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Natural Product Synthesis

Redox Divergent Synthesis of Fawcettimine-Type *Lycopodium* Alkaloids

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Abstract: A new approach for synthesis of fawcettimine-type *Lycopodium* alkaloids is described. A divergent strategy was achieved by applying stereoselective Diels–Alder reaction followed by redox-controlled elaboration. Eventually, (−)-8-deoxyserratinine, (+)-fawcettimine, (−)-lycopoclavamine-A, (−)-serratine, (−)-lycopoclavamine-B and (−)-serratanidine were successfully accessed.

Introduction

More than 300 alkaloids have been isolated from the *Lycopodium* genus to date, and they have unique and complex cyclic structures.[1] In addition, recent studies have revealed that some of them have remarkable biological activity.[1] These facts imply that *Lycopodium* alkaloids are potentially a rich vein of medicinal seeds. *Lycopodium* alkaloids consist of some subclasses. The fawcettimine class, which contains over 80 alkaloids, recently received much attention in the field of chemistry. (+)-Fawcettimine is a representative alkaloid in this class and bears a *cis*-fused [4.3.0]bicyclo structure and an azonane ring with a quaternary carbon (Figure 1, Core **B**).[2] (−)-8-Deoxyserratinine also belongs in the same class because its skeleton is built up by connecting a nitrogen atom of the azonane ring with a C-4 carbon (Figure 1, Core **A**). In addition, many miscellaneous skeletal derivatives are known. Thus, fawcettimine-type alkaloids can be classified by differences in functional groups (position, number or stereochemistry). In category **A**, there are four related alkaloids, (−)-8-deoxyserratinine,[3] (−)-serratinine[4] (not shown in Figure 1, see Scheme 8), (−)-serratine[4] and (−)-serratanidine,[5a,d,6] and they differ in the number or position of hydroxyl groups. Some newcomers relevant to (+)-fawcettimine were recently isolated. (−)-Lycopoclavamine-A is an atypical example of fawcettimine-type *Lycopodium* alkaloids because it has a methyl group of which the stereochemistry is opposite to that of other related alkaloids.[7] (−)-Lycopoclavamine-B has a tertiary hydroxyl group on the C-15 position as does (−)-serratine.[7] In any case, an oxygen functional group (hydroxyl or ketone group) on a C-13 position emerge as a common component in most of fawcettimine-type alkaloids. Indeed, fawcettimine-type *Lycopodium* alkaloids have recently provided a platform for synthetic chemists. Many elegant approaches to construct complex cyclic structures of these alkaloids have been reported.[1,8] On the other hand, most of the synthetic studies focused on (−)-8-deoxyserratinine, (+)-fawcettimine, and their skeletal derivatives (defined as "Standard") because easily available chiral cyclohexenones **1**, which is often prepared from (+)-pulegone, could be an origin of the 15-(*R*)-methyl group in these alkaloids.[1e,f] Consequently, they are "skeletal divergent synthesis" of these standard alkaloids. In contrast, synthetic studies of irregular types of the alkaloids, such as (−)-lycopoclavamine-A having an "unusual methyl group", "highly oxygenated" (−)-serratine and (−)-serratanidine, are sparse.[8a,9,10] This is probably because the strategy using convenient material **1** is not applicable to synthesis of these alkaloids unlike that of (−)-8-deoxyserratinine and (+)-fawcettimine. In such cases, stereocontrolled introduction of methyl and hydroxy groups is required. Inubushi and co-workers reported the results of their pioneer study on the synthesis of (±)-serratinine in 1974,[11] but insufficient stereocontrol was unavoidable at that time. Quite recently, we reported the first syntheses of (±)-serratine and related alkaloids using a stereocontrolled strategy based on Diels–Alder reaction between a 2-alkynylcyclopetenone and (*E*)-1-(trimethylsilyloxy)-3-methylbutadiene.[12]

In this paper, we present a concept of redox divergent synthesis of fawcettimine-type *Lycopodium* alkaloids by expanding our previous synthetic strategy. The present work addresses representative alkaloids consisting of major core structure **A** or **B** to plainly demonstrate this concept (Figure 1). Our synthetic study can be placed in "redox divergent synthesis" of fawcettimine-type alkaloids complementing precedent reports of "skeletal divergent synthesis". We herein describe that this strategy is a general method to access various fawcettimine-type alkaloids.

Results and Discussion

An outline of our synthetic strategy is shown below. Diastereoselective Diels–Alder reaction between (*E*)-1-(trimethylsilyloxy)-

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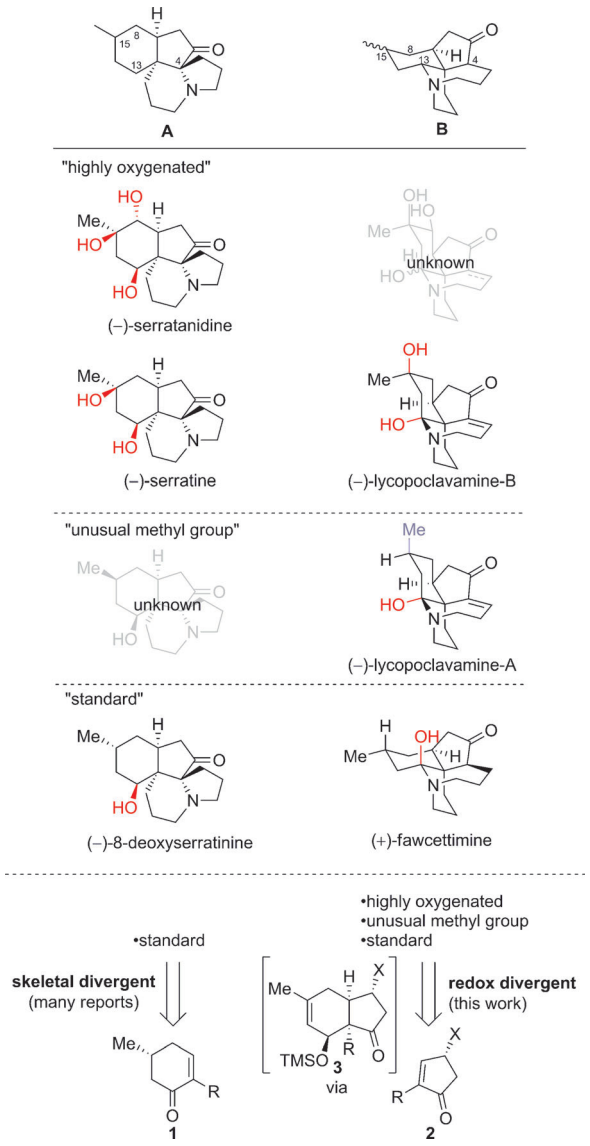
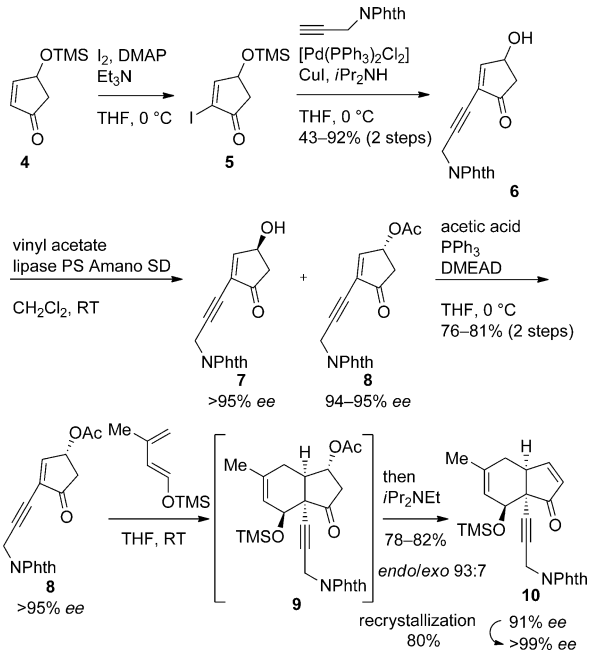


Figure 1. Target natural products and the concept of synthesis. TMS = trimethylsilyl.

3-methylbutadiene and chiral cyclopentenone **2** (X = OPG; PG = protecting group) could be designed to obtain chiral bicyclo[4.3.0] compound **3** (Figure 1).[13] Stereoselective reduction of the olefin of compound **3** would each provide a saturated bicyclo compound having an (*R*) or (*S*)-methyl group on a cyclohexane ring, which corresponds to partial structures of (–)-8-deoxyserratinine or (–)-lycopoclavamine-A, respectively. We observed palladium-catalyzed olefin isomerization of a racemic derivative of compound **3** (X = H) in a previous study.[12] Therefore, hydroxyl groups of highly oxygenated alkaloids such as (–)-serratine and (–)-serratanidine could be introduced via isomerization of **3** and following stereoselective oxygenation of an olefin. Construction of an azonane skeleton would be achievable by a common established procedure, and final elaboration would lead to the corresponding alkaloids.[14]

First, we set out to prepare chiral cyclopentenone **8** to test the diastereoselective Diels–Alder reaction. Chiral 4-hydroxy-2-cyclopentenone derivatives are known to work as good dienophiles of diastereoselective Diels–Alder reactions.[13] Although chiral 4-hydroxy-2-cyclopentenones are easily available and could be used as a starting material of **8**,[15] kinetic resolution of a racemic 2-substituted 4-hydroxy-2-cyclopentenone derivative using a lipase was chosen as a simple and reliable method to prepare it on a multigram scale.[16] An iodine atom was introduced to a 2-position of racemic protected 4-hydroxy-2-cyclopentenone **4**[17] by treatment with iodine (1.5 equiv) in the presence of *N*,*N*-dimethyl-4-aminopyridine (DMAP, 20 mol%) and triethylamine (2.0 equiv),[18] and the crude product **5** was subjected to Sonogashira conditions (2 mol% of catalysts) with *N*-propargylphthalimide (1.5 equiv) to give racemic 2-alkynyl-4-hydroxy-2-cyclopentenone **6** in good yield (Scheme 1).[19] A 2-alkynyl group is essential to improve the poor reactivity of 2-substituted cyclopetenones in the Diels–Alder reaction.[20] When compound **6** was exposed to vinyl acetate (3.0 equiv) and Lipase PS Amano SD (30 wt%), optical resolution was readily achieved to provide (*S*)-4-hydroxy-2-cyclopentenone **7** and (*R*)-4-acetoxy-2-cyclopentenone **8**. HPLC analysis of a small amount of sample taken from the reaction mixture indicated high enantiomeric excess values of **7** (>95% *ee*) and **8** (94–95% *ee*). The mixture of **7** and **8** was subjected to Mitsunobu conditions with acetic acid and converged to **8** in good yield and an optical purity (>95% *ee*). When a mixture of dienophile **8** and (*E*)-1-(trimethylsilyloxy)-3-methylbutadiene (90% geometrical purity, 2.0 equiv) was stirred for 48–72 h at room temperature, the Diels–Alder reaction readily proceeded to form cycloadduct **9**, though heating was required in the reaction of dienophile having no acetoxy group.[12] Probably, an acetoxy group activated the dienophile by an inductive effect. Subsequent treatment with diisopropylethylamine (1.5 equiv) set off elimination of the acetoxy group to afford chiral bicyclo[4.3.0] compound **10** in good yield. Cycloaddition should occur from the less hindered β-face of **8**,[13] and facial selectivity could be estimated to be good because the optical purity of **10** did not significantly decrease (91% *ee*). The optical purity of **10** could be improved by recrystallization (>99% *ee*: minor enantiomer not detected).

Hydrogenation of compound **10** with 10% palladium carbon was a key step for redox-divergent synthesis (Table 1). A work-up procedure with acidification followed hydroxylation of compound **10** to remove a trimethylsilyl group. Tracing the reaction (20 wt% of 10% Pd/C) by ^{1}H NMR analysis indicated that alkyne and cyclopentenone moieties were saturated faster than was a cyclohexene moiety. When compound **10** was exposed to hydrogenation conditions for a limited time (24 h) in the presence of a small catalytic amount of 10% Pd/C, cyclohexenol product **11** was isolated as a major product along with isomerized cyclohexenol product **12** and thoroughly saturated product **13** bearing an (*S*)-methyl group (entry 1).[21] The above NMR experiment also indicated that isomerization of the cyclohexene moiety was promoted in the presence of 20 wt% of the catalyst. In fact, isomerized product **12** could be obtained as a major product by increasing the catalytic amount of 10% Pd/C to 20 wt% and prolonging the reaction time (120 h) (entry 2). Further increase of the catalytic amount

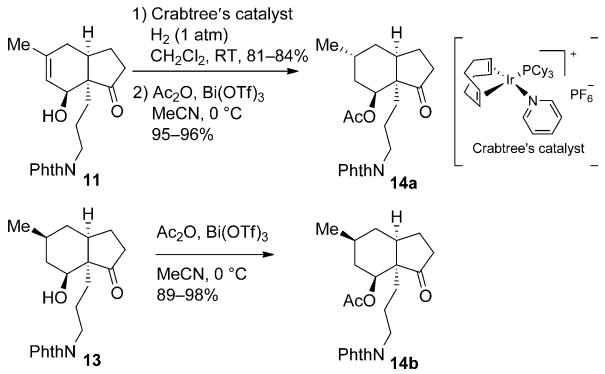


Scheme 1. Preparation of chiral dienophile **8** and Diels–Alder reaction. DMAP = *N*,*N*-dimethyl-4-aminopyridine; Phth = phthaloyl; DMEAD = di-2-methoxyethyl azodicarboxylate.

(50 wt%) provided saturated product **13** as a major product (entry 3). The reaction under high pressured hydrogen gas promoted production of **13** (entry 4). Although selectivity of these reactions was not perfect, all of the products obtained could be used for synthesis of each alkaloid.

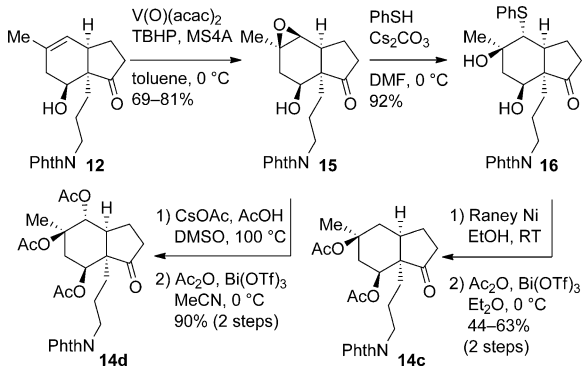
Saturated compound **14a** bearing an (*R*)-methyl group was obtained by hydroxyl group-directed diastereoselective hydrogenation of cyclohexenol compound **11** by Crabtree's catalyst (1 mol%)[22] and the following bismuth triflate-catalyzed (5 mol%) acetylation of the hydroxyl group.[23] A hydroxyl group of saturated compound **13** bearing an (*S*)-methyl group was also protected by an acetyl group to give compound **14b** (Scheme 2).

Sharpless diastereoselective oxidation of compound **12** exclusively gave the corresponding epoxide **15** in good yield.[24] Addition of thiophenol (2.0 equiv) to epoxide **15** proceeded in



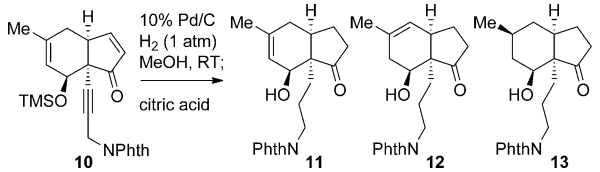
Scheme 2. Synthesis of **14a** and **14b**. Ac = acetyl; Tf = trifluoromethanesulfonyl.

the presence of cesium carbonate (2.0 equiv) at low temperature (0 °C) and provided diol **16** in good yield. Desulfurization of **16** with Raney nickel (W-2) followed by acetylation of two hydroxyl groups gave diacetate **14c** having a protected tertiary hydroxyl group. Another oxygen atom could be introduced into epoxide **15** by a combination of cesium acetate (1.0 equiv) and acetic acid (2.0 equiv), and protection of the two remaining hydroxyl groups by acetyl groups gave triacetate **14d** (Scheme 3).



Scheme 3. Synthesis of **14c** and **14d** by stereoselective introduction of oxygen functional groups. acac = acetylacetone; TBHP = *tert*-butyl hydroperoxide; MS = molecular sieves; DMF = *N*,*N*-dimethylformamide.

Table 1. Hydrogenation of **10**.

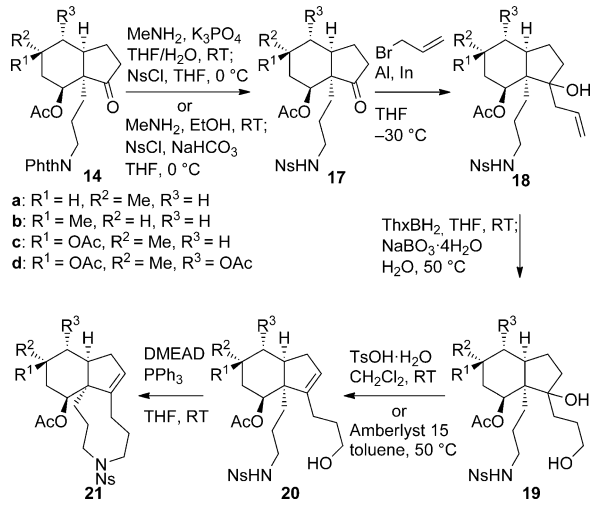


Entry	10% Pd/C [wt%]	*t* [h]	Yield [%][a] 11	12	13
1	10	24	59	13	4
2	20	120	24	52	17
3	50	120		34	40
4[b]	20	36			62

[a] Isolated yield. [b] 50 atm of H_2.

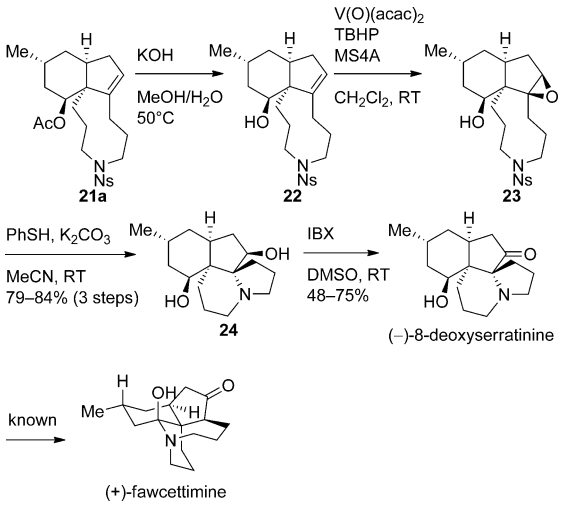
Since we succeeded in obtaining four synthetic intermediates by elaborating desired functional groups from common synthetic intermediate **10**, we next set out to construct an azonane skeleton from each compound. A common procedure could be applied to this transformation basically (Table 2). Phthaloyl groups of compounds **14a–d** were removed by treatment with an excessive amount of methylamine, and 2-nitrobenzenesulfonamides (nosylamides) **17a–d** were obtained by subsequent treatment with 2-nitrobenzenesulfonyl chloride (2.0 equiv) after quick removal of excess methylamine by simple evaporation.[25] Reproducibility of these reactions was somewhat sensitive to reaction scale because the corresponding cyclic imines were partially produced by evaporation after removal of the phthaloyl group. Introduction of a three-carbon

Table 2. Construction of the azonane ring. Ns = 2-nitrobenzenesulfonyl; Thx = thexyl; Ts = *p*-toluenesulfonyl.



Entry	Yield [%][a]		
	17	**19** (2 steps)	**21** (2 steps)
a	58–85	54–63	38–50
b	77–92	57–66	49–64
c	58	58	52
d	65–83	44–46	36–46

[a] Isolated yield.



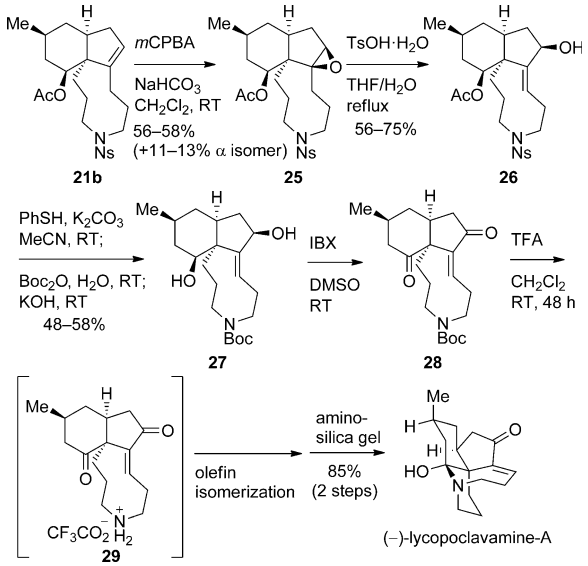
Scheme 4. Total synthesis of (−)-8-deoxyserratinine. IBX = 2-iodoxybenzoic acid; DMSO = dimethylsulfoxide.

unit to a ketone group of compounds **17a–d** was achieved by an indium (5 mol%)-catalyzed addition reaction of an allyl aluminum reagent prepared by allyl bromide (6.0 equiv) and metal aluminum (6.0 equiv) and provided homoallyl alcohols **18a–d** as single isomers (stereochemistry not determined).[26] Terminal alkenes of compounds **18a–d** were converted to primary alcohols by hydroboration with thexylborane (ca. 4 equiv), and the following oxidative treatment with sodium perborate (10 equiv) gave 1,4-diols **19a–d**. Elimination of tertiary hydroxyl groups of compounds **19a–d** readily proceeded by treatment with *p*-toluenesulfonic acid (20 mol%) or Amberlyst 15 to give cyclopentene derivatives **20a–d**.[27] An azonane ring of tricyclic compounds **21a–d** was constructed by intramolecular amination between primary alcohols and nosyl amides of compounds **20a–d** under Mitsunobu conditions with di-2-methoxyethyl azodicarboxylate (DMEAD, 1.5 equiv).[25,28,29]

End games to lead to each alkaloid from four azonane compounds **21a–d** are shown in Schemes 4–7. Alcohol **22** produced by hydrolysis of compound **21a** was subjected to Sharpless epoxidation conditions to give β-epoxide **23** exclusively (Scheme 4). When crude epoxide **23** was treated with thiophenol (2.0 equiv) and potassium carbonate (2.0 equiv), tetracyclic compound **24** was produced by a sequence of transformation including removal of a nosyl group and cyclization onto an epoxide. Interestingly, we found that chemoselective oxidation of a cyclopentanol moiety of diol **24** was successful by using 2-iodoxybenzoic acid (IBX, 2.0 equiv) and directly afforded (−)-8-deoxyserratinine. Although the corresponding diketone (8-deoxy-13-dehydroserratinine) was hardly detected in this reaction, the diketone would have been obtained if another stronger oxidizer had been used.[29] Despite many reports of synthesis of (−)-8-deoxyserratinine, this observation has been overlooked because synthesis of (−)-8-deoxyserratinine has usually been achieved by chemoselective reduction of (−)-8-deoxy-13-dehydroserratinine.[1e,f] (−)-8-Deoxyserratinine can become a precursor of other related alkaloids, such as (+)-fawcettimine, (+)-fawcettidine and (+)-lycoflexine, via (−)-8-deoxy-13-dehydroserratinine.[1e,f,30] This implies that our synthetic route leads to various related alkaloids. Optical rotation data for synthesized (−)-8-deoxyserratinine ($[\alpha]_D^{18} = -10.2$ ($c = 0.58$, EtOH)) were consistent with previously reported values ($[\alpha]_D^{17} = -17.2$ ($c = 1.01$, EtOH);[3] $[\alpha]_D^{18} = -15.6$ ($c = 1.00$, EtOH);[30] $[\alpha]_D^{21} = -12.0$ ($c = 0.1$, EtOH)[1e]), and this result proved that absolute configurations of all chiral synthesized compounds were correct.

Treatment of compound **21b** with *m*-chloroperbenzoic acid (*m*CPBA, 2.0 equiv) predominantly gave β-epoxide **25**. Elimination of epoxide **25** with *p*-toluenesulfonic acid (1.0 equiv) produced allyl alcohol **26** as a single geometric isomer (Scheme 5). In our previous study, we found that a similar epoxide to compound **25** gave the corresponding allyl alcohol stereospecifically under the same reaction conditions.[12] By comparing with the previous results, it was presumed that **26** had a (*Z*)-olefin. After exchanging the Ns group on the nitrogen atom of compound **26** for a *tert*-butoxycarbonyl (Boc) group, subsequent removal of the acetoxy group gave diol **27**. Oxidation of two hydroxyl groups of **27** with IBX (5.0 equiv) afforded diketone **28**, which was successively exposed to an excessive amount of trifluoroacetic acid (TFA) to remove the Boc group. ^{1}H NMR analysis of the crude product obtained from the reaction mixture showed production of TFA salt **29** and gradual transformation into another product. A significant change in the chemical shift of alkene C-H peaks was observed (**29**: $\delta = 5.80$, new product: $\delta = 6.95$). After complete disappearance of **29**, purification of the crude product by amino-

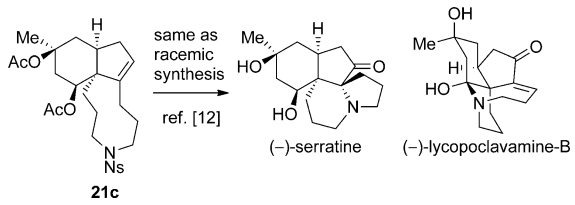
silica gel (CHROMATOREX NH-DM1020) afforded lycopoclavamine-A. All physical data including the optical rotation data ($[\alpha]_D^{23} = -56.3$ ($c = 0.58$, $CHCl_3$)) of synthesized lycopoclavamine-A accorded with those of the natural product ($[\alpha]_D^{25} = -48.8$ ($c = 0.11$, $CHCl_3$)).[7] In this point, we suspected that a (*Z*)-olefin of compound **28** was isomerized into an (*E*)-olefin by TFA, and the following cyclization produced lycopoclavamine-A. If salt **29** originally had an (*E*)-olefin, the following cyclization would occur faster.[31] Actually, transformation of salt **29** into another product was very slow (48 h), and it would therefore include not only the cyclization step but also the isomerization step.



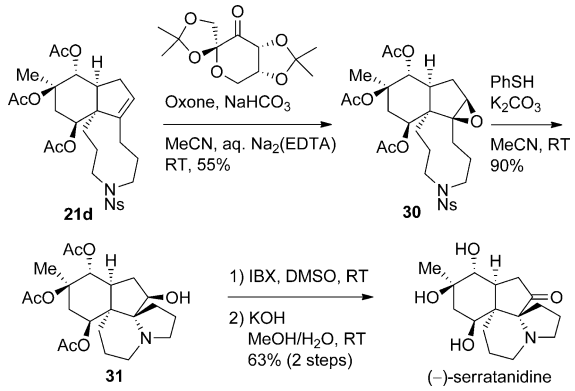
Scheme 5. Total synthesis of (−)-lycopoclavamine-A. *m*CPBA = *m*-chloroperbenzoic acid; Boc = *tert*-butoxycarbonyl; TFA = trifluoroacetic acid.

Transformation of **21 c** into (−)-serratine and (−)-lycopoclavamine-B was performed according to the procedure described by us previously (Scheme 6).[12] Optical rotation values of synthesized compounds ((−)-serratine: $[\alpha]_D^{29} = -7.9$ ($c = 0.073$, EtOH); (−)-lycopoclavamine-B: $[\alpha]_D^{23} = -14.0$ ($c = 0.087$, $CHCl_3$)) were consistent with those of natural products ((−)-serratine: $[\alpha]_D^{22} = -15.0$ ($c = 1.02$, EtOH);[5c] $[\alpha]_D^{24} = -11.8$ ($c = 0.39$, EtOH);[5d] (−)-lycopoclavamine-B: $[\alpha]_D^{25} = -13.9$ ($c = 0.06$, $CHCl_3$)[7]).

Epoxidation of highly oxygenated compound **21 d** with *m*CPBA produced undesired α-epoxide as a main product along with β-epoxide **30** (α/β ca. 80:20). Fortunately, we found that Shi epoxidation of **21 d** provided β-epoxide **30** as a main product.[32,33] Removal of the Ns group of **30** set off intramolecular addition of the resultant secondary amine to the epoxide to give tetracyclic compound **31** having seven stereocenters. Finally, after oxidation of alcohol **31** with IBX (2.0 equiv), removal of three acetyl groups afforded (−)-serratanidine for which physical data including optical rotation data ($[\alpha]_D^{20} = -34.7$ ($c = 0.17$, EtOH)) were identical to those of the natural product ($[\alpha]_D^{12.5} = -52.0$ ($c = 1.01$, EtOH);[6] $[\alpha]_D^{26} = -31.0$ ($c = 0.049$, EtOH)[5d]) (Scheme 7).



Scheme 6. Total synthesis of (−)-serratine and (−)-lycopoclavamine-B.

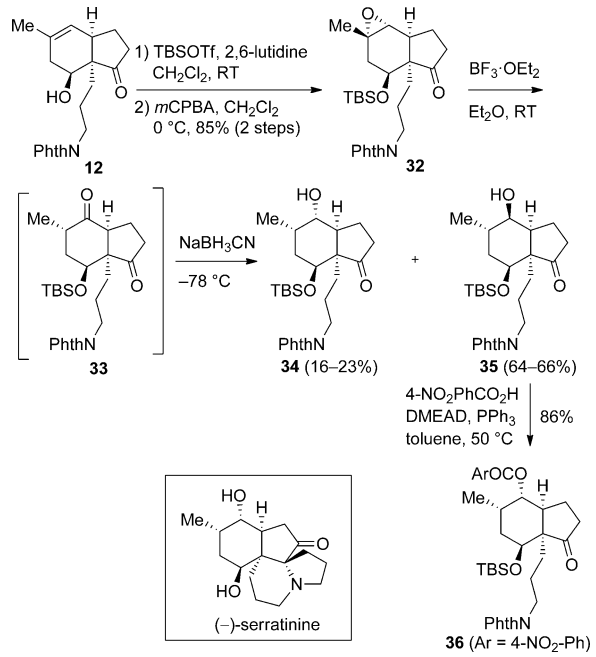


Scheme 7. Total synthesis of (−)-serratanidine. Oxone = potassium peroxymonosulfate; EDTA = ethylenediaminetetraacetate.

We also made efforts to synthesize (−)-serratinine from our synthetic intermediate **12** (Scheme 8). A hydroxyl group of compound **12** was protected by a *tert*-butyldimethylsilyl group, and epoxidation of the obtained product with *m*CPBA gave α-epoxide **32** exclusively. Treatment of epoxide **32** with boron·trifluoride diethyl etherate (2.0 equiv) caused a stereospecific 1,2-hydride shift to produce α-methylcyclohexanone **33**. Subsequent treatment of the reaction mixture with sodium cyanoborohydride (2.0 equiv) in one pot gave desired alcohol **34** as a minor diastereomer due to a hydride approach from a concave face. Stereochemistry of a hydroxyl group of major isomer **35** could be inverted by Mitsunobu reaction with 4-nitrobenzoic acid to provide a 4-nitrobenzoate derivative of **36**.[34] Although the current procedure to introduce the hydroxyl group is still circuitous, the possibility of synthesis of (−)-serratinine has been shown. Further study will be continued to improve the procedure to introduce the secondary alcohol and complete the total synthesis of (−)-serratinine.

Conclusion

We have achieved the total synthesis of (−)-8-deoxyserratinine, (+)-fawcettimine (formal), (−)-lycopoclavamine-A, (−)-serratine, (−)-lycopoclavamine-B and (−)-serratanidine. The main carbon core was enantioselectively constructed on the basis of Diels–Alder reaction, and plural synthetic intermediates were derived from the product by stereoselective introduction of desired functional groups. The present synthetic study is a robust approach to fawcettimine-type *Lycopodium* alkaloids by applying the redox divergent strategy. The outstanding aspect of the synthetic route was emphasized by the successful synthesis of



Scheme 8. The synthetic study toward (−)-serratinine. TBS = *tert*-butyldimethylsilyl.

(−)-serratanidine because it was accessible to derivatives having dense stereocenters. In short, many previous synthetic studies of them pursued elegance of skeletal construction, whereas we demonstrated how structurally close natural products and various derivatives could be generally synthesized.

The meaning of natural product synthesis is currently diverse and somewhat wandering.[35] In addition, the reliability of product yield has been vacillating in recent studies on organic synthesis.[36] In such situations, at least, it is crucial to synthesize more natural products and derivatives systematically as long as they are potential candidates of pharmaceuticals.[37] The potential of *Lycopodium* alkaloids is still unknown because their ability as pharmaceuticals has not been investigated sufficiently and new derivatives are currently being isolated. We believe that our synthetic study will serve as a motif of derivative synthesis when *Lycopodium* alkaloids will be taken up as important targets in pharmaceutical science.

Experimental Section

All experimental details including procedures, characterization and copies of spectra are available in the Supporting Information.

Acknowledgements

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Keywords: asymmetric synthesis · cycloaddition · divergent synthesis · natural products · total synthesis

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