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Ten new fawcettimine-related alkaloids from three species of *Lycopodium*

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ABSTRACT

Ten new fawcettimine-related alkaloids, i.e., lycopoclavamines, lycoposquarrosamine-A, and other hydroxylated fawcettimine derivatives, were isolated from three species of *Lycopodium* (*Lycopodium clavatum*, *Lycopodium serratum*, *and Lycopodium squarrosum*). The structures of the new alkaloids were elucidated by spectroscopic methods and chemical correlation.

1. Introduction

Lycopodium plants have sustained interest because they contain alkaloids having complex polycyclic structures[1] and biological activities, such as acetylcholine esterase inhibitory activity.[2] In the course of our chemical studies on *Lycopodium* plants,[3] we investigated the constituents in three species of *Lycopodium*, i.e., *Lycopodium clavatum*, *Lycopodium serratum*, and *Lycopodium squarrosum*, and our effort resulted in the isolation of ten new alkaloids having fawcettimine-related skeletons. In this paper, we describe the structure elucidation of these new alkaloids (**1**–**10**) (Fig. 1).

2. Results and discussion

L. clavatum was collected in Toyama Prefecture, Japan and the alkaloid extract was prepared by following a conventional procedure. The alkaloid fraction was purified by repeated column chromatography using silica gel, alumina, and amino-silica gel, and two new alkaloids named lycopoclavamines-A (**1**) and -B (**2**) were isolated together with fawcettimine (**11**).[4]

Lycopoclavamine-A (**1**) was obtained as a colorless amorphous solid and its molecular formula was deduced from HREIMS analysis to be $C_{16}H_{23}NO_2$. ^1H and ^{13}C NMR spectra (Table 1) showed the presence of one carbonyl group (δ_C 206.6), one tri-substituted olefinic function (δ_H 6.91, δ_C 136.3, 141.4), and one carbinolamine moiety (δ_C 85.0). Particularly, the presence of the carbinolamine moiety suggested that **1** had a fawcettimine-related skeleton. ^1H–^1H COSY and HSQC analyses indicated the presence of three carbon chains (**a**–**c**) shown by the bold lines in Fig. 2. The existence of 3,4-didehydrofawcettidane skeleton in **1** was elucidated by HMBC spectroscopic analysis as follows. HMBC correlation between the olefinic hydrogen [δ_H 6.91 (H-3)] and the carbonyl carbon [δ_C 206.6 (C-5)] as well as the correlation between the terminal hydrogen [δ_H 1.90 (H-6)] in fragment **b** and another olefinic carbon [δ_C 141.4 (C-4)] indicated that fragments **a** and **b** were connected by an enone moiety. The presence of a cyclopentanone ring (C-4–C-7 and C-12) was elucidated by HMBC correlations between the methylene hydrogen [δ_H 1.90 (H-6)] in fragment **b** and the quaternary carbon [δ_C 53.4 (C-12)] as well as between the methine hydrogen [δ_H 2.08 (H-7)] in fragment **b** and the olefinic carbon [δ_C 141.4 (C-4)]. Fragment **c** should be connected to the quaternary carbon [δ_C 53.4 (C-12)] described above based on the correlation between the methine hydrogen [δ_H 2.08 (H-7)] in fragment **b** and the methylene carbon [δ_C 30.5 (C-11)]. Finally, the connectivity of the three fragments

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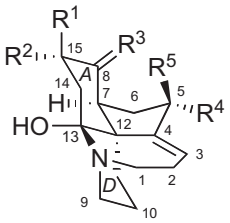
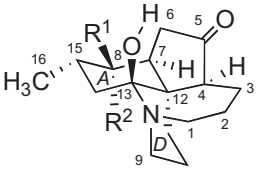
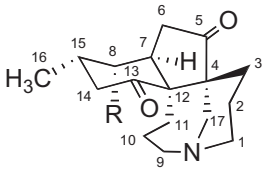


1: $R^1 = CH_3$, $R^2 = H$, $R^3 = H_2$, R^4 & R^5 = carbonyl
2: $R^1 = OH$, $R^2 = CH_3$, $R^3 = H_2$, R^4 & R^5 = carbonyl
3: $R^1 = CH_3$, $R^2 = H$, $R^3 = H_2$, $R^4 = OH$, $R^5 = H$
4: $R^1 = CH_3$, $R^2 = H$, $R^3 = O$, $R^4 = H$, $R^5 = OH$



5: $R^1 = H$, $R^2 = OAc$
6: $R^1 = H$, $R^2 = OH$
7: $R^1 = OAc$, $R^2 = H$
8: $R^1 = OH$, $R^2 = H$
11: $R^1 = R^2 = H$



9: R = OAc
10: R = H, *N*-oxide
12: R = H
13: R = OH

Fig. 1. Structures of new (**1**–**10**) and known (**11**–**13**) alkaloids.

Table 1
^{13}C NMR data of **1**–**4** and **11**

Position	1	2	3	4	11
1	46.7	46.9	47.3	47.4	50.0
2	29.9	29.7	29.8	29.4	22.6
3	136.3	136.6	125.9	125.6	35.9
4	141.4	140.7	150.1	148.4	60.2
5	206.6	205.7	75.7	74.6	220.4
6	43.2	42.8	38.3	32.0	41.9
7	37.3	36.2	42.8	55.1	43.2
8	40.5	46.1	40.1	212.6	31.9
9	46.0	45.6	46.1	46.1	53.4
10	23.0	22.8	22.9	22.3	28.8
11	30.5	29.9	30.9	32.3	28.2
12	53.4	53.3	54.7	57.5	48.2
13	85.0	86[a]	85.4	83.9	88 (br)
14	43.1	46.8	43.5	43.5	44.4
15	27.3	71.5	27.7	41.2	23.7
16	22.3	29.2	22.5	14.6	21.8

[a] Based on HMBC correlation.

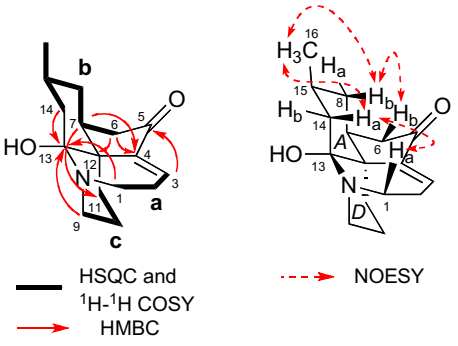


Fig. 2. Selected 2D NMR data of lycopoclavamine-A (**1**).

through a carbinolamine moiety was elucidated by the correlations between the four hydrogens located at the terminus of each fragment [δ_H 2.93 (H-1), 2.72 (H-9), 1.91 (H-14), and 1.30 (H-14)] and the carbinolamine carbon [δ_C 85.0 (C-13)], respectively. NOESY correlation between H-1a and H-14a indicated a *trans*-decahydroquinoline ring system at the *A*/*D*-ring junction. This configuration is enabled by taking an opposite configuration at the hemiaminal carbon (C-13) relative to that in fawcettimine (**11**). Furthermore, NOESY correlations H-16/H-8b and H-16/H-14a indicated that **1** had a β-oriented methyl group at C-15, which differs from that in common fawcettimine-type *Lycopodium* alkaloids. Following lycovatin A isolated by Kobayashi and co-workers,[5] this is the second example of fawcettimine-related alkaloids possessing a *trans*-decahydroquinoline ring system at the *A*/*D*-ring junction as well as a β-oriented methyl group at C-15.

Lycopoclavamine-B (**2**) was obtained as a colorless amorphous solid and its molecular formula was deduced from HREIMS analysis to be $C_{16}H_{23}NO_3$, which implied that **2** was an oxygenated derivative of **1**. The NMR spectra of **2** resembled those of **1** except that the methyl group was detected as a singlet signal in the lower field relative to that of **1**, and one oxygenated quaternary carbon resonance was observed instead of a methine signal corresponding to C-15 in **1**. These NMR data implied that **2** must be a 15-hydroxy derivative of **1**. ^{1}H–^{1}H COSY and HSQC analysis of **2** indicated two carbon chains ascribable to fragments **a** and **c** in **1** as well as a snapped chain corresponding to fragment **b** (Fig. 3). HMBC correlations between the singlet methyl hydrogen [δ_H 1.49 (H_3-16)] and three carbons [δ_C 46.1 (C-8), 46.8 (C-14), and 71.5 (C-15)] showed the connectivity of the carbon chain corresponding to fragment **b** in **1**. NOESY correlations between H-7 and H-16 indicated that the tertiary hydroxy group at C-15 should have a β-equatorial orientation. Other stereochemistry was elucidated based on NOESY correlations, such as H-1a/H-14a, H-6b/H-8b, and H-8b/H-14a. Therefore, **2** was elucidated to be the 15-hydroxy derivative of **1**.

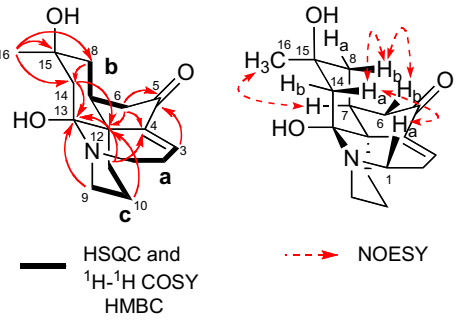
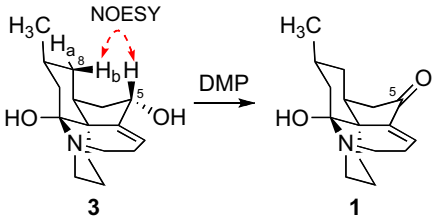


Fig. 3. Selected 2D NMR data of lycopoclavamine-B (**2**).

L. serratum was collected in Chiba Prefecture, Japan. The alkaloid fraction prepared in the previous study[3f] was purified by repeated column chromatography to give one new alkaloid named dihydrolycopoclavamine-A (**3**).

Dihydrolycopoclavamine-A (**3**) was obtained as a colorless amorphous solid and its molecular formula was deduced from HREIMS analysis to be $C_{16}H_{25}NO_2$, which was two hydrogens more than that of **1**. The NMR spectra of **3** resembled those of **1** except for the presence of an oxymethine signal instead of a carbonyl carbon and an olefinic hydrogen signal that shifted to the higher field relative to that of **1**. This suggested that **3** was a dihydro derivative of **1**. Extensive NMR analysis supported the α-orientation of a secondary hydroxy group at C-5, which was elucidated from the NOESY correlation between H-5 and H-8b (Scheme 1). Oxidation of **3** with Dess–Martin periodinane (DMP) afforded **1**, whose

spectroscopic data were completely identical with those of the natural product. Therefore, the structure of **3** was confirmed to be dihydrolycopoclavamine-A.



Scheme 1. Selected NOESY correlation of dihydrolycopoclavamine-A (**3**) and chemical correlation of **3** and lycopoclavamine-A (**1**).

L. squarrosum was purchased at a flower market in Bangkok, Thailand, and the alkaloid extract was obtained by following a conventional procedure similar to that used for *L. clavatum*. The alkaloid fraction was separated by column chromatography to afford seven new alkaloids **4**–**10** together with fawcettimine (**11**) and lycoflexine (**12**).[6]

Lycoposquarrosamine-A (**4**) was obtained as a colorless solid and its molecular formula was established as $C_{16}H_{23}NO_3$ by HREIMS analysis, which was identical with that of **2**. NMR data showed that **4** had a 3,4-didehydrofawcettidane skeleton with a *trans*-decahydroquinoline ring, one carbonyl group, and one secondary hydroxy group, which was almost the same as that of **2** except for the chemical shifts of the carbonyl and olefinic functions and the presence of a secondary hydroxy group. Among them, the chemical shift of the carbonyl carbon resonated at δ_C 212.6 (C-8), indicating that this function did not constitute an α,β-unsaturated carbonyl moiety present in **2**. HMQC and $^1H-^1H$ COSY analyses indicated the presence of four partial structures [**a**: $-CH_2CH_2CH-$ (C-1–C-3), **b**: $-CH(OH)CH_2CH-$ (C-5–C-7), **c**: $-CH_2CH_2CH_2-$ (C-9–C-11), and **d**: $-CH_2CH(CH_3)-$ (C-14–C-16)] (Fig. 4). HMBC correlation between the olefinic hydrogen [δ_H 5.87 (H-3)] located at the terminus of unit **a** and the oxygenated methine carbon in unit **b** [δ_C 74.6 (C-5)] indicated the presence of an allylic alcohol moiety. HMBC correlation between the methyl hydrogen [δ_H 1.02 (H_3-16)] and the ketonic carbon [δ_C 212.6 (C-8)] as well as correlation between the central methylene hydrogen in unit **b** [δ_H 1.61 (H-6)] and the same carbonyl carbon implied that **4** had a carbonyl function at position 8. Furthermore, the plane structure of **4** was elucidated by HMBC analysis based on correlations H-3/C-12, H-9/C-13, H-11/C-4, H-11/C-7, and H-14/C-13. The β-orientation of the secondary hydroxy group was elucidated from the NOE correlation H-5/H-7. The NOE correlation between H-14b (δ_H 1.68) and H-15 (δ_H 3.11) as well as the large coupling constant (13.2 Hz) between H-14a (δ_H 2.49) and H-15 indicated the β-equatorial orientation of the C-16 methyl group. Thus, **4** was elucidated to be a 5-hydroxy-8-keto derivative of **1**.

Compound **5** was obtained as a colorless amorphous solid and its molecular formula was established as $C_{18}H_{27}NO_4$ by HREIMS analysis. NMR analysis (Table 2) indicated the presence of one secondary acetoxy group (δ_H 2.11, 5.00; δ_C 21.3, 73.5, and 170.5) besides the characteristic resonance for the fawcettimine-type skeleton (eg. carbinolamine carbon resonated at δ_C 88.6) and implied that **5** must be an acetoxy derivative of fawcettimine (**11**). Extensive NMR analyses (particularly HMQC and $^1H-^1H$ COSY) indicated the presence of four fragment carbon chains [**a**: $-CH_2CH_2CH_2CH-$ (C-1–C-4), **b**: $-CH_2CHCH-$ (C-6–C-8), **c**: $-CH_2CH_2CH_2-$ (C-9–C-11), and **d**: $-CH_2CH(CH_3)-$ (C-14–C-16)] (Scheme 2). HMBC correlation between the secondary methyl hydrogen (δ_H 0.94, H_3-16) and the oxymethine carbon (δ_C 73.5, C-8) as well as HMBC correlations between the oxymethine hydrogen (δ_H 5.00, H-8) and the acetyl carbonyl carbon (δ_C 170.5) and between the methylene hydrogen (δ_H 1.05, H-14) and the two quaternary carbons [δ_C 48.2 (C-12) and 88.6 (C-13)] indicated that the acetoxy group was located at C-8. The α-orientation of the C-8 acetoxy group was indicated from the enhancement of the signals for H-6 methylene hydrogens (δ_H 2.44, 2.33) by H-8 irradiation in the NOE experiment. Thus, **5** was confirmed to be an 8α-acetoxy derivative of fawcettimine, which was reported to be a synthetic intermediate (acetylaposerratinine) in the literature,[7] and this is the first isolation from nature.

Table 2
^{13}C NMR data of **5**–**8**

Position	5	6	7	8
1	53.5	54.3	53.4	53.4
2	28.4	29.5	28.6	28.5
3	28.0	29.2	28.0	27.9
4	60.4	61.7	60.3	60.6
5	218.1	222.9 (br)	218.5	219.0
6	40.9	42.5	38.3	37.8
7	47.7	51.7	45.6	49.1
8	73.5	72.2	75.7	73.7
9	50.2	51.3	50.1	50.1
10	22.5	23.6	22.4	22.4
11	37.4	38.6	36.8	36.8
12	48.2	50.0	49.8	49.9
13	88.6	89.5	88.1	88 (br)
14	39.0	37.4	43.6	43.6
15	26.7	29.2	28.1	30.5
16	16.9	17.8	17.6	17.8
CH_3CO	21.3		21.0	
CH_3CO	170.5		170.9	

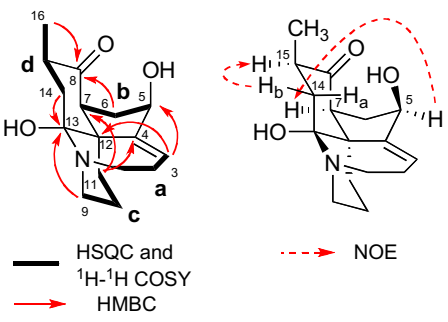
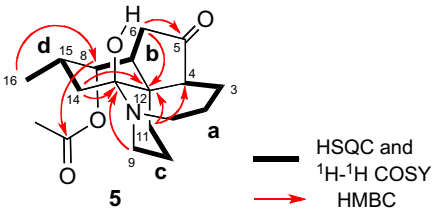
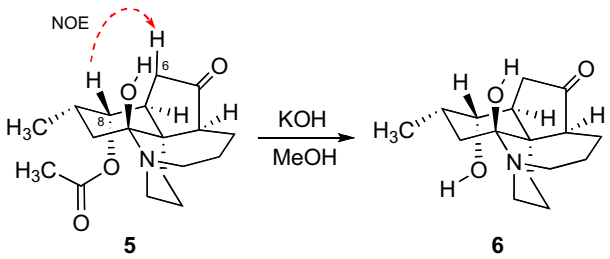


Fig. 4. Selected NMR data of lycoposquarrosamine-A (**4**).



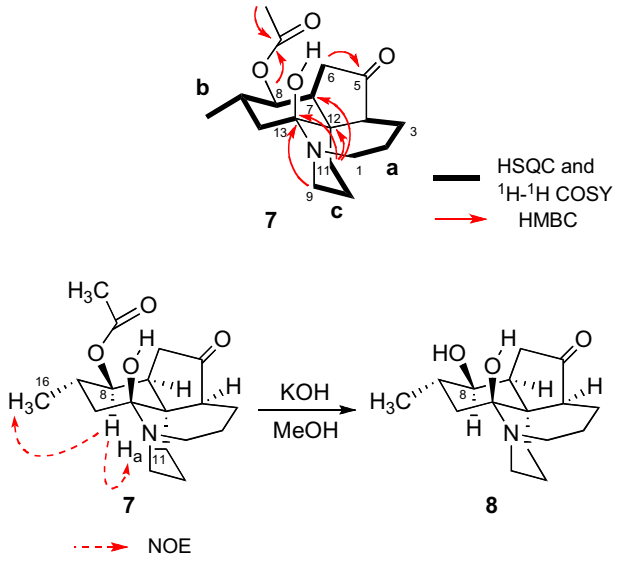


Scheme 2. Selected NMR data of acetylaposerratinine (**5**) and chemical correlation of **5** and 8α-hydroxyfawcettimine (**6**).

Compound **6** was obtained as a colorless solid and its molecular formula was analyzed by HREIMS analysis to be $C_{16}H_{25}NO_3$. ^1H and

^{13}C NMR spectra resembled those of **5** except for the absence of an acetoxy function and the existence of a higher-field-shifted oxymethine signal (δ_H 3.74, H-8). When **6** was dissolved in methanol-d_4, a methine signal ascribable to hydrogen at C-4 adjacent to the carbonyl group disappeared and C-4 methine carbon was observed as broad signal, which was caused by the proton–deuterium exchange. From the spectroscopic analysis, the structure of **6** was deduced to be a deacetylated **5** and therefore, the hydrolysis of **5** was conducted. When **5** was treated with KOH/MeOH, a deacetylated product was obtained, the spectroscopic data of which were completely identical with those of **6**. Thus, **6** was elucidated to be 8α-hydroxyfawcettimine.

Compound **7** was obtained as a colorless solid. Its molecular formula was established as $C_{18}H_{27}NO_4$ by HREIMS analysis and was identical with that of **5**. Although the ^{1}H and ^{13}C NMR signals well resembled those of **5**, the coupling pattern of the oxymethine resonance at δ_H 4.90 (dd, J=10.7, 6.1 Hz, H-8) differed from that in **5** (δ_H 5.00, s). The plane structure was identical with that of **5**, as elucidated by extensive NMR analysis. The presence of three fragments (**a**–**c**) was inferred from ^{1}H – ^{1}H COSY and HMQC measurements and the connectivities of the fragments were analyzed from the results of HMBC (particularly H-6/C-5, H-9/C-13, H-11/C-7, H-11/C-12, and H-11/C-13) (Scheme 3). The β-orientation of the acetoxy function located at C-8 was elucidated based on the NOE correlation between H-8 and H-11a. Thus, **7** was deduced to be 8β-acetoxyfawcettimine.

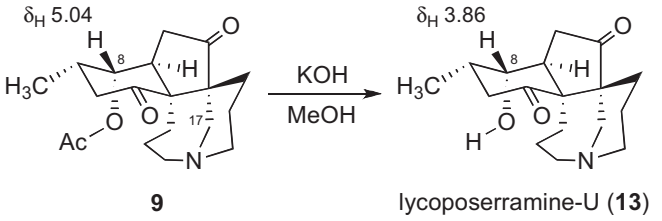


Scheme 3. Selected NMR data of 8β-acetoxyfawcettimine (**7**) and chemical correlation of **7** and 8β-hydroxyfawcettimine (**8**).

Compound **8** was obtained as a colorless amorphous solid and its molecular formula was analyzed by HREIMS analysis to be $C_{16}H_{25}NO_5$. ^{1}H and ^{13}C NMR data resembled those of **7** except for the absence of the acetyl signal and the existence of a higher-field-shifted oxymethine hydrogen signal (δ_H 3.71, H-8) compared to that in **7** (δ_H 4.90). Intensive NMR analysis indicated that **8** had a fawcettimine skeleton that possessed a hydroxy group at C-8. NOE correlation between the oxymethine hydrogen (H-8) and both H-11 and H-14 indicated the C-8 hydroxy group must be β-oriented. Compound **7** was hydrolyzed with KOH/MeOH to give **8**, which was completely identical with the natural product. Thus, **8** was confirmed to be 8β-hydroxyfawcettimine.

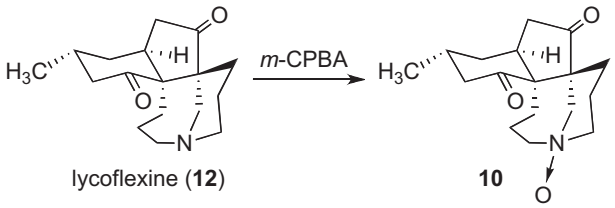
The absolute configurations of compounds **5**–**8** were identical with that of fawcettimine (**11**), whose absolute configuration was already established,[4] based on comparison of the cotton curves in the CD spectra.

Compound **9** was obtained as a colorless amorphous solid and its molecular formula was established as $C_{19}H_{27}NO_4$ by HREIMS. ^{1}H and ^{13}C NMR analysis implied the presence of two ketonic functions [δ_C 216.1 (C-5) and 212.4 (C-13)] and one additional methylene group [δ_H 3.18 and 2.62 (H_2-17), δ_C 54.8 (C-17)], which indicated that **9** had a lycoflexine-type skeleton. The NMR data of **9** well resembled those of lycoposerramine-U (**13**),[7] which was previously isolated from *L. serratum*. In the ^{1}H NMR spectra, **9** showed an acetyl methyl signal (δ_H 2.13) and an oxymethine signal (δ_H 5.04, H-8) was observed at a lower field than that of **13** (δ_H 3.86, H-8) (Scheme 4). The same coupling pattern of the oxymethine signal in **9** and **13** (dd, J=2.4, 2.4 Hz) suggested that **9** was an acetylated **13**. When **9** was treated with KOH, the deacetylated derivative was obtained, the spectroscopic properties, including the CD spectra, of which were completely identical with those of **13**. Thus, we concluded that **9** was acetyllycoposerramine-U.



Scheme 4. Chemical correlation of acetyllycoposerramine-U (**9**) and lycoposerramine-U (**13**).

Compound **10** was obtained as a colorless solid and its molecular formula was elucidated by HRFABMS analysis to be $C_{17}H_{25}NO_3$. The NMR data of **10** and lycoflexine (**12**) very much resembled each other except for the lower-field-shifted methylene signals around nitrogen in **10**. This fact, plus the mass spectral data, indicated that **10** was an *N*-oxide derivative of **12**. To inspect this assumption, the oxidation of **12** was examined (Scheme 5). When **12** was treated with *m*-CPBA, an *N*-oxide derivative was obtained, the spectroscopic data of which were completely identical with those of **10**. Thus, **10** was elucidated to be lycoflexine *N*-oxide.



Scheme 5. Chemical conversion of lycoflexine (**12**) to lycoflexine *N*-oxide (**10**).

In conclusion, ten new fawcettimine-related alkaloids, i.e., lycopoclavamines (**1**–**3**), lycoposquarrosamine-A (**4**), and other hydroxylated fawcettime derivatives (**5**–**10**), were isolated from three species of *Lycopodium* (*L. clavatum*, *L. serratum*, *and L. squarrosum*). Lycopoclavamines (**1**–**3**) and lycoposquarrosamine-A (**4**) are the second examples of fawcettimine-related alkaloids possessing a *trans*-decahydroquinoline ring system at the *A*/*D*-ring junction as well as a β-oriented methyl group at C-15.

3. Experimental

3.1. General experimental procedure

^{1}H and ^{13}C NMR spectra: JEOL JNM ECP-600 at 600 MHz (^{1}H) or 150 MHz (^{13}C), JEOL JNM A-500 at 500 MHz (^{1}H) or 125 MHz (^{13}C), and JEOL ECP-400 and JEOL JNM ECX-400 at 400 MHz (^{1}H) or

100 MHz (^{13}C), respectively. EIMS and HREIMS: JEOL JMS-GC mate and JEOL JMS-GC mate II (BU-25). FABMS: JEOL JMS-AX500. HRFABMS: JEOL JMS-HX110. Optical rotation: JASCO P-1020 and JASCO DIP-140. CD: JASCO J-720WI. TLC: Precoated silica gel 60 F_{254} plates (Merck, 0.25 mm thick), Precoated amino-silica gel plates (Fuji Silysia Chemical), Aluminum oxide F_{254} (Merck, Type-E). Column chromatography: Silica gel 60 (Merck, 70–230 mesh), Silica gel 60 N [Kanto Chemical, 40–50 mm (for flash chromatography)], Chromatorex NH [Fuji Silysia Chemical, 100–200 mesh (for amino-silica gel column chromatography)], Aluminum oxide 60 (Merck, 70–230 mesh).

3.2. Plant material

The club moss *L. clavatum* L. was collected in Toyama City, Toyama Prefecture, Japan, and identified by one of the authors (M. Arisawa). A voucher specimen was deposited at the Herbarium of the Faculty of Pharmaceutical Sciences, International University of Health and Welfare. The club moss *L. squarrosum* was purchased at a flower market in Bangkok, Thailand. A voucher specimen was deposited at the Herbarium of the Faculty of Pharmaceutical Sciences, Chiba University.

3.3. Extraction and isolation of alkaloids from *L. clavatum*

The air-dried *L. clavatum* (219 g) was extracted with MeOH (1 L) six times and the extracts were filtered. The combined filtrates were concentrated under reduced pressure to give the crude extract (58.1 g), which was then suspended in 2% tartaric acid and filtered. The aqueous filtrate was washed with AcOEt, rendered basic with $NaHCO_3$ (pH 9), and then exhaustively extracted with 5% MeOH/$CHCl_3$ (300 mL) five times. The organic layer was dried over $MgSO_4$ and evaporated to give the crude alkaloid fraction (1.03 g). The crude alkaloid fraction was separated by silica gel flash column chromatography using MeOH/$CHCl_3$ (0–30%) gradient, MeOH/$CHCl_3$/aqueous ammonia (28%)=4:7:1, and then MeOH to give five fractions (A–E). The 5% MeOH/$CHCl_3$ eluate (fraction C) was purified over amino-silica gel using $CHCl_3$/*n*-hexane gradient (10–60%) to give **1** (2.0 mg). The 15–30% MeOH/$CHCl_3$ and MeOH/$CHCl_3$/aqueous ammonia (28%)=4:7:1 eluate (fraction E) was rechromatographed on silica gel using MeOH/AcOEt/aqueous ammonia (28%)=10:90:0 to 20:80:1 to give **2** (0.8 mg).

*3.3.1. Lycopoclavamine-A (**1**).* Colorless amorphous solid; $[\alpha]_D^{25}$ −48.8 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1642, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): 6.91 (dd, *J* 7.4, 2.3 Hz, H-3), 3.73 (ddd, *J* 14.0, 14.0, 4.4 Hz, H-9), 3.52 (ddd, *J* 15.7, 11.8, 4.2 Hz, H-1a), 2.93 (dd, *J* 15.6, 6.9 Hz, H-1b), 2.78 (m, H-2), 2.72 (dd, *J* 14.2, 5.5 Hz, H-9), 2.55 (dd, *J* 17.6, 6.6 Hz, H-6a), 2.28 (m, H-2), 2.25 (m, H-11), 2.10 (m, H-15), 2.08 (m, H-7), 1.91 (dd, *J* 12.1, 12.1 Hz, H-14a), 1.90 (d, *J* 17.9 Hz, H-6b), 1.67 (2H, m, H-8a and 10), 1.57 (m, H-11), 1.49 (m, H-10), 1.30 (ddd, *J* 12.7, 2.4, 2.4 Hz, H-14b), 0.87 (3H, d, *J* 6.9 Hz, H_3-16), 0.55 (ddd, *J* 13.7, 12.4, 12.4 Hz, H-8b); ^{13}C NMR ($CDCl_3$, 100 MHz): see Table 1; EIMS *m*/*z* (%): 261 (M^+, 100), 243 (24); HREIMS *m*/*z* 261.1734 (M^+, Δ+0.5 mmu).

*3.3.2. Lycopoclavamine-B (**2**).* Colorless amorphous solid; $[\alpha]_D^{25}$ −13.9 (*c* 0.06, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1645, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): 6.93 (dd, *J* 7.6, 2.1 Hz, H-3), 3.73 (ddd, *J* 13.8, 13.8, 4.4 Hz, H-9), 3.51 (ddd, *J* 16.3, 11.8, 4.5 Hz, H-1a), 2.96 (dd, *J* 15.4, 6.7 Hz, H-1b), 2.79 (m, H-2), 2.70 (dd, *J* 14.2, 5.5 Hz, H-9), 2.60 (dd, *J* 17.4, 6.4 Hz, H-6a), 2.51 (d, *J* 12.8 Hz, H-14a), 2.32 (m, H-2), 2.26 (m, H-11), 2.13 (m, H-7), 1.93 (d, *J* 17.9 Hz, H-6b), 1.77 (ddd, *J* 13.5, 5.3, 2.5 Hz, H-8a), 1.67 (m, H-10), 1.56 (m, H-11), 1.52 (2H, m, H-10 and 14b), 1.49 (3H, s, H_3-16), 1.10 (dd, *J* 13.3, 13.3 Hz, H-8b); ^{13}C NMR ($CDCl_3$, 100 MHz): see Table 1; EIMS *m*/*z* (%): 277 (M^+, 100), 259 (36), 241 (41); HREIMS *m*/*z* 277.1680 (M^+, Δ+0.2 mmu).

3.4. Isolation of alkaloids from *L. serratum*

Alkaloid fraction E, which was prepared from *L. serratum* Thunb. in the previous study,[3f] was purified over amino-silica gel using 50–100% $CHCl_3$/*n*-hexane and then 1–10% MeOH/$CHCl_3$ gradient to give **3** (2.7 mg).

*3.4.1. Dihydrolycopoclavamine-A (**3**).* Colorless amorphous solid; $[\alpha]_D^{25}$ +34.7 (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 5.94 (d, *J* 7.3 Hz, H-3), 4.55 (dd, *J* 7.8, 7.8 Hz, H-5), 3.68 (ddd, *J* 14.2, 14.2, 4.7 Hz, H-9), 3.50 (ddd, *J* 15.2, 13.0, 4.7 Hz, H-1), 2.88 (dd, *J* 15.1, 6.4 Hz, H-1), 2.71 (dd, *J* 14.2, 5.5 Hz, H-9), 2.67 (m, H-2), 2.14 (m, H-11), 2.09 (m, H-2), 1.99 (m, H-15), 1.97 (m, H-14), 1.90 (m, H-7), 1.86 (m, H-10), 1.80 (2H, m, H_2-6), 1.73 (m, H-11), 1.56 (m, H-8a), 1.47 (m, H-10), 1.24 (m, H-14), 0.86 (3H, d, *J* 6.0 Hz, H_3-16), 0.53 (ddd, *J* 12.5, 12.5, 12.5 Hz, H-8b); ^{13}C NMR ($CDCl_3$, 100 MHz): see Table 1; EIMS *m*/*z* (%): 263 (M^+, 100); HREIMS *m*/*z* 263.1885 (M^+, Δ 0 mmu).

*3.4.2. DMP oxidation of compound **3**.* To a stirred solution of **3** (0.63 mg, 0.0024 mmol) in dry CH_2Cl_2 (0.2 mL) was added DMP (1.2 mg, 0.0028 mmol) under argon atmosphere. After the reaction mixture was stirred at room temperature for 1 h, it was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (0–15% MeOH/$CHCl_3$) to give semi-synthetic **1** (0.59 mg, 94%). All the spectroscopic data (^{1}H and ^{13}C NMR, $[\alpha]_D$, and MS) were identical with those of natural **1**.

3.5. Isolation of alkaloids from *L. squarrosum*

The air-dried *L. squarrosum* (1.65 kg) was extracted with MeOH (10 L) four times and the extracts were filtered. The combined filtrates were concentrated under reduced pressure to give the crude extract (394 g), and the alkaloid extract (2.31 g) was obtained by following a conventional procedure that was similar to the case of *L. clavatum*. The crude alkaloid fraction was separated by silica gel flash column chromatography using MeOH/$CHCl_3$ (0–30%) gradient, 30% MeOH/$CHCl_3$ saturated with ammonia, and then MeOH to give six fractions (A–F). The 5–10% MeOH/$CHCl_3$ eluate (fraction B) was purified over silica gel using 8% MeOH/$CHCl_3$ to give **9** (29.2 mg). The 15% MeOH/$CHCl_3$ eluate (fraction C) was purified over silica gel using 0–25% MeOH/AcOEt gradient to give six fractions (C1–C6). The 8% MeOH/AcOEt eluate (fraction C4) was purified over amino-silica gel using 50–100% $CHCl_3$/*n*-hexane to give **7** (3.2 mg). The 5–25% MeOH/AcOEt eluate (fraction C5) was purified over silica gel using 3–20% $CHCl_3$/*n*-hexane to give **5** (59.5 mg). The 20–30% MeOH/$CHCl_3$ eluate (fraction D) was purified over silica gel using 0–25% MeOH/AcOEt gradient to give seven fractions (D1–D7). The 8% MeOH/AcOEt eluate (fraction D3) was purified over aluminum oxide using 0–100% $CHCl_3$/*n*-hexane to give **4** (58.0 mg). The MeOH eluate (fraction F) was purified over silica gel using 0–100% MeOH/AcOEt gradient to give five fractions (F1–F5). The 50–70% MeOH/AcOEt eluate (F4) was rechromatographed over amino-silica gel using 80–100% $CHCl_3$/*n*-hexane and then 1–10% MeOH/$CHCl_3$ to give seven sub-fractions. The 0–2% MeOH/$CHCl_3$ eluate (F4E) was purified over silica gel using 1–5% MeOH/$CHCl_3$ saturated with ammonia to give **6** (9.9 mg). The 2–5% MeOH/$CHCl_3$ eluate (F4F) was purified over silica gel using 0–20% MeOH/AcOEt to give **8** (5.9 mg). The MeOH eluate (F5) was purified over silica gel using 10–50% MeOH/$CHCl_3$ saturated with ammonia to give **10** (6.1 mg).

*3.5.1. Lycoposquarrosamine-A (**4**).* Colorless solid; CD (0.42 mM, MeOH, 24 °C) λ nm (Δε): 317 (0), 268 (+0.6), 263 (0), 239 (+1.0),

222 (0), 227 (−0.9); ^{1}H NMR ($CDCl_3$, 600 MHz): 5.87 (d, *J* 7.7 Hz, H-3), 4.30 (dd, *J* 8.3, 8.3 Hz, H-5), 3.72 (ddd, *J* 14.0, 14.0, 4.4 Hz, H-9), 3.41 (m, H-1), 3.11 (ddddd, *J* 13.2, 6.6, 6.6, 6.6, 5.2 Hz, H-15), 2.92 (dd, *J* 15.4, 6.0 Hz, H-1), 2.85 (dd, *J* 12.9, 8.0 Hz, H-6), 2.78 (dd, *J* 14.0, 5.5 Hz, H-9), 2.70 (m, H-2), 2.50 (d, *J* 6.9 Hz, H-7), 2.49 (dd, *J* 13.2, 13.2 Hz, H-14a), 2.41 (ddd, *J* 12.8, 4.4, 4.4 Hz, H-11), 2.07 (br ddd, *J* 18.1, 7.6, 4.8 Hz, H-2), 1.87 (m, H-10), 1.81 (m, H-11), 1.68 (dd, *J* 12.9, 5.2 Hz, H-14b), 1.61 (ddd, *J* 15.4, 8.5, 7.1 Hz, H-6), 1.51 (m, H-10), 1.02 (3H, d, *J* 6.6 Hz, H_3-16); ^{13}C NMR ($CDCl_3$, 150 MHz): see Table 1; EIMS *m*/*z* (%): 277 (M^+, 100), 259 (55), 160 (39); HREIMS *m*/*z* 277.1687 (M^+, Δ +0.9 mmu).

*3.5.2. Acetylaposerratinine (**5**).* Colorless amorphous solid; CD (0.42 mM, MeOH, 24 °C) λ nm (Δε): 334 (0), 289 (+2.3), 243 (0); ^{1}H NMR ($CDCl_3$, 500 MHz): 5.00 (s, H-8), 3.43 (ddd, *J* 14.6, 8.5, 4.3 Hz, H-1), 3.26 (ddd, *J* 14.0, 14.0, 3.7 Hz, H-9), 2.88 (br dd, *J* 14.3, 4.6 Hz, H-9), 2.71 (m, H-1), 2.53 (m, H-14), 2.48 (m, H-11), 2.44 (2H, m, H-6 and 15), 2.33 (dd, *J* 17.7, 8.9 Hz, H-6), 2.18 (m, H-3), 2.11 (3H, s, H_3-18), 2.06 (3H, m, H-3, 4, and 7), 1.92 (br s, H-2), 1.85 (m, H-2 and 10), 1.49 (dd, *J* 14.0, 4.9 Hz, H-11), 1.42 (br d, *J* 14.0 Hz, H-10), 1.05 (dd, *J* 13.4, 2.7 Hz, H-14), 0.94 (3H, d, *J* 6.7 Hz, H_3-16); ^{13}C NMR ($CDCl_3$, 150 MHz): see Table 2; EIMS *m*/*z* (%): 321 (M^+, 100), 262 (29), 123 (98); HREIMS *m*/*z* 321.1929 (M^+, Δ −1.1 mmu).

*3.5.3. Hydrolysis of compound **5**.* To a stirred solution of **5** (1.8 mg, 0.0056 mmol) in MeOH (0.2 mL) was added aqueous 1 M KOH (0.1 mL). After the reaction mixture was stirred at room temperature for 6.5 h, it was diluted with water and extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$/28% aqueous ammonia=10:90:1 to 20:80:1) to give semi-synthetic **6** (0.7 mg, 45%). All the spectroscopic data (^{1}H and ^{13}C NMR and MS) were identical with those of natural **6**.

*3.5.4. 8α-Hydroxyfawcettimine (**6**).* Colorless solid; CD (0.39 mM, MeOH, 24 °C) λ nm (Δε): 320 (0), 286 (+3.0), 243 (0); ^{1}H NMR (CD_3OD, 500 MHz) 3.74 (s, H-8), 3.45 (ddd, *J* 13.7, 8.9, 4.3 Hz, H-1), 3.22 (ddd, *J* 14.0, 14.0, 4.0 Hz, H-9), 2.84 (dd, *J* 14.6, 4.9 Hz, H-9), 2.78 (ddd, *J* 15.0, 15.0, 6.4 Hz, H-11a), 2.67 (ddd, *J* 14.3, 4.9, 4.9 Hz, H-1), 2.47 (dd, *J* 12.8, 12.8 Hz, H-14), 2.37 (dd, *J* 17.4, 13.7 Hz, H-6), 2.27 (m, H-15), 2.14 (2H, m, H-3 and 6), 2.08 (m, H-7), 2.02 (m, H-3), 1.93 (m, H-2), 1.89 (m, H-10), 1.83 (m, H-2), 1.52 (br dd, *J* 14.3, 4.9 Hz, H-11b), 1.40 (br d, *J* 13.8 Hz, H-10), 1.04 (dd, *J* 13.7, 3.4 Hz, H-14), 1.04 (3H, d, *J* 7.0 Hz, H_3-16); ^{13}C NMR (CD_3OD, 125 MHz): see Table 2; EIMS *m*/*z* (%): 279 (M^+, 100), 221 (38), 193 (35), 152 (38), 83 (75); HREIMS: *m*/*z* 279.1833 (M^+, Δ −0.1 mmu).

*3.5.5. 8β-Acetoxyfawcettimine (**7**).* Colorless solid; CD (0.36 mM, MeOH, 24 °C) λ nm (Δε): 334 (0), 289 (+2.3), 243 (0); ^{1}H NMR ($CDCl_3$, 500 MHz): 4.90 (dd, *J* 10.7, 6.1 Hz, H-8), 3.42 (ddd, *J* 14.6, 8.9, 4.0 Hz, H-1), 3.22 (ddd, *J* 14.0, 14.0, 4.3 Hz, H-9), 2.89 (dd, *J* 14.6, 5.5 Hz, H-9), 2.72 (m, H-1), 2.68 (dd, *J* 18.3, 13.4 Hz, H-6), 2.35 (3H, m, H-7, 14, and 15), 2.29 (ddd, *J* 14.1, 14.1, 6.0 Hz, H-11), 2.19 (m, H-3), 2.07 (3H, m, H-3, 4, and 6), 2.05 (3H, s, H_3-18), 1.91 (2H, m, H-2 and 10), 1.82 (m, H-2), 1.62 (dd, *J* 14.3, 5.5 Hz, H-11), 1.48 (br d, *J* 14.3 Hz, H-10), 1.29 (br d, *J* 11.0 Hz, H-14), 0.94 (3H, d, *J* 5.8 Hz, H_3-16); ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 2; EIMS *m*/*z* (%): 321 (M^+, 100), 262 (39), 123 (61), 83 (72); HREIMS *m*/*z* 321.1949 (M^+, Δ +0.9 mmu).

*3.5.6. 8β-Hydroxyfawcettimine (**8**).* Colorless amorphous solid; CD (0.41 mM, MeOH, 24 °C) λ nm (Δε): 323 (0), 286 (+2.4), 244 (0); ^{1}H NMR ($CDCl_3$, 500 MHz): 3.71 (dd, *J* 10.1, 5.2 Hz, H-8), 3.41 (ddd, *J* 14.6, 9.2, 4.3 Hz, H-1), 3.20 (ddd, *J* 14.7, 14.7, 3.9 Hz, H-9), 2.87 (dd, *J* 14.9, 5.2 Hz, H-9), 2.69 (ddd, *J* 14.6, 6.4, 4.3 Hz, H-1), 2.64 (dd, *J* 16.5, 15.9 Hz, H-6), 2.43 (dd, *J* 14.0, 12.5 Hz, H-14), 2.22 (4H, m, H-3, 6, 7, and 11), 2.14 (m, H-15), 2.07 (2H, m, H-3 and 4), 1.94 (m, H-2), 1.89 (m, H-10), 1.82 (m, H-2), 1.62 (br dd, *J* 14.0, 5.2 Hz, H-11), 1.45 (br d, *J* 13.7 Hz, H-10), 1.23 (dd, *J* 14.3, 3.4 Hz, H-14), 1.05 (3H, d, *J* 6.4 Hz, H_3-16); ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 2; EIMS *m*/*z* (%): 279 (M^+, 100), 261 (30), 236 (28), 193 (58), 151 (56), 123 (45), 70 (42); HREIMS: *m*/*z* 279.1834 (M^+, Δ 0 mmu).

*3.5.7. Hydrolysis of compound **7**.* To a stirred solution of **7** (1.3 mg, 0.0041 mmol) in MeOH (0.2 mL) was added aqueous 1 M KOH (0.1 mL). After the reaction mixture was stirred at room temperature for 14.5 h, it was diluted with water and the whole was extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$/28% aqueous ammonia=10:90:1 to 20:80:1) to give semi-synthetic **8** (1.2 mg, quant.). All the spectroscopic data (^{1}H and ^{13}C NMR and MS) were identical with those of natural **8**.

*3.5.8. Acetyllycoposerramine-U (**9**).* Colorless amorphous solid; CD (0.20 mM, MeOH, 24 °C) λ nm (Δε): 328 (0), 307 (−1.7), 281 (0), 243 (+3.1), 208 (0); ^{1}H NMR ($CDCl_3$, 500 MHz): 5.04 (dd, *J* 2.4, 2.4 Hz, H-8), 3.18 (br dd, *J* 14.3, 1.8 Hz, H-17), 3.07 (m, H-9), 2.94 (ddd, *J* 14.0, 14.0, 4.0 Hz, H-1), 2.89 (br d, *J* 4.0 Hz, H-1), 2.85 (m, H-9), 2.81 (ddd, *J* 9.8, 9.8, 2.7 Hz, H-7), 2.62 (3H, m, H-6, 14, and 17), 2.33 (m, H-15), 2.28 (2H, m, H-11 and 14), 2.15 (3H, m, H-3, 10, and 11), 2.13 (3H, s, H_3-19), 2.06 (m, H-6), 1.99 (ddd, *J* 14.0, 14.0, 4.6 Hz, H-3), 1.82 (m, H-2), 1.74 (m, H-10), 1.35 (m, H-2), 1.00 (3H, d, *J* 6.4 Hz, H_3-16); ^{13}C NMR ($CDCl_3$, 125 MHz): 216.1 (C-5), 212.4 (C-13), 170.3 (C-18), 73.9 (C-8), 59.3 (C-12), 58.3 (C-4), 56.9 (C-9), 54.8 (C-17), 52.8 (C-1), 44.3 (C-7), 42.8 (C-14), 39.4 (C-11), 39.3 (C-6), 30.0 (C-15), 28.2 (C-3), 27.2 (C-10), 21.1 (C-19), 19.3 (C-2), 17.6 (C-16); FABMS (NBA): *m*/*z* 334 (MH^+); HRFABMS: *m*/*z* 333.1941 (M^+, Δ −0.1 mmu).

*3.5.9. Hydrolysis of compound **9**.* To a stirred solution of **9** (1.7 mg, 0.0051 mmol) in MeOH (0.5 mL) was added aqueous 1 M KOH (0.1 mL). After the reaction mixture was stirred at room temperature for 1 h, it was evaporated to dryness. The residue was purified by silica gel column chromatography (0–10% MeOH/$CHCl_3$) to give semi-synthetic **13** (1.5 mg, quant.). All the spectroscopic data (^{1}H and ^{13}C NMR, CD, and MS) were identical with those of natural **13**.

*3.5.10. Lycoflexine N-oxide (**10**).* Colorless solid; CD (0.57 mM, MeOH, 24 °C) λ nm (Δε): 344 (0), 302 (+2.1), 244 (+0.2), 238 (+0.4), 220 (0), 202 (−1.5); ^{1}H NMR ($CDCl_3$, 500 MHz): 3.70 (4H, m, H-1, 9, 9, and 17), 3.09 (ddd, *J* 13.1, 13.1, 3.4 Hz, H-1), 3.04 (d, *J* 14.0 Hz, H-17), 2.69 (m, H-7), 2.40 (dd, *J* 18.3, 7.9 Hz, H-6), 2.34 (2H, m, H_2-14), 2.25 (3H, m, H-2, 6, and 10), 2.17 (4H, m, H-3, 11, 11, and 15), 2.08 (m, H-3), 1.99 (m, H-2), 1.93 (m, H-10), 1.90 (m, H-8), 1.73 (ddd, *J* 14.6, 12.5, 4.6 Hz, H-8), 1.07 (3H, d, *J* 6.4 Hz, H_3-16); ^{13}C NMR ($CDCl_3$, 125 MHz): 213.1 (C-5), 211.8 (C-13), 75.2 (C-9), 70.7 (C-1), 68.1 (C-17), 60.1 (C-12), 57.6 (C-4), 46.8 (C-14), 41.3 (C-7), 39.6 (C-6), 34.2 (C-11), 30.8 (C-8), 28.2 (C-15), 27.0 (C-10), 22.0 (C-2), 21.9 (C-16), 21.2 (C-3); FABMS (NBA): *m*/*z* 292 (MH^+); HRFABMS (NBA/PEG): *m*/*z* 292.1931 (MH^+, Δ +1.8 mmu).

*3.5.11. m-CPBA oxidation of lycoflexine (**12**).* To a stirred solution of **12** (3.4 mg, 0.0124 mmol) in dry CH_2Cl_2 (0.6 mL) was added *m*-CPBA (77%, 3.3 mg, 0.0147 mmol) under argon atmosphere. After the reaction mixture was stirred at 0 °C for 1 h, it was directly subjected to aluminum oxide column chromatography (0–20% MeOH/$CHCl_3$) to give semi-synthetic **10** (2.5 mg, 69%). All the spectroscopic data (^{1}H and ^{13}C NMR, CD, and MS) were identical with those of natural **10**.

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