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A General and Efficient Strategy for 7-Aryloctahydroindole and *cis*-3a-Aryloctahydroindole Alkaloids: Total Syntheses of (±)-γ-Lycorane and (±)-Crinane

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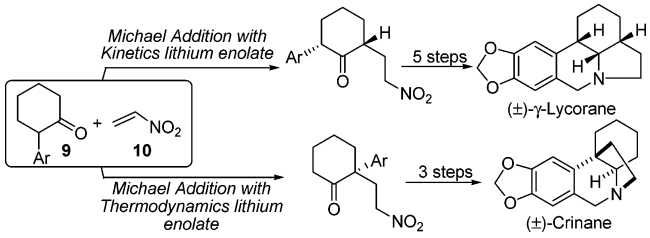

A general and efficient approach to both 7-aryloctahydroindole and *cis*-3a-aryloctahydroindole alkaloids has been developed. The key step involves Michael additions of the corresponding kinetics and thermodynamics lithium enolates of ketone **9** to the versatile building blocks: nitroethylene **10**. Two representative members, (±)-γ-lycorane and (±)-crinane, have been synthesized in 22 and 36% overall yields, respectively.

The lycorine-type and crinine-type alkaloids, which possess 7-aryloctahydroindole and *cis*-3a-aryloctahydroindole nuclei, respectively (as shown in Figure 1), constitute a large class of structurally diverse natural products existing widely in the *Amaryllidaceae* alkaloids,[1] such as γ-lycorane (**1**),[2] lycorine (**2**),[3] and crinine (**4**),[4] as well as some nonnatural products, such as crinane (**3**).[5] Due to their intriguing structures, the wide range of biological activities, and ability to be a proving ground for new strategy and synthetic methods, these two groups of

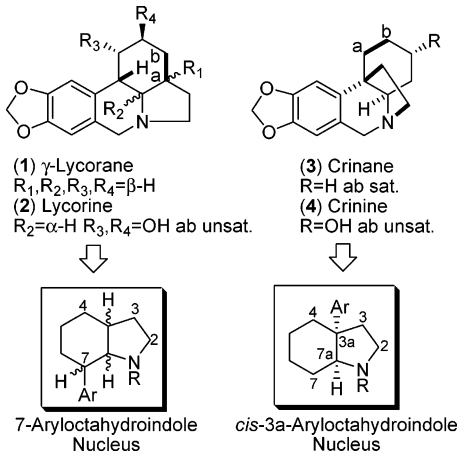

FIGURE 1. Representative lycorine-type and crinine-type alkloids.

alkaloids have been attracting considerable attention from organic chemists over the years. Because establishment of the five-membered nitrogen-containing ring of the above two aryl substituted octahydroindole nuclei is critical, a number of synthetic efforts have emerged to address appropriate "C−C−NH_2" synthons. Up to now, Mitsunobu reaction,[2b,5b] Wadsworth−Emmons reaction,[2e] and nucleophilic displacement[2d] have been intermolecularly utilized to create the "C−C−NH_2" segment. Despite the above strategies for the different "C−C−NH_2" synthons, there have been no reports on the application of the nitroethylene[6] as a key building block for the construction of the above two types of alkaloids.

In connection with our previous investigations, we have recently reported the total syntheses of (±)-crinane and its analogue.[7] This achievement encouraged us to develop other kinds of conceptually new strategies, especially the more general and efficient, for these two types and other more complex alkaloids. Herein, we wish to present a highly concise tactic for both of the above two aryl

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(1) For recent reviews of *Amaryllidacea* alkaloids, see: (a) Martin, S. F. In *The Alkaloids: Chemistry and Physiology*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251. (b) Hoshino, O. *The Alkaloids: Chemistry and Physiology*; Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 51, p 323. (c) Lewis, J. R. *Nat. Prod. Rep*. **1998**, *15*, 107. (d) Jin, Z.; Li, Z. G.; Huang, R. Q. *Nat. Prod. Rep*. **2002**, *19*, 454.

(2) Recent synthesis of γ-lycorane: (a) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016. (b) Bäckvall, J. E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988. (c) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716. (d) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783. (e) Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671. (f) Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, N.; Yamada, K.-i.; Muraoka, O.; Tomioka, K. *Org. Lett*. **2003**, *5*, 1123.

(3) For some previous syntheses of lycorine, see: (a) Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Irie, H.; Tanaka, H.; Takagi, S.; Yamaki, M.; Murata, M. *J. Chem. Soc., Chem. Commun*. **1975**, 933. (b) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K. *Heterocycles* **1979**, *12*, 1475. (c) Sano, T.; Kashiwaba, N.; Tada, J.; Tsuda, Y.; Irie, H. *Heterocycles* **1980**, *32*, 1097. (d) Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634. (e) Boeckman, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250. (f) Umezawa, B.; Hoshino, O.; Sawaki, H.; Mori, K.; Hamada, Y.; Kotera, K.; Iitaka, Y. *Tetrahedron* **1984**, *40*, 1783. (g) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc*. **1996**, *118*, 6210. (h) Hoshino, O.; Ishizaki, M.; Kamei, K.; Taguchi, M.; Nagao, T.; Iwaoka, K.; Sawai, S.; Umezawa, B.; Iitaka, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 571. (i) Martin, S. F.; Tu, C. *J. Org. Chem.* **1981**, *46*, 3763. (j) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc*. **1993**, *115*, 7904.

(4) For some previous syntheses of crinine, see: (a) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670. (b) Whitlock, H. W.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600. (c). Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184. (d) Pearson, W. H.; Lovering, F. E. *J. Org. Chem*. **1998**, *63*, 3607.

(5) For some previous syntheses of crinane, see: (a) Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. H. *J. Org. Chem*. **2001**, *66*, 3119. (b) Schkeryantz, J. M.; Pearson, W. H. *Tetrahedron* **1996**, *52*, 3107. (c) Keck, G. E.; Webb, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3173. (d) Song, Z.-L.; Wang, B.-M.; Tu, Y.-Q.; Fan, C.-A.; Zhang S.-Y. *Org. Lett*. **2003**, *5*, 2319.

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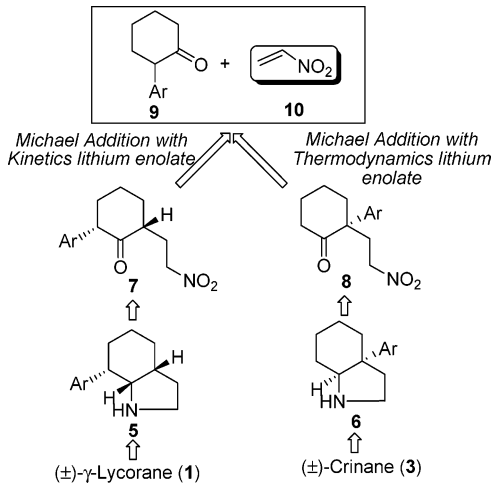
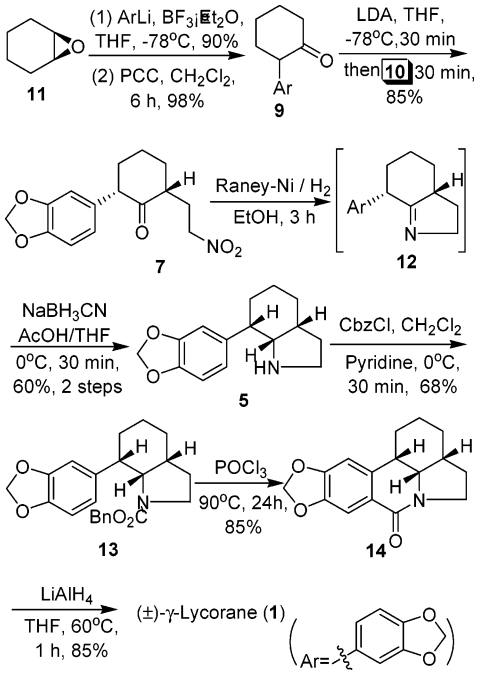
SCHEME 1. Retrosynthetic Analysis of (±)-γ-Lycorane and (±)-Crinane



substituted octahydroindole nuclei and its application to the total synthesis of (±)-γ-lycorane (**1**) and (±)-crinane (**3**) from the same starting compound. Meanwhile, it is worthy to note that, as the powerful acceptor of the strategy key Michael addition reaction, nitroethylene[6] is a particularly versatile building block and can serve as the needed "C−C−NH_2" synthon.[8] Herein, we hope this work will enrich and expand its present limited utility in organic chemistry,[9] especially the total synthesis of natural products.

Our retrosynthetic considerations (Scheme 1) on **1** and **3** were focused on establishment of 7-aryloctahydroindole **5** and *cis*-3a-aryloctahydroindole **6**, which can be converted to the target molecules by some facile steps. In turn, **5** and **6** might be prepared from γ-nitro carbonyl compounds **7** and **8** through several transformations involving the reductive cyclization and further reduction. As the key strategy level step, Michael additions to

SCHEME 2. Total Synthesis of (±)-γ-Lycorane



nitroethylene **10** using the corresponding kinetics and thermodynamics lithium enolates of ketone **9** would provide the desired precursors **7** and **8**, respectively. Thus, two different routes were connected and could be started from the same starting materials.

Initially, we selected (±)-γ-lycorane (**1**), possessing the basic structural elements of lycorine-type alkaloids, as an optimal target to test our strategy. As demonstrated in Scheme 2, 2-arylcyclohexanone **9**[10] could be readily synthesized from the commercially available cyclohexene oxide **11** in 88% overall yield via two steps involving the nucleophilic addition promoted by $BF_3{\cdot}Et_2O$[11] and oxidation of the formed alcohol by PCC. With **9** in hand, the key Michael reaction was then investigated. As expected, subjection of the kinetics lithium enolates of ketone **9** to the nitroethylene **10**[12] gave rise to the desired γ-nitro carbonyl compounds as a 25:1 mixture of diastereoisomers in 85% combined yield, and the major isomer **7**[13] was easily isolated by silica gel column chromatography. The following reductive cyclization of γ-nitro carbonyl compound **7** with Ni−Raney/H_2 led to the unstable cycloimine **12**, which was transformed to the amine **5** directly by further reduction with $NaBH_3CN$.[2b] Unfortunately, attempted direct conversion of **5** to γ-lycorane (**1**) by Pictet−Spengler cyclization using either Eschenmoser's salt or paraformaldehyde and CF_3COOH was unsuccessful to result in recovery of starting material **5**. Then, treatment of **5** with benzyl chloroformate in the presence of pyridine afforded carbamate **13**, which is the

(6) Historically, the utility of nitroolefins in conjugate addition reactions has been limited by their facile polymerization in the presence of nucleophiles. For the successful addition of ketones to nitroolefins via their lithium enolates, enol silanes, enol ethers, or enamines, see: (a) Yoshikoshi, A.; Mayashita, M. *Acc. Chem. Res.* **1985**, *18*, 284. (b) Brook, M. A.; Seebach, D. *Can. J. Chem*. **1987**, *65*, 836. (c) Seebach, D.; Brook, M. A. *Helv. Chim. Acta* **1985**, *68*, 319. (d) Seebach, D.; Leitz, H. F.; Ehrig, V. *Chem. Ber.* **1975**, *108*, 1924. (e) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413. (f) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637. (g) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857. (h) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem*. **1993**, *58*, 1859. (i) Denmark, S. E.; Senanayake, C. B. W. *J. Org. Chem*. **1993**, *58*, 1853. (j) Cory, R. M.; Anderson, P. C.; Bailey, M. D.; McLaren, F. R.; Renneboog, R. M.; Yamamoto, B. R. *Can. J. Chem*. **1985**, *63*, 2618. (k) Cory, R. M.; Anderson, P. C.; McLaren, F. R.; Yamamoto, B. R. *J. Chem. Soc., Chem. Commun*. **1981**, 73. (l) Bradamente, P.; Pitacco, G.; Risaliti, A.; Valentin, E. *Tetrahedron Lett.* **1982**, *23*, 2683. (m) Flintoft, R. J.; Buzby, J. C.; Tucher, J. A. *Tetrahedron Lett.* **1999**, *40*, 4485. For synthetic utility of nitroethylene, see: (n) Glassco, W.; Suchocki, J.; George, C.; Martin, B. R. May, E. L. *J. Med. Chem.* **1993**, *36*, 3381. (o) Johnson, M. R.; Fazio, M. J.; Ward, D. L.; Sousa, L. R. *J. Org. Chem*. **1983**, *48*, 494.

(7) (a) Song, Z.-L.; Wang, B.-M.; Tu, Y.-Q.; Fan, C.-A.; Zhang, S.-Y. *Org. Lett*. **2003**, *5*, 2319. (b) Fan, C.-A.; Tu, Y.-Q.; Song, Z.-L.; Zhang, E.; Shi, L.; Wang, M.; Wang, B.; Zhang, S.-Y. *Org. Lett*. **2004**, *6*, 4691.

(8) (a) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (b) Perlmutter, P. *Conjugate Addition in* Organic Synthesis; Tarrytown, NY, 1992.

(9) The utility of nitroethylene as a key building block for the construction of *Aspidosperma* alkaloids has been reported by the Dugat group: Nora, B. M.; Dugat, D.; Gramain, J. C.; Husson, H. P. *J. Org. Chem.* **1993**, *58*, 6457.

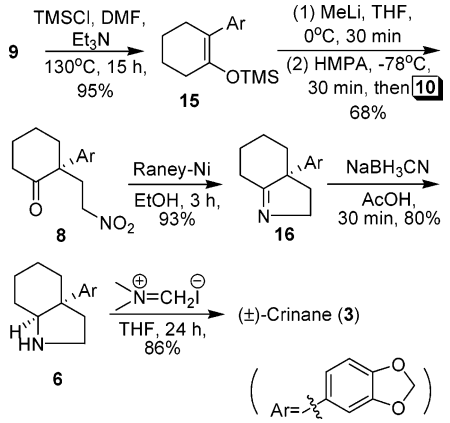
(10) (a) Bunsuke U.; Osamu H.; Shohei S.; Seiichi S.; Naganori N. *J. Org. Chem.* **1977**, *42*, 4272. (b) Hoshino, O.; Sawaki, S.; Shimamura, N.; Onadera, A.; Umezawa, B. *Chem. Pharm. Bull.* **1987**, *35*, 2734.

(11) Eis, M. J.; Wrobel, J. E.; Ganem B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

(12) For preparation of nitroethylene, see: Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem*. **1980**, *45*, 1185.

(13) The stereochemical assignment of **7** was confirmed by the spectral properties of further reaction products **5** which were in agreement with those previously reported.

SCHEME 3. Total Synthesis of (±)-Crinane



known intermediate for the synthesis of **1**.[2b] Finally, the total synthesis of **1** was accomplished according to the reported sequence through Bischler−Napieralski cyclization and the final lithium aluminum hydride reduction.[2b]

The successful synthesis of (±)-γ-lycorane **1** encouraged us to focus on another more challenging molecule, (±)-crinane (**3**), which contains a sterically congested quaternary carbon center located at the hydroindolone bridgehead, and a number of synthetic efforts have emerged to address this problem.[14] As shown in Scheme 3, our synthesis is started from the identical ketone **9**, which could be converted to the thermodynamics silyl enol ethers **15** smoothly according to the reported protocol.[15] By Li−Si exchange reaction of **15** with 1.0 equiv of MeLi,[16] the corresponding thermodynamics lithium enolate was formed, and the subsequent Michael addition to nitroethylene **10** furnished the key intermediate **8** in 68% yield. Following the crucial construction of the quaternary carbon center, the *cis*-3a-aryloctahydroindole core structure **6** was readily obtained via the similar transformations of reductive cyclization and the further reduction in 75% overall yield. Its spectral properties were in agreement with those previously reported.[5b] Finally, according to the reported Pictet−Spengler cyclization procedure, treatment of **6** with Eschenmoser's salt at 40 °C in THF for 24 h yielded (±)-crinane (**3**).

In summary, we have developed a general and highly concise strategy for syntheses of both 7-aryloctahydroindole and *cis*-3a-aryloctahydroindole alkaloids. The key step is the Michael additions to nitroethylene **10** with the corresponding kinetics and thermodynamics lithium enolates of ketone **9**, and the total syntheses of (±)-γ-lycorane and (±)-crinane have been achieved. Application of this methodology to other kinds of more complex alkaloids is currently under investigation in our group.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For recent reviews on stereoselective construction of a quaternary carbon center, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708. (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(15) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120.

(16) (a) Roberk K.; Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 6179. (b) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399.