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Synthesis of Highly Oxidized Quinolizidine via Reduction of Acylpyridinium Cations, and Total Syntheses of Quinolizidines 207I and 1-*epi*-207I

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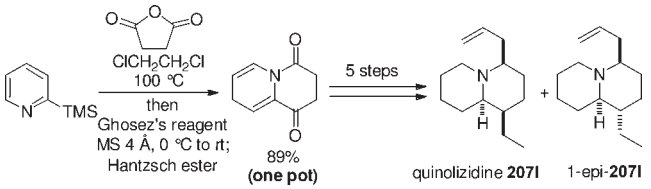
ABSTRACT



A new strategy for synthesizing quinolizidine skeletons by reductive cyclization via acylpyridinium cations was developed. Several functional groups, including carbonyl, silyl, and acetal, were tolerated under mild reaction conditions. The reaction was successfully extended to a one-pot synthesis of a bicyclic compound, and the synthetic strategy was applied to concise total syntheses of quinolizidines 207I and 1-*epi*-207I, without protecting groups.

Quinolizidine is a 6,6-bicyclic scaffold with a bridgehead nitrogen atom. Various types of quinolizidine alkaloids, from simple bicyclic to polycyclic compounds, have been isolated from bacteria, fungi, plants, invertebrates, and vertebrates.[1] Although there is no common biosynthetic pathway, these compounds often have significant biological activities, and some of them are major components of traditional medicines. Because of their promising structures with respect to biological activities, chemists and pharmacists are interested in the quinolizidine skeleton. Various synthetic methods for quinolizidines have been developed. The skeletons are generally constructed from piperidine derivatives by formation of the second six-membered ring using nitrogen nucleophilic substitution, intramolecular reductive amination, or ring-closing metathesis.[1,2] Comins et al. accomplished the total syntheses of quinolizidine natural products from *N*-acyl-1,2-dihydropyridines and *N*-acyl-2,3-dihydro-4-pyridinones, which were prepared by nucleophilic addition to *N*-acylpyridinium salts.[3] Synthesis via iminium intermediates is another route to this skeleton.[4] Direct conversion of a pyridinium salt fused with a six-membered ring has also been reported, but this required a relatively stable pyridinium cation.[5] Recently, Charette et al. described an intramolecular pyridine activation−dearomatization

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(2) Recent examples: (a) Wong, H.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 7517. (b) Ying, Y.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 796. (c) Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108. (d) Airiau, E.; T. Spangenberg, R.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528. (e) Dalton, D. M.; Oberg, K. M.; Yu, R. T.; Lee, E. E.; Perreault, S.; Oinen, M. E.; Pease, M. L.; Malik, G.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 15717. (f) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394.

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(5) Selected examples: (a) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082. (b) Kutney, J. P.; Fortes, C. C.; Honda, T.; Murakami, Y.; Preston, A.; Ueda, Y. *J. Am. Chem. Soc.* **1977**, *99*, 964.

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strategy via a *N*-pyridinium imidate.[6] In their paper, quinolizidine ring formation, dearomatization of pyridine, and C−C bond formation were accomplished in one pot. Although dearomatization strategies are powerful, they would be difficult to apply to substrates with carbonyl functionalities because they require strong nucleophiles such as Grignard reagents. We therefore focused on reducing reagents as mild nucleophiles. If the quinolizidine skeleton is constructed by one-pot activation−reduction via an unstable pyridinium cation, this synthetic strategy can be applied to a broader range of substrates. Using pyridine instead of piperidine would make the synthesis simple and free from protecting groups.[7] In this paper, we report a new strategy for the synthesis, without protecting groups, of quinolizidine skeletons via reduction of acylpyridinium cations and its application to total syntheses of related natural products.

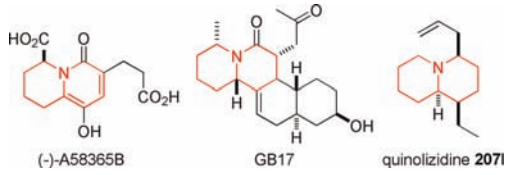
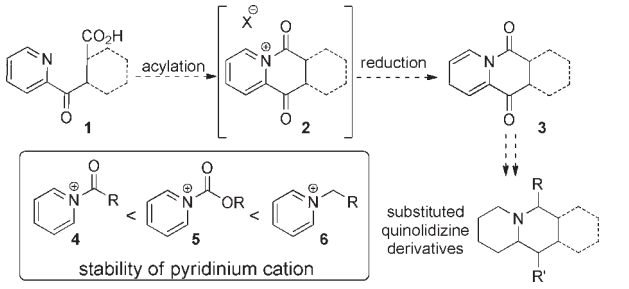


Figure 1. Quinolizidine alkaloids.

We devised a synthesis of quinolizidine **3**, bearing in mind natural products with carbonyl functionalities and carbon side chains, for example A58365B[8] and GB17[9] (Figure 1, Scheme 1). Because **3** contains amide and ketone groups, it would also be a useful intermediate for substituted quinolizidine derivatives such as quinolizidine **207I**.[10] The quinolizidine skeleton could be constructed by reduction of acylpyridinium cation **2**, which is obtained by activation of carboxylic acid **1**, as shown in Scheme 1. There are many examples of nucleophilic addition and reduction of alkoxycarbonylpyridinium cation **5** and alkylpyridinium cation **6**;[3,5,11−14] Charette et al. focused on nucleophilic addition to *N*-pyridinium imidates.[15] However, there have been few reports of reduction of acylpyridinium cation **4**.[16] Also, the reported yields were often low, and specific functional groups were required because the lability of **4**, unlike **5** and **6**, would hamper reduction under these conditions. To realize our strategy, we needed mild reducing agents.

Scheme 1. Synthetic Strategy for Highly Oxidized Quinolizidines



For the initial survey, a model compound **7**[17] was used to examine reductive cyclization using an activator and a reductant (Table 1). After treatment of **7** with oxalyl chloride and a catalytic amount of DMF, we tried several reagents for reduction of the resultant acylpyridinium intermediate **8**. Reduction using $NaBH_4$, $LiBH_4$, DIBAL-H, and Et_3SiH did not proceed and only the starting carboxylic acid was recovered. In the case of $BH_3\cdot THF$ and Bu_3SnH, **9b** was obtained via 1,2-reduction (Table 1, entries 1 and 2). In contrast, the reaction using Comins' conditions[16a] gave 1,2-dihydropyridine as a 1:0.7 mixture of isomers **9c** (entry 3). When a Hantzsch ester **10**[18,19] was

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(13) For recent examples of reduction of alkoxy carbonylpyridinium cation **5** and alkyl pyridinium cation **6**, see: (a) Donohoe, T. J.; Connolly, M.; Rathi, A. H.; Walton, L. *Org. Lett.* **2011**, *13*, 2074. (b) Shaw, A. P.; Ryland, B. L.; Franklin, M. J.; Norton, J. R.; Chen, J. Y.-C.; Hall, M. L. *J. Org. Chem.* **2008**, *73*, 9668. (c) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Bamford, M. J.; Ichihara, O. *Org. Lett.* **2005**, *7*, 435.
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(17) Compound **7** was prepared from methyl picolinate by modifying our previous report: Tsukano, C.; Zhao, L.; Takemoto, Y.; Hirama, M. *Eur. J. Org. Chem.* **2010**, 4198. Also see Supporting Information.
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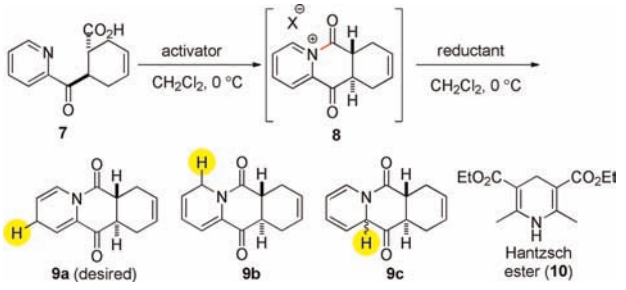
used as the reducing reagent, 1,4-reduction proceeded, giving **9a** as a single isomer along with recovered starting material **7** (entry 4). Considering the obtained yields, **10** was used for further investigations. To obtain a full conversion of **7**, several reagents were investigated for carboxylic acid activation (entries 5−7). It was found that 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (Ghosez's reagent), which is used under mild and neutral conditions,[20] gave good yields, and addition of MS4 Å resulted in excellent conversion (entry 8). It should be noted that the 1,4-dihydropyridine **9a** was unstable; for example, lengthy exposure to silica gel caused decomposition of the cyclized 1,4-dihydropyridine.

Table 1. Reduction of Acylpyridinium Cation



			yield (%)[a]	
entry	conditions A	conditions B	**9a**−**c**	**7**
1	$(COCl)_2$, cat. DMF	BH_3·THF[b]	**9b** 47%	0%
2	$(COCl)_2$, cat. DMF	Bu_3SnH[c]	**9b** 32%	53%
3	$(COCl)_2$, cat. DMF	Li(tBuO)$_3$AlH, CuBr	**9c** 33%[d]	0%
4	$(COCl)_2$, cat. DMF	Hantzsch ester (**10**)	**9a** 60%[e]	18%
5	$(SOCl)_2$, cat. DMF	Hantzsch ester (**10**)	**9a** 54%[e]	36%
6	BzCl, Et_3N	Hantzsch ester (**10**)	**9a** 23%[e]	48%
7	Ghosez's reagent	Hantzsch ester (**10**)	**9a** 89%[e]	trace
8	Ghosez's reagent	Hantzsch ester[f]	**9a** 96%[e]	0%

[a] Isolated yield. [b] THF was used as a cosolvent. [c] −78 °C. [d] The ratio of mixture was 1:0.7. [e] Isolated yield based oxidized Hantzsch ester. [f] MS 4 Å was added.

Next we investigated the scope and limitations of the optimized reaction conditions. Treatment of **11a** with a methyl group on the pyridine ring with Ghosez's reagent following treatment with Hantzsch ester **10** gave the cyclized product **12a** in 87% yield (Table 2, entry 1). In the case of a phenyl substituent, the reaction proceeded smoothly to give **12b** (entry 2). Electron-withdrawing groups, such as bromine and trifluoromethyl, on the pyridine ring were tolerated under these conditions (entries 3 and 4). The reaction of **11e**, bearing a methoxy group, resulted in decomposition of the starting material, probably because of the instability of the intermediate (entry 5). The sterically hindered carboxylic acid **11f** could be used for this cyclization (entry 6). The double bond was

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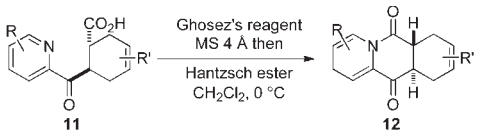
Table 2. Substrate Scopes and Limitations[a]



entry	starting material	product	yield[b]
1	**11a** (R = Me)	**12a** (R = Me)	87%
2	**11b** (R = Ph)	**12b** (R = Ph)	62%
3	**11c** (R = Br)	**12c** (R = Br)	81%
4	**11d** (R = CF_3)	**12d** (R = CF_3)	66%
5	**11e**	**12e**	0%
6	**11f**	**12f**	70%
7	**11g**	**12g**	50%
8	**11h**	**12h**	83%
9	**11i**	**12i**	58%
10	**11j**	**12j**	trace

[a] Conditions: **11** (1 equiv), Ghosez's reagent (1.5 equiv), and MS 4 Å were stirred for 20 min at 0 °C, and then Hantzsch ester (3 equiv) was added. [b] Isolated yield based oxidized Hantzsch ester.

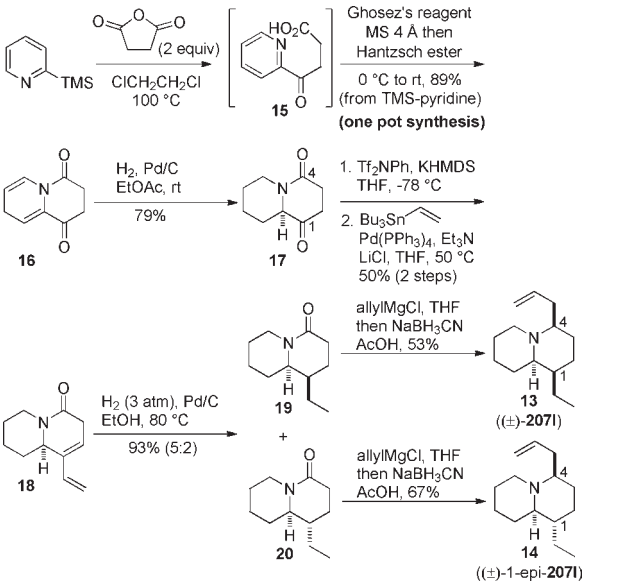
not essential for this reductive cyclization, although the yield was slightly decreased (entry 7). Acetal and *tert*-butyldimethylsilyl (TBS) groups were compatible under these conditions (entries 8 and 9). In contrast, the reaction of **11j** afforded only trace amounts of **12j** (entry 10). These results indicated that the ketone moiety was essential for increasing product stability.

To show that our strategy is powerful for preparing quinolizidine skeletons, the total syntheses of quinolizidines **207I** (**13**) and 1-*epi*-**207I** (**14**) were performed

(Scheme 2). **207I** was isolated in trace quantities from skin extracts of a Madagascan mantelline frog, *Mantella baroni*, by Daly et al.[10a] It was first assigned as the C1 epimer (i.e., 1-*epi*-**207I**) using GC-FTIR and GC-MS, but this was revised after the syntheses of **207I** and 1-*epi*-**207I**.[10b,21a] The first total synthesis of racemic **207I**, involving 17 steps, was reported by Michel and Rassat.[21a,b] Toyooka et al. determined the absolute stereochemistry of **207I** using their 23-step enantioselective synthesis.[21c] Interestingly, 1-*epi*-**207I** selectively blocks α7 nicotinic receptors (IC_{50} = 0.6 μM), but **207I** is less potent than 1-*epi*-**207I** and shows no selectivity for α4β2 nicotinic receptors.[22] Concise routes to both quinolizidines are important for further biological studies.

Our syntheses commenced with construction of the quinolizidine skeleton by reductive cyclization. The coupling of trimethylsilylpyridine and succinic anhydride, using Thames's procedure,[23] was followed by cyclization under the developed conditions to give **16** in 89% yield without isolation of intermediate **15**. The bicyclic core was readily obtained by a one-pot synthesis based on an extension of our method. After hydrogenation of **16**, we tried to install an ethyl group at the C1 position. After several investigations, ketone **17**[24] was converted to diene **18** by formation of an enol triflate and Stille coupling. Hydrogenation of **18** gave a 5:2 mixture of diastereomers **19** and **20** under medium pressure. After separation by HPLC, products **19** and **20** were each treated with allyl magnesium chloride and then sodium cyanoborohydride in one pot[3a,25] to give racemic **207I** (**13**) and 1-*epi*-**207I** (**14**), respectively; **207I** and 1-*epi*-**207I** were the only observed products in each one-pot reduction and cyclization. The ^{1}H NMR, ^{13}C NMR, and high-resolution MS data were identical to previously reported data.[10,21] This seven-step synthetic route using no protecting groups is more concise compared to previous syntheses.

Scheme 2. Total Synthesis of Quinolizidine **207I**



In summary, we have developed reduction of acylpyridinium cations under mild conditions as a one-pot synthesis of quinolizidine skeletons. Several functional groups, including silyl and acetal, were tolerated under these conditions. The method was successfully applied to the seven-step syntheses of quinolizidine alkaloids **207I** and 1-*epi*-**207I**, without protecting groups. Because the cyclized products are highly oxidized quinolizidines containing enamide and α,β-unsaturated ketone functionalities, these compounds have the potential for conversion to more-substituted quinolizidines. Extension of the strategy and its application to syntheses of related quinolizidine natural products are now underway.

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Supporting Information Available. Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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