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Syntheses of (±)-Serratine, (±)-Lycoposerramine T, and (±)-Lycopoclavamine B

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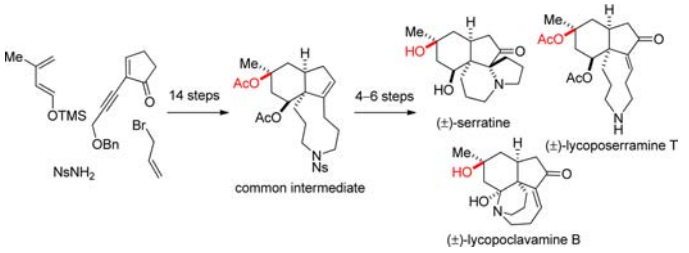
ABSTRACT



The first total syntheses of (±)-serratine, (±)-lycoposerramine T, and (±)-lycopoclavamine B have been accomplished. The functionalized octahydroindane skeleton of these natural products was constructed by an efficient Diels–Alder reaction of an α-alkynylcyclopentenone and the stereoselective introduction of a tertiary hydroxyl group. Two of these natural products were divergently synthesized from the same synthetic intermediate at a later stage.

A great number of *Lycopodium* alkaloids have been isolated from plant sources. These alkaloids have been shown to have complex polycyclic structures and potential biological activities.[1] These characteristics have attracted the attention of synthetic chemists, and many successful total syntheses of *Lycopodium* alkaloids have been reported.[2] (−)-Serratine (**1**), which possesses a tetracyclic framework with five stereocenters, was isolated from *Lycopodium serratum* by Inubushi and co-workers in the 1960s (Figure 1).[3] Other related alkaloids such as (−)-serratinine (**2**),[4] (−)-serratanidine (**3**),[3a,5] and its deoxy derivative[6] have also been isolated in succession. Recently, (+)-lycoposerramine T (**4**),[7] (−)-lycopoclavamine B (**5**),[8] and (+)-lycojaponicumin A (**6**),[9] which have a tertiary hydroxyl or acetoxy group like (−)-serratine (**1**), have been

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(1) Recent reviews of the *Lycopodium* alkaloids: (a) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772. (b) Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2005; Vol. 61, pp 1–57. (c) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729. (d) Kitajima, M.; Takayama, H. *Top. Curr. Chem.* **2012**, *309*, 1–31.

(2) Selected recent examples of total synthesis of the *Lycopodium* alkaloids: (a) Otsuka, Y.; Inagaki, F.; Mukai, C. *J. Org. Chem.* **2010**, *75*, 3420–3426. (b) Yang, Y.-R.; Shen, L.; Huang, J.-Z.; Xu, T.; Wei, K. *J. Org. Chem.* **2011**, *76*, 3684–3690. (c) Nakayama, A.; Katajima, M.; Takayama, H. *Synlett* **2012**, 2014–2024. (d) Lin, H.-Y.; Causey, R.; Garcia, G. E.; Snider, B. B. *J. Org. Chem.* **2012**, *77*, 7143–7156. (e) Pan, G.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 4801–4811. (f) Saha, M.; Carter, R. G. *Org. Lett.* **2012**, *15*, 736–739. (g) Shimada, N.; Abe, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 11824–11826. (h) Canham, S. M.; France, D. J.; Overman, L. E. *J. Org. Chem.* **2013**, *78*, 9–34. (i) Li, H.; Wang, X.; Hong, B.; Lei, X. *J. Org. Chem.* **2013**, *78*, 800–821. (j) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3243–3247.

(3) (a) Inubushi, Y.; Tsuda, Y.; Ishii, H.; Sano, T.; Hosokawa, M.; Harayama, T. *Yakugaku Zasshi* **1964**, *84*, 1108–1113 (written in Japanese). (b) Inubushi, Y.; Ishii, H.; Harayama, T. *Chem. Pharm. Bull.* **1967**, *15*, 250–252. (c) Inubushi, Y.; Harayama, T.; Akatsu, M.; Ishii, H.; Nakahara, Y. *Chem. Pharm. Bull.* **1968**, *16*, 2463–2470. The detailed spectroscopic data of (−)-serratine (**1**) have been reported by Takayama et al.: (d) Katakawa, K.; Nozoe, A.; Kogure, N.; Kitajima, M.; Hosokawa, M.; Takayama, H. *J. Nat. Prod.* **2007**, *70*, 1024–1028.

(4) (a) Inubushi, Y.; Ishii, H.; Yasui, B.; Hashimoto, M.; Harayama, T. *Tetrahedron Lett.* **1966**, 1537–1549. (b) Inubushi, Y.; Ishii, H.; Yasui, B.; Harayama, T. *Tetrahedron Lett.* **1966**, 1551–1559. (c) Inubushi, Y.; Ishii, H.; Yasui, B.; Hashimoto, M.; Harayama, T. *Chem. Pharm. Bull.* **1968**, *16*, 82–91. (d) Inubushi, Y.; Ishii, H.; Yasui, B.; Hashimoto, M.; Harayama, T. *Chem. Pharm. Bull.* **1968**, *16*, 92–100.

(5) Inubushi, Y.; Harayama, T.; Akatsu, M.; Ishii, H.; Nakahara, Y. *Chem. Pharm. Bull.* **1968**, *16*, 561–563.

(6) (a) Inubushi, Y.; Ishii, H.; Yasui, B.; Harayama, T.; Hosokawa, M.; Nishino, R.; Nakahara, Y. *Yakugaku Zasshi* **1967**, *87*, 1394–1404 (written in Japanese).

(7) Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Helv. Chim. Acta* **2009**, *92*, 445–452.

(8) Katakawa, K.; Mito, H.; Kogure, N.; Kitajima, M.; Wongseripipatana, S.; Arisawa, M.; Takayama, H. *Tetrahedron* **2011**, *67*, 6561–6567.

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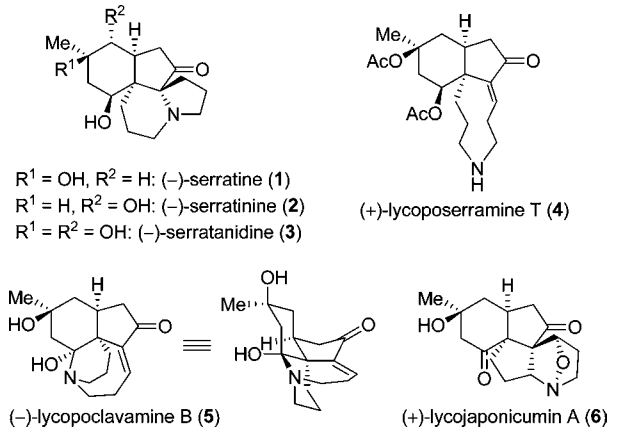
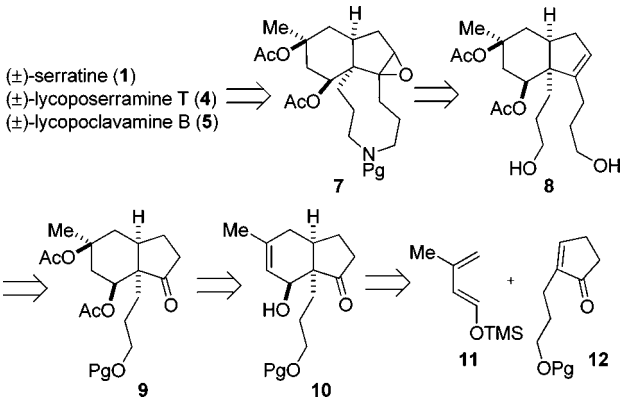


Figure 1. Serratine and related natural products.

isolated by Takayama et al. (for **4** and **5**) and Yu et al. (for **6**). Surprisingly, the total synthesis of (−)-serratine (**1**) has never been reported,[10] though syntheses of structurally close (−)-serratinine (**2**)[11] and its deoxy derivatives[12] have been reported. This might be due to the existence of the tertiary hydroxyl group, which appears to make the synthesis of (−)-serratine (**1**) difficult. With the goal of succeeding in the first total synthesis of (−)-serratine (**1**) and related alkaloids, we decided to try to synthesize racemic forms of these natural products.

As shown in Scheme 1, (±)-serratine (**1**), (±)-lycoposerramine T (**4**), and (±)-lycopoclavamine B (**5**) could potentially be synthesized from a common intermediate **7**. Azonane compounds, such as **7**, are intermediates in the synthesis of many *Lycopodium* alkaloids.[2] Compound **7** could possibly be constructed from diol **8** by epoxidation of an alkene and double alkylation with a protected amine (Pg = protecting group). The ketone group of compound **9** could serve as a precursor for the introduction of a C3 unit on the right side. Sharpless diastereoselective epoxidation of allyl alcohol **10** followed by reduction could offer a reliable method for stereoselective introduction of the tertiary hydroxyl group. As a starting reaction for this synthetic study, the Diels–Alder reaction between diene **11**[13] and the α-alkylcyclopentenone **12** was envisaged for the preparation of compound **10**.

Scheme 1. Outline of a Synthetic Strategy



We performed some model experiments of the Diels–Alder reaction using α-alkylcyclopentenones, but the reactions with diene **11** (*E*/*Z*, 90:10) were extremely slow, even under conditions at high temperature, hardly giving any desired products. The use of Lewis acids induced decomposition of these substrates.[14] In 2007, Danishefsky et al. reported that α-alkynyl dienophiles show high reactivity and *endo* selectivity in Diels–Alder reactions.[15] Encouraged by this report, we examined the Diels–Alder reaction between diene **11** and α-alkynylcyclopentenone **13** (see the Supporting Information) at 90 °C and obtained the desired *endo*-adduct **14** in good yield, along with a small amount of the *exo*-adduct **15**, after 40 h (Table 1, entry 1). The use of a microwave significantly promoted this reaction, but the yield of **14** on a multigram scale (2–6 g) was somewhat low (ca. 50%) (entry 2).[16] Eventually, we found that heating the neat mixture of **11** and **13** for 24 h at 80 °C gave **14** in good yield with high reproducibility (entry 3).

Chemoselective reduction of the alkyne and hydrogenolysis of the benzyl group in compound **14** with palladium hydroxide on carbon (20%) in isopropanol for 5 h, and subsequent treatment with citric acid, gave the unexpected homoallyl alcohol **16** (Scheme 2). The reason for the olefin isomerization is unclear, but fortunately, Sharpless diastereoselective epoxidation[17] of **16** succeeded, and subsequent treatment of the crude epoxide with benzenethiol (2 equiv) and cesium carbonate (2 equiv) gave the triol compound **17** in good yield. Desulfurization of **17** with Raney nickel (W-2) readily provided the corresponding 1,3-diol compound **18**. After protection of the primary hydroxy group by a *tert*-butyldiphenylsilyl group (TBDPS) and bismuth triflate (5 mol %)-catalyzed acetylation[18] of

(9) Wang, X.-J.; Zhang, G.-J.; Zhuang, P. Y.; Zhang, Y.; Yu, S.-S.; Bao, X.-Q.; Zhang, D.; Yuan, Y.-H.; Chen, N.-H.; Ma, S.-g.; Qu, J.; Li, Y. *Org. Lett.* **2012**, *14*, 2614–2617.

(10) A synthetic study of (±)-serratine (**1**) has been reported: Luedtke, G.; Livinghouse, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2369–2371.

(11) (a) Harayama, T.; Ohtani, M.; Oki, M.; Inubushi, Y. *J. Chem. Soc., Chem. Commun.* **1974**, 827–828. (b) Harayama, T.; Ohtani, M.; Oki, M.; Inubushi, Y. *Chem. Pharm. Bull.* **1975**, *23*, 1511–1515.

(12) (a) Harayama, T.; Takatani, M.; Inubushi, Y. *Tetrahedron Lett.* **1979**, *20*, 4307–4310. (b) Harayama, T.; Takatani, M.; Inubushi, Y. *Chem. Pharm. Bull.* **1980**, *28*, 2394–2402. (c) Cassayre, J.; Gagosz, F.; Zard, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1783–1785. (d) Yang, Y.-R.; Lai, Z.-W.; Shen, L.; Huang, J.-Z.; Wu, X.-D.; Yin, J.-L.; Wei, K. *Org. Lett.* **2010**, *12*, 3430–3433. See also ref 2b and 2i.

(13) Colvin, E. W.; Thom, I. G. *Tetrahedron* **1986**, *42*, 3137–3146.

(14) A recent example of Lewis acid catalyzed Diels–Alder reactions of α-alkylcyclopentenones: Inokuchi, T.; Okano, M.; Miyamoto, T.; Madon, H. B.; Takagi, M. *Synlett* **2000**, 1549–1552.

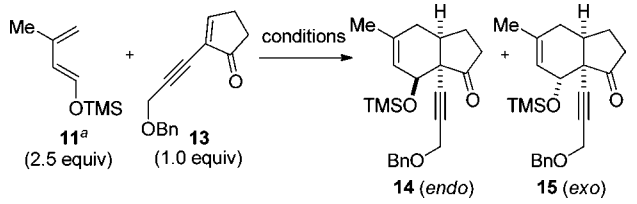
(15) Min, S.-J.; Jones, G. O.; Houk, K. N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10078–10079.

(16) Reviews on microwave use in organic synthesis: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284. (b) Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem., Int. Ed.* **2012**, *52*, 1088–1094.

(17) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.

(18) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, *66*, 8926–8934.

Table 1. Diels–Alder Reactions between **11** and **13**



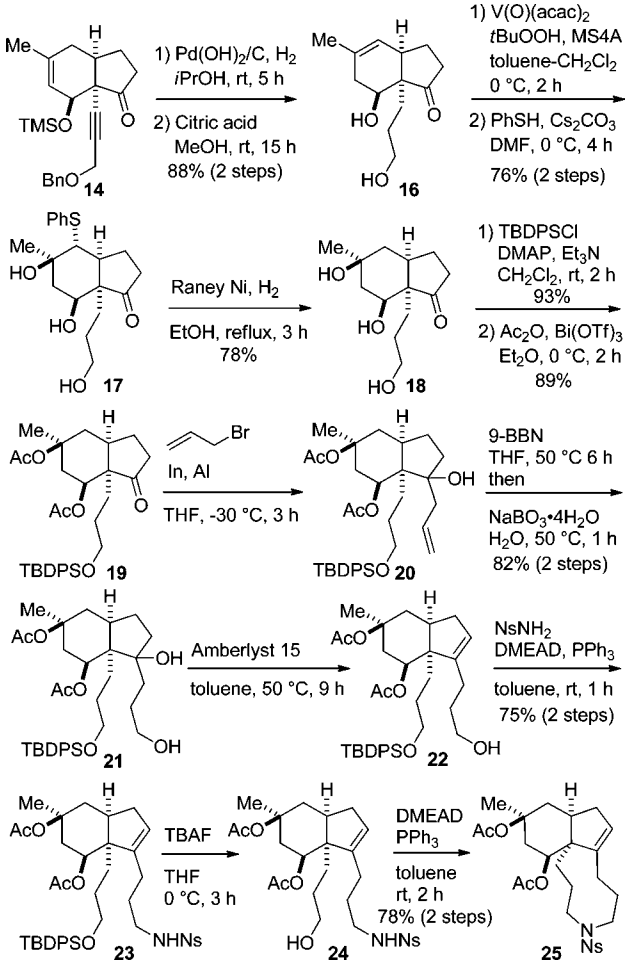
		yield (%)	
entry	conditions	**14**	**15**
1	toluene, 90 °C, 40 h	69	7
2	toluene, μwave, 190 °C, 20 min	75[b]	11[b]
3[c]	neat, 80 °C, 24 h	70	7

[a] 90% geometrical purity (*E*/*Z*, 90:10). [b] On a milligram scale (40–100 mg). [c] 2.0 equiv of **11** were used.

two other hydroxyl groups, reactions with various organometallic reagents were examined to introduce a C3 unit into compound **19**. Through many failed attempts, we realized that only an allyl group could be delivered as a C3 unit to **19**, and Takai's indium (20 mol %)-catalyzed allylation using allyl bromide (4 equiv) and aluminum (4 equiv) quantitatively afforded the adduct **20** as a single isomer (the putative product is an α-adduct).[19] After subsequent hydroboration using 9-borabicyclo[3.3.1]nonane (9-BBN, ca. 3 equiv) followed by oxidative treatment, 1,4-diol **21** was isolated in 82% yield. Treatment of compound **21** with Amberlyst 15 caused elimination of the tertiary hydroxyl group to give compound **22**.[20] A nitrogen atom was introduced into **22** by Fukuyama's method[21] using *o*-nitrobenzenesulfonamide ($NsNH_2$) under Mitsunobu conditions (all reagents: 1.5 equiv) with di-2-methoxyethyl azodicarboxylate (DMEAD)[22] to give compound **23**. After removal of the TBDPS group with tetrabutylammonium fluoride (TBAF), Fukuyama's method was again applied to construct the azonane ring of compound **25**. We also tried a direct synthesis of azonane **25** from diol **8**, prepared by one-pot dehydration and deprotection of **21** (conditions: $TsOH \cdot H_2O$, CH_2Cl_2, rt, then MeOH, rt, 87%) according to the plan shown in Scheme 1. However, the double Mitsunobu reaction of **8** with $NsNH_2$ gave **25** in only a low yield (8%).[2e] Efforts toward the optimization of this transformation will be continued.

When compound **25** was treated with *m*-chloroperbenzoic acid (*m*CPBA, 2 equiv), two epoxide diastereomers **26** and **27** were produced in similar yields (Scheme 3). Removal of the Ns group of β-epoxide **26** using benzenethiol (2 equiv) and potassium carbonate (2 equiv) caused a subsequent annulation onto the epoxide group to give

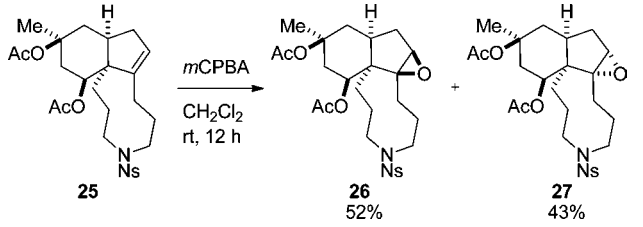
Scheme 2. Synthesis of Intermediate **25**



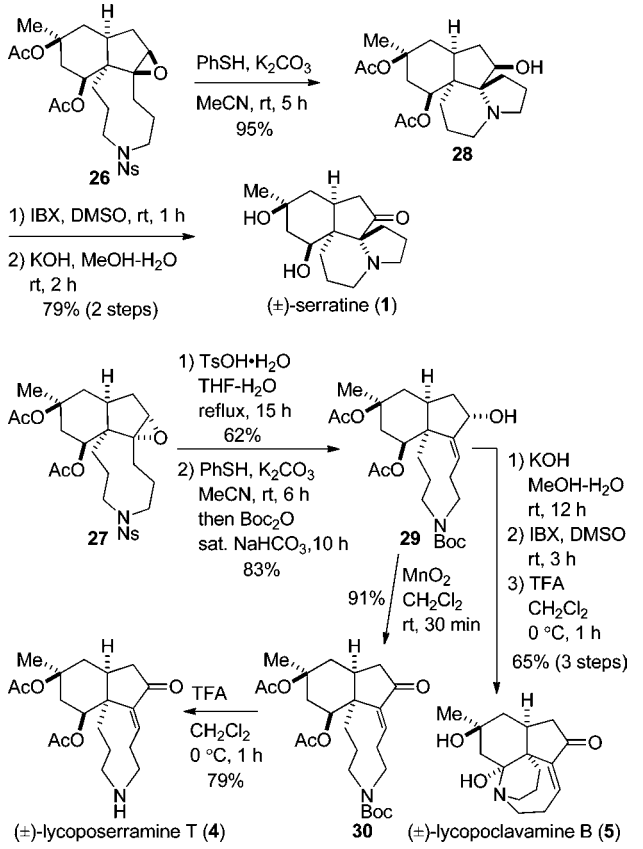
tetracyclic compound **28** (Scheme 4). The hydroxyl group of **28** was oxidized into ketone **29** with 2-iodoxybenzoic acid (IBX, 2 equiv), and the final hydrolysis of the acetyl groups with potassium hydroxide (5 equiv) in $MeOH/H_2O$ (10:1) afforded (±)-serratine (**1**). Although we did not succeed in transforming α-epoxide **27** into (±)-**1**, **27** served as an intermediate for the synthesis of (±)-lycoposerramine T (**4**) and (±)-lycopoclavamine B (**5**). Epoxide **27** was transformed into the corresponding (*E*)-allyl alcohol **29** by elimination with *p*-toluenesulfonic acid monohydrate (20 mol %) in THF/H_2O (10:1) at reflux and by replacement of the protecting group (Ns → *tert*-butoxycarbonyl; Boc). Finally, oxidation of the allylic hydroxy group of compound **29** with an excess of manganese dioxide (MnO_2) and removal of the Boc group of compound **30** led to (±)-lycoposerramine T (**4**). On the other hand, after removal of the acetyl groups of **29**, the two secondary hydroxyl groups were oxidized with 2-iodoxybenzoic acid (IBX, 5 equiv), and subsequent removal of the Boc group set off cyclization upon the resultant cyclohexanone moiety to afford (±)-lycopoclavamine B (**5**). The spectral data of synthetic (±)-**1**, (±)-**4**, and (±)-**5** were in accordance with those of each natural product.[3d,7,8]

(19) Takai, K.; Ikawa, Y. *Org. Lett.* **2002**, *4*, 1727–1729.
(20) A review on reactions using Amberlyst 15: Pal, R.; Sarkar, T.; Khasnobis, S. *ARKIVOC* **2012**, 570–609.
(21) Review: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359 and references therein.
(22) Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, *36*, 566–567.

Scheme 3. Epoxidation of **25**

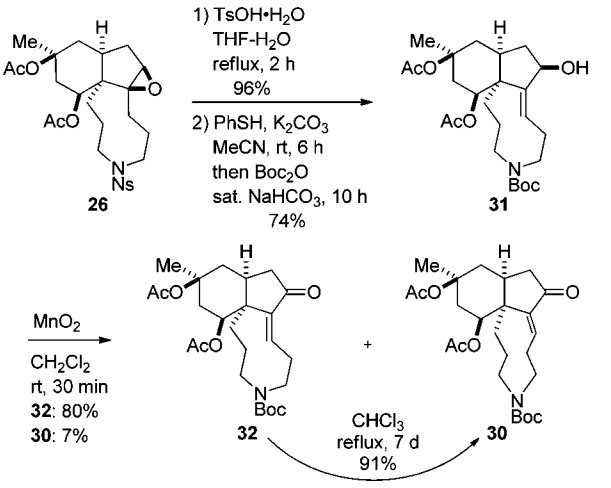


Scheme 4. Accomplishment of Total Syntheses of Three Alkaloids



Interestingly, (*Z*)-allyl alcohol **31** was obtained from *β*-epoxide **26** in almost quantitative yield by the same procedure as that used to obtain **29** from **27** (Scheme 5). We realized this fact by obtaining the (*Z*)-α,*β*-unsaturated ketone **32** (80% yield) along with a small amount of (*E*)-isomer **30** (7%) by oxidation of **31** with MnO_2. Apparently, the nine-membered ring of (*Z*)-isomer **32** is strained. Therefore, **32** completely isomerized to the thermodynamically more stable (*E*)-isomer **30**, which was converted into (±)-**4**, in chloroform at reflux for 7 days.

Scheme 5. Production of (*Z*)-Isomer **31** from **26** and Transformation into **30**



In conclusion, we have achieved the first total syntheses of three *Lycopodium* alkaloids, (±)-serratine (**1**), (±)-lycoposerramine T (**4**), and (±)-lycopoclavamine B (**5**). The present syntheses feature a Diels–Alder reaction promoted by an alkyne substituent and a subsequent stereoselective introduction of a tertiary hydroxyl group to construct the bicyclic systems of the three alkaloids. This synthetic route is efficient because the total syntheses were completed divergently from a common intermediate **25**. We anticipate that a synthesis of (±)-lycojaponicumin A (**6**) from intermediate **29** or **30** will be possible by intramolecular cycloaddition of the corresponding nitrone. In addition, unexpected production of **16** from **14** suggested an entry into (±)-serratanidine (**3**) because stereoselective introduction of the third hydroxy group to the cyclohexane ring should be possible by basic hydrolysis of epoxide **17**. Further synthetic studies including attempts at enantioselective syntheses of alkaloids **1**–**6** are currently underway in our laboratory.

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Supporting Information Available. Expermental detail and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.