ORGANIC LETTERS

2006
Vol. 8, No. 2
247−250

# An Efficient Synthesis of (±)-Lycoricidine Featuring a Stille–IMDAF Cycloaddition Cascade

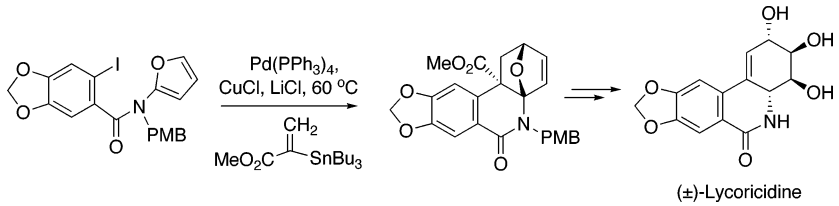
**Hongjun Zhang and Albert Padwa***

*Department of Chemistry, Emory University, Atlanta, Georgia 30322*

*chemap@emory.edu*

**Received October 18, 2005**

## ABSTRACT




**A highly efficient total synthesis of (±)-Lycoricidine is described. The synthesis features the ready preparation of the Lycoricidine skeleton by a Stille–IMDAF cycloaddition cascade. The resulting cycloadduct is then used for the stereocontrolled installation of the other functionality present in the C-ring of the target molecule.**

Many of the lycorine-type *Amaryllidaceae* alkaloids display useful biological properties,[1] and as a consequence this family has captured the interest of a number of synthetic groups as targets for total synthesis.[2] The history of the hydroxylated phenanthridones of the *Amaryllidaceae* group, their biological profiles, and various syntheses have been reviewed on several occasions,[3] most recently by Hudlicky and Rinner in 2005.[4] Lycoricidine (**1**),[5] the structurally related Narciclasine (**2**),[6] as well as Pancratistatin (**3**)[7] and 7-Deoxypancratistatin (**4**)[8] are popular synthetic targets primarily because their heterocyclic framework provides a means to demonstrate the utility of new synthetic strategies.[4] In addition, the narcissus alkaloids are available only in small quantities from natural sources,[9] and their use as therapeutic agents[10] depends on their ready availability. The principle hurdles to their

(1) (a) Hartwell, J. L. *Lloydia* **1967**, *30*, 379. (b) Fitzgerald, D. B.; Hartwell, J. L.; Leiter, J. *J. Nat. Cancer Inst.* **1958**, *20*, 763. (c) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995. (d) Ceriotti, G. *Nature* **1967**, *213*, 595. (e) Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860.

(2) For some leading references, see: (a) Hudlicky, T. *J. Heterocycl. Chem.* **2000**, *37*, 535. (b) Martin, S. F. The Amaryllidaceae Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, Chapter 3, pp 251−376.

(3) (a) Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT; 1997; Vol. 3, p 109. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, p 323. (c) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 606.

(4) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365.

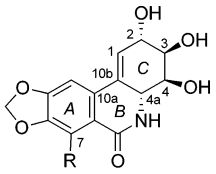
(5) For syntheses of Lycoricidine, see: (a) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2977. (b) Paulsen, H.; Stubbe, M. *Tetrahedron Lett.* **1982**, *23*, 3171. (c) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535. (d) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525. (e) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (f) Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441. (g) Martin, S. F.; Tso, H. H. *Heterocycles* **1993**, *35*, 85. (h) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108. (i) Keck, G. E.; Wager, T. T. *J. Org. Chem.* **1996**, *61*, 8366. (j) Elango, S.; Yan, T. H. *Tetrahedron* **2002**, *58*, 7375.

(6) For syntheses of Narciclasine, see: (a) Mondon, A.; Krohn, K. *Tetrahedron Lett.* **1972**, *13*, 2085. (b) Mondon, A.; Krohn, K. *Chem. Ber.* **1975**, *108*, 445. (c) Krohn, K.; Mondon, A. *Chem. Ber.* **1976**, *109*, 855. (d) Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655. (e) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624. (f) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077.

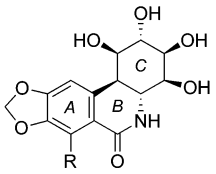
(7) For syntheses of Pancratistatin, see: (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. (b) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643. (c) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143. (d) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (e) Hudlicky, T.; Tian, X. R.; Königsberger, K.; Mauray, R.; Rouden, J.; Fan. B. *J. Am. Chem. Soc.* **1996**, *118*, 10752. (f) Chida, N.; Jitsuoka, M.; Yamamoto, Y.; Ohtsuka, M.; Ogawa, S. *Heterocycles* **1996**, *43*, 1385. (g) Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153. (h) Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509. (i) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341. (j) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583. (k) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343. (l) Ko, H. J.; Park, J. E.; Kim, S. *J. Org. Chem.* **2004**, *69*, 112.

10.1021/ol052524f CCC: $33.50 
**Published on Web 12/16/2005**

synthesis include the introduction of the aryl group and the stereocontrolled construction of the fused BC ring system.



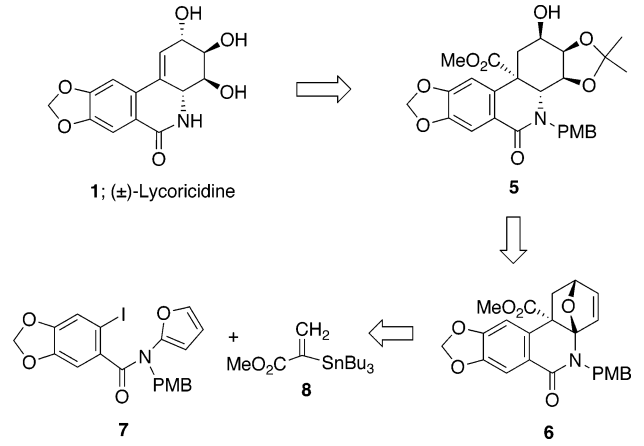
**1;** R = H; Lycoricidine
**2;** R = OH; Narciclasine



**3;** R = OH; Pancratistatin
**4;** R = H; Deoxypancratistatin

A major strategy that is routinely employed for the synthesis of the lycorine group consists of constructing two fragments representing the A and C cycles, which are then coupled together to form the B ring. This approach often involves formation of the *10a-10b* carbon−carbon bond by either a palladium-based[11] or photocyclization[6d] reaction, although other coupling methods have also been used.[3,4] An alternate synthetic route would be the formation of the C-ring from a suitable precursor in which the *10a-10b* bond of the target is already present.[12,13] It is against this background that we report a short and efficient synthesis of (±)-Lycoricidine. Our approach derives from a general program underway in our laboratory that is designed to exploit the facile Diels−Alder reaction of amidofurans for the purposes of natural product synthesis.[14] Our retrosynthetic analysis of (±)-Lycoricidine is shown in Scheme 1 and makes use

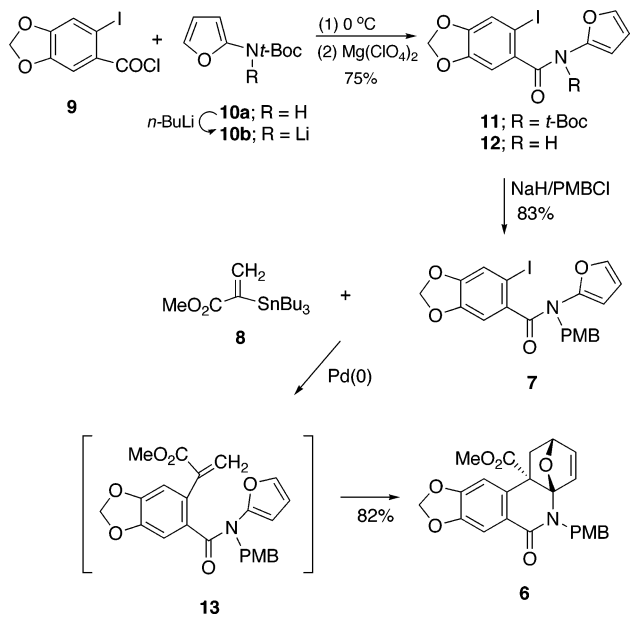
**Scheme 1**



of a tandem cascade sequence consisting of a Stille coupling[15] followed by a spontaneous intramolecular [4 + 2]-cycloaddition of an amidofuran (IMDAF). The resulting cycloadduct **6** is then used for the stereocontrolled installation of the other functionality present in the C-ring of Lycoricidine. The carbomethoxy substituent is utilized as a critical control element not only to facilitate the [4 + 2]-cycloaddition but also to provide a handle for the introduction of the required $\pi$-bond and to set the stereochemistry at the $C_{4a}$-ring juncture.

Our synthesis of amidofuran **7** began by coupling the known acid chloride **9**[16] with the lithiated carbamate **10b** derived by treating furanyl-2-ylcarbamic acid *tert*-butyl ester (**10a**) with *n*-BuLi. Removal of the *t*-Boc protecting group from the resulting carbamate **11** with $Mg(ClO_4)_2$ afforded NH amide **12** in 75% yield, and this was followed by reaction with NaH and *p*-methoxybenzyl chloride to give **7** in 83% yield.[17] The methyl acrylate moiety was introduced by means of a Stille coupling[15] using methyl 2-tri-*n*-butylstannylacrylate[18] (Scheme 2). The optimum conditions for this reaction

**Scheme 2**



were eventually determined to be those described by Corey that utilize a combination of CuCl/Pd(0)/LiCl for the key coupling.[19] The use of DMSO with rigorous exclusion of

(8) (a) Akgun, H.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3081. (b) Rinner, U.; Siengalewicz, P.; Hudlicky, T. *Org. Lett.* **2002**, *4*, 115. (c) Tian, X.; Maurya, R.; Königsberger, K. *Synlett* **1995**, 1125. (d) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164. (e) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (f) Acena, J. L.; Arjona, O.; Leon, M. L.; Plumet, J. *Org. Lett.* **2000**, *2*, 3683.

(9) Pettit, G. R.; Backhaus, R. A.; Boettner, F. E. *J. Nat. Prod.* **1995**, *58*, 37.

(10) (a) Pettit, G. R.; Freeman, S.; Simpson, M. J.; Thompson, M. A.; Boyd, M. R.; Williams, G. R.; Pettit, G. R., III; Doubek, D. L. *Anti-Cancer Drug Des.* **1995**, *10*, 243. (b) Pettit, G. R.; Orr, S.; Ducki, S. *Anti-Cancer Drug Des.* **2000**, *15*, 389.

(11) Grubb, L. M.; Dowdy, A. L.; Blanchette, H. S.; Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1999**, *40*, 2691.

(12) (j) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176.

(13) Khaldi, M.; Chre'tien, F.; Chapleur, Y. *Tetrahedron Lett.* **1995**, *36*, 3003.

(14) (a) Wang, Q.; Padwa, A. *Org. Lett.* **2004**, *6*, 2189. (b) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197. (c) Padwa, A.; Bur, S. K.; Zhang, H. *J. Org. Chem.* **2005**, *70*, 6833.

(15) Farina, V.; Krishnamurphy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

(16) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823.

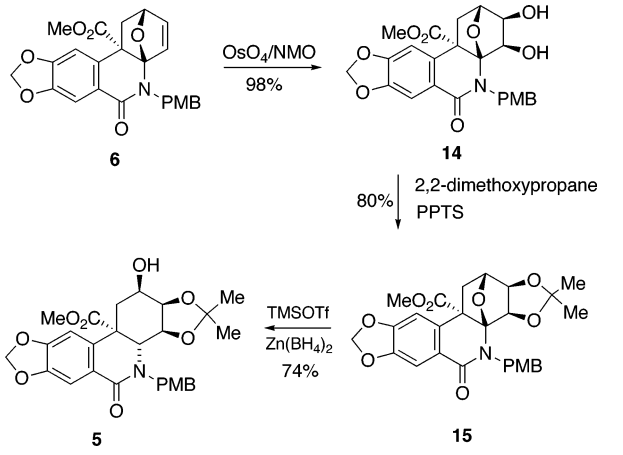
(17) Replacement of the *t*-Boc group with the PMB functionality was necessary for the subsequent Stille reaction.

(18) (a) Zhang, H. X.; Guiibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (b) Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, 981. (c) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Philips, H. K. *Tetrahedron Lett.* **1990**, *31*, 6621.

oxygen and moisture at 60 °C gave the best results. The expected cross-coupled amidofuran **13**, however, was not isolated as it spontaneously underwent an intramolecular [4 + 2]-cycloaddition to furnish cycloadduct **6** in 82% overall yield for the two-step cascade. The increase in reactivity of **13** when compared to related furanyl carbamates[20] (>150 °C) is due to both the placement of the carbonyl center within the dienophilic tether and the presence of the carbomethoxy group, which lowers the LUMO energy of the $\pi$-bond thereby facilitating the cycloaddition. Dramatic effects on the rate of the Diels−Alder reaction were previously noted to occur when an amido group was used to anchor the diene and dienophile.[21] Our ability to isolate oxabicyclic adduct **6** is presumably a result of the lower reaction temperature employed (i.e., 60 °C) as well as the presence of the amido carbonyl group, which diminishes the basicity of the nitrogen atom thereby retarding the ring cleavage/rearrangement reaction generally encountered with these systems.[20] Moreover, the IMDAF cycloaddition proceeds by a transition state where the sidearm of the tethered vinyl group is oriented *exo* with respect to the oxygen bridge.[22] As a consequence of this preferred orientation, the carbomethoxy group and oxy-bridge are disposed in an *anti* relationship in the resulting cycloadduct **6**.

With the rapid construction of the Lycoricidine framework in hand, installation of the other functional groups present on the C-ring with the correct relative stereochemistry was investigated. To continue the synthesis, cycloadduct **6** was transformed to diol **14** by reaction with catalytic $OsO_4$ in the presence of 4-methyl-morpholine-*N*-oxide. The dihydroxylation reaction occurred exclusively from the less hindered *exo* face, producing **14** in 98% yield (Scheme 3).

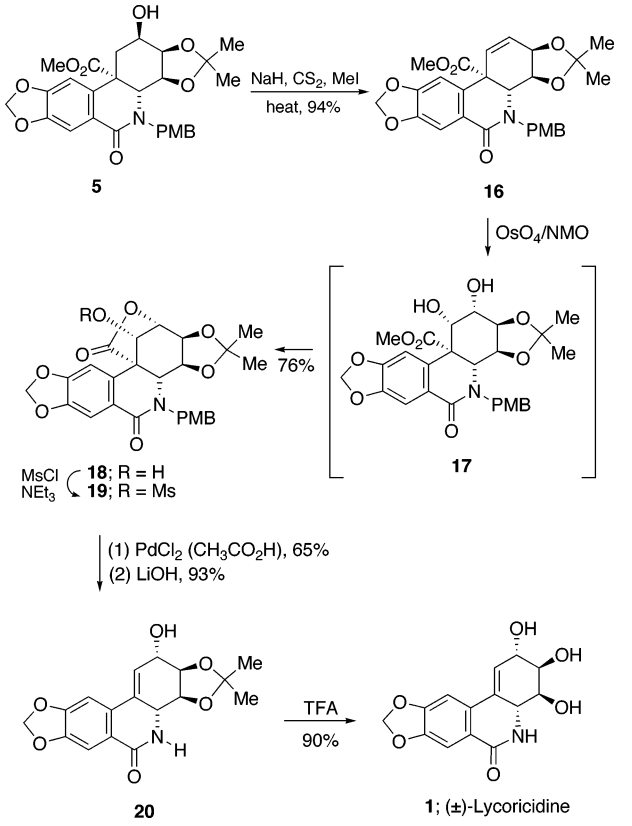
**Scheme 3**




Having introduced the correct *cis*-stereochemistry of the hydroxyl groups at the $C_3$,$C_4$ positions, we then proceeded to set the stereochemistry at the $C_{4a}$ position, insert the remaining α-hydroxyl group at $C_2$, and ultimately introduce the required $\pi$-bond. All of these operations were facilitated by making use of the available carbomethoxy group (vide infra). First, diol **14** was converted to the corresponding acetonide **15** in 80% yield by treatment with 2,2-dimethoxypropane and catalytic pyridinium *p*-toluenesulfonate. The uniquely functionalized oxabicyclic adduct **15** contains a "masked" *N*-acyliminium ion that can be released by treatment with a Lewis acid such as TMSOTf. When the resulting ring-opened iminium ion was treated with $Zn(BH_4)_2$,[23] alcohol **5** was obtained in 74% yield.

What was required for the end game leading to Lycoricidine (**1**) was to invert the stereochemistry of the $C_2$-hydroxyl group, remove the carbomethoxy moiety, and generate a double bond between the $C_1$−$C_{10b}$ position of the C-ring. To this end, compound **5** was treated with NaH followed by the addition of $CS_2$ and MeI to give the corresponding xanthate ester, which upon heating at reflux in 1,2-dichlorobenzene for 12 h afforded the expected olefin derived from a Chugaev elimination[24] in 94% yield (Scheme 4). Since the

**Scheme 4**




$\beta$-face of the $\pi$-bond of **16** was blocked by the bulky acetonide, a dihydroxylation reaction was expected to take place from the less hindered α-face, *syn* to the carbomethoxy group, thereby setting the correct stereochemistry of the $C_2$-hydroxyl group. Indeed, when **16** was treated with $OsO_4$/NMO, the desired diol **17** was formed as a transient species but underwent spontaneous cyclization with the adjacent

(19) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(20) (a) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304. (b) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473. (c) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.

carbomethoxy group to deliver $\gamma$-lactone **18**. A subsequent mesylation reaction afforded mesylate **19** in 76% yield for the two-step sequence starting from **16**. The $\gamma$-lactonization of **17** to **18** permits the selective activation of the $C_1$-hydroxyl group. The PMB group was removed by the reaction of **19** with $PdCl_2$ in the presence of acetic acid[25] to furnish the deprotected amide. Gratifyingly, the reaction of this amide with LiOH in aqueous THF induced a novel tandem hydrolysis/decarboxylation/elimination sequence[26] to furnish allylic alcohol **20**. Deprotection of the acetonide with TFA afforded (±)-Lycoricidine in 90% yield.

In summary, we have described here a novel and highly efficient synthesis of (±)-Lycoricidine, which was achieved in 14 steps with a 12.6% overall yield. The synthesis illustrates (a) the use of a one-pot Stille−IMDAF cycloaddition cascade to construct the ring skeleton, (b) a stereocontrolled dihydroxylation and *N*-acyliminium ion reduction to set the correct stereochemistry at carbon atoms $C_3$, $C_4$, and $C_{4a}$, and (c) the novel introduction of the $C_1$−$C_{10b}$ $\pi$-bond by a one-pot hydrolysis−decarboxylation−elimination sequence. The application of this approach to other members of the lycorine family of alkaloids is currently under investigation, the results of which will be disclosed in due course.

**Acknowledgment.** We appreciate the financial support provided the The National Institutes of Health (GM059384) and The National Science Foundation (CHE-0450779).

**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.

OL052524F

(21) (a) Oppolzer, W.; Fröstl, W. *Helv. Chem. Acta* **1975**, *58*, 590. (b) White, J. D.; Demnitz, F. W. J.; Oda, H.; Hassler, C.; Snyder, J. P. *Org. Lett.* **2000**, *2*, 3313. (c) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412. (d) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938.

(22) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617.

(23) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

(24) Nace, H. R. *Org. React.* **1962**, *12*, 57.

(25) Keck, G. E.; Boden, E.; Sonnewald, U. *Tetrahedron Lett.* **1981**, *22*, 2615.

(26) For a related fragmentation reaction, see: Khim, S.; Dai, M.; Zhang, X.; Chen, L.; Pettus, L.; Thakkar, K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7728.