizidines by the reduction of acylpyridinium cations under mild conditions.[5] It was envisaged that this method could be used as a powerful tool for the concise synthesis of quinolizidine alkaloids, because the resulting products could be readily derivatized. With this in mind, we became interested in investigating the application of our method to the stereoselective synthesis of the AB rings of matrine-type alkaloids with *cis-cis* stereochemistry.

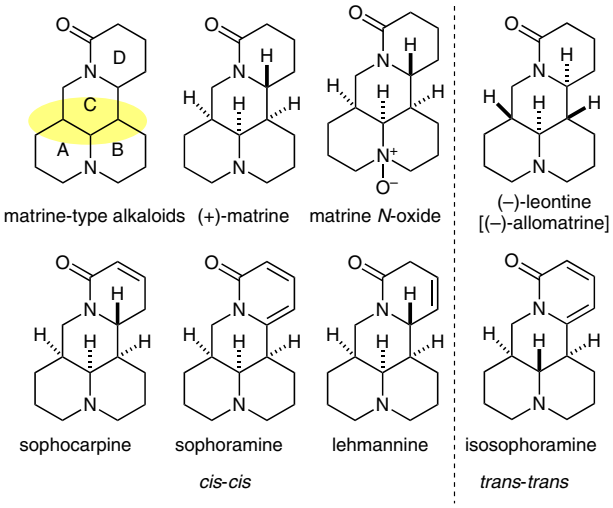

Figure 1 Matrine and related quinolizidine alkaloids

Retrosynthetically, alcohol **1** was set as a suitable synthetic target, because it was envisaged that this compound would provide comprehensive access to matrine and several related alkaloids through cyclization of the C ring and adjustment of the oxidation levels (Scheme 1). The *cis-cis* stereochemistry of **1** could be successfully installed by hydrogenation of **2** or **5**. Compound **2** could be accessed through the introduction of a C1 unit to the quinolizidine core of compound **3**, which could be constructed by reduction of the acylpyridinium cation derived from carboxylic acid **4** (route a). Alternatively, the addition of a pyridyl moiety to compound **6**, which could be derived from **7**, could also be used to provide access alcohol **1** (route b). Herein, we report the development of a stereoselective synthesis of the key *cis-cis* intermediate **1** based on our reductive cyclization strategy by examining both possibilities.

To begin, we examined route a, which required the challenging selective reduction of one of two pyridines. The synthesis of the cyclization precursor **4** started with the Stille coupling of 2-iodopicolinate methyl ester **8**[12] and pyridylstannane **9**[13] by using catalytic amounts of

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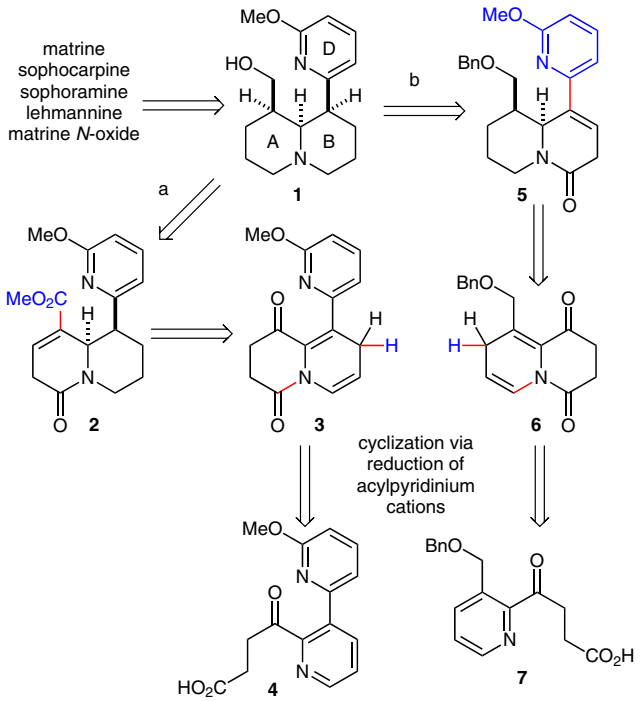
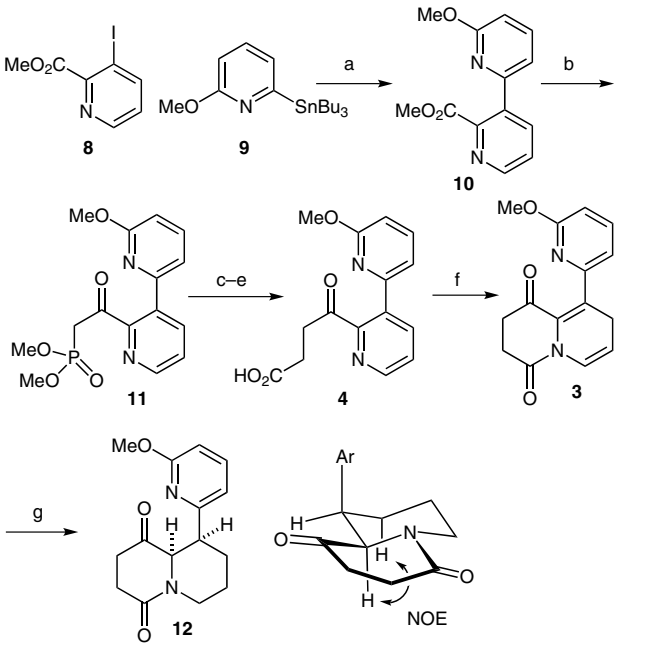


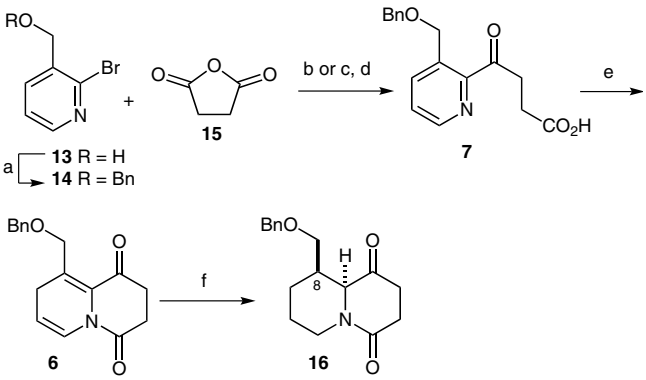
Scheme 1 Retrosynthetic analysis of matrine-type alkaloids



Scheme 2 Synthesis and cyclization of bipyridine **4**. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, CuI, DMF, 110 °C, 74%; (b) *n*-BuLi, $MeP(O)(OMe)_2$, THF, –78 °C; (c) *t*-BuOK, EtO_2CCHO, DME, –20 °C, 57% (two steps); (d) H_2, Pd/C, EtOAc; (e) LiOH, THF–H_2O, 88% (two steps); (f) Ghosez reagent, 4 Å MS then Hantzsch ester, DCE, 36%; (g) H_2, Pd/C, EtOH, 70%.

$Pd(PPh_3)_4$ and CuI (Scheme 2). CuI was essential for the production of bipyridine **10**.[14] Compound **10** was converted into carboxylic acid **4** by the Horner–Wadsworth–Emmons reaction of **11** with ethyl glyoxylate, followed by sequential hydrogenation and hydrolysis reactions, which gave the cyclization precursor **4** in 50% yield from the coupling product **10**.[15] The quinolizidine skeleton was constructed by reduction of the acylpyridinium cation intermediate, which was produced by the activation of one of the two pyridine rings of **4**. Treatment of **4** with Ghosez's reagent followed by the Hantzsch ester gave the desired product **3** in 36% yield. This low yield was attributed to unfavorable nucleophilic attack of the nitrogen of the second pyridine on the acid chloride generated in situ. Hydrogenation of the cyclized product **3** proceeded stereoselectively to give the desired compound **12** as a single isomer. The newly generated stereochemistry was confirmed by NOE experiments. Although ketone **12** was accessed in a stereoselective manner, quinolizidine ring formation was low-yielding, and we decided to focus our efforts on the second route for accessing the *cis-cis* intermediate **1**.

The second route started from 2-bromo-3-hydroxymethylpyridine (**13**),[16] which was converted into the corresponding benzyl ether **14** by using standard techniques (Scheme 3). Subsequent treatment of **14** with *n*-butyllithium followed by addition of succinic anhydride (**15**) gave carboxylic acid **7**, albeit in low yield (45%). To improve the yield and reproducibility of this step, compound **14** was first converted into the 2-TMS-pyridine species, which was treated with succinic anhydride **15** to give carboxylic acid **7** in 65% yield over two steps.[5,17] Compound **7** was then successfully converted into **6** by treatment with Ghosez's reagent followed by the Hantzsch ester.[18] Compound **6** was found to be unstable, and was immediately hydrogenated over Pd/C to give ketone **16**, the stereochemistry of which was confirmed by NOE experiments and the coupling constants in its ^1H NMR spectrum (Figure 2). The second route performed more effectively than the first in terms of both the number of steps required and the yield of the key cyclization step.



Scheme 3 Synthesis of quinolizidine **16**. *Reagents and conditions*: (a) BnBr, NaH, DMF, 68%; (b) *n*-BuLi then succinic anhydride **15**, Et_2O, –78 °C to r.t., 45%; (c) *n*-BuLi, TMSCl, Et_2O, –78 °C to r.t.; (d) **15**, DCE, 100 °C, 65% (two steps); (e) (i) Ghosez reagent, 4 Å MS; (ii) Hantzsch ester, DCE, 0°C to r.t., 61%; (f) H_2, Pd/C, EtOH, 53%.

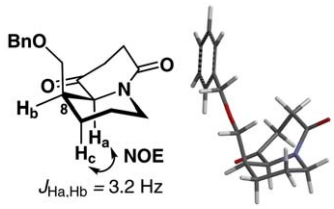


Figure 2 ^{1}H NMR coupling constant and NOESY experiments with compound **16** (left) and a stable conformation calculated by Spartan at the B3LYP/6-31+G(d) level of theory (DFT) (right)

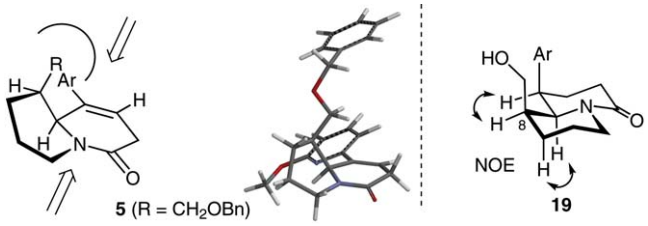


Figure 3 Regioselectivity of hydrogenation of compound **5** (left), a stable conformation calculated by Spartan at the B3LYP/6-31+G(d) level of theory (DFT) (middle), NOESY experiments of compound **19** (right).

We then investigated the stereoselective introduction of the pyridyl moiety into compound **16**. Preliminary studies revealed that the structurally related ketone **12** was readily enolized rather than attacked by nucleophiles such as $TMSCH_2Li$ and $Ph_3P{=}CH_2$.[19] Treatment of **16** with NaHMDS and Comins' reagent gave enol triflate **17** together with a significant amount of its regioisomer **18** in a combined yield of 61% (**17**/**18** = 1.3:1; Scheme 4). A variety of different bases (i.e., LDA, LiTMP, TrLi, KHMDS, NaHMDS, LiHMDS, Et_3N) and triflating reagents (i.e., Tf_2O, Tf_2NPh, and Comins' reagent[20]) were evaluated for this transformation, but none of these combinations led to an improvement in the low regioselectivity. Pleasingly, it was possible to separate these two compounds by silica gel column chromatography, and this allowed for sufficient quantities of the enol triflate **17** to be obtained for the subsequent Stille coupling. Following an extensive investigation of the conditions required for the coupling of **17** with **9** using several copper salts such as CuTC,[21] $CuBr{\cdot}SMe_2$, and CuDPP,[22] it was found that the reaction proceeded smoothly in the presence of catalytic $Pd(PPh_3)_4$ with copper(I) diphenylphosphinate (CuDPP) and LiCl in THF at 50 °C to give the coupling product **5** in good yield. Hydrogenation of **5** gave compound **19** as a single isomer, because the α-face was shielded by the hydroxymethyl group (Figure 3, left). The newly generated stereochemistry was confirmed by NOE experiments (Figure 3, right). Finally, reduction with $LiAlH_4$ gave the common intermediate **1** with the required *cis-cis* stereochemistry.[23]

In summary, we have developed a concise synthesis of quinolizidine **1** in a stereoselective manner. The key features of this method include: (i) construction of the quinolizidine ring by reduction of an acylpyridinium cation; and (ii) late-stage introduction of a pyridyl group by sequential Stille coupling and hydrogenation reactions. This synthetic strategy represents a reasonable technique for the stereoselective construction of quinolizidine rings with *cis-cis* stereochemistry. The synthesis of matrine-type alkaloids such as sophoramine, sophocarpine, and matrine from quinolizidine **1** through construction of the C ring and subsequent adjustment of the oxidation levels is underway in our laboratory.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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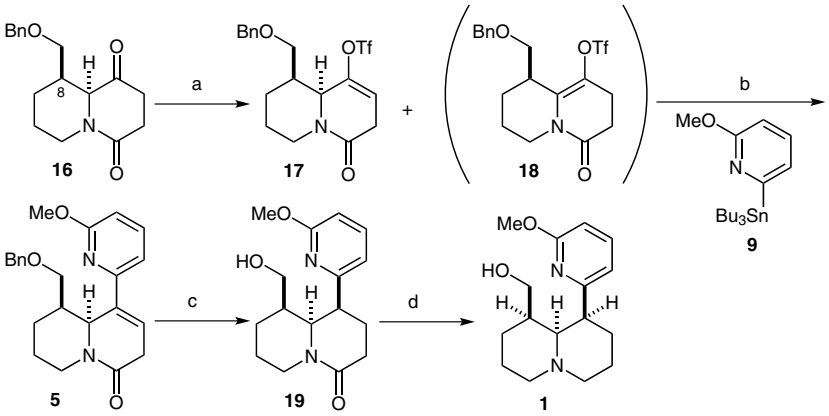

Scheme 4 Synthesis of common intermediate **1**. *Reagents and conditions*: (a) NaHMDS, Comins reagent, THF, –78 to 0 °C, 61%, (**17**/**18** = 1.3:1); (b) **9**, $Pd(PPh_3)_4$, CuDPP, LiCl, THF, 50 °C, 67%; (c) Pd/C, H_2 (5 atm), EtOH, 70 °C, 65%; (d) $LiAlH_4$, THF, 50 °C, 80%.

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(18) **Synthesis of 1,4-Dihydropyridine 6**: To a solution of carboxylic acid **7** (2.20 g, 7.34 mmol) and MS (4 Å; ca. 5 g) in CH_2Cl_2 (50 mL) at 0 °C was added Ghosez reagent (1.00 mL, 7.41 mmol). The mixture was stirred at 0 °C for 30 min, then Hantzsch ester (5.58 g, 22.0 mmol) was added. After stirring at room temperature for 2 h, the mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O–toluene, 2–3%) to afford dihydropyridine **6** (1.28 g, 4.52 mmol, 61%) as a solid. IR (ATR): 2979, 2721, 1689, 1235, 1089, 893 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 7.08 (dt, *J* = 8.0, 1.7 Hz, 1 H), 5.13 (dt, *J* = 8.3, 3.5 Hz, 1 H), 4.60–4.57 (m, 2 H), 4.49 (s, 2 H), 3.19–3.17 (m, 2 H), 2.74 (ddd, *J* = 8.3, 6.0, 1.5 Hz, 2 H), 2.67 (ddd, *J* = 8.3, 6.0, 1.5 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.3, 165.3, 138.1, 132.8, 128.9, 128.5, 127.8, 127.7, 122.7, 108.1, 73.0, 69.7, 35.9, 29.7, 25.9; MS (FAB): *m*/*z* = 284 $[M + H]^+$. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{18}NO_3$: 284.1287; found: 284.1296.

(19) We also found that a related ketone that did not have a substituent on the quinolizidine ring, enolized under the conditions of the Grignard and Wittig reactions. See ref. 5.

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(23) **Synthesis of Quinolizidine 1**: To a solution of alcohol **19** (11.3 mg, 0.0390 mmol) in THF (1 mL) was added dropwise a solution of $LiAlH_4$ (2.2 mg, 0.058 mmol, 1.5 equiv) in anhydrous THF (0.6 mL) at 0 °C under argon, and the resulting mixture was stirred at 50 °C for 30 min. After careful hydrolysis with 3 M aq NaOH (1 mL), EtOAc (1 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography ($CHCl_3$–MeOH, 20:1) to give alcohol **1** (10.8 mg, 0.035 mmol, 80%) as an oil. IR (ATR): 3356, 2928, 2857, 2754, 2683, 1578, 1466 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 8.0, 7.4 Hz, 1 H), 7.00 (d, *J* = 7.4 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 3.91 (s, 3 H), 3.65–3.54 (m, 2 H), 3.46 (dd, *J* = 11.2, 3.0 Hz, 1 H), 3.20 (dd, *J* = 8.5, 6.3, 4.0 Hz, 1 H), 2.98 (br d, *J* = 11.7 Hz, 1 H), 2.87–2.83 (m, 2 H), 2.30–2.14 (m, 3 H), 2.10–2.02 (m, 2 H), 1.86–1.81 (m, 2 H), 1.59–1.43 (m, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.1, 160.8, 138.3, 116.2, 107.7, 67.2, 64.9, 57.7, 53.3, 45.2, 37.9, 31.9, 30.7, 29.6, 21.7, 21.6. MS (FAB): *m*/*z* = 277.2 $[M + H]^+$. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_2$: 277.1911; found: 277.1913.

