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Total Synthesis of the Putative Structure of the Lupin Alkaloid Plumerinine

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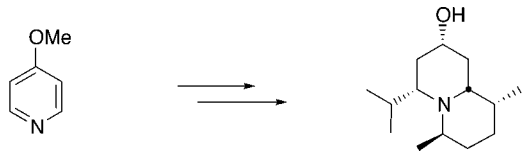
ABSTRACT



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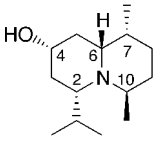
A stereocontrolled synthesis of quinolizidine 1, the reported structure of plumerinine, has been accomplished in 10 steps from 4-methoxypyridine. The key step is a highly facial selective intramolecular [2 + 2] photocycloaddition of a 2,3-dihydro-4-pyridone. The reported spectral data for plumerinine did not match that of our synthetic 1.

In 1989, Malik and co-workers reported the isolation of a novel lupin alkaloid from the stem of *Plumeria rubra* which commonly grows as an ornamental plant in southeast Asia. This plant is reputed to possess purgative, diuretic, abortificient, and antituberculotic properties and is also used as a remedy for rheumatism, diarrhea, blennorrhea, gonorrhea, syphilis, venereal sores, and leprosy. The alkaloid was named plumerinine and assigned the structure **1** on the basis of extensive spectral studies using NMR, IR, HRMS, and UV.[1] Structure **1** contains a quinolizidine skeleton, four substituents, and five stereogenic centers in a relatively compact molecule. The interesting structure of **1** and its potential biological activities prompted us to pursue its synthesis.



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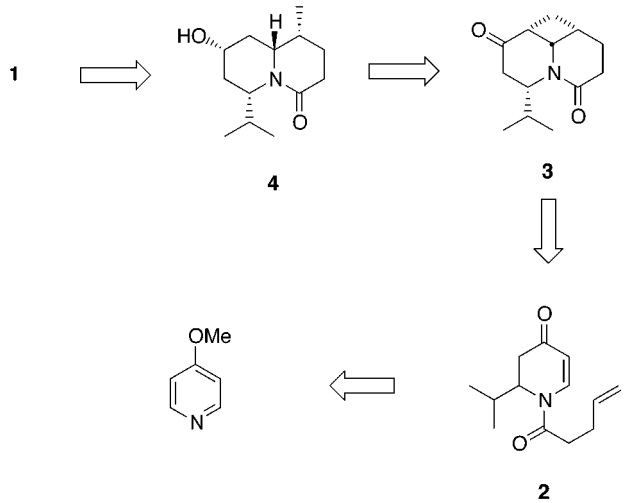
Our synthesis plan for the preparation of **1** starting from 4-methoxypyridine is depicted in Scheme 1. The strategy uses a facial selective [2 + 2] photocyclization of dihydropyridone **2** to prepare the key tricyclic intermediate **3**. It was anticipated that cyclobutane ring opening of **3** would lead to **4**, a viable precursor to **1**.

Treatment of 4-methoxypyridine with 4-pentenoyl chloride and isopropylmagnesium bromide gave the 1-acyl-2,3-

Scheme 1



(1) Kazmi, S. N.; Ahmed, W.; Malik, A. *Heterocycles* **1989**, *29*, 1901.

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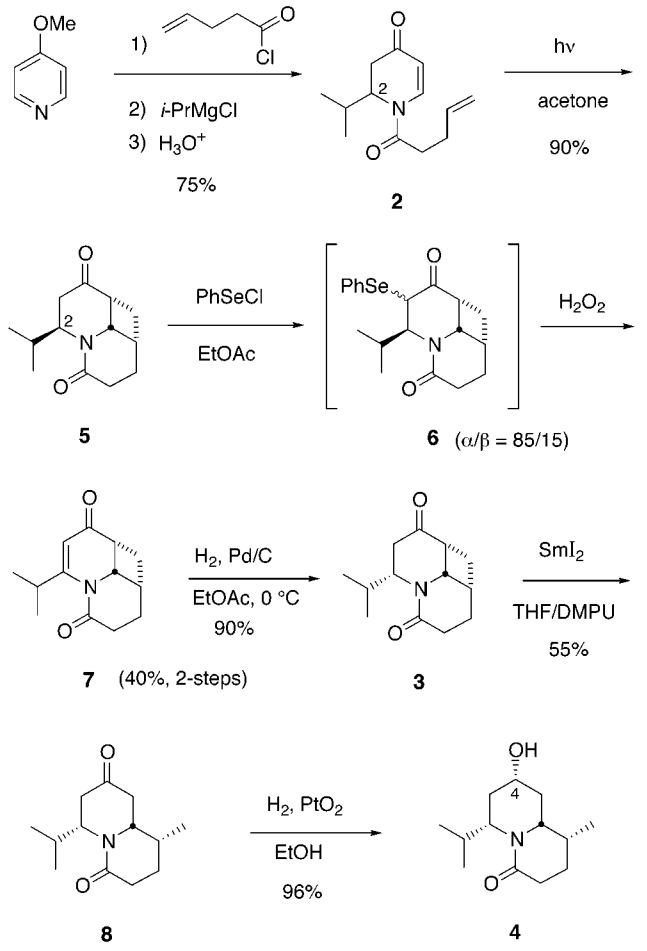
Scheme 2



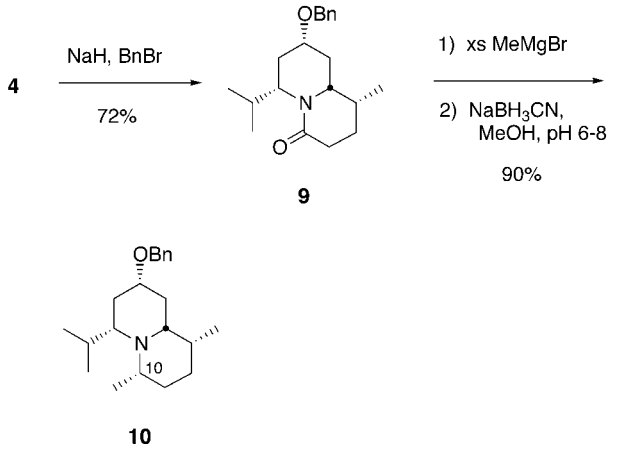
dihydro-4-pyridone **2** in 75% yield[2] (Scheme 2). On irradiation of **2** in acetone (460 W Hanovia Hg lamp), an intramolecular [2 + 2] photocycloaddition occurred to provide a 90% yield of cycloadduct **5** as a single diastereomer. Since the C-2 substituent of **2** is axial, due to $A^{1,3}$ strain,[3] cycloaddition occurred exclusively from the less hindered olefin face.[4] In this key step, the quinolizidine ring system was constructed and three of the five stereocenters of **1** were established. The center at C-2 of **5** has the incorrect stereochemistry relative to the target, so epimerization was required.

When phenylselenyl chloride was added to an ethyl acetate solution of **5**, an 80% yield of *trans*-α-phenylselenyl ketone **6** was obtained along with 15% of the corresponding *cis*-isomer. Oxidative elimination of **6** with hydrogen peroxide gave the desired enone **7** in moderate yield. It was anticipated that catalytic hydrogenation would occur from the less hindered convex side of **7** to provide the needed stereochemistry at C-2. Hydrogenation of **7** over 5% Pd/C in EtOAc at 0 °C gave a quantitative yield of a 10/1 mixture of **3** and epimer **5**. The structure of **3** was confirmed by single-crystal X-ray analysis.

Treatment of **3** with SmI_2 (THF, DMPU) effected cyclobutane ring opening[4b,d] to give bicyclic ketone **8** in 55% yield. Reduction of **8** with L-Selectride or hydrogenation over washed[5] PtO_2 gave exclusively the desired alcohol **4** in near quantitative yield. With the stereoselective introduction of the C-4 hydroxyl group, four of the five required stereocenters of **1** were established.

Conclusion of the synthesis required the conversion of the γ-lactam to a piperidine ring with incorporation of a β-methyl group at C-10. The hydroxyl group of **4** was protected as a benzyl ether (Scheme 3). The lactam **9** was then subjected to methylation/reduction conditions. After considerable study, a one-pot sequence was developed. Addition of excess methylmagnesium bromide to **9**, followed by acidic methanol/$NaCNBH_3$, provided a 90% yield of amine **10** as a single diastereomer. Unfortunately, this highly stereoselective transformation afforded the C-10 epimer of the desired compound as confirmed by X-ray analysis of its hydrobromide salt. The stereochemical outcome of this conversion can be explained through stereoelectronic control[6] during axial hydride addition to a low-energy iminium ion intermediate as depicted in Figure 1.

Scheme 3



After several unsuccessful attempts at in situ reduction/methylation of **9**, stepwise processes to prepare the desired bicyclic amine were investigated. Treatment of **9** with

(2) (a) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press Inc.; Greenwich, CT, 1996; Vol. 2, pp 251−294. (b) Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; McKillop, A., Ed.; Pergamon Press: Oxford, England, 1996; Vol. 5, pp 37−89. (c) Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491.

(3) For reviews on $A^{1,3}$ strain, see: Hoffmann, R. *Chem. Rev.* **1989**, *89*, 1841. Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(4) For previous [2 + 2] photocycloaddition reactions of 2,3-dihydro-4-pyridones, see: (a) Guerry, P.; Neier, R. *Chimia* **1987**, *41*, 341. Guerry, P.; Neier, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1727. Guerry, P.; Blanco, P.; Brodbeck, H.; Pasteris, O.; Neier, R. *Helv. Chem. Acta* **1991**, *74*, 163. (b) Comins, D. L.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1994**, 2681. (c) Comins, D. L.; Lee, Y.; Boyle, P. D. *Tetrahedron Lett.* **1998**, *39*, 187. (d) Comins, D. L.; Zhang, Y.-M.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1998**, 2509.

(5) Mitsui, S.; Saito, H.; Yamashita, Y.; Kaminaga, M.; Senada, Y. *Tetrahedron* **1973**, *29*, 1531.

(6) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 6. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296 and references therein.

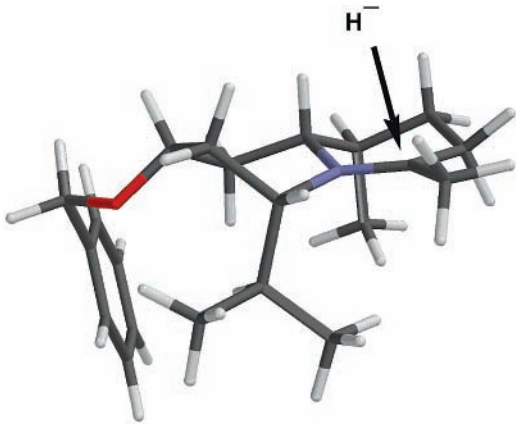
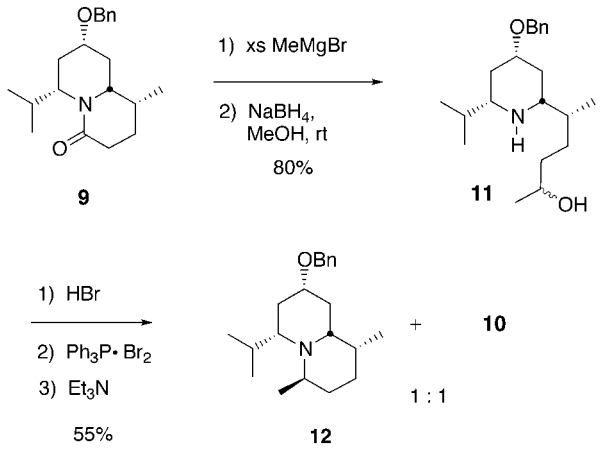


Figure 1. Axial attack of hydride on iminium ion (MMFF).

methylmagnesium bromide followed by workup with $NaBH_4$/MeOH provided alcohols **11** as an equal mixture of diastereomers (Scheme 4). The alcohols **11** on treatment with HBr

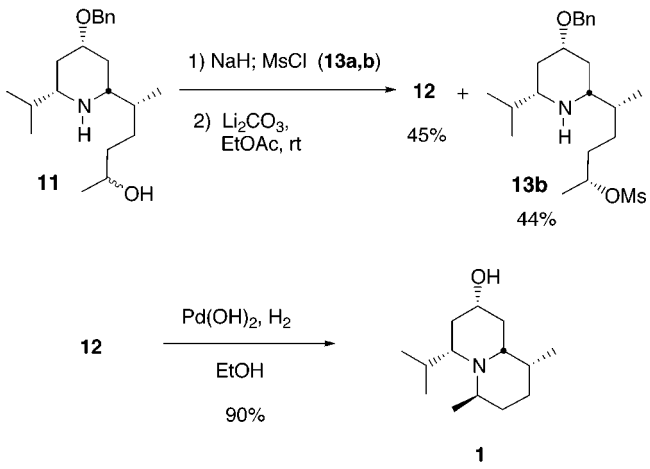
Scheme 4



formed the crude corresponding salts, which were cyclized using Oliver and Sonnet's conditions ($Ph_3P{\cdot}Br_2$; TEA)[7] to provide quinolizidines **12** and **10** as a 1:1 mixture. Purification of the crude reaction products proved difficult, so an alternative procedure was developed. The alcohols **11** were converted to the corresponding crude mesylates **13** (NaH, MsCl), which were treated with lithium carbonate in EtOAc at room temperature (Scheme 5). Under these conditions, only diastereomer **13a** cyclized and the desired product **12**

(7) Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1974**, *39*, 2662.

Scheme 5



could be easily isolated by chromatography. The benzyl ether of **12** was cleaved using standard catalytic hydrogenolysis to provide **1** in 90% yield. The structure of **1** was confirmed by X-ray analysis of its hydrobromide salt. Unfortunately, the ^1H and ^{13}C NMR data of our synthetic **1**, or its hydrobromide salt, did not match the corresponding data reported by Malik for "plumerinine". It appears that a structure reassignment is in order for this natural product.

In summary, a stereocontrolled synthesis of quinolizidine **1** has been accomplished in 10 steps from 4-methoxypyridine. A novel approach to the quinolizidine skeleton using a photocycloaddition/cyclobutane ring-opening sequence was developed. A highly facial selective intramolecular [2 + 2] photocycloaddition of a 2,3-dihydro-4-pyridone containing a terminal olefin tethered to nitrogen was key to the success of this synthesis.

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Supporting Information Available: Characterization data for compounds **2**−**5**, **7**−**10**, and **12** and comparison tables of NMR data for synthetic **1**. ^1H NMR spectra of **1**, **4**, **9**, **10**, and **12** and ORTEP plots and X-ray crystal data for **1**, **3**, **4**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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