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Total Synthesis of (±)-α- and β-Lycoranes by Sequential Chemoselective Conjugate Addition–Stereoselective Nitro-Michael Cyclization of an ω-Nitro-α,β,ψ,ω-unsaturated Ester

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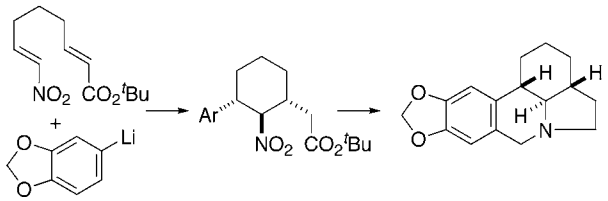
ABSTRACT



An ω-nitro-α,β,ψ,ω-unsaturated ester underwent a chemoselective conjugate addition of a nitroolefin moiety with aryllithium to produce a ψ-aryl-ω-nitro-α,β-unsaturated ester, which was then stereoselectively cyclized by intramolecular nitro-Michael reaction giving a functionalized cyclohexane applicable to the total synthesis of (±)-α- and β-lycoranes.

The Amaryllidaceae alkaloids are a gold mine of pharmaceutical candidates as is evidenced by galanthamine, whose hydrobromide salt, galamtamine, is currently in clinical trial for the treatment of Alzheimer's disease.[1] Lycoranes **1** (α) and **2** (β) are deoxygenated skeletons of this class alkaloid lycorine **3**[2] and were converted from **3** by Kotera early in 1960s (Figure 1).[3,4] The class of its attracts wide attention of synthetic chemists because of challenging tetracyclic galanthan skeleton[5−8] and potent biological activities.[9]

We have recently discovered and developed a tandem conjugate addition-cyclization protocol for α,β,ψ,ω-unsatur-

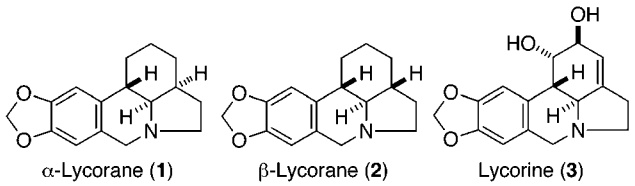


Figure 1. Lycoranes **1** and **2** and lycorine **3**.

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(1) (a) Holl, G.; Straschill, M.; Thomsen, T.; Fischer, J. P.; Kewitz, H. *Electroencephalogr. Clin. Neurophysiol.* **1992**, *82*, 445−452. (b) WHO Drug Information **1998**, *12*, 205.

(2) (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251−376. (b) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 79−84. (c) Lewis, J. R. *Nat. Prod. Rep.* **1995**, *11*, 339−345. (c) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, pp 323−424.

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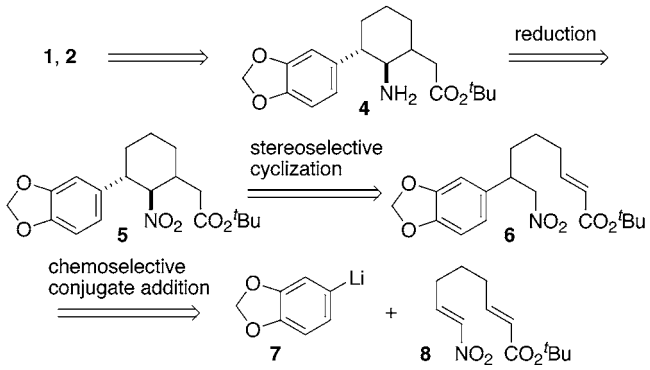
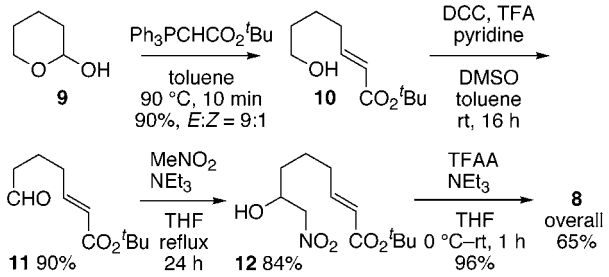
ated bisphosphonate and bisphosphine oxide[10] as well as a tandem conjugate addition-aldol cyclization method for ω-oxo-α,β-unsaturated esters.[11] We have also been involved in development of catalytic asymmetric conjugate addition methodologies[12] of carbo-[13] and heteronucleophiles.[14] We describe herein development of a novel chemoselective conjugate addition[15,16] of aryllithium **7** to a nitroolefin[17] moiety of an ω-nitro-α,β,ψ,ω-unsaturated ester **8** and subsequent stereoselective intramolecular nitro-Michael cyclization reaction[18] of an adduct **6** affording **5** and its application to a total synthesis of **1** and **2** via **4** (Scheme 1).

Scheme 1. Synthetic Strategy of Lycoranes Based on Chemoselective Conjugate Addition−Stereoselective Intramolecular Nitro-Michael Cyclization Reaction of **8** with **7**



An ω-nitro-α,β,ψ,ω-unsaturated ester **8** was prepared by the modified procedure developed by Denmark[19] (Scheme 2). Wittig reaction of **9** gave an alcohol **10**, which was then

Scheme 2. Synthesis of ω-Nitro-α,β,ψ,ω-Unsaturated Ester **8** in Four Steps from **9**



oxidized by the Pfitzner−Moffat method to give an aldehyde **11** after chromatographical separation of *Z*-isomer. Nitroaldol reaction of **11** with nitromethane was catalyzed by triethylamine and was followed by dehydration with trifluo-

(3) **1**: (a) Takeda, K.; Kotera, K.; Mizukami, S.; Kobayashi, M. *Chem. Pharm. Bull*. **1960**, *8*, 483−486. **2**: (b) Kotera, K. *Tetrahedron* **1961**, *12*, 240−247. γ- and δ-lycoranes: (c) Kotera, K. *Tetrahedron* **1961**, *12*, 248−261.

(4) Tsuda, Y.; Isobe, K. *J. Synth. Org. Chem. Jpn*. **1976**, *34*, 625−640.

(5) Synthesis of **3**: (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**, 933−934. (b) Møller, O.; Steinberg, E.-M.; Torssell, K. *Acta Chem. Scand., Sect. B* **1978**, *32*, 98−104. (c) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K. *Heterocycles* **1979**, *12*, 1475−1478. (d) Sano, T.; Kashiwaba, N.; Tada, J.; Tsuda, Y.; Irie, H. *Heterocycles* **1980**, *32*, 1097−1100. (e) Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634−3643. (f) Boeckman, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250−8252. (g) Umezawa, B.; Hoshino, O.; Sawaki, H.; Mori, K.; Hamada, Y.; Kotera, K.; Iitaka, Y. *Tetrahedron* **1984**, *40*, 1783−1790. (h) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc*. **1996**, *118*, 6210−6219. (i) 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**, 571−580.

(6) Synthesis of **1**: (a) Hill, R. K.; Joule, J. A.; Loerrler, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 1−4956. (b) Umezawa, B.; Hoshino, O.; Sawaki, S. Sato, S.; Numao, N. *J. Org. Chem.* **1977**, *26*, 4272−4275. (c) Tanaka, H.; Nagai, Y.; Irie, H.; Uyeo, S.; Kuno, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 874−878. (d) Wang, C.-L. J.; Ripka, W. C.; Confalone, P. N. *Tetrahedron Lett*. **1984**, *25*, 4613−4616. (e) Bäckwell, J.-E.; Anderson, G. B. S.; Goggoll, A. *J. Org. Chem.* **1991**, *56*, 2988−2993. (f) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139−3140. (g) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569−10582. (h) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 1135−1138. (i) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537−5545. See also ref 5e.

(7) Synthesis of **2**: see refs 5e, 6a, and 6c.

(8) Recent synthesis of γ-lycorane: (a) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016−2021. (b) Cossy, J.; Tresnard, L.; Pard, D. G. *Eur. J. Org. Chem.* **1999**, *1925*, 5−1933. (c) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716−1724.

(9) Yui, S.; Mikami, M.; Kitahara, M.; Yamazaki, M. *Immunopharmacology* **1998**, *40*, 151−162.

(10) (a) Nagaoka, Y.; Tomioka, K. *Org. Lett*. **1999**, *1*, 1467−1469. (b) Nagaoka, Y.; Inoue, H.; Nawal, E.-K.; Tomioka, K. *Chem. Commun*. **2002**, 122−123. (c) Inoue, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem*. **2002**, *67*, 5864−5867. (d) Nagaoka, Y.; Nawal, El-K.; Uesato, S.; Tomioka K. *Tetrahedron Lett*. **2002**, *43*, 4355−4359.

(11) (a) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K.*Tetrahedron Lett*. **1999**, *40*, 6979−6982. (b) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem*. **2001**, *66*, 8199−8203. (c) Nishimura, K.; Tsubouchi, H.; Ono, M.; Hayama, T.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett*. **2003**, *44*, 2323−2326.

(12) (a) Tomioka, K. *Synthesis* **1990**, 541−549. (b) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, Chapter 31. (c) Tomioka, K. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 12. (d) Iguchi, M.; Yamada, K.; Tomioka, K. In *Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer: Heidelberg, in press.

(13) (a) Tomioka, K.; Shindo, M.; Koga. K. *J. Am. Chem. Soc*. **1989**, *111*, 8266−8268. (b) Kanai, M.; Tomioka, K. *Tetrahedron Lett*. **1995**, *36*, 4273−4274, (c) Shindo, M.; Koga, K.; Tomioka K. *J. Org. Chem*. **1998**, *63*, 9351−9357. (d) Asano, Y.; Yamashita, M.; Nagai, K.; Kuriyama, M.; Yamada K.; Tomioka, K. *Tetrahedron Lett*. **2001**, *42*, 8493−8495. (e) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc*. **2002**, *124*, 8932−8939.

(14) (a) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc*. **1997**, *119*, 12974−12975. (b) Nishimura, K.; Tomioka, K. *J. Org. Chem*. **2002**, *67*, 431−434. (c) Tanaka, Y.; Nishimura, K.; Tomioka, K. *Heterocycles* **2002**, *58*, 71−73. (d) Nishimura, K.; Tomioka, K. *Yakugaku Zasshi* **2003**, *123*, 9−18. (e) Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc*. **2003**, *125*, in press.

(15) Review on asymmetric Michael additions to nitroalkenes: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem*. **2002**, 1877−1894.

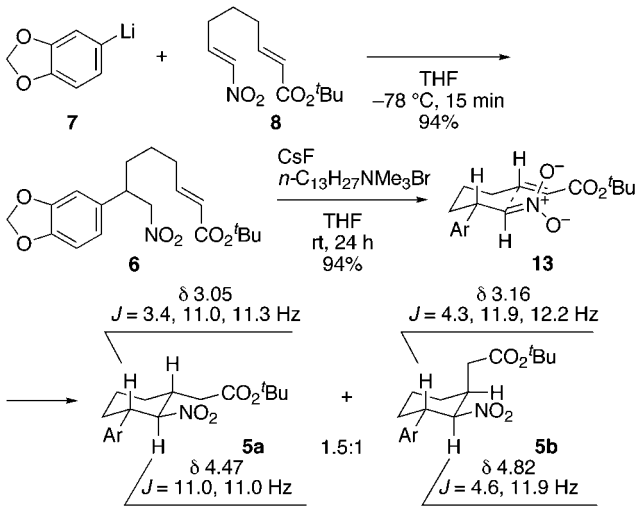
(16) Conjugate addition of nitroalkene: (a) Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chem. Acta* **1979**, *62*, 2695−2698. (b) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305−2324. (c) Sewald, N.; Wendish, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341−1344. (d) Versleijer, J. P. G.; van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett*. **1999**, *40*, 5803−5806. (e) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc*. **2000**, *122*, 10716−10717. (f) Alexakis, A.; Benhaim, C. *Org. Lett*. **2000**, *2*, 2579−2581. (g) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc*. **2001**, *123*, 1004−1005. (h) Alexakis, A.; Benhaim, C.; Rosset, S.; Human, M. *J. Am. Chem. Soc*. **2002**, *124*, 5262−5263. (i) Luchaco-cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 8192−8193. (j) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc*. **2002**, *124*, 11689−11698. (k) Rimkus, A.; Sewald, N. *Org. Lett*. **2002**, *4*, 3289−3291. (l) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773−5778.

(17) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

roacetic anhydride and triethylamine to afford **8** in 65% overall yield from **9**.

Reaction of **8** with 1.5 equiv of **7**, generated by treating the corresponding bromide with butyllithium at −78 °C for 0.5 h, in THF at −78 °C for 15 min gave, after aqueous workup followed by silica gel column chromatography, an adduct **6** as a sole product in 94% yield with perfect chemoselectivity (Scheme 3). No direct cyclization product

Scheme 3. Chemoselective Conjugate Addition and Stereoselective Nitro-Michael Cyclization Reaction of **8** with **7** Giving **6** and **5** via **13**



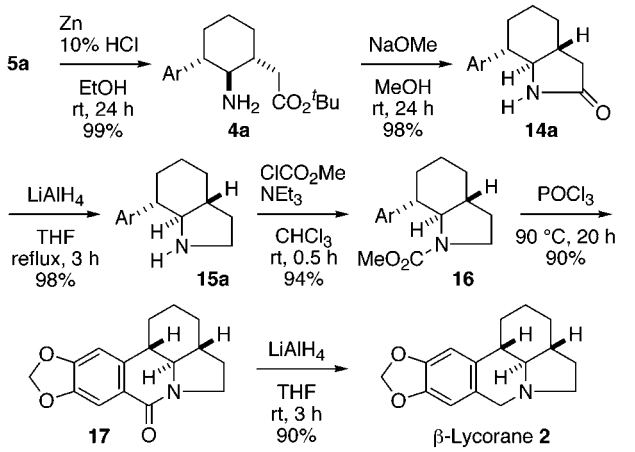
was observed even under forced conditions. Fortunately, intramolecular nitro-Michael cyclization of **6** was possible with 2 equiv of cesium fluoride and 0.1 equiv of myristyltrimethylammonium bromide[18f] in THF at room temperature for 24 h to give, via **13**, a 1.5:1 mixture of only two diastereomers **5a** and **5b** in 94% combined yield among possible four diastereomers. It is worthy to note that the configuration between aryl and nitro groups in **5** is trans, and cis isomer was not observed.

The stereochemistry of **5a** and **5b** was determined by ^{1}H NMR (Scheme 3). Coupling constants of methine protons indicate that all substituents on a cyclohexane ring are equatorial in **5a**, while aryl and nitro groups are equatorial and an acetate group is axial in **5b**.

High diastereoselectivity is attributable to a nitronate intermediate **13** of which conformation is fixed by an allylic strain.[20] Approach of an unsaturated ester moiety to a nitronate takes place anti to an Ar−C bond resulting in trans configuration of aryl and nitro groups.[21]

Crystallization of the 1.5:1 mixture of **5** from chloroform−hexane afforded diastereomerically pure **5a** as colorless cubes of mp 123−125 °C in 43% yield together with a mother liquid in 51% yield (**5a**/**5b** = 1:3). The isolation of pure **5a** encouraged us to proceed to the total synthesis of **2** (Scheme 4). Reduction of a nitro group of **5a** with zinc powder in

Scheme 4. Total Synthesis of (±)-*β*-Lycorane **2** from **5a**



10% aq HCl/ethanol[22] at room temperature for 24 h gave an amine **4a** in 99% yield. Treatment of **4a** with sodium methoxide in methanol at room temperature for 24 h afforded a lactam **14a** in 98% yield. Lithium aluminum hydride reduction of **14a** in THF under reflux for 3 h gave an amine **15a** in 98% yield, which is the known intermediate[5e] for the synthesis of **2**. Unfortunately, attempted direct conversion of **15a** to *β*-lycorane **2** by Pictet−Spengler-type cyclization[6f,22,23] using paraformaldehyde and mineral acids was unsuccessful to result in recovery of starting **15a**. Then, the total synthesis of **2** was accomplished in high yield according to the reported sequence[5e] through methoxycarbonylation, Pictet-type cyclization, and finally lithium aluminum hydride reduction. Spectroscopic data and the melting point[24] of synthetic (±)-**2** were identical with those reported.

α-Lycorane **1** was also synthesized from **5b** (Scheme 5). A 1:3 mixture of **5a** and **5b**, the recrystallization mother liquid of **5**, was treated with zinc powder in 10% aq HCl/ethanol at room temperature for 18 h to give a mixture of chromatographically easily separable amines **4a** and **4b** in 19% and 77% yields, respectively. Treatment of **4b** with sodium methoxide in methanol at room temperature for 48 h gave a lactam **14b** in 88% yield. Lithium aluminum hydride reduction of **14b** in THF under reflux for 2 h gave an amine

(18) Nitro-Michael addition: (a) Baum, K.; Guest, A. M. *Synthesis* **1979**, 311−312. (b) Matsumoto, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1046−1051. (c) Ono, N.; Kamimura, A.; Kaji, A. *Synthesis* **1984**, 226−227. (d) Bergbreiter, D. E.; Lalonde, J. J. *J. Org. Chem.* **1987**, *52*, 1601−1603. (e) Ballini, R.; Bosica, G. *Tetrahedron Lett.* **1996**, *37*, 8027−8030. (f) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257−4259. (g) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555−3560.

(19) Denmark, S. E.; Senanayake, B. W. *J. Org. Chem.* **1993**, *58*, 1835−1858.

(20) (a) Kamimura, A.; Sasatani, H.; Hashimoto, T.; Kawai, T.; Hori, K.; Ono, N. *J. Org. Chem.* **1990**, *55*, 2437−2442. (b) Hori, K.; Higuchi, S.; Kamimura, A. *J. Org. Chem.* **1990**, *55*, 5900−5905.

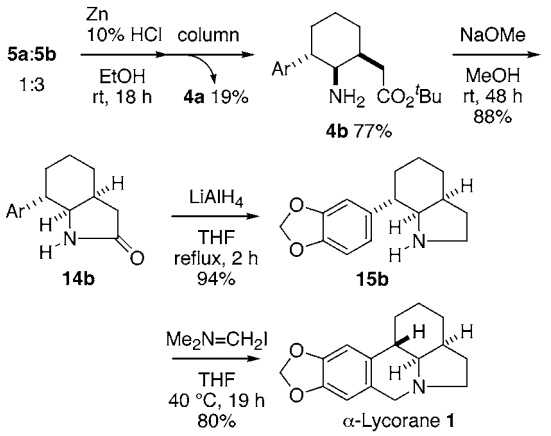
(21) The possibility of thermodynamic control is not excluded.

(22) Michaelides, M. R.; Hong, Y.; DiDomenico, S., Jr.; Bayburt, E. K.; Asin, K. E.; Britton, D. R.; Lin, C. W.; Shosaki, K. *J. Med. Chem.* **1997**, *40*, 1585−1599.

(23) Tomioka, K.; Kubota, Y.; Koga, K. *Tetrahedron Lett.* **1993**, *49*, 1891−1900.

(24) Melting point of (±)-**2**: 86−87 °C (lit.[5e] mp 86−88 °C).

Scheme 5. Total Synthesis of (±)-α-Lycorane **1** from **5b**



15b,[6f] the known synthetic intermediate of **1**, in 94% yield. Pictet−Spengler type cyclization[6f] of **15b** with Eschenmoser's salt gave **1** in 80% yield without any trouble. Spectroscopic data and melting point[25] of synthetic (±)-**1** were identical with those reported.

(25) Melting point of (±)-**1**: 93−94 °C (lit.[5e] mp 92−94 °C).

In conclusion, we have succeeded in the development of a perfectly chemoselective conjugate addition of aryllithium to a nitroolefin moiety of an ω-nitro-α,β,ψ,ω-unsaturated ester and subsequent stereoselective nitro-Michael cyclization reaction producing functionalized cyclohexanes, which were applied to the total synthesis of α-lycorane **1** in 24% through six steps and β-lycorane **2** in 34% overall yields through eight steps from **8**. The synthetic scheme to lycorine on this line seems available by a simple functionalization of **8**. Currently, our focus is a development of asymmetric methodology for synthesis of lycorine.

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

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