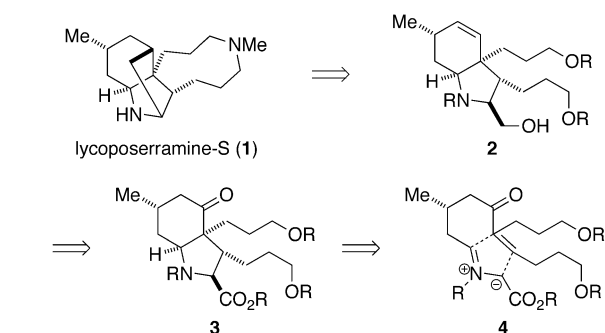# Total Synthesis of (−)-Lycoposerramine-S**

Naoaki Shimada, Yuzo Abe, Satoshi Yokoshima, and Tohru Fukuyama*

Lycopodium alkaloids have attracted the attention of synthetic chemists because of their intriguing structural features and the remarkable bioactivities.[1] Among them is (−)-lycoposerramine-S (**1**; Figure 1), which was isolated from *Lycopodium serratum* by Takayama and co-workers in 2002[2] and has a unique structure including a highly fused tetracyclic skeleton with two nitrogen atoms and one quaternary carbon center. Although synthetic studies of (−)-lycoposerramine-S were reported by Elliott and co-workers,[3] its total synthesis has not been reported to date. Although the biological activity of this molecule has not yet been determined, we were interested in exploring this unique molecule and its derivatives for drug discovery. Herein, we report the first total synthesis of (−)-lycoposerramine-S (**1**). Key to the straightforward construction of the tetracyclic skeleton was the unexpected stereoselectivity in the intramolecular cycloaddition of an azomethine ylide.

Figure 1. Structure of lycoposerramine-S.

Our retrosynthesis is shown in Scheme 1. Formation of the nine-membered ring and the cyclopentane ring could be achieved by alkylation of a nosyl amide and radical cyclization, respectively. The requisite precursor **2** would be derived from the ketoester **3**. The bicyclic system of **3** could in turn be constructed by an intramolecular cycloaddition of the azomethine ylide **4**.[4]

Our synthesis commenced with preparation of the precursor of the azomethine ylide (Scheme 2). Reaction of the alkyl iodide **5**[5] with an anion derived from the terminal
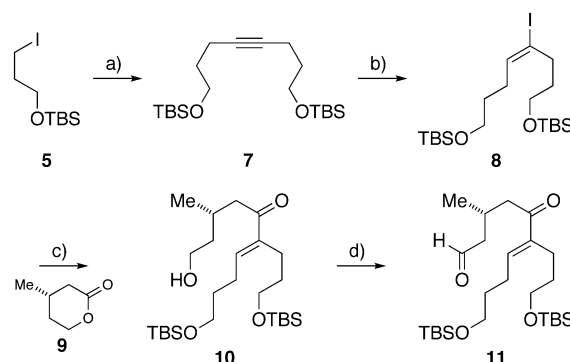
Scheme 2. Preparation of a precursor for the azomethine ylide.
a) *n*BuLi, HCC(CH$_2$)$_3$OTBS (**6**), THF/DMPU, −78 °C to RT, 87%; b) [Cp$_2$ZrCl$_2$], DIBAL, THF, 0 °C to RT; I$_2$, −78 °C, 87%; c) *n*BuLi, Et$_2$O, −78 °C; **9**, −78 °C, 66%; d) TPAP, NMO, 4Å M.S., CH$_2$Cl$_2$, RT, 75%. Cp = cyclopentadienyl, DIBAL = diisobutylaluminum hydride, DMPU = *N,N′*-dimethylpropyleneurea, M.S. = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide, TBS = *tert*-butyldimethylsilyl, TPAP = tetrapropylammonium perruthenate.

Scheme 1. Retrosynthesis.

[*] N. Shimada, Dr. Y. Abe, Dr. S. Yokoshima,[+] Prof. T. Fukuyama
Graduate School of Pharmaceutical Sciences, University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: fukuyama@mol.f.u-tokyo.ac.jp

[+] Current address: Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601 (Japan)

alkyne **6** afforded the alkyne **7**, which was subjected to hydrozirconation and subsequent addition of iodine to give the alkenyl iodide **8**.[6] Halogen–lithium exchange of **8** generated the corresponding alkenyllithium species, which was reacted with the known lactone **9**[7] to afford **10**. Subsequent oxidation of the hydroxy group in **10** furnished the ketoaldehyde **11**, which was used for the cycloaddition of the azomethine ylide.

Treatment of **11** with *N*-benzylglycine ethyl ester in refluxing toluene formed an azomethine ylide, which underwent cycloaddition to afford the product as a 4:3 mixture of two diastereomers which differed in the relative configuration at C15. This result indicated that the distant methyl group on C15 did not control the facial selectivity of the cycloaddition. Therefore we decided to employ chiral amino esters as reagents for the cycloaddition. Using (5*S*,6*R*)-5,6-diphenylmorpholin-2-one,[8] the cycloaddition proceeded stereoselectively, albeit in low yield. After intensive screening of chiral amino esters, we found that the morpholinone **12** gave the best selectivity and yield.[9] Thus, heating **11** with **12** in toluene furnished the adduct **13** in 86% yield as a single isomer
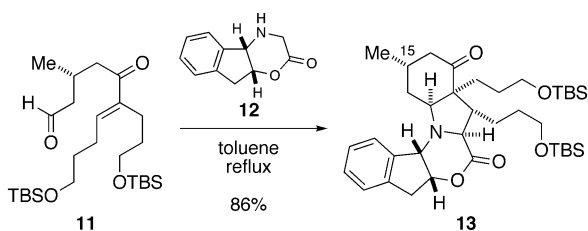
Scheme 3. Stereoselective intramolecular cycloaddition of azomethine ylide.

(Scheme 3). The stereochemistry of **13** was determined by a NOESY experiment.[10]

The intermolecular cycloaddition reactions of azomethine ylides, derived from 5-substituted or 5,6-disubstituted morpholin-2-one with aldehydes, have been reported to give a mixture of 2,5-*trans*- and 2,5-*cis*-disubstituted pyrrolidines via the *E* and *Z* ylides, respectively (Scheme 4). However, the analogous cycloadditions with ylides derived from sterically
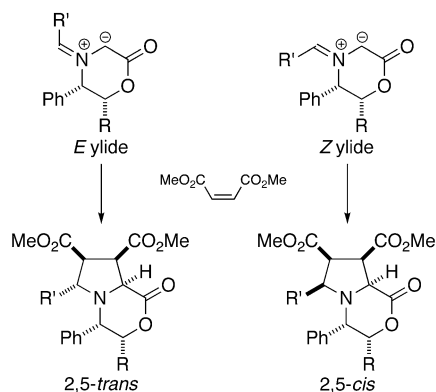
Scheme 4. Stereochemical outcome of cycloaddition of azomethine ylides.

demanding aldehydes preferentially proceed via *E* ylides to furnish the 2,5-*trans* isomers.[8,11] As shown in Scheme 3, the reaction of **11** with **12** unexpectedly afforded a 2,5-*cis*-disubstituted pyrrolidine via the *Z*-ylide intermediate.[12,13]

The unexpected stereoselectivity can be rationalized by considering the possible transition states for the cycloaddition (Figure 2). In the cycloaddition, the double bond would approach the azomethine ylide from the convex face. To minimize steric repulsion between the two siloxypropyl chains on the double bond and the indane moiety, the transition state
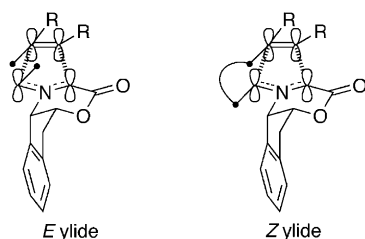
Figure 2. Possible transition states for the cycloaddition.

is expected to have the conformations as shown in Figure 2. In the case of the *E* ylide, the substituents on the double bond and the azomethine ylide (shown as dots) would be oriented anti to each other. As a result, the four-atom linkage between these moieties would be too short to provide good overlap of the orbitals for the cycloaddition. In contrast, in the case of the *Z* ylide these two moieties can be connected with the linkage without any constraints. The reaction, therefore, proceeds through the latter transition state with the *Z* ylide, giving the adduct **13** which has the correct stereochemistry required for the synthesis of (−)-lycoserramine-S.

Having constructed the bicyclic skeleton with complete stereoselectivity, we turned our attention to forming the cyclopentane ring of the natural product by radical cyclization. Reduction of **13** with Red-Al afforded a triol, which was subjected to hydrogenolysis in the presence of Boc₂O to afford **14** as a single diastereomer (Scheme 5).[14] Selective dehydration of the secondary alcohol in the diol **14** was efficiently achieved in a one-pot procedure, involving acylation of the primary alcohol with methoxyacetyl chloride, activation of the secondary alcohol with chloromethanesul-
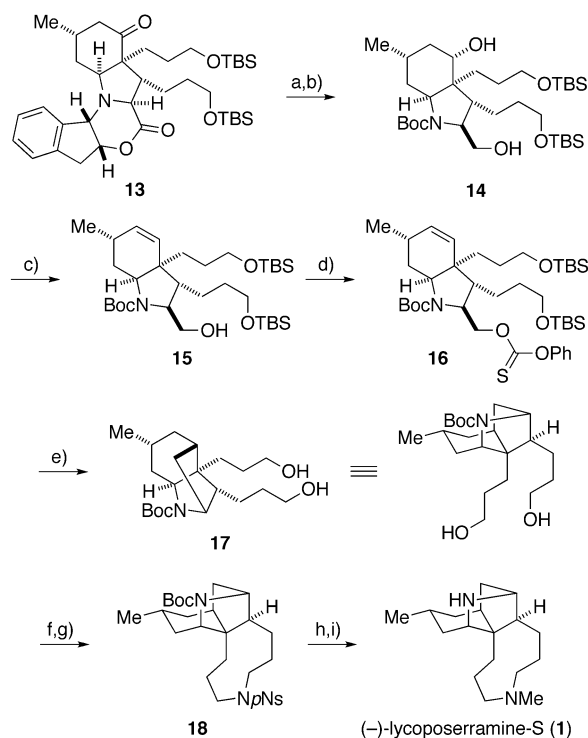
Scheme 5. Completion of the synthesis. a) Red-Al, toluene, 0°C to RT, 81%; b) H₂, Pd(OH)₂/C, Boc₂O, EtOAc, RT, 98%; c) methoxyacetyl chloride, TMEDA, toluene, RT; ClCH₂SO₂Cl, TMEDA, RT; K₂CO₃, MeOH, reflux, 75%; d) phenyl chlorothionoformate, DMAP, MeCN, 50°C; e) V-70, (Me₃Si)₃SiH, toluene, 50°C; CSA, MeOH, RT, 69% (2 steps); f) MsCl, TMEDA, CH₂Cl₂, RT, 91%; g) *p*NsNH₂, Cs₂CO₃, TBAI, DMF, 50°C, 48%; h) PhSH, Cs₂CO₃, MeCN, 50°C; aq HCHO, NaBH(OAc)₃, RT, 88%; i) TFA, CH₂Cl₂, RT, 91%. Boc = *tert*-butoxycarbonyl, CSA = 10-camphorsulfonic acid, DMAP = 4-(dimethylamino)pyridine, DMF = *N,N*-dimethylformamide, Ms = methanesulfonyl, Ns = nitrobenzenesulfonyl, Red-Al = sodium bis(2-methoxyethoxy)aluminium hydride, TBAI = tetra-*n*-butylammonium iodide, TFA = trifluoroacetic acid, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine, V-70 = 2,2′-azobis(4-methoxy-2.4-dimethylvaleronitrile).

fonyl chloride[15] and TMEDA,[16] and methanolysis/elimination with K_2CO_3 in refluxing methanol, to give the olefin **15** in 75% yield. Conversion of **15** into the thionocarbonate **16** with phenyl chlorothionoformate and subsequent subjection to radical reaction conditions[17] led to a smooth 5-*exo-trig* cyclization to give, after acidic treatment, the tricyclic compound **17**.

After mesylation of the two hydroxy groups, the nine-membered ring was constructed by alkylation with 4-nitrobenzenesulfonamide to furnish **18**.[18] Finally, cleavage of the *p*-Ns group, reductive methylation, and removal of the Boc group under acidic conditions furnished (−)-lycoposerramine-S (**1**).[19]
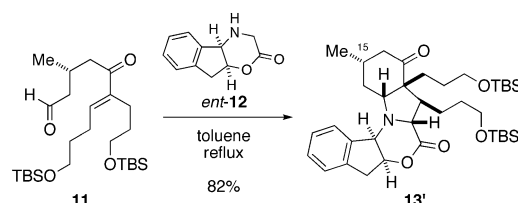
In summary, the total synthesis of (−)-lycoposerramine-S has been accomplished in 14 steps from the known alkyl iodide **5**. Key steps of our synthesis involved facile construction of the tetracyclic system through an intramolecular 1,3-dipolar cycloaddition of an azomethine ylide with unexpected stereoselectivity, a 5-*exo-trig* radical cyclization, and alkylation of a nosyl amide.

[1] For reviews of the *Lycopodium* alkaloids, see: a) D. B. MacLean in *The Alkaloids*, *Vol. 10* (Ed.: R. H. F. Manske), Academic Press, New York, **1968**, pp. 305–382; b) D. B. MacLean in *The Alkaloids*, *Vol. 14* (Ed.: R. H. F. Manske), Academic Press, New York, **1973**, pp. 347–405; c) D. B. MacLean in *The Alkaloids*, *Vol. 26* (Ed.: A. Brossi), Academic Press, New York, **1985**, pp. 241–298; d) W. A. Ayer, *Nat. Prod. Rep.* **1991**, *8*, 455–463; e) W. A. Ayer, L. S. Trifonov in *The Alkaloids*, *Vol. 45* (Eds.: G. A. Cordell, A. Brossi), Academic Press, New York, **1994**, pp. 233–266; f) X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752–772; g) J. Kobayashi, H. Morita in *The Alkaloids*, *Vol. 61* (Ed: G. A. Cordell), Academic Press, New York, **2005**, pp. 1–57; h) Y. Hirasawa, J. Kobayashi, H. Morita, *Heterocycles* **2009**, *77*, 679–729; i) H. Takayama, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 457–469.

[2] H. Takayama, K. Katakawa, M. Kitajima, K. Yamaguchi, N. Aimi, *Tetrahedron Lett.* **2002**, *43*, 8307–8311. For a proposed biogenetic route, see: K. Katakawa, M. Kitajima, N. Aimi, H. Seki, K. Yamaguchi, K. Furihata, T. Harayama, H. Takayama, *J. Org. Chem.* **2005**, *70*, 658–663.

[3] a) M. C. Elliott, N. N. E. El Sayed, J. S. Paine, *Org. Biomol. Chem.* **2008**, *6*, 2611–2618; b) M. C. Elliott, J. S. Paine, *Org. Biomol. Chem.* **2009**, *7*, 3455–3462.

[4] I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2810.

[5] K. Miura, M. Tomita, J. Ichikawa, A. Hosomi, *Org. Lett.* **2008**, *10*, 133–136.

[6] Z. Huang, E. Negishi, *Org. Lett.* **2006**, *8*, 3675–3678.

[7] L. Poppe, L. Novák, P. Kolonits, Á. Bata, C. Szántay, *Tetrahedron* **1988**, *44*, 1477–1487.

[8] R. M. Williams, W. X. Zhai, D. J. Aldous, S. C. Aldous, *J. Org. Chem.* **1992**, *57*, 6527–6532.

[9] The morpholinone **12** was readily prepared from (1*S*,2*R*)-1-amino-2-indanol by treatment with phenyl bromoacetate in the presence of *N*,*N*-diisopropylethylamine. For details, see the Supporting information.

[10] Reaction of **11** with *ent*-**12** gave **13′** as a single isomer in 82% yield. The product **13′** was an epimer of *ent*-**13** at C15. This result clearly suggested that the stereoselectivity of the cycloaddition was completely controlled by the morpholinone.

[11] a) A. S. Anslow, L. M. Harwood, H. Phillips, D. Watkin, L. F. Wong, *Tetrahedron: Asymmetry* **1991**, *2*, 1343–1358; b) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.

[12] Harwood and Lilley reported that the reaction of 5-phenyl-morpholin-2-one with 6-heptenal resulted in an intramolecular cycloaddition of an azomethine ylide and proceeded via the *E* ylide to give the 2,5-*trans*-disubstituted pyrrolidine derivative. L. M. Harwood, I. A. Lilley, *Tetrahedron Lett.* **1993**, *34*, 537–540.

[13] For examples of 2,5-*cis* products by cycloadditions of azomethine ylides derived from 2,2-disubstituted 6-heptenals and N-alkyl glycine esters, see: I. Coldham, K. M. Crapnell, J. D. Moseley, R. Rabot, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1758–1763.

[14] Using $LiAlH_4$ instead of Red-Al gave a 3.3:1 mixture of **14** and its epimer. The epimer of **14** did not undergo the subsequent dehydration.

[15] T. Shimizu, S. Hiranuma, T. Nakata, *Tetrahedron Lett.* **1996**, *37*, 6145–6148.

[16] Y. Yoshida, K. Shimonishi, Y. Sakakura, S. Okada, N. Aso, Y. Tanabe, *Synthesis* **1999**, 1633–1636.

[17] Y. Kita, A. Sano, T. Yamaguchi, M. Oka, K. Gotanda, M. Matsugi, *Tetrahedron Lett.* **1997**, *38*, 3549–3552.

[18] a) T. Kan, H. Kobayashi, T. Fukuyama, *Synlett* **2002**, 697–699; b) T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353–359; c) Y. Kaburagi, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2004**, *126*, 10246–10247. Pan and Williams carried out extensive investigations on the inter- and intramolecular Mitsunobu reaction of a diol with $NsNH_2$ for construction of a nine-membered ring in *Lycopodium* alkaloids: G. Pan, R. M. Williams, *J. Org. Chem.* **2012**, *77*, 4801–4811.

[19] Spectral data of the synthetic lycoposerramine-S were consistent with the reported data (ref [2]).