

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

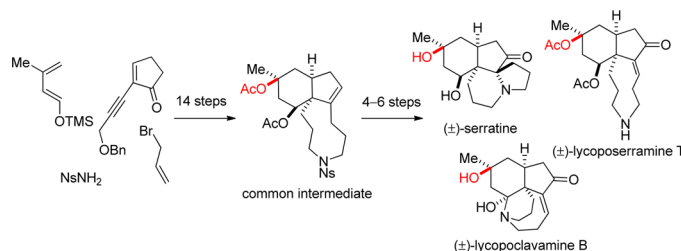
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ABSTRACT



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 derivative⁶ have also been isolated in succession. Recently, (+)-lycoposerramine T (**4**),⁷ (–)-lycopoclavamine B (**5**),⁸ and (+)-lycojaponicum A (**6**),⁹ which have a tertiary hydroxyl or acetoxy group like (–)-serratine (**1**), have been

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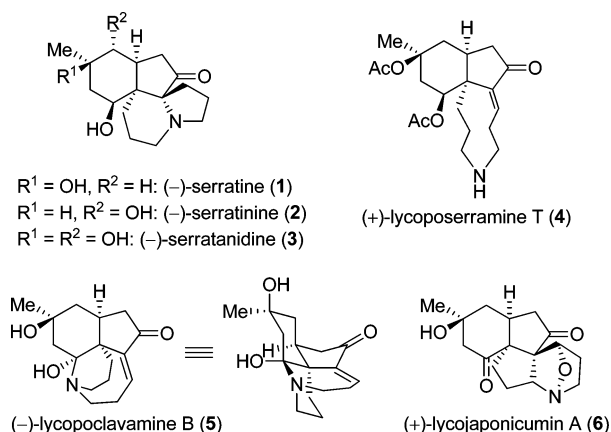
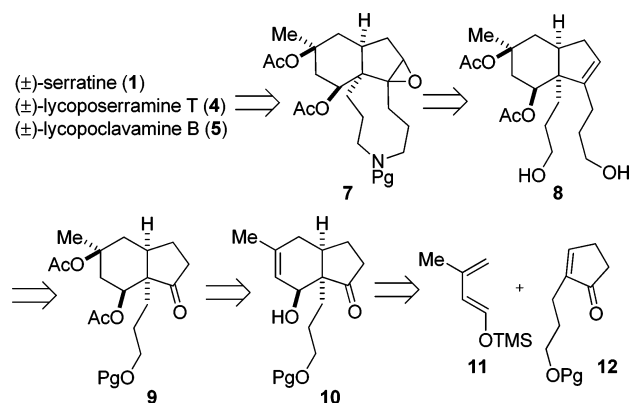


Figure 1. Serratine and related natural products.

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 derivatives¹² 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**), (±)-lycopserramine 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 epoxidation¹⁷ 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 acetylation¹⁸ of

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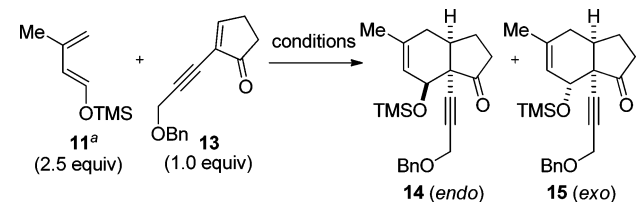
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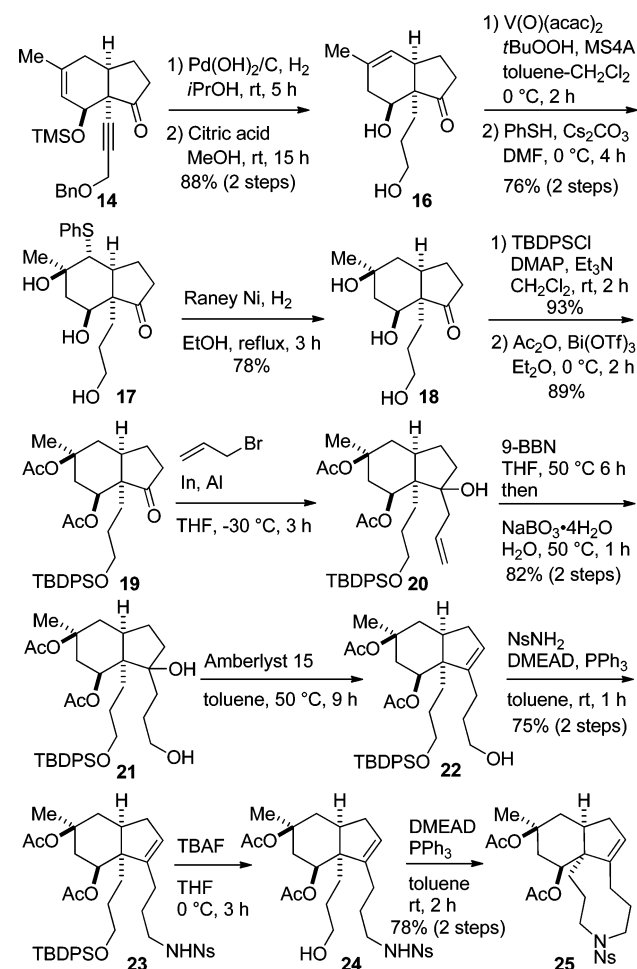
Table 1. Diels–Alder Reactions between **11** and **13**

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

^a90% geometrical purity (*E/Z*, 90:10). ^bOn a milligram scale (40–100 mg). ^c2.0 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 method²¹ using *o*-nitrobenzenesulfonamide (NsNH₂) 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·H₂O, CH₂Cl₂, rt, then MeOH, rt, 87%) according to the plan shown in Scheme 1. However, the double Mitsunobu reaction of **8** with NsNH₂ gave **25** in only a low yield (8%).^{2c} 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**

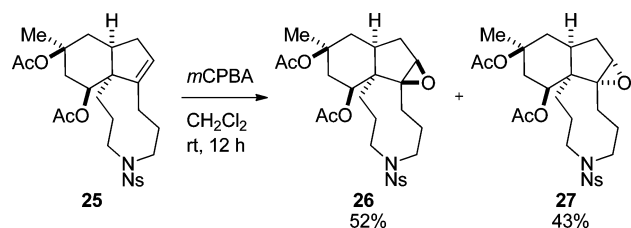
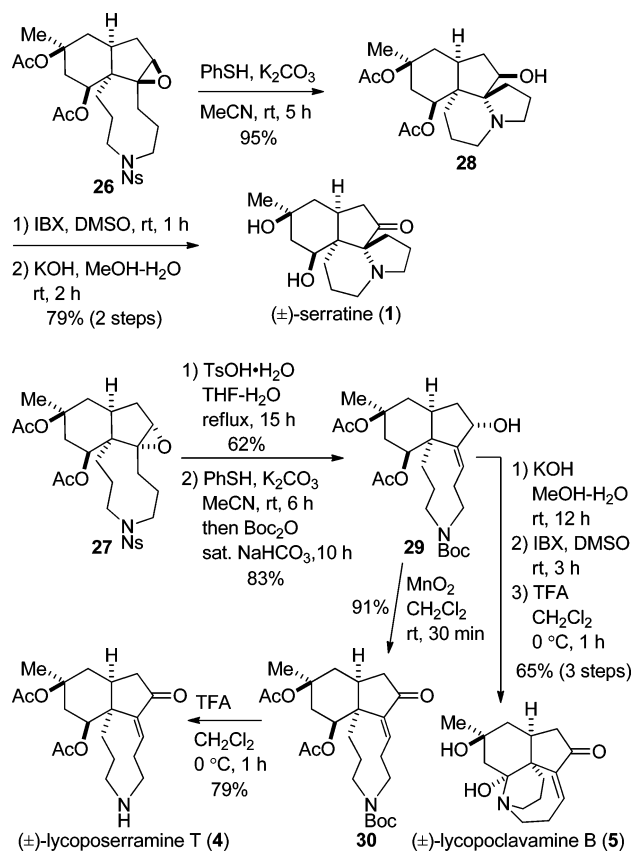
tetracyclic compound **28** (Scheme 4). The hydroxyl group of **28** was oxidized into ketone **29** with 2-iodoxybenzoic acid (IBX, 2 equiv), and the final hydrolysis of the acetyl groups with potassium hydroxide (5 equiv) in MeOH/H₂O (10:1) afforded (\pm)-serratine (**1**). Although we did not succeed in transforming α -epoxide **27** into (\pm)-**1**, **27** served as an intermediate for the synthesis of (\pm)-lycoposerramine T (**4**) and (\pm)-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/H₂O (10:1) at reflux and by replacement of the protecting group (Ns \rightarrow *tert*-butoxycarbonyl; Boc). Finally, oxidation of the allylic hydroxy group of compound **29** with an excess of manganese dioxide (MnO₂) and removal of the Boc group of compound **30** led to (\pm)-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 (\pm)-lycopoclavamine B (**5**). The spectral data of synthetic (\pm)-**1**, (\pm)-**4**, and (\pm)-**5** were in accordance with those of each natural product.^{3d,7,8}

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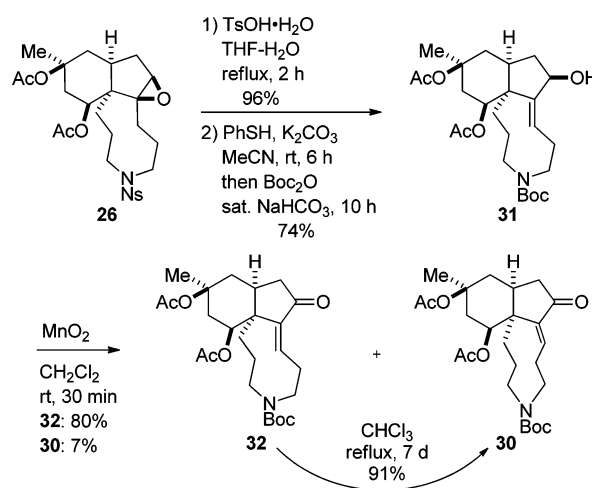
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Scheme 3. Epoxidation of **25****Scheme 4.** Accomplishment of Total Syntheses of Three Alkaloids

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 (\pm)-**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, (\pm)-serratine (**1**), (\pm)-lycoposerramine T (**4**), and (\pm)-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 (\pm)-lycojaponicum A (**6**) from intermediate **29** or **30** will be possible by intramolecular cycloaddition of the corresponding nitron. In addition, unexpected production of **16** from **14** suggested an entry into (\pm)-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. Experimental 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.