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Total Synthesis of (+)-Epilupinine via An Intramolecular Nitrile Oxide-Alkene Cycloaddition

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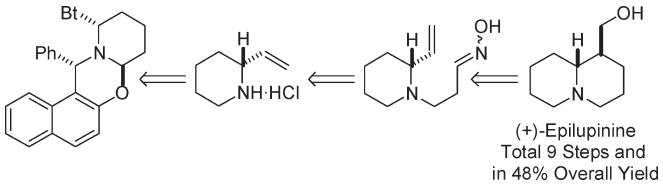

Total synthesis of (+)-epilupinine was accomplished in nine steps and in 48% overall yield, in which INOC was used as the key step for the construction of the quinolizidine skeleton. We found that it was an extremely difficult task to prepare the key intermediates (*R*)-*N*-(3-nitropropyl)-2-vinylpiperidine or (*R*)-(2-vinylpiperid-1-yl)propanal by routine methods. Thus, by using Fukuyama's oxime synthesis, a general method was developed for highly efficient conversion of 3-(*N*,*N*-dialkylamino)propanols into 3-(*N*,*N*-dialkylamino)-propanal oximes without using the corresponding aldehydes.

Introduction

Quinolizidine alkaloid is one of three major types of chiral nitrogen-bridged bicyclic alkaloids found in nature, along with indolizidine and pyrrolizidine alkaloids.[1] The diastereoisomers of (−)-lupinine (**1**) and (+)-epilupinine (**2**) are the simplest members of quinolizidine alkaloids isolated from lupine seeds or as derivatives isolated from seedlings of *L. luteus*.[2] They are characterized by a hydroxymethyl group substituted on C1 position of quinolizidine ring with opposite configurations (Chart 1). When (−)-lupinine (**1**) is heated under basic conditions, it can be isomerized to the thermodynamically stable (+)-epilupinine (**2**).[3]

Almost two decades ago, (+)-epilupinine (**2**) was reported to show *in vitro* inhibitory activity against P-388 (LD_{50} = 28 μg/mL) and L1210 (LD_{50} = 20 μg/mL) cell lines.[4] In recent years, it has been widely employed as intermediates or pharmacophores in drug discovery. Many molecules bearing epilupinyl unit are potential ligands for 5-HT_3, 5-HT_4 or Sigma receptors[5] as well as antiviral, antiarrhythmic, antimalarial or platelet antiaggregating agents.[6] Since its typical structure and biologically important properties, especially the fact that it often served as an excellent vehicle for the validation of new synthetic methodology and strategy, (+)-epilupinine (**2**) has attracted great interest as a challenging target for total synthesis.

Many novel routes have been developed for the total synthesis of (+)-epilupinine (**2**) based on the different cyclization methods in literature.[4,7] Surprisingly, the well-known intramolecular nitrile oxide−alkene cycloaddition (INOC)[8]

(1) For reviews, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–165. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191–222. (c) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.

(2) For reviews, see: (a) Takamatsu, S.; Saito, K.; Murakoshi, I.; Ohmiya, S. *J. Nat. Prod.* **1991**, *54*, 477–482. (b) Beck, A. B.; Goldspink, B. H.; Knox, J. R. *J. Nat. Prod.* **1979**, *42*, 385–398. (c) Aslanov, K. A.; Kushmuradow, Y. K.; Sadykov, A. S. in *The alkaloids*; Brossi, A., Ed.; Academic Press, Inc.: New York, 1987; Vol. 31, pp 140−146.

(3) Sparatore, A.; Tasso, B.; Boido, V.; Sparatore, F. *Helv. Chim. Acta* **2005**, *88*, 245–251.

(4) Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970–974.

(5) (a) Sparatore, A.; Novelli, F.; Sparatore, F. *Helv. Chim. Acta* **2004**, *87*, 580–591. (b) Sparatore, A.; Cagnotto, A.; Sparatore, F. *IL Farmaco* **1999**, *54*, 248–254.

(6) (a) Tonelli, M.; Vazzana, I.; Tasso, B.; Boido, V.; Sparatore, F.; Fermeglia, M.; Paneni, M. S.; Posocco, P.; Pricl, S.; La Colla, P.; Ibba, C.; Secci, B.; Collu, G.; Loddo, R. *Bioorg. Med. Chem.* **2009**, *17*, 4425–4440. (b) Tonellia, M.; Pagliettib, G.; Boidoa, V.; Sparatore, F.; Marongiuc, F.; Marongiuc, E.; La Collac, P.; Loddoc, R. *Chem. Biodiv.* **2008**, *5*, 2386–2481. (c) Casagrande, M.; Basilico, N.; Parapini, S.; Romeo, S.; Taramelli, D.; Sparatore, A. *Bioorg. Med. Chem.* **2008**, *16*, 6813–6823. (d) Vazzana, I.; Budriesi, R.; Terranova, E.; Ioan, P.; Ugenti, M. P.; Tasso, B.; Chiarini, A.; Sparatore, F. *J. Med. Chem.* **2007**, *50*, 334–343. (e) Sparatore, A.; Basilico, N.; Parapini, S.; Romeo, S.; Novelli, F.; Sparatorec, F.; Taramelli, D. *Bioorg. Med. Chem.* **2005**, *13*, 5338–5345. (f) Ercoli, M.; Mina, L.; Boido, C. C.; Boido, V.; Sparatore, F.; Armani, U.; Piana, A. *IL Farmaco* **2004**, *59*, 101–109.

(7) For asymmetric syntheses of optical epilupinine, see: (a) Ahari, M.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473–2476. (b) Ma, S.; Ni, B. *Chem.—Eur. J.* **2004**, *10*, 3286–3300. (c) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349–10362. (d) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565–16574. (e) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420–8421. (f) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc. Perkin Trans 1* **1994**, 2903–2907. (g) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289–291.

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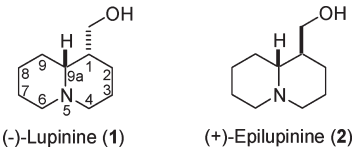
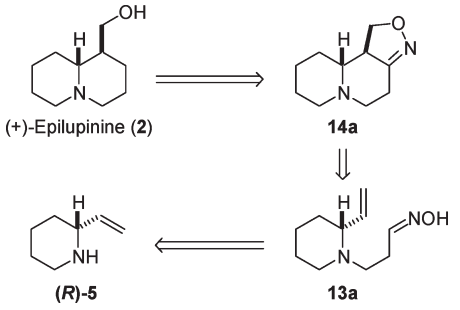
CHART 1



SCHEME 1



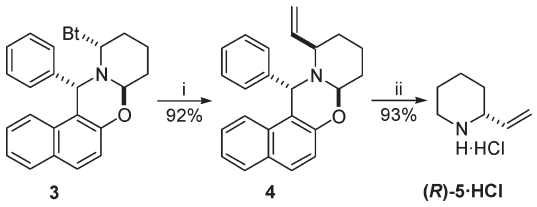
has never been employed for such purpose, even though it was often used for the construction of substituted piperidine rings.[9] However, when a *retro*-synthetic route was proposed for (+)-epilupinine (**2**) by using INOC as a key step (Scheme 1), we realized that it may be hampered by three obstacles: (a) efficient preparation of chiral (*R*)-2-vinylpiperidine [(***R*)-5**)]; (b) efficient preparation of (*R*)-(2-vinylpiperid-1-yl)propanal oxime (**13a**); (c) efficient preparation of **14a** by a oxidative INOC of tertiary amine **13a**.

Herein, we report a novel route for the total synthesis of enantiopure (+)-epilupinine (**2**) by using INOC as a key step, in which all three obstacles in Scheme 1 are overcome efficiently. This practical and scalable route is characterized by easy performance, short steps and high overall yield.

Results and Discussion

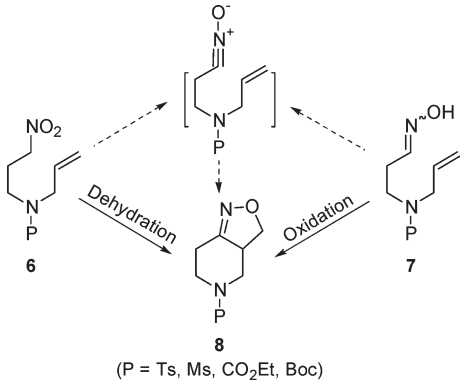
Efficient Preparation of (*R*)-2-Vinylpiperidine Hydrochloride [(*R*)-5·HCl]. The investigation shows that nonracemic 2-vinylpiperidine (**5**) is a versatile precursor in the total syntheses of alkaloids.[10] But its application is far from that expected, most possibly because its preparation is still a challenging subject to date.[10,11]

SCHEME 2[a]



[a]Conditions: i. $H_2C{=}CHMgBr$, THF, 0 °C, 1 h, 92%; ii. (a) $LiAlH_4$, THF, 0 °C, 0.5 h; (b) aq. NaOH, MeOH, THF, 60 °C, 6 h; (c) sat. HCl in MeOH, 93% yield for three steps.

SCHEME 3



Recently, we reported a general method for the preparation of enantiopure 2-alkene substituted piperidines from Betti base derivative **3**.[10a,b] Its high efficiency owes to a novel base-catalyzed *N*-debenzylation. As shown in Scheme 2, when **3** was treated with $H_2C{=}CHMgBr$ in THF, its Bt-group (1,2,3-benzotriazol-1-yl) was substituted by a vinyl group to give a single diastereomer **4** in 92% yield. When **4** was subjected to a reductive cleavage of C−O bond followed by a *N*-debenzylation in one-pot, (*R*)-2-vinylpiperidine hydrochloride [(***R*)-5·HCl**] was obtained in 93% yield. This method is so practical that (***R*)-5·HCl** can be prepared in gram scale within a few hours.

Efficient Preparation of (*R*)-(2-Vinylpiperid-1yl)propanal Oxime (13a). INOC has been proved to be a powerful tool for the preparation of bicyclic derivatives of 4,5-dihydroisoxazole.[8] By using the substrates that two functional groups are linked by a nitrogen atom, the nitrogen-containing heterocyclic products are expected. As shown in Scheme 3, when the derivatives of *N*-allyl-3-nitropropylamine (**6**)[9e] or 3-(allylamino)propanal oxime (**7**)[9a] were treated under INOC conditions, 4,5-dihydroisoxazolo[4,3-*c*]piperidines (**8**) can be prepared stereoselectively with satisfactory yields.

Thus, we tried to convert (***R*)-5·HCl** into the corresponding (*R*)-*N*-(3-nitropropyl)-2-vinylpiperidine (**9**) or (*R*)-(2-vinylpiperid-1-yl)propanal (**10**) (Scheme 4). Unfortunately, when

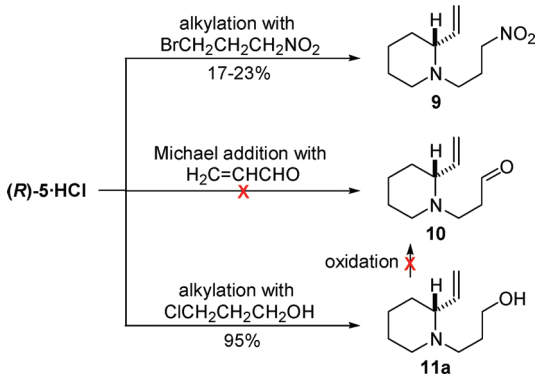
(8) Recent reviews for intramolecular nitrile oxide−alkene cycloaddition (INOC), see: (a) Rai, K. M. L. *Top. Heterocycl. Chem.* **2008**, *13*, 1–69. (b) Namboothiri, I. N. N.; Rastogi, N. *Top. Heterocycl. Chem.* **2008**, *12*, 1–44. (c) Jager, V.; Colinas, P. A. Nitrile Oxides. In *The Chemistry of Heterocyclic Compounds*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons Inc.: New York, 2002; Vol. 59. (d) Namboothiri, I. N. N.; Hassner, A. *Top. Curr. Chem.* **2001**, *216*, 1–49.

(9) Recent references for the construction of substituted piperidine rings by INOC, see: (a) Noguchi, M.; Tsukimoto, A.; Kadowaki, A.; Hikata, J.; Kakehi, A. *Tetrahedron Lett.* **2007**, *48*, 3539–3542. (b) Kadowaki, A.; Nagata, Y.; Uno, H.; Kaminura, A. *Tetrahedron Lett.* **2007**, *48*, 1823–1825. (c) Nath, M.; Mukhopadhyay, R.; Bhattacharjya, A. *Org. Lett.* **2006**, *8*, 317–320. (d) Andres, J. I.; Alcazar, J.; Alonso, J. M.; Alvarez, R. M.; Bakker, M. H.; Biesmans, I.; Cid, J. M.; De Lucas, A. I.; Fernandez, J.; Font, L. M.; Hens, K. A.; Iturrino, L.; Lenaerts, I.; Martinez, S.; Megens, A. A.; Pastor, J.; Vermote, P. C. M.; Steckler, T. *J. Med. Chem.* **2005**, *48*, 2054–2071. (e) Akritopoulou-Zanze, I.; Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 3421–3423. (f) Falb, E.; Nudelman, A.; Gottlieb, H. E.; Hassner, A. *Eur. J. Org. Chem.* **2000**, 645–655.

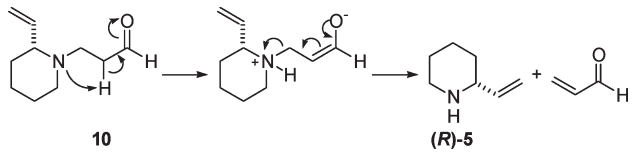
(10) (a) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911–1916. (b) Liu, H.; Su, D.; Cheng, G.; Xu, J.; Wang, X.; Hu, Y. *Org. Biomol. Chem.* **2010**, 1899–1904. (c) Friestad, G. K.; Korapala, C. S.; Ding, H. *J. Org. Chem.* **2006**, *71*, 281–289. (d) Zheng, J.-F.; Jin, L.-R.; Huang, P.-Q. *Org. Lett.* **2004**, *6*, 1139–1142. (e) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056–9062. (f) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700–709.

(11) (a) Spiess, S.; Welter, C.; Franck, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7652–7655. (b) Yamauchi, S.; Omi, Y. *Biosci., Biotechnol., Biochem.* **2005**, *69*, 1589–1594. (c) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896–897.

SCHEME 4



SCHEME 5[a]



[a] A *retro*-Micheal addition by an intramolecular E1cB elimination

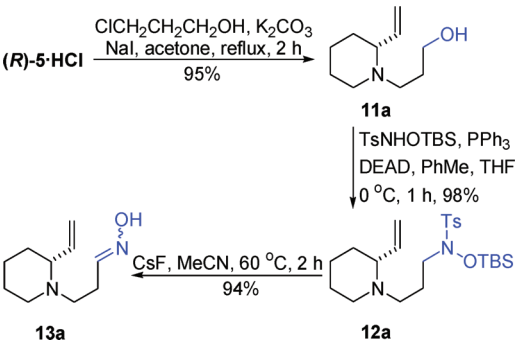
(***R***)**-5·HCl** was subjected to an alkylation with $BrCH_2CH_2CH_2NO_2$, the expected product **9** was obtained in poor yield (17−23%). It was worse that a complex mixture was produced in Michael addition between (***R***)**-5·HCl** and CH_2=CHCHO at room temperature. We observed a major product on TLC plate when Michael addition proceeded at 0 °C, but a similar mixture was obtained after a routine workup. Although the alkylation of (***R***)**-5·HCl** with $ClCH_2CH_2CH_2OH$ gave **11a** in excellent yield, the conversion of **11a** to **10** failed too by oxidation with PCC, DMSO-$(COCl)_2$ or Dess-Martin periodinane. In fact, Marko's early works have demonstrated that the preparation, isolation, storage and application of 3-(*N*,*N*-dialkylamino)propionals were extremely difficult tasks.[12]

These results strongly indicate that the problems may be from the structural natures of **9** and **10** rather than from the synthetic methods used. We hypothesized that the instability of **9** and **10** may be caused by their intramolecular E1cB elimination, in which the amine group may play dual roles as shown in Scheme 5 (by using **10** as a model). (a) Initially, amine is used as a base to remove the α-proton to generate an ammonium intermediate. (b) After amine is converted into ammonium, it is used as a good leaving group to lead to a *retro*-Michael addition. Thus, the amide-protected[9] (as a weak base) or α,α-disubstituted[13] (without α-protons) aldehydes were successfully prepared in literature because they could not carry out an intramolecular E1cB elimination. That may be the reason that INOC was rarely used as a key step to construct the piperidine ring in the syntheses of polycyclic alkaloids. Therefore, both *N*,*N*-dialkyl-3-nitropropylamines and 3-(*N*,*N*-dialkylamino)propionals are not suitable intermediates in INOC and there is a great need to develop new methods to avoid using them.

(12) (a) Chesney, A.; Marko, I. E. *Synth. Commun.* **1990**, *20*, 3167–3180. (b) Marko, I. E.; Chesney, A. *Synlett* **1992**, 275–278. (c) Marko, I. E.; Southern, J. K.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 4657–4660.

(13) Noguchi, M.; Okada, H.; Tanaka, M.; Matsumoto, S.; Kakehi, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 917–925.

SCHEME 6



In the further investigation, a novel two-step conversion of alcohols into oximes reported by Fukuyama[14] drew our attention, by which the aldehyde oxime can be prepared without using the corresponding aldehyde. This method has a wide range of substrates,[14,15] but no 3-(*N*,*N*-dialkylamino)propanol (**11**) was determined as a substrate. Thus, we tried to use this method for the preparation of the required oxime **13a** from alcohol **11a**.

As shown in Scheme 6, **11a** was prepared in 95% yield by a normal alkylation of (***R***)**-5a·HCl** and $ClCH_2CH_2CH_2OH$. Following Fukuyama's step, when **11a** was treated with TsNHOTBS under Mitsunobu conditions at 0 °C for 1 h, its hydroxyl group was substituted by *N*-Ts-*N*-OTBS-amino group to give the intermediate **12a** in 98% yield. As was expected, the desired product **13a** was produced in 94% yield by treatment of **12a** with CsF in MeCN.

To generalize this method, different 3-(*N*,*N*-dialkylamino)-propanols **11b**−**11k** were tested under the similar conditions. As shown in Table 1, all of them were converted into the corresponding tosylamides **12b**−**12k** in excellent yields under Mitsunobu conditions. In *N*-detosylation, the acyclic amines **12b-12f** gave the corresponding 3-(*N*,*N*-dialkylamino)propanal oximes **13b**−**13f** in high yields. The double bonds in those substrates stayed intact in both steps. When cyclic amines **11g**−**11k** were used as substrates, desired products **13g**−**13k** were obtained in moderate to high yields. Since numerous biologically important alkaloids are polycycles with different types and sizes, therefore, the successful syntheses of **13g**−**13k** provides a new pathway to build their skeletons.

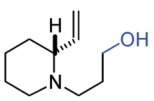
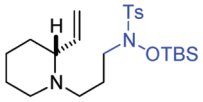
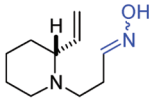
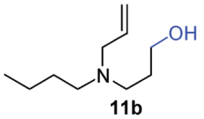
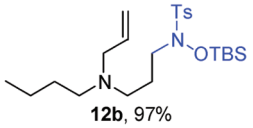
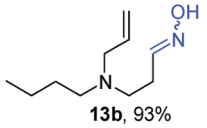
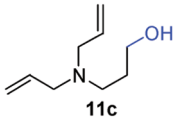
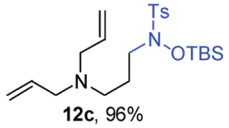
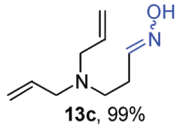
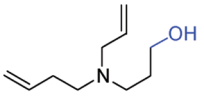
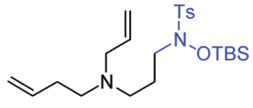
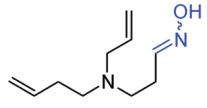
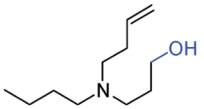
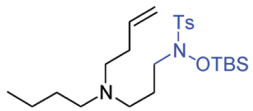
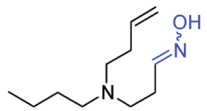
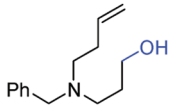
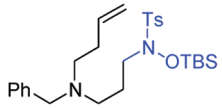
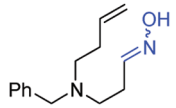
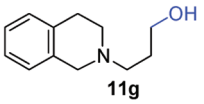
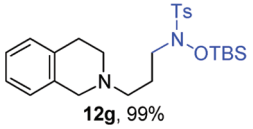
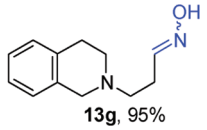
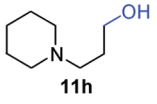
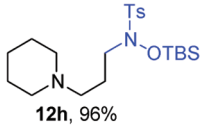
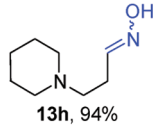
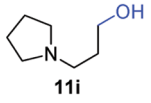
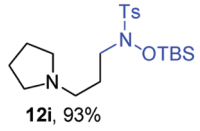
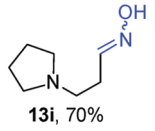
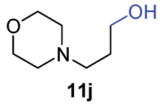
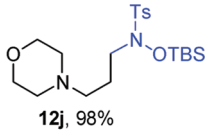
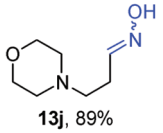
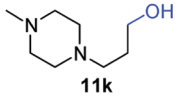
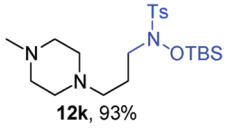
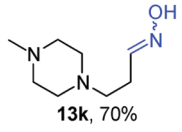
INOC of (*R*)-(2-Vinylpiperid-1yl)propanal Oxime (13a). Oxidative INOC usually proceeds in the presence of an oxidant, by which the oxime is oxidized to the corresponding nitrile oxide. Although many oxidants[8] have been reported for this purpose, there is no general rule to follow. Thus, different oxidants were tested by using oxime **13a** as a model substrate. We found that **13a** was almost inert to chloramine-T under the reference conditions,[9d] but it was completely decomposed by $PhI(OAc)_2$/TFAA[16] within 30 min. When **13a** was treated with NCS for 72 h, the expected product **14a** was obtained in only 28% yield.[9c] To our delight, the simplest oxidant NaOCl[9a,f] gave the best result. As shown in Scheme 7, after the mixture of

(14) Kitahara, K.; Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 2259–2261.

(15) (a) Rai, G.; Thomas, C. J.; Leister, W.; Maloney, D. J. *Tetrahedron Lett.* **2009**, *50*, 1710–1713. (b) Singh, M. K.; Lakshman, M. K. *J. Org. Chem.* **2009**, *74*, 3079–3084.

(16) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539–1542.

TABLE 1. Preparation of 3-(*N*,*N*-Dialkylamino)propanal Oximes 13a−13k[a]

Entry	11a-11k	12a-12k	13a-13k
1	 **11a**	 **12a**, 98%	 **13a**, 94%
2	 **11b**	 **12b**, 97%	 **13b**, 93%
3	 **11c**	 **12c**, 96%	 **13c**, 99%
4	 **11d**	 **12d**, 96%	 **13d**, 93%
5	 **11e**	 **12e**, 97%	 **13e**, 93%
6	 **11f**	 **12f**, 96%	 **13f**, 98%
7	 **11g**	 **12g**, 99%	 **13g**, 95%
8	 **11h**	 **12h**, 96%	 **13h**, 94%
9	 **11i**	 **12i**, 93%	 **13i**, 70%
10	 **11j**	 **12j**, 98%	 **13j**, 89%
11	 **11k**	 **12k**, 93%	 **13k**, 70%

[a]Isolated yields were obtained.

13a and NaOCl (10% aqueous solution) in CH_2Cl_2 was stirred at room temperature for 2 h, a single product **14a** was obtained in 88% yield. Since its two chiral carbons were formed in separated steps, **14a** was easily confirmed to be an enantiopure product by its ^1H and ^{13}C NMR spectra. The favored transition state **17** was proposed because the new formed chiral carbon has *R*-configuration [it was deducted from the final product (+)-epilupinine (**2**)].

SCHEME 7

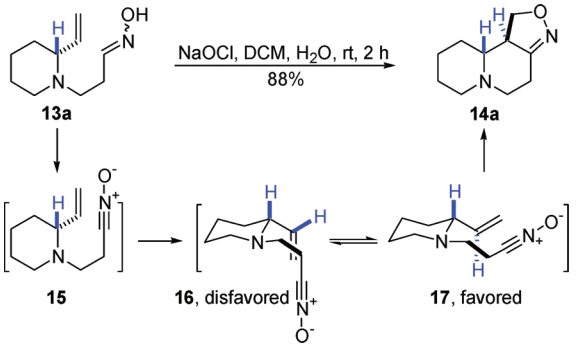
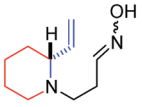
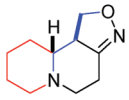
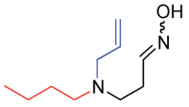
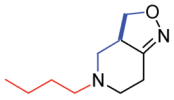
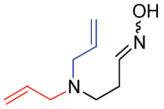
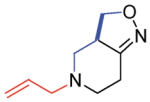
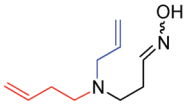
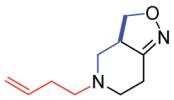
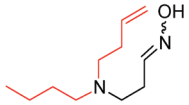
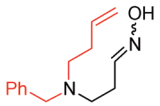


TABLE 2. Chemo- and Stereoselective INOC of 13a−13f[a]

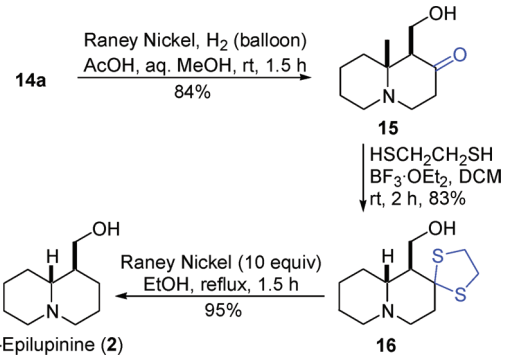
Entry	13a-13f	14a-14d
1	 13a	 14a, 88%
2	 13b	 14b, 90%
3	 13c	 14c, 86%
4	 13d	 14d, 85%
5	 13e	No desired product
6	 13f	No desired product

[a]Isolated yields were obtained.

Thus, the oximes **13b−13f** were treated with aqueous NaOCl by the similar procedure. As shown in Table 2, the desired cyclic product **14b** was obtained in 90% yield from **13b** (entry 2). When *N*,*N*-diallyl **13c** was used as a substrate, one allyl group involved in INOC reaction and another one stay intact (entry 3). In entry 4, the *N*-allyl group in **13d** took a highly chemoselective INOC to give **14d** in 85% yield, while the *N*-butene group stayed intact. It was not surprise that **13e−13f** could not give desired seven-membered ring products (entries 5 and 6).

Total Synthesis of Natural Alkaloid (+)-Epilupinine (2). So far, we have successfully overcome all three obstacles in the total synthesis of (+)-epilupinine (**2**). As shown in Scheme 8, when **14a** was routinely treated by Raney nickel in the presence of HOAc, its 4,5-dihydroisoxazole was cleaved to

SCHEME 8



give desired product **15** in 84% yield. Then, **15** was smoothly converted into *S,S*-ketal **16** by reaction with ethane-1,2-dithiol. Finally, **16** was subjected to a highly efficient Raney nickel promoted desulfurization to give the target product (+)-epilupinine (**2**) in 95% yield. Since the stereochemistry of (+)-epilupinine (**2**) has been well established in literature,[7,17] its structure was confirmed easily by its optical rotation data and NMR spectra. Thus, the total synthesis of enantiopure **2** was accomplished in nine steps [starting from (*R*)-**3**] and in 48% overall yield.

Conclusion

Total synthesis of enantiopure (+)-epilupinine was accomplished in nine steps and in 48% overall yield by using INOC as the key step for the construction of the quinolizidine skeleton. Three obstacles to hamper this total synthesis were overcome efficiently. Prominent among them is the preparation of (*R*)-(2-vinylpiperid-1-yl)propanal oxime (**13a**) from (*R*)-(2-vinylpiperid-1-yl)propanol (**11a**), by which (*R*)-(2-vinylpiperid-1-yl)propanal (**10**) was avoided to using as an essential intermediate because it is a highly unstable Michael adduct and its preparation is an extremely difficult task. Finally, a general method was developed for highly efficient conversion of 3-(*N*,*N*-dialkylamino)propanols into the corresponding 3-(*N*,*N*-dialkylamino)propanal oximes without using the corresponding aldehydes. Since numerous natural alkaloids are nitrogen-bridged polycycles, it is expected that the method will promote the application of INOC in total syntheses of alkaloids in future.

Experimental Section

The starting material **3**[18] and the intermediate **4**[10b] were prepared by the reference methods.

Preparation of (*R*)-2-Vinylpiperidine Hydrochloride [(*R*)-5·HCl]. To a cold solution (ice−water bath) of compound **4** (1.02 g, 3 mmol) in dry THF (20 mL) was added $LiAlH_4$ (170 mg, 4.5 mmol) under N_2. After the reaction was stirred at 0 °C for 30 min (monitored by TLC), a saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction. Then the resultant mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O and brine and dried over Na_2SO_4.

(17) Koziol, A. E.; Gdaniec, M.; Kosturkiewicz, Z. *Acta Crystallogr.* **1980**, *B36*, 982–983.

(18) (a) Dong, Y.; Li, R.; Lu, J.; Xu, X.; Wang, X.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 8617–8620. (b) Wang, X.; Dong, Y.; Sun, J.; Li, R.; Xu, X.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897–1900.

After removal of the solvent, the residue was diluted by a solution of THF (4 mL), CH_3OH (4 mL) and aq NaOH (6.0 M, 2 mL). The resultant mixture was stirred at 60 °C for 6 h and then was cooled to room temperature. It was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. After the solid was filtered off, the filtrate was immediately treated with saturated solution of HCl in MeOH (6 mL) at 0 °C for 30 min. Then, the solvent was removed in vacuum and the residue was recrystallized from MeOH-Et_2O to give product (***R*)-5·HCl** as a white crystal (410 mg, 93%). It had mp 199−200 °C (MeOH−Et_2O). $[\alpha]_D^{20}$ = +5.5 (c 0.2, $CHCl_3$); IR: *v* 3440, 2983, 1252, 1013 cm^{-1}. ^1H NMR: δ 9.53−9.40 (m, 2H), 6.13−6.02 (m, 1H), 5.56−5.37 (m, 2H), 3.60−3.43 (m, 2H), 2.95−2.88 (m, 1H), 2.04−1.82 (m, 5H), 1.55−1.52 (m, 1H). ^{13}C NMR: δ 133.3, 120.5, 58.1, 44.2, 28.1, 21.8, 21.5. MS *m*/*z* (%): 111 (M^+ − HCl, 1.71), 84 (100). Anal. calcd for $C_7H_{14}ClN$: C, 56.94; H, 9.56; N, 9.49. Found: C, 56.67; H, 9.43; N, 9.66.

Preparation of (*R*)-3-(2-Vinylpiperidin-1-yl)propan-1-ol (11a). The mixture of compound **(*R*)-5·HCl** (2.00 g, 13.5 mmol), $ClCH_2CH_2CH_2OH$ (1.42 g, 15 mmol), dry K_2CO_3 (4.14 g, 30 mmol) and KI (2.49 g, 15 mmol) in acetone (50 mL) was refluxed for 2 h. Then the solid was filtrated off and the solvent was evaporated. The residue was purified by chromatography (silica gel, EtOAc) to give 2.18 g (95%) of product **11a** as a colorless oil, $[\alpha]_D^{20}$ = +76.4 (c 0.2, $CHCl_3$). IR: *v* 3387, 2933, 2857, 1053 cm^{-1}. ^1H NMR: δ 5.78−5.67 (m, 1H), 5.49 (s, 1H), 5.10−4.99 (m, 2H), 3.70−3.63 (m, 2H), 3.10−2.87 (m, 2H), 2.53−2.48 (m, 1H), 2.23−2.14 (m, 1H), 1.86−1.25 (m, 9H). ^{13}C NMR: δ 141.0, 116.0, 66.9, 64.2, 54.9, 51.7, 33.5, 27.1, 25.5, 23.3. MS *m*/*z* (%): 169 (M^+, 1.87), 124 (100). Anal. calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.21; H, 11.24; N, 8.32.

Preparation of *N*-[(2*R*)-2-Vinyl-1-piperidine-propyl]-*N*-[(*tert*-butyl-dimethylsilyl)oxy]-4-methyl-benzenesulfonamide (12a), a Typical Procedure of Mutsunobu Reaction. To a stirred solution of **11a** (508 mg, 3 mmol), TsNHOTBS (915 mg, 3.15 mmol), PPh_3 (1.58 g, 6 mmol) and THF (3 mL) in toluene (9 mL) was added a solution of DEAD (784 mg, 4.5 mmol) in toluene (3 mL) at 0 °C under N_2. One hour later, the solvent was removed to give a residue, which was purified by chromatography (silica gel, 10% EtOAc in PE) to give 1.33 g (98%) of product **12a** as a colorless oil, $[\alpha]_D^{20}$ = +21.0 (c 0.2, $CHCl_3$). IR: *v* 2932, 2856, 1465 cm^{-1}. ^1H NMR: δ 7.73 (d, *J* = 8.2, 2H), 7.33 (d, *J* = 7.9, 2H), 5.71−5.62 (m, 1H), 5.12−4.98 (m, 2H), 3.02−2.83 (m, 3H), 2.71−2.51 (m, 2H), 2.44 (s, 3H), 2.16−2.06 (m, 1H), 1.97−1.91 (m, 1H), 1.74−1.23 (m, 8H), 0.93 (s, 9H), 0.30 (s, 6H). ^{13}C NMR: δ 144.3, 141.8, 129.9, 129.7 (2C), 129.1 (2C), 115.3, 66.4, 54.3, 52.4, 51.9, 33.5, 25.9 (3C), 25.8, 23.7, 23.5, 21.5, 18.0. −4.4 (2C). MS *m*/*z* (%): 452 (M^+, 1.08), 44 (100). Anal. calcd for $C_{23}H_{40}N_2O_3SSi$: C, 61.02; H, 8.91; N, 6.19. Found: C, 61.25; H, 8.99; N, 6.06.

By similar procedure, 3-aminopropanols **11b−11k** were converted into the corresponding 4-methyl-benzenesulfonamides **12b−12k** (see Supporting Information).

Preparation of (*R*)-2-Vinyl-1-piperidinepropanal Oxime (13a), a Typical Procedure of Oximation. A stirred mixture of compound **12a** (453 mg, 1.0 mmol) and CsF (301 mg, 2 mmol) in MeCN (10 mL) was heated at 60 °C under N_2 for 2 h. After it was cooled to room temperature, saturated aqueous NH_4Cl was added to quench the reaction. The resultant mixture was extracted by EtOAc (3 × 30 mL) and combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by chromatography (silica gel, 30% EtOAc in PE) to give 171 mg (94%, *E*:*Z* = 72:28) of product **13a** as a white crystal. It had mp 43−45 °C (PE/EtOAc), $[\alpha]_D^{20}$ = +11.2 (c 0.2, $CHCl_3$). IR: *v* 3305, 3179, 3073, 2931, 2854, 2789, 2726 cm^{-1}. ^1H NMR (as a mixture of *E*:*Z* isomers): δ 11.06 (s, br, 1H), 7.37−7.32 (m, 0.28H, minor), 6.70−6.67 (m, 0.72H, major), 5.88−5.74 (m, 1H), 5.18−5.04 (m, 2H), 3.02−2.87 (m, 2H), 2.75−2.63 (m, 1H), 2.62−2.33 (m, 3H), 2.17−2.08 (m, 1H), 1.74−1.45 (m, 5H), 1.37−1.25 (m, 1H). ^{13}C NMR: δ 149.8, 149.1, 140.7, 115.9, 66.2, 66.0, 51.9, 51.7, 51.5, 51.2, 32.8, 25.8, 25.2, 23.5, 21.4. MS *m*/*z* (%): 182 (M^+, 0.42), 124 (100). Anal. calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37; Found: C, 65.95; H, 9.92; N, 15.26.

By similar procedure, 4-methyl-benzenesulfonamides **12b−12k** were converted into **13b−13k** (see Supporting Information).

Preparation of (10a*R*,9b*R*)-Octahydro-1H-isoxazolo[4,3-a]quinolizine (14a), A Typical Procedure of INOC. To a stirred solution of compound **13a** (91 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added an aqueous solution of NaOCl (10%, 0.9 mL) at 0 °C within 30 min. Then the reaction was stirred at room temperature for 2 h (monitored by TLC). After the reaction was quenched by H_2O (20 mL), the resultant mixture was extracted by CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by chromatography (silica gel, 50% EtOAc in PE) to give 79 mg (88%) of product **14a** as a yellowish oil, $[\alpha]_D^{20}$ = −30.4 (c 0.9, $CHCl_3$). IR: *v* 2929, 2856, 2800, 2763 cm^{-1}. ^1H NMR: δ 4.50−4.43 (m, 1H), 3.83−3.77 (m, 1H), 3.08−2.93 (m, 3H), 2.76−2.70 (m, 1H), 2.55−2.45 (m, 1H), 2.20−2.03 (m, 2H), 1.80−1.54 (m, 5H), 1.38−1.16 (m, 2H). ^{13}C NMR: δ 157.7, 70.5, 67.3, 55.2, 55.1, 54.0, 32.3, 25.2, 24.7, 23.4. MS *m*/*z* (%): 180 (M^+, 42.12), 179 (100). Anal. calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54. Found: C, 66.81; H, 8.89; N, 15.42.

By similar procedure, 3-aminopropanal oximes **13b−13d** were converted into **14b−14d** (see Supporting Information).

(1*S*,9a*R*)-Octahydro-1-hydroxymethyl-2*H*-quinolizin-2-one (15). At room temperature, a suspension of compound **14a** (400 mg, 2.22 mmol), Raney nickel (13 mg, 0.22 mmol) and HOAc (1.33 g, 22.2 mmol) in aqueous MeOH (75%, 20 mL) under H_2 (balloon) was vigorously stirred for 1.5 h. Then the reaction was quenched by saturated aqueous Na_2CO_3 (20 mL) and the catalyst was filtrated off. The filtration was extracted with EtOAc (3 × 20 mL) and combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by chromatography (silica gel, EtOAc) to give 342 mg (84%) of product **15** as a white solid. It had mp 69−71 °C (EtOAc), $[\alpha]_D^{20}$ = +8.8 (c 0.04, $CHCl_3$). IR: *v* 3440, 1714, 1092, 647 cm^{-1}. ^1H NMR: δ 3.97−3.93 (m, 1H), 3.74−3.68 (m, 1H), 3.14−3.05 (m, 1H), 3.00−2.96 (m, 1H), 2.83−2.70 (m, 2H), 2.46−2.33 (m, 3H), 2.17−2.07 (m, 2H), 1.98−1.95 (m, 1H), 1.83−1.56 (m, 3H), 1.40−1.20 (m, 2H). ^{13}C NMR: δ 211.9, 63.0, 58.3, 56.6, 55.69, 55.67, 41.7, 31.1, 25.3, 23.3. MS *m*/*z* (%): 183 (M^+, 28.76), 28 (100). Anal. calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.81; H, 9.42; N, 7.56.

(1*S*,9a*R*)-Octahydro-1-hydroxymethyl-spiro[1,3-dithiolane-2,2′-[2*H*]quinolizine] (16). To a solution of compound **15** (293 mg, 1.60 mmol) in dry CH_2Cl_2 was added a mixture of ethane-1,2-dithiol (1.23 mL, 14.7 mmol) in $BF_3 \cdot Et_2O$ (0.46 mL, 3.68 mmol). Two hours later, the reaction was quenched by aqueous NaOH (2.0 M, 3 mL). The resultant mixture was extracted by CH_2Cl_2 (3 × 20 mL) and combined organic layers were washed with H_2O (20 mL) and brine (20 mL) and dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by chromatography (silica gel, EtOAc) to give 344 mg (83%) of product **16** as a white solid. It had mp 128−130 °C (EtOAc), $[\alpha]_D^{20}$ = −13.0 (c 0.1, $CHCl_3$). IR: *v* 3452, 1641, 1048, 1025 cm^{-1}. ^1H NMR: δ 4.21−4.17 (m, 1H), 3.90−3.86 (m, 1H), 3.39−3.23 (m, 4H), 2.94−2.77 (m, 3H), 2.47−2.24 (m, 2H), 2.16−1.95 (m, 4H), 1.82−1.73 (m, 2H), 1.65−1.52 (m, 2H), 1.38−1.14 (m, 2H). ^{13}C NMR: δ 71.8, 63.7, 61.3, 56.3, 55.2, 52.7, 44.9, 39.3, 38.7, 29.9, 25.3, 24.2. MS *m*/*z* (%): 259 (M^+, 28.33), 97 (100). Anal. calcd for $C_{12}H_{21}NOS_2$: C, 55.56; H, 8.16; N, 5.40. Found: C, 55.51; H, 8.17; N, 5.44.

Preparation of (+)-Epilupinine (2). A suspension of compound **16** (260 mg, 1.00 mmol), Raney nickel (secondary grad, 900 mg, 15.3 mmol) in anhydrous EtOH (20 mL) was refluxed for 1.5 h. After the reaction was cooled to room temperature, the catalyst was filtrated off. Removal of the solvent gave a residue, which was purified by

chromatography (silica gel, 25% MeOH in EtOAc) to give 161 mg (95%) of product **2** as a white solid. It had mp 77−79 °C (lit.[7b,g] 78−79 °C), $[\alpha]_D^{20} = +31.8$ (c 0.60, EtOH) [lit.[7b] $[\alpha]_D^{20} = +32.6$ (c 0.72, EtOH), lit.[7g] $[\alpha]_D^{22} = +31.2$ (c 0.86, EtOH)]. IR: *v* 3183, 2929, 2860, 1064 cm^{-1}. ^1H NMR: δ 3.62−3.56 (m, 1H), 3.50−3.45 (m, 1H), 2.77−2.69 (m, 2H), 2.33 (s, br, 1H), 2.00−1.50 (m, 9H), 1.38−1.28 (m, 1H), 1.26−1.11 (m, 4H). ^{13}C NMR: δ 64.4, 64.3, 56.8, 56.6, 43.9, 29.7, 28.2, 25.5, 24.9, 24.5. MS *m*/*z* (%): 169 (M^+, 42.96), 83 (100). Anal. calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.91; H, 11.34; N, 8.23.

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Supporting Information Available: Experiments, characterization, ^1H and ^{13}C NMR spectra for products (***R*)-5·HCl**, **11a−11k**, **12a−12k**, **13a−13k**, **14a−14d**, **15**, **16**, and (+)-epilupinine (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.