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THE *LYCOPODIUM* ALKALOIDS

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Abstract – *Lycopodium* alkaloids are unique heterocyclic alkaloids having $C_{11}N$, $C_{15}N_2$, $C_{16}N$, $C_{16}N_2$, $C_{22}N_2$, and $C_{27}N_3$ types from genus *Lycopodium* and have attracted great interest from biogenetic and biological points of view as well as providing challenging targets for total synthesis. This review covered the structure elucidation and biological activity of new *Lycopodium* alkaloids and total synthesis of some *Lycopodium* alkaloids reported in the literature from 2004 to July in 2008.

INTRODUCTION

Lycopodium species produce a number of structurally diverse alkaloids, which often possess unusual skeletons, and many of them continue to be of interest from the biogenetic and biological points of view, as well as providing challenging targets for total synthesis. There are over 500 species in the genus *Lycopodium* (family Lycopodiaceae), but the alkaloid content has been studied about 50 species.[1-7] Most of the species are low, evergreen, coarsely moss-like plants, which are commonly known as club mosses. They are non-flowering plants which reproduce by means of spores rather than seeds. In many species, the spore-bearing bodies, known as strobili, appear as club-shaped growths at the tips of the moss like branches, hence the name club mosses. The taxonomy of the genus and the family is still in a state of flux. Some botanists have subdivided the genus into four genera (*Lycopodium*, *Diphasiastrum*, *Lycopodiella*, and *Huperzia*), and some have placed *Huperzia* in a separate family.[8,9] We prefer to retain the single genus name, *Lycopodium* that can be easily recognized as being closely related.

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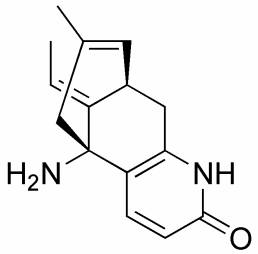
†Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



huperzine A (**1**)

In 1986, Liu and co-workers isolated two new *Lycopodium* alkaloids, huperzines A (**1**) and B from *Huperzia serrata* (*Lycopodium serratum*), which is a Chinese traditional medicine.[10] Huperzine A (**1**) has been shown to be a potent, reversible inhibitor of acetylcholinesterase and shows promise in the treatment of Alzheimer's disease and myasthenia gravis.[10-13] The inherent inhibition of acetylcholinesterase has promoted the pursuit of the total synthesis[14-19] and SAR[11,12] studies of huperzine A. Since the inhibition of acetylcholinesterase activity of huperzine A was detected, clinical trials with *Lycopodium* alkaloids have been carried out. Many reports on clinical trials of huperzine A and its analogue have been published in recent years.

The biosynthesis of the alkaloids is still not completely understood, and only limited biosynthetic studies have been reported.[20-33] Plants of the genus *Lycopodium* have not been cultivated, and labeling experiments must be carried out in the field. Because the club mosses often are not easily accessible, very few feeding studies have been conducted.[34-36] This is an area where plant tissue culture may prove extremely useful in future biosynthetic studies.

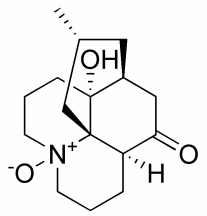
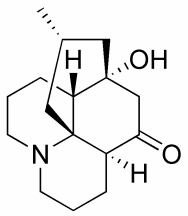
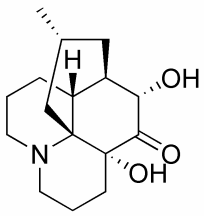
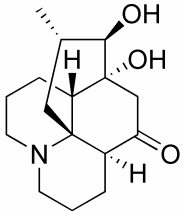
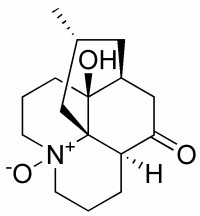
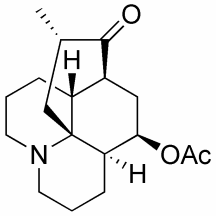
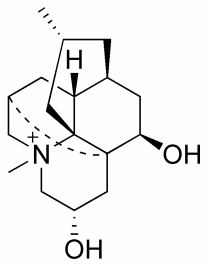
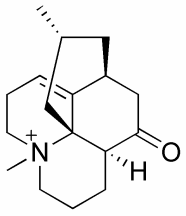
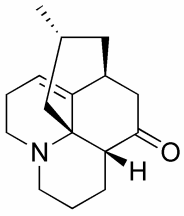
Ther are some reviews of the chemistry of *Lycopodium* alkaloids,[1-7] and of the biology and chemistry of huperzine A (**1**).[10-13] Since the last review by us in Volume 61[7] of The Alkaloids, a number of new *Lycopodium* alkaloids have been discovered. As a result, the number of known *Lycopodium* alkaloids has grown markedly in recent years to a present count of ca. 250. These alkaloids, isolated chiefly by Manske and Ayer *et al.*, are classified into different frameworks of $C_{16}N$, $C_{16}N_2$, and $C_{27}N_3$ types.[1-4] These unusual ring systems have attracted great interest as challenging targets for total synthesis or biosynthetic studies.

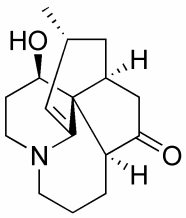
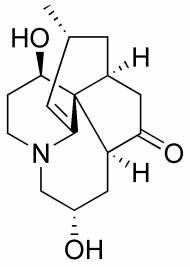
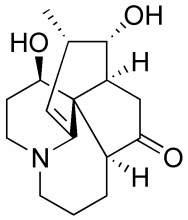
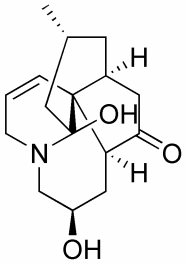
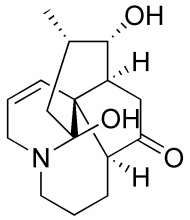
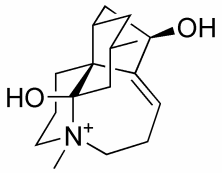
This review covers the reports on *Lycopodium* alkaloids that have been published between 2004 to July in 2008, and provides an update of the previous our review[7] in 2005. The natural *Lycopodium* alkaloids published between 2004 to July 2008 (compounds **2-51**) are listed in Table 1.

This review describes the recent studies on *Lycopodium* alkaloids isolated from the genus *Lycopodium* and *Huperzia*, and the syntheses of *Lycopodium* alkaloids.

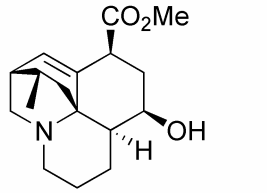
Table 1.

New *Lycopodium* Alkaloids.

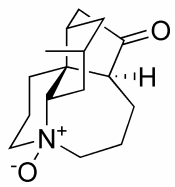
A and B. Lycopodine related alkaloids and lycopodatines				
				
12-epilycodoline *N*-oxide (**2**)[37]	7-hydroxylycopodine (**3**)[37]	4,6α-dihydroxylycopodine (**4**)[37]	sauroine (**5**)[38]	
$C_{16}H_{25}NO_3$	$C_{16}H_{25}NO_2$	$C_{16}H_{25}NO_3$	$C_{16}H_{25}NO_3$	
				
obscurumine A (**6**)[39]	obscurumine B (**7**)[39]	lycopodatine A (**8**)[40]	lycopodatine B (**9**)[40]	lycopodatine C (**10**)[40]
$C_{16}H_{25}NO_3$	$C_{18}H_{27}NO_3$	$C_{17}H_{28}NO_2^+$	$C_{17}H_{26}NO$	$C_{16}H_{23}NO$

C and D. Fawcettimine related alkaloids and lycovatine A			
			
11α-hydroxyfawcettidine (**11**)[41]	2α,11α-dihydroxyfawcettidine (**12**)[41]	8α,11α-dihydroxyfawcettidine (**13**)[41]	
$C_{16}H_{23}NO_2$	$C_{16}H_{23}NO_3$	$C_{16}H_{23}NO_3$	
			
2β-hydroxylycothunine (**14**)[41]	8α-hydroxylycothunine (**15**)[41]	lycovatine A (**16**)[42]	
$C_{16}H_{23}NO_3$	$C_{16}H_{23}NO_3$	$C_{17}H_{28}NO_2^+$	

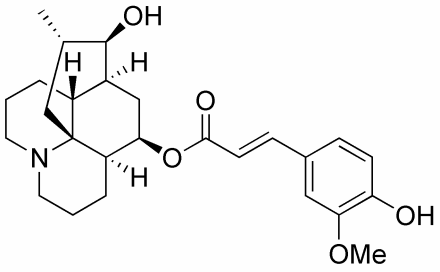
E. Lannotinidines



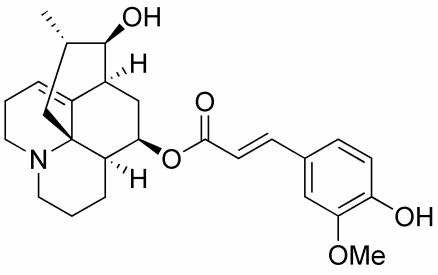
lannotinidine A (**17**)[43]
$C_{17}H_{25}NO_3$



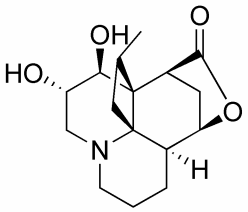
lannotinidine B (**18**)[43]
$C_{16}H_{25}NO_2$



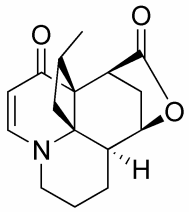
lannotinidine C (**19**)[43]
$C_{26}H_{35}NO_5$



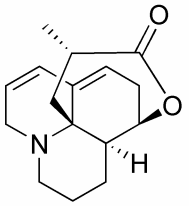
lannotinidine D (**20**)[43]
$C_{26}H_{33}NO_5$



lannotinidine E (**21**)[43]
$C_{16}H_{23}NO_4$

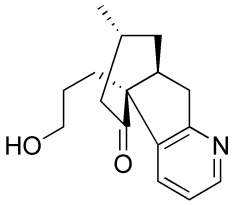


lannotinidine F (**22**)[43]
$C_{16}H_{19}NO_3$

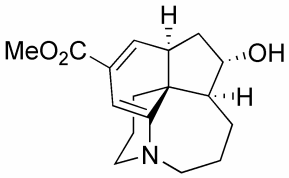


lannotinidine G (**23**)[43]
$C_{16}H_{21}NO_2$

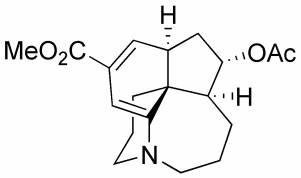
F. Lycopladines



lycopladine A (**24**)[44]
$C_{16}H_{21}NO_2$



lycopladine B (**25**)[45]
$C_{17}H_{23}NO_3$



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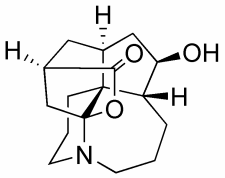
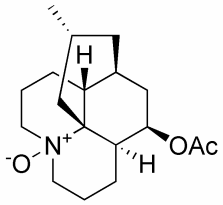
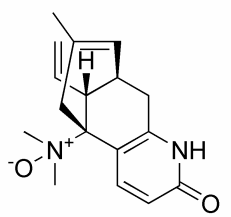


lycopladine D (**27**)[45]
$C_{16}H_{23}NO_3$

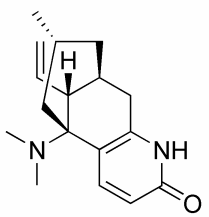


lycopladine E (**28**)[46]
$C_{18}H_{29}NO_3$

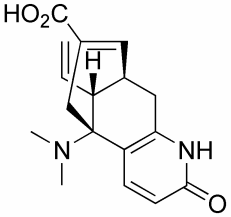
G. Huperzinine related alkaloids



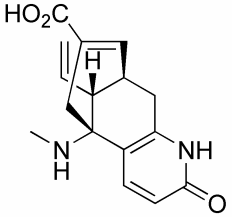
huperzinine *N*-oxide (**29**)[47]
$C_{17}H_{22}N_2O_2$



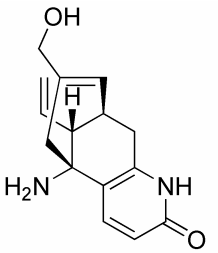
8,15-dihydrohuperzinine (**30**)[47]
$C_{17}H_{24}N_2O$



lycoparin A (**31**)[48]
$C_{17}H_{20}N_2O_3$

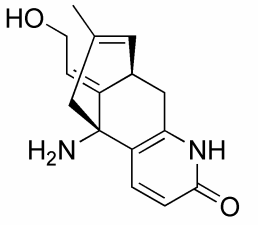


lycoparin B (**32**)[48]
$C_{16}H_{18}N_2O_3$

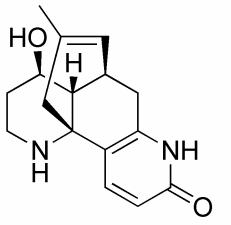


lycoparin C (**33**)[48]
$C_{15}H_{18}N_2O_2$

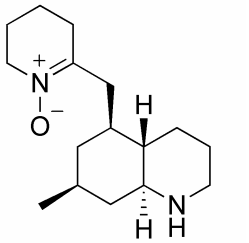
H. Carinatumins



carinatumin A (**34**)[49]
$C_{15}H_{18}N_2O_2$

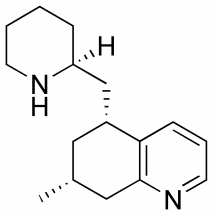


carinatumin B (**35**)[49]
$C_{16}H_{20}N_2O_2$

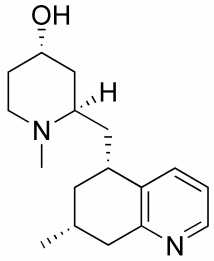


carinatumin C (**36**)[49]
$C_{16}H_{28}N_2O$

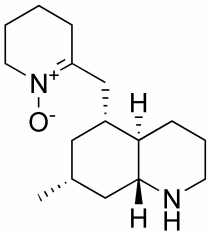
I. Lycoposerramines



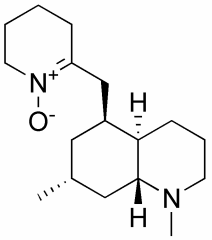
lycoposerramine-V (**37**)[50]
$C_{16}H_{24}N_2$



lycoposerramine-W (**38**)[50]
$C_{17}H_{26}N_2O$



lycoposerramine-X (**39**)[51]
$C_{16}H_{28}N_2O$



lycoposerramine-Y (**40**)[51]
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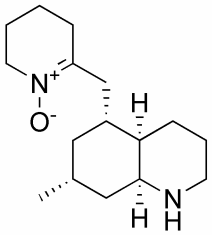
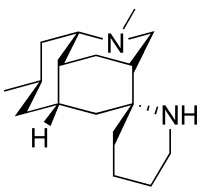
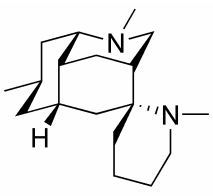


lycoposerramine-Z (**41**)[51]
$C_{16}H_{28}N_2O$

J. Nankakurines

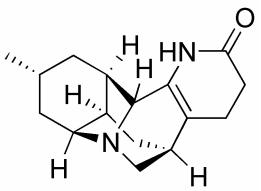


nankakurine A (**42**)[52,53]
$C_{17}H_{30}N_2$



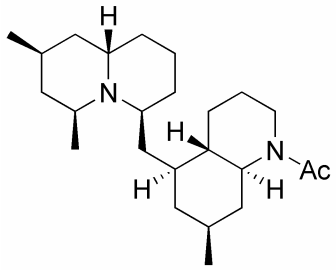
nankakurine B (**43**)[53]
$C_{18}H_{32}N_2$

K and L. Lyconadin B and senepodine F



lyconadin B (**44**)[45]

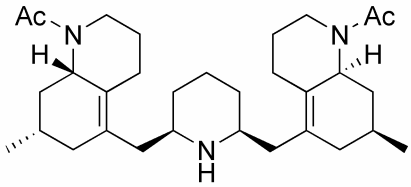
$C_{16}H_{22}N_2O$



senepodine F (**45**)[54]

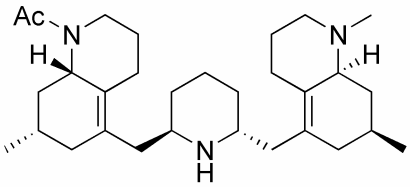
$C_{24}H_{42}N_2O$

M. Lycoperine A and cryptadines



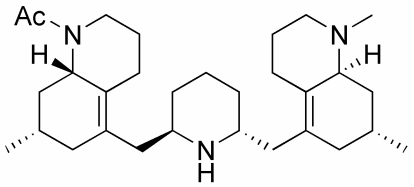
lycoperine A (**46**)[55]

$C_{31}H_{49}N_3O_2$



cryptadine A (**47**)[56]

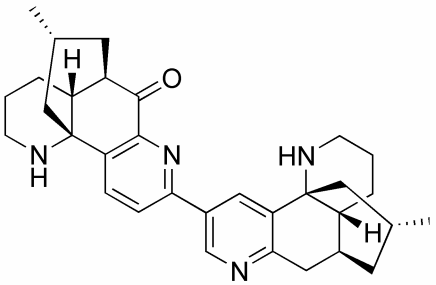
$C_{30}H_{49}N_3O$



cryptadine B (**48**)[56]

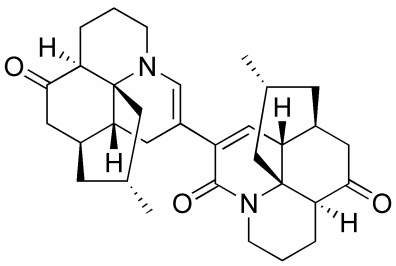
$C_{30}H_{49}N_3O$

N. Complanadines



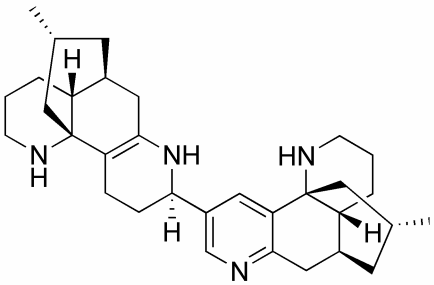
complanadine B (**49**)[39]

$C_{32}H_{40}N_4O$



complanadine C (**50**)[57]

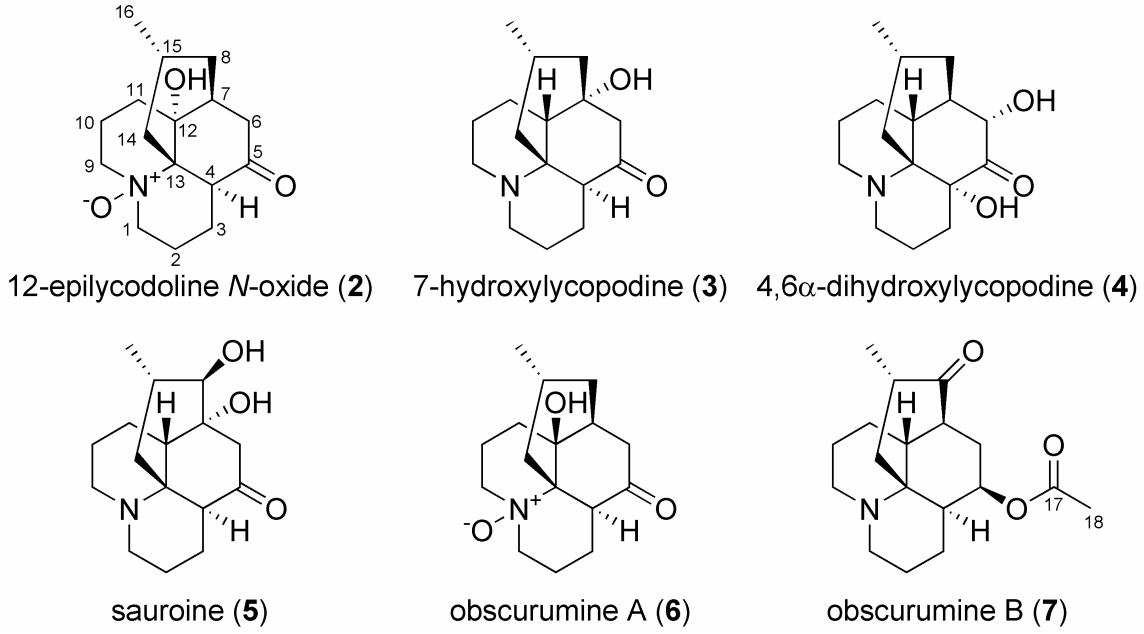
$C_{32}H_{42}N_2O_3$



complanadine D (**51**)[57]

$C_{32}H_{46}N_4$

A. LYCOPODINE RELATED ALKALOIDS



Six new lycopodine related alkaloids were isolated from some *Lycopodium* species. These alkaloids possess fused tetra-6-membered rings system, so-called lycopodane skeleton.

12-Epilycodoline-*N*-oxide (**2**), 7-hydroxylycopodine (**3**), and 4,6α-dihydroxylycopodine (**4**) were isolated from the basic material of the whole plant of *Huperzia serrata* (Thunb.).[37] Their structures were elucidated spectroscopically, especially by means of 1D and 2D NMR.

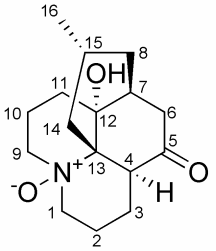
A new alkaloid, sauroine (**5**) was isolated from the aerial parts of *Lycopodium saururus*.[38] The relative stereochemistry of sauroine was 7α,8-endo-dihydroxylycopodine. Sauroine did not inhibit acetylcholinesterase with 10 μg/mL.

With an aim to isolate structurally interesting alkaloids and key intermediates to clarify the biogenetic pathway, purification of extracts of *L. obscurum* led to isolate two new alkaloids, obscurumines A (**6**) and B (**7**).[39] The structure and stereochemistry of **6** and **7** were assigned as *N*-oxide form of lycodoline[58] and 8-dehydro form of fawcettiine[59] respectively from combination of 2D NMR spectra. The absolute configuration of obscurumine A (**6**) was assigned by chemical transformation of lycodoline with *m*-CPBA.

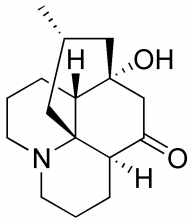
Table 2. ^{13}C NMR Data of 12-Epilycodoline-*N*-oxide (**2**), 7-Hydroxylycopodine (**3**), 4,6α-Dihydroxylycopodine (**4**), Sauroine (**5**), and Obscurumines A (**6**) and B (**7**).

	2[a]	**3**[b]	**4**[b]	**5**[c]	**6**[d]	**7**[e]
1	63.2	49.0	48.7	47.2	64.3	47.6
2	21.4	18.9	16.4	18.3	22.0	18.9
3	17.8	19.1	26.1	19.1	18.7	22.8
4	49.9	44.1	78.9	42.0	49.0	31.5
5	207.0	206.8	205.9	209.4	209.2	71.5
6	44.1	51.0	79.5	44.3	44.8	29.9
7	41.2	72.5	44.2	74.4	42.5	47.3
8	35.2	50.9	40.8	83.1	36.4	217.0
9	59.7	49.5	52.8	46.9	60.8	46.8
10	16.4	24.2	25.4	25	17.4	24.8
11	29.6	18.8	26.9	19.3	30.3	22.3
12	71.0	51.8	46.4	48.8	74.7	38.3
13	72.8	66.3	65.7	59.4	73.1	56.0
14	29.6	40.6	44.0	40.7	30.6	38.1
15	24.7	26.6	27.8	32.0	25.9	40.2
16	22.5	22.6	23.4	19.2	22.8	22.5
17						169.6
18						20.8

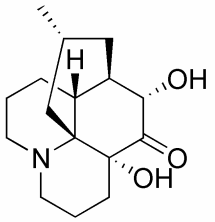
[a] Solution in $CDCl_3$ referenced to $SiMe_4$.
[b] Solution in CD_3OD referenced to $SiMe_4$.
[c] Solution in $CDCl_3$ referenced to $CHCl_3$ at 77.7.
[d] Solution in CD_3OD referenced to CD_3OD at 49.0.
[e] Solution in $CDCl_3$ referenced to $CDCl_3$ at 77.0.



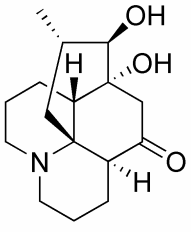
12-epilycodoline *N*-oxide (**2**)



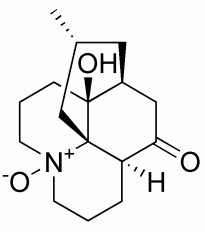
7-hydroxylycopodine (**3**)



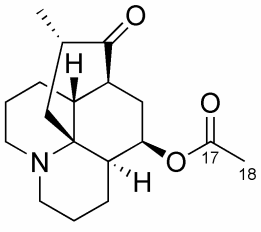
4,6α-dihydroxylycopodine (**4**)



sauroine (**5**)

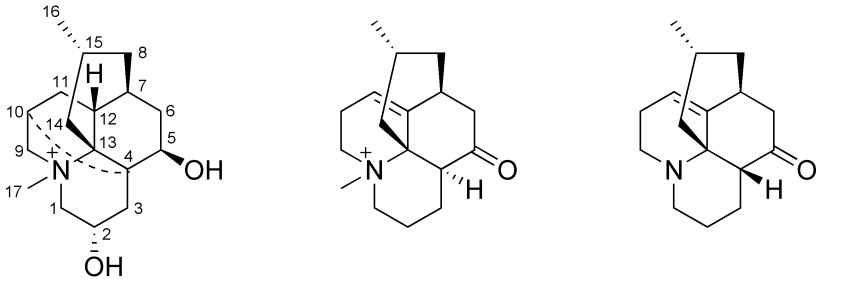


obscurumine A (**6**)



obscurumine B (**7**)

B. LYCOPODATINES



lycopodatine A (**8**) lycopodatine B (**9**) lycopodatine C (**10**)

Further investigation on extracts of *L. inundatum* resulted in the isolation of three new $C_{16}N$ type alkaloids, lycopodatines A-C (**8**-**10**),[40] as well as known related alkaloids, inundatine,[60,61] debenzoylalopecurine, [60,61] and anhydrolycodoline.[62]

Lycopodatine A (**8**) had a molecular formula of $C_{17}H_{28}NO_2$ by HRESIMS [*m*/*z* 278.2117, $(M)^+$, Δ −0.3 mmu]. The IR spectrum was indicative of the presence of a hydroxy group (3440 cm^{-1}). ^1H and ^{13}C NMR data of **8** were analogous to those of debenzoylalopecurine, although the three carbons C-1 (δ_C 67.7; δ_H 3.25, 3.82), C-9 (δ_C 72.1; δ_H 3.04, 4.66), and C-13 (δ_C 80.7) were remarkably shifted to lower field as compared to those of debenzoylalopecurine. Furthermore, a methyl signal (δ_C 3.00; δ_H 45.4) was observed in the ^1H and ^{13}C NMR spectra of **8**. The molecular structure of **8** was deduced from extensive analyses of the two-dimensional NMR data, including the $^1H-^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Figure 1). The ^1H-^1H COSY and HOHAHA spectra revealed connectivities of two partial structures **a** (C-1−C3) and **b** (C-5−C-8, C-9−C-12, and C-14−C-16), as shown in Figure 1. Connectivities of C-17 to C-1, C-9, and C-13 through a nitrogen atom were implied by HMBC correlations for H_3-17 to C-1, C-9, and C-13. HMBC correlations were observed for H-2, H-5, and H-9a to C-4 (δ_C 54.6), suggesting that C-3, C-5, and C-10 were connected through C-4. HMBC cross-peaks for H-14 to C-4, C-12, and C-13 indicated that C-4, C-12, and C-14 were connected through C-13. Thus, the molecular structure of lycopodatine A was elucidated to be **8**, possessing an alopecurane skeleton with two hydroxy groups at C-2 and C-5 and an *N*-methyl group. The relative configuration of **8** was elucidated by NOESY correlations and $^3J_{H-H}$ couplings as depicted in the computer-generated three-dimensional drawing (Figure 1). The chair conformation of the cyclohexane ring (C-7−C-8, C-12−C-15) was deduced from NOESY correlations, as shown in Figure 1. The methyl group at C-15 was assigned to be equatorial from the large ^3J coupling (12.4 Hz) between H-14a and H-15. The NOESY correlation of H-2/H-14b and H-5/H-10 indicated that the hydroxy groups at C-2 and C-5 were α- and β-orientated, respectively.

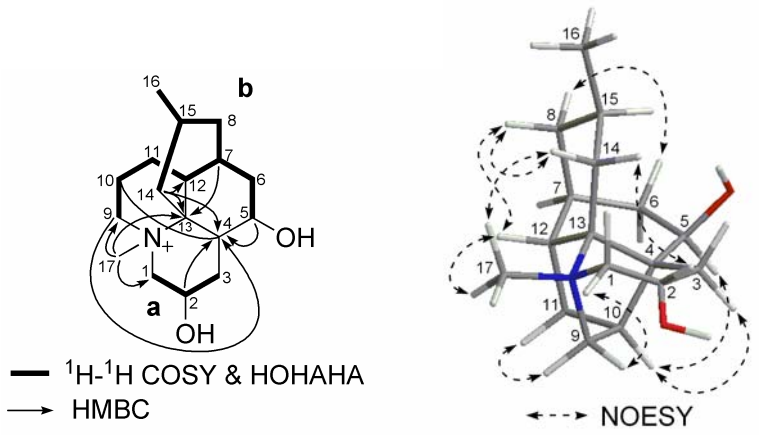


Figure 1. Selected 2D NMR correlations for lycopodatine A (**8**).

Treatment of debenzoylalopecurine with methyl iodide afforded an *N*-methyl derivative, whose spectroscopic data and specific rotation were identical with lycopodatine A (**8**). Thus, the absolute configuration of lycopodatine A was assigned as **8**.

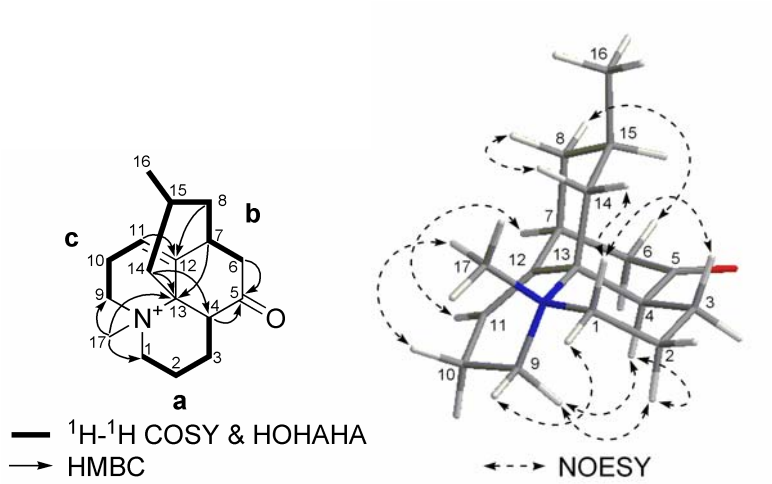


Figure 2. Selected 2D NMR correlations for lycopodatine B (**9**).

Lycopodatine B (**9**) had a molecular formula of $C_{17}H_{26}NO$ by HRESIMS [*m/z* 260.2037, $(M)^+$, Δ +2.3 mmu]. The IR spectrum indicated the presence of a carbonyl group (1770 cm^{-1}). ^{1}H and ^{13}C NMR data of **9** were similar to those of anhydrolycodoline, although the three carbons C-1 (δ_C 61.8; δ_H 3.40, 3.79), C-9 (δ_C 54.9; δ_H 3.23, 4.29), and C-13 (δ_C 72.5) were remarkably shifted to lower field. Furthermore, a methyl signal (δ_H 3.16; δ_C 48.9) was observed in the ^{1}H and ^{13}C NMR of **9**. Two-dimensional NMR data, including the ^{1}H–^{1}H COSY, HOHAHA, HMQC, HMBC, and NOESY spectra in CD_3OD (Figure 2), supported the structure of **9**. Thus, the structure of lycopodatine B was assigned as the *N*-methylammonium form of anhydrolycodoline.

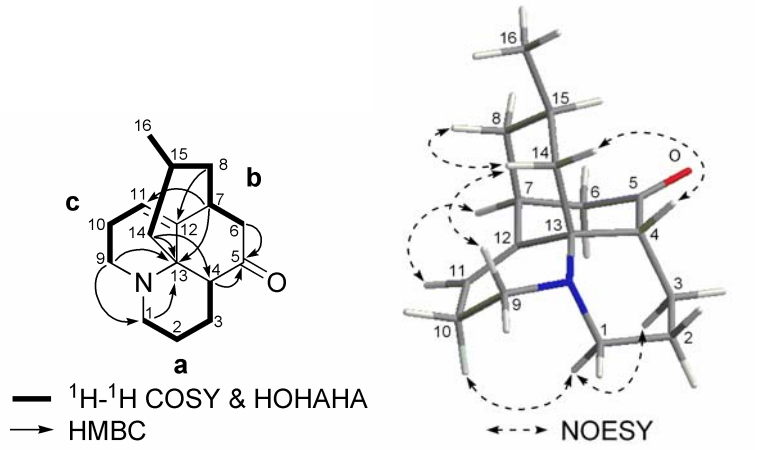


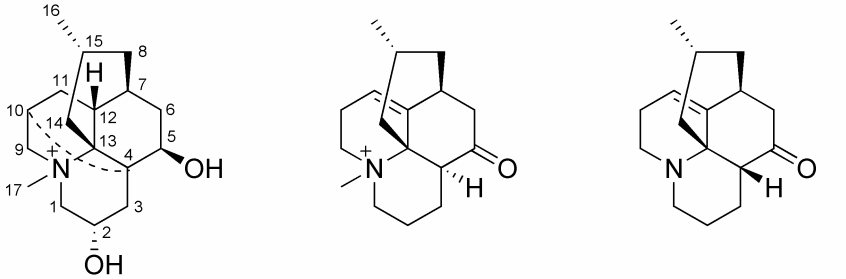
Figure 3. Selected 2D NMR correlations for lycopodatine C (**10**).

Lycopodatine C (**10**) had a molecular formula of $C_{16}H_{23}NO$ by HRESIMS [*m*/*z* 246.1855 $(M + H)^+$, Δ −0.3 mmu]. IR absorptions implied the presence of a carbonyl (1700 cm^{-1}) group. $^1H–^1H$ COSY, HOHAHA, HMQC, HMBC and NOESY spectra suggested that **3** was the 4-*epi* form of anhydrolycodoline (Figure 3).

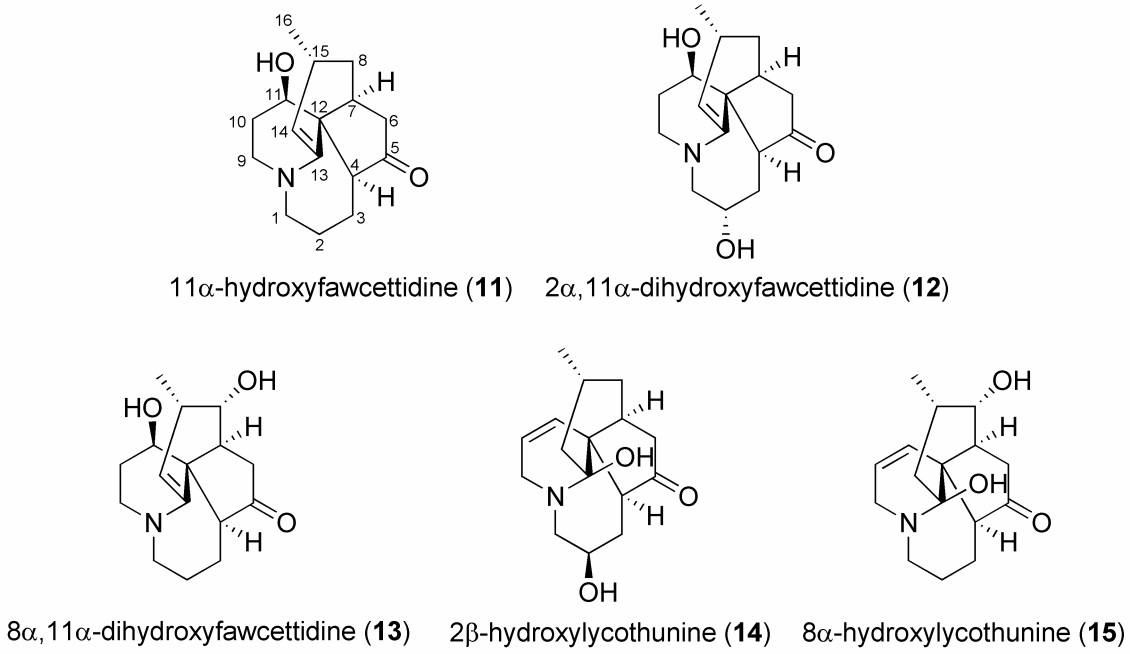
Table 3. ^{13}C NMR Data of Lycopodatines A (**8**), B (**9**), and C (**10**).

	8[a]	**9**[a]	**10**[a]		**8**[a]	**9**[a]	**10**[a]
1	67.7	61.8	49.8	10	45.6	22.2	20.3
2	61.5	20.7	25.2	11	33.1	117.2	119.4
3	31.7	18.8	29.8	12	40.4	138.8	139.8
4	54.6	56.8	60.2	13	80.7	72.5	60.2
5	68.4	207.6	215.9	14	31.2	35.1	52.3
6	35.2	50.0	44.1	15	25.8	26.6	27.2
7	38.2	40.5	42.0	16	22.9	22.1	22.4
8	40.9	41.0	45.9	17	45.4	48.9	
9	72.1	54.9	46.2				

[a] Solution in CD_3OD referenced to CD_3OD at 49.0.

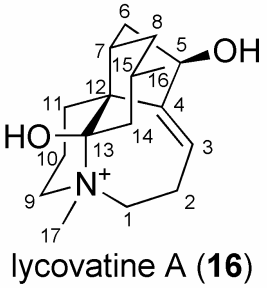


C. FAWCETTIMINE RELATED ALKLAOIDS



Five new *Lycopodium* alkaloids, 11α-hydroxyfawcettidine (**11**), 2α,11α-dihydroxyfawcettidine (**12**), 8α,11α-dihydroxyfawcettidine (**13**), 2β-hydroxylycothunine (**14**), and 8α-hydroxylycothunine (**15**) having the fawcettimine skeleton were isolated from *L. serratum* by Takayama and co-workers.[41] The structures including absolute configuration of the alkaloids were elucidated on the basis of spectroscopic analysis.

D. LYCOVATINE A



A new $C_{16}N$-type quaternary alkaloid, lycovatine A, was isolated from the club moss *Lycopodium clavatum* var. *robustum*.[42] The relative stereochemistry of **16** was deduced from detailed analyses of 2D NMR data of **16** (Figure 4). The absolute configuration of C-5 in lycovatine A was deduced to be *R* configuration by applying the modified Mosher's method.[63]

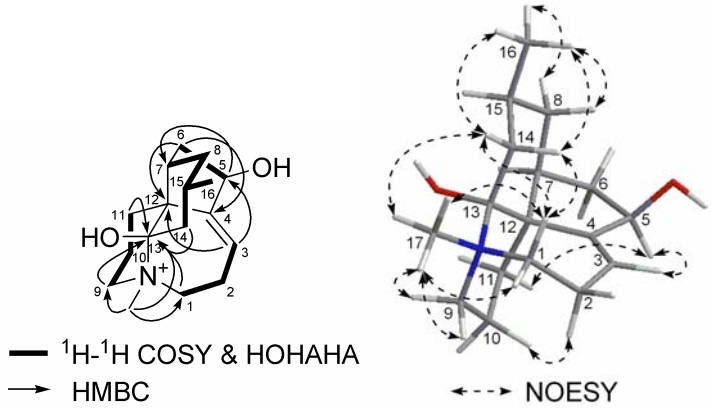


Figure 4. Selected 2D NMR correlations for lycovatine A (**16**).

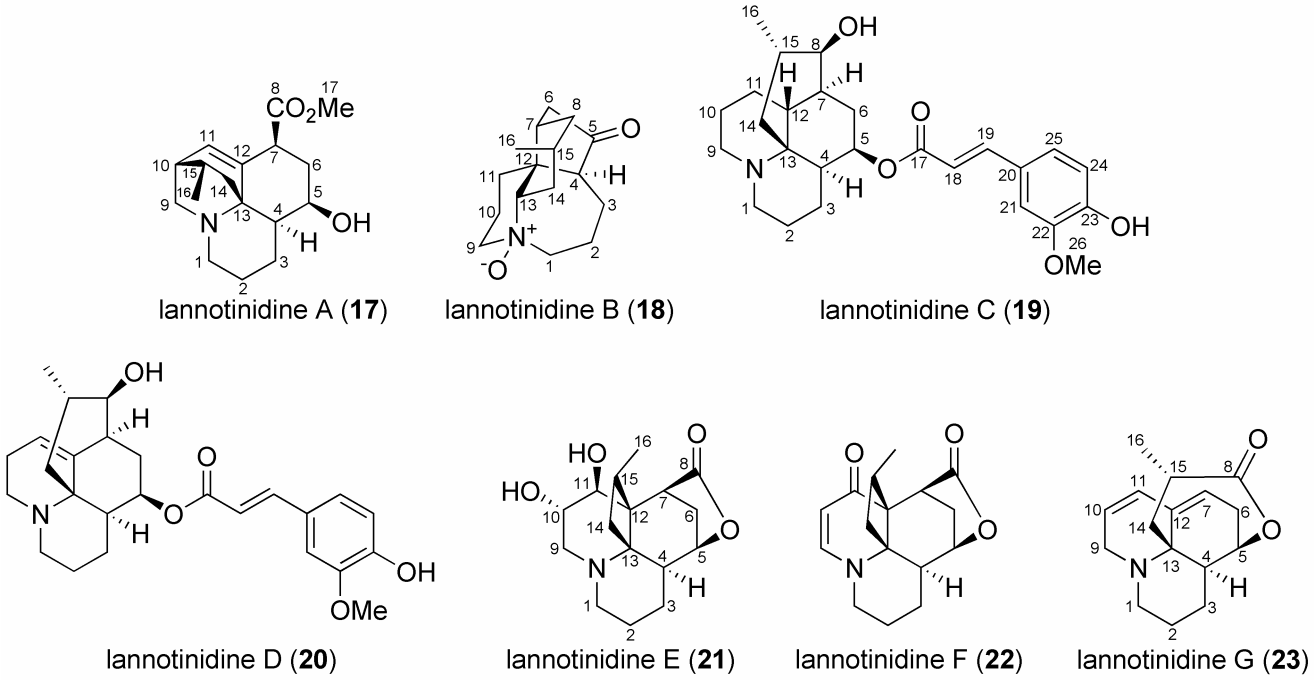
Effects of lycovatine A on neurotrophic factor biosynthesis in 1321N1 human astrocytoma cell were examined by a semiquantitative RT-PCR method[39,64] to find that the mRNA expressions for NGF were enhanced by **16**. Lycovatine A did not show cytotoxicity against murine leukemia L1210 cells and human epidermoid carcinoma KB cells (IC_{50} > 10 μg/mL). Lycovatine A exhibited antimicrobial activity against *Cryptococcus neoformans* (MIC, 0.52 μg/mL) and *Aspergillus niger* (MIC, 2.05 μg/mL).

Table 4. ^{13}C NMR Data of 11α-Hydroxyfawcettidine (**11**), 2α,11α-Dihydroxyfawcettidine (**12**), 8α,11α-Dihydroxyfawcettidine (**13**), 2β-Hydroxylycothunine (**14**), 8α-Hydroxylycothunine (**15**), and Lycovatine A (**16**).

	11[a]	**12**[a]	**13**[a]	**14**[a]	**15**[a]	**16**[b]
1	61.3	65.9	60.8	60.6	54.6	59.5
2	31.3	70.6	31.6	65.1	23.6	28.2
3	29.2	34.8	30.8	37.8	28.8	125.9
4	55.1	47.4	56.0	54.8	56.9	149.1
5	217.1	219.8	217.4	218.4	217.9	75.6
6	43.8	44.2	40.7	39.9	39.5	38.3
7	30.9	30.3	30.7	43.4	50.4	48.2
8	34.2	34.1	70.4	32.6	72.3	39.9
9	45.8	46.6	45.7	51.4	51.2	59.4
10	30.0	28.0	29.9	128.4	127.0	21.2
11	71.8	71.6	73.5	135.0	136.3	28.7
12	52.4	53.2	51.4	49.7	49.0	57.3
13	141.9	141.4	143.0	87.2	87.5	100.7
14	132.9	131.9	128.1	44.5	38.1	36.3
15	27.9	28.2	31.8	22.7	27.1	30.4
16	21.0	21.0	16.2	21.7	17.3	32.3
17						51.3

[a] Solution in $CDCl_3$.
[b] Solution in CD_3OD referenced to CD_3OD at 49.5.

E. LANNOTINIDINES



Seven new *Lycopodium* alkaloids, lannotinidines A−G (**17**-**23**), have been isolated from the club moss *Lycopodium annotinum* and *L. annotinum* var. *acrifolium*.[43] Lannotinidine A (**17**) is structural isomer of annopodine.[65,66] Lannotinidine B (**18**) has similar stereostructure with lyconesidine A.[67] Lannotinidine C (**19**) and D (**20**) are new alkaloids consisting of deacetylfawcettiine[59,68] or lycofoline[59,69] with ferulic acid ester at C-5, respectively. Treatment of annotinine[70,71] with sulfuric acid gave a dihydroxy derivative, whose spectral data and $[\alpha]_D$ value were identical with those of lannotinidine E (**21**). Lannotinidine F {**22**, $[\alpha]_D^{24}$ −22° (*c* 1.0, MeOH)} was revealed to have the molecular formula, $C_{16}H_{19}NO_3$, by HRFABMS [*m*/*z* 274.1432 $(M+H)^+$, Δ −1.1 mmu]. IR absorptions implied the presence of carbonyl (1770 and 1680 cm^{-1}) groups. ^1H and ^{13}C NMR data suggested the presence of two ketones, two sp^2 methines, five sp^3 methylenes, four sp^3 methines, one methyl, and two sp^3 quaternary carbon. Among them, one sp^2 methine (δ_C 153.6), one methylene (δ_C 49.9), and one quaternary carbon (δ_C 66.6) were ascribed to those bearing a nitrogen. The ^1H–^1H COSY and HOHAHA spectra of **22** revealed four structural units as shown in Figure 5. The presence of 2,3-dihydro-4-pyridinone and γ-lactone moieties was suggested by HMBC correlations for H-9 of C-11 and C-13, H-5 and H-6 of C-8, respectively. Connectivities among C-1, C-9, and C-13 through a nitrogen were elucidated by HMBC cross-peaks for H-1 of C-9 and C-13. HMBC correlations for H-1, H-5, and H-14 of C-13, H-7, H-14, and H-16 of C-12, H-7 and H-16 of C-11, and H-4 of C-14 gave rise to connectivities among the four units through a nitrogen atom, C-11, C-12, and C-13. Thus, the gross structure of lannotinidine F was elucidated to be **22**.

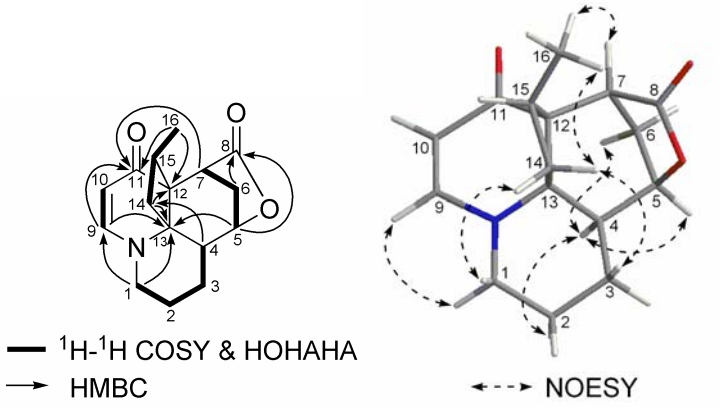


Figure 5. Selected 2D NMR correlations for lannotinidine F (**22**).

The relative stereochemistry of **22** was deduced from cross-peaks observed in the phase sensitive NOESY spectrum as shown in computer-generated 3D drawing (Figure 5).

Lannotinidine G (**23**) was revealed to have the molecular formula, $C_{16}H_{21}NO_2$, by HRFABMS [*m*/*z* 260.1653 $(M+H)^+$, Δ +0.3 mmu]. IR absorptions implied the presence of carbonyl (1685 cm^{-1}) group. ^1H and ^{13}C NMR data suggested the presence of one ketone, three sp^2 methines, one sp^2 quaternary carbon, six sp^3 methylenes, three sp^3 methines, one methyl, and one sp^3 quaternary carbon. Among them, signals due to three nitrogen-bearing carbons at δ_C 49.6, 49.8, and 62.0, and an oxygen-bearing carbon at δ_C 75.2 appeared.

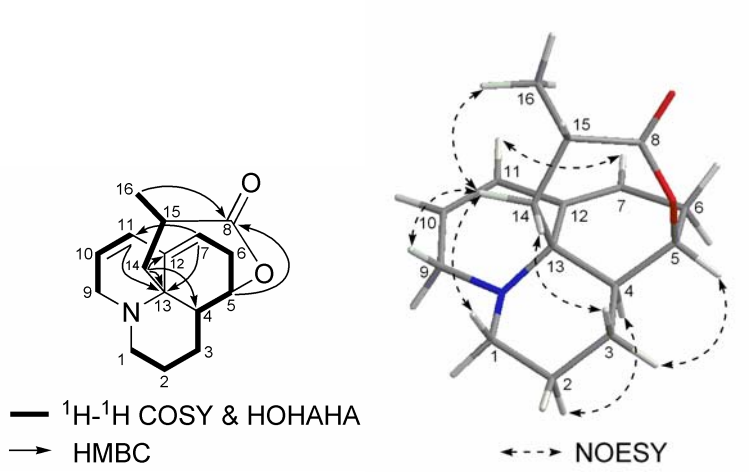


Figure 6. Selected 2D NMR correlations for lannotinidine G (**23**).

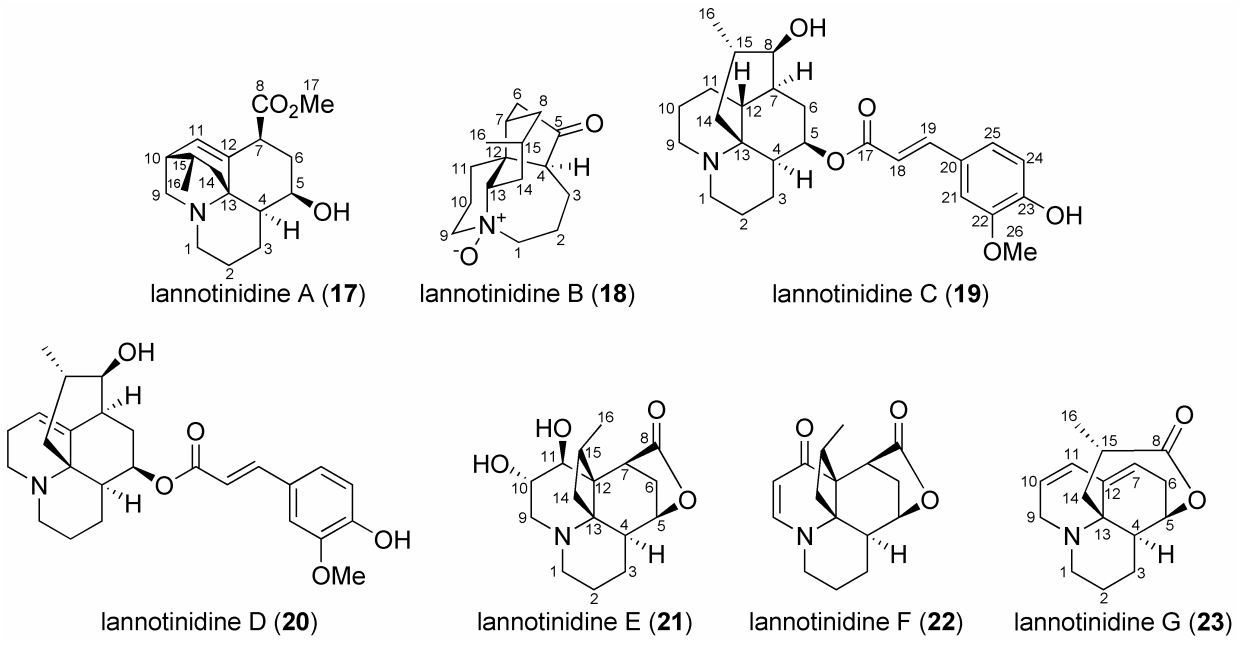
The structure of **23** was elucidated by 2D NMR (^1H–^1H COSY, HOHAHA, HMQC, and HMBC) data (Figure 10). The ^1H–^1H COSY and HOHAHA spectra revealed connectivities of C-1−C-7, C-9−C-11, and C-14−C-16. These three partial units were connected to one another on the basis of HMBC correlations as shown in Figure 6. Lannotinidine G (**23**) was identical with a compound produced by

hydrolysis of lyconnotine with KOH/MeOH followed by acidification. The relative stereochemistry of **23** was deduced from NOESY correlations (Figure 6).

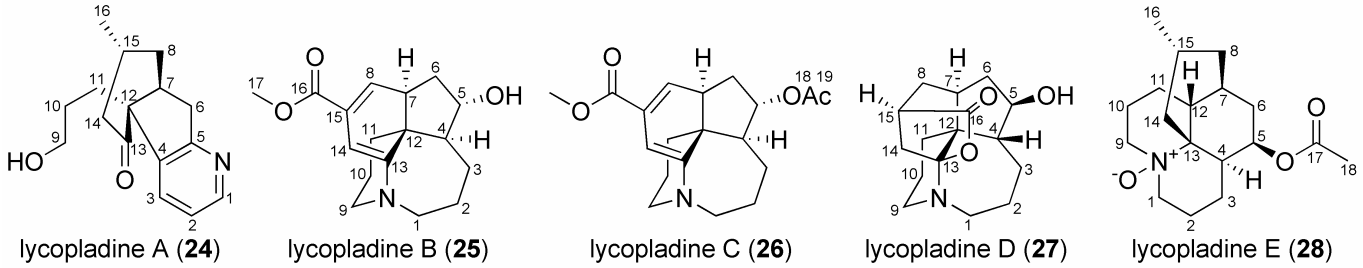
Table 5. ^{13}C NMR Data of Lannotinidine A (**17**), B (**18**), C (**19**), D (**20**), E (**21**), F (**22**), and G (**23**).

	17[a]	**18**[a]	**19**[a]	**20**[a]	**21**[a]	**22**[a]	**23**[a]
1	50.4	72.1	48.3	50.3	49.9	49.9	49.6
2	24.8	22.7	20.6	20.1	24.8	28.8	24.1
3	20.7	39.6	25.2	22.1	25.5	24.3	21.8
4	42.2	57.0	32.5	44.0	38.1	47.9	43.8
5	67.0	218.0	70.6	70.0	82.6	81.1	75.2
6	35.0	44.9	24.8	31.0	36.1	37.2	32.7
7	42.2	39.1	42.8	47.8	43.6	40.4	130.9
8	173.7	37.6	79.4	77.8	182.2	181.3	177.2
9	49.7	69.2	47.4	46.0	53.8	153.6	49.8
10	36.0	26.6	23.4	23.5	73.4	92.7[b]	119.9
11	131.6	24.8	24.8	117.4	77.2	190.8	127.1
12	141.4	46.3	44.6	141.3	53.6	55.7	133.1
13	62.6	78.6	57.3	63.8	63.9	66.6	62.0
14	28.8	28.7	41.5	37.9	35.6	40.3	28.3
15	30.1	28.2	32.4	32.1	33.2	37.0	34.2
16	18.0	17.5	21.1	20.1	14.2	12.9	18.8
17	52.5		167.5	168.1			
18			115.6	115.6			
19			145.6	147.1			
20			134.6	127.7			
21			112.7	112.0			
22			149.5	149.4			
23			153.0	150.8			
24			116.7	116.6			
25			124.3	124.2			
26			56.4	56.5			

[a] Solution in CD_3OD referenced to CD_3OD at 49.0.
[b] Solution in $CDCl_3$ referenced to $CDCl_3$ at 77.0.



F. LYCOPLADINES



Five new *Lycopodium* alkaloids lycopladine A−E (**24**-**28**) were isolated from the club moss *Lycopodium complanatum*,[43] together with lyconadin A.[72]

Lycopladine A (**24**) showed the pseudomolecular ion peak at *m*/*z* 260 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{16}H_{21}NO_2$, was established by HRESIMS [*m*/*z* 260.1653, $(M+H)^+$, Δ +0.2 mmu]. IR absorptions implied the presence of hydroxyl group (3380 cm^{-1}) and ketone carbonyl (1700 cm^{-1}). ^{13}C NMR data of **24** revealed 16 carbon signals due to one carbonyl carbon, two sp^2 quaternary carbons, three sp^2 methines, one sp^3 quaternary carbon, two sp^3 methines, six sp^3 methylenes, and one methyl group. Among them, two olefinic carbons [δ_C 148.8 (d), 164.3 (s)] assignable to nitrogen-bearing carbons were elucidated to form a disubstituted pyridine ring together with the remaining three olefinic carbons [δ_C 123.0 (d), 136.1 (d), 140.0 (s)]. The UV absorption [270 nm (ε 2800)] also supported the presence of the pyridine ring. Since five out of seven unsaturations were accounted for, **24** was inferred to possess two more rings.

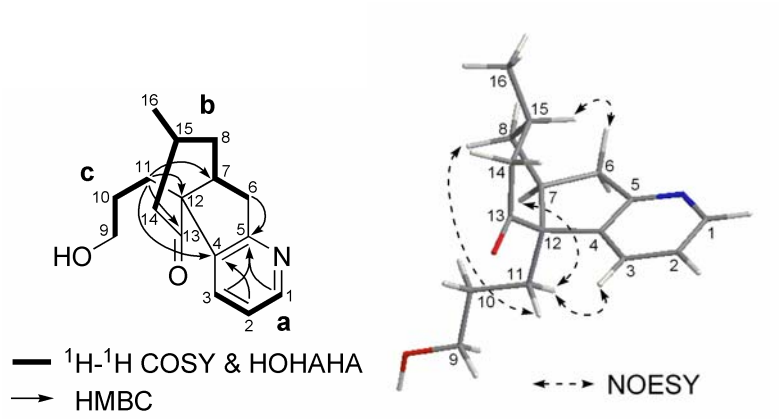


Figure 7. Selected 2D NMR correlations for lycopladine A (**24**).

The gross structure of **24** was elucidated by analyses of 2D NMR data including $^1H-^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD. The $^1H-^1H$ COSY and HOHAHA spectra of **24** revealed three structural units **a** (C-1–C-3), **b** (C-6−C-8, C-8−C-15, and C-14−C-16), and **c** (C-9−C-11) (Figure 7). It was elucidated that unit **a** constituted a 2,3-disubstituted pyridine ring by HMBC correlations of H-1 and H-3 (δ_H 8.30, 7.67, respectively) to C-5, and H-2 (δ_H 7.24) to C-4. HMBC

correlations of H-11a (δ_H 2.06) to C-4, C-7, and C-12 revealed the connectivities from C-11 to C-4 and C-7 through C-12. The HMBC correlations of H_2-11 and H_2-14 (δ_H 2.29) to C-13 indicated the connectivities from C-11 to C-14 through C-12 and C-13. HMBC cross-peaks of H_2-6 (δ_H 3.09, 2.83) to C-5 suggested the connectivity from C-6 to C-5. The remaining C-9 (δ_H 3.53, δ_C 62.8) was elucidated to be connected with a hydroxyl group. Thus, the gross structure of lycopladine A was assigned as **24**.

The NOESY spectrum of **24** showed cross-peaks as shown in computer-generated 3D drawing. The relative configurations of C-7, C-12, and C-15 in the cyclohexanone ring (C-7, C-8, and C-12 to C-15) were deduced from NOESY correlations of H-3/H_2-11, H-6b/H-15, H-7/H_2-11, H-8b/H_2-11, and H_2-14/H_2-11. Thus, the relative configurations of lycopladine A (**24**) were elucidated as shown in Figure 7.

Lycopladine A (**24**) showed weak cytotoxicity against murine lymphoma L1210 cells (IC_{50}, 7 μg/mL) in vitro, while **24** did not show such activity against human epidermoid carcinoma KB cells (IC_{50} > 10 μg/mL).

Lycopladine B (**25**) showed the pseudomolecular ion peak at *m*/*z* 290 $(M+H)^+$ in the ESI-MS, and the molecular formula, $C_{17}H_{23}NO_3$, was established by HRESIMS [*m*/*z* 290.1759, $(M+H)^+$, Δ +0.3 mmu]. IR absorptions implied the presence of hydroxy (3380 cm^{-1}) and ester carbonyl (1710 cm^{-1}) functionalities. ^{13}C NMR data of **25** revealed 17 carbon signals due to one carbonyl carbon, two sp^2 quaternary carbons, two sp^2 methines, one sp^3 quaternary carbon, three sp^3 methines, seven sp^3 methylenes, and one *O*-methyl group.

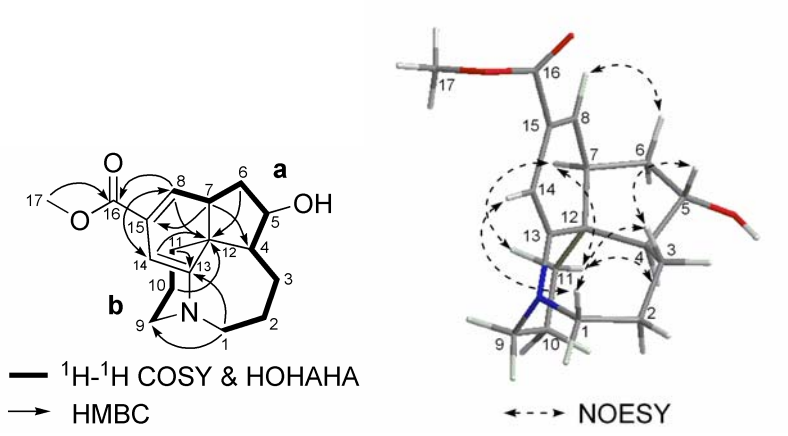


Figure 8. Selected 2D NMR correlations for lycopladine B (**25**).

The gross structure of **25** was elucidated by analyses of 2D NMR data including ^1H–^1H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Figure 8). ^1H–^1H COSY and HOHAHA spectra of **25** revealed two structural units **a** (C-1 to C-8) and **b** (C-9 to C-11). In unit **a**, C-5 was deduced to be connected to a hydroxy group from the ^1H and ^{13}C NMR chemical shifts (δ_H 3.59 and δ_C 80.8). HMBC

correlations of H_2-6 (δ_H 2.08 and 1.96) and H-8 (δ_H 6.51) to C-12 (δ_C 48.2), and H-7 (δ_H 2.76) to C-4 (δ_C 59.9) suggested a connection of C-7 to C-4 through C-12, indicating the presence of a cyclopentane ring (C-4 to C-7 and C-12). HMBC cross-peaks of H-1b (δ_H 3.09) to C-9 (δ_C 53.5) and H-1a to C-13 revealed connections of C-1 to C-9, C-1 to C-13, and C-9 to C-13 through a nitrogen atom. While HMBC cross-peaks of H-10b (δ_H 1.61) and H-14 (δ_H 6.22) to C-12 (δ_C 48.2) and H-11a (δ_H 2.02) to C-13 (δ_C 147.9) indicated a connection of C-11 to C-14 through C-12 and C-13. HMBC cross-peaks of H-8 (δ_H 6.51) to C-14 and C-16 (δ_C 114.9 and 167.1, respectively) and H-7 (δ_H 2.76) to C-15 (δ_C 127.6) suggested that C-8 was connected to C-14 and C-16 through C-15. The presence of a methyl ester group was elucidated by the HMBC correlation of H-17 (δ_H 3.74) to C-16 (δ_C 167.1). Thus, the gross structure of lycopladine B was elucidated to be **25**.

The NOESY spectrum of **25** showed cross-peaks as shown in computer-generated 3D drawing (Figure 8). The relative stereochemistry of H-5 was deduced to be a β-configuration from NOESY correlations of H-1b/H-3b, H-1b/H-14, and H-3b/H-5. While the relative stereochemistry of H-4 was deduced to be an α-configuration from the NOESY correlation of H-4/H-11a. A chair-like conformation of the piperidine ring (N-1 and C-9 to C-13) and an α-configuration of H-7 were suggested by NOESY correlations of H-7/H_2-11.

The absolute configuration of C-5 in lycopladine B (**25**) was elucidated by the modified Mosher's method for the MTPA esters of **25**. The values of $\Delta\delta$[δ(*S*-MTPA ester)−δ(*R*-MTPA ester)] for H_2-6, H-7, and H-8 were negative, while the values of $\Delta\delta$ for H_2-1, H_2-2, H_2-3, H-4, H_2-9, H_2-10, and H_2-11 were positive. These data suggested that the absolute configuration at C-5 was *S*. Thus, the absolute stereochemistry of **25** was assigned as shown.

Lycopladine C (**26**) showed the pseudomolecular ion peak at *m*/*z* 332 $(M+H)^+$ in the ESI-MS, and the molecular formula, $C_{19}H_{25}NO_4$, was established by HRESIMS [*m*/*z* 332.1858, $(M+H)^+$, Δ −0.4 mmu]. IR absorptions implied the presence of ester carbonyl (1735 cm^{-1}) functionality. Comparison of the ^1H and ^{13}C NMR spectra of **26** with those of **25** suggested that they were almost identical with each other except for the presence of signals for an acetate group [δ_H 2.04 (s, 3H) and δ_C 170.8 and 21.2] and low field shift of signal of H-5 (δ_H 4.67) in **26**. The spectral data of the product which was obtained by acetylation of **25** were identical with those of **26**. Thus, lycopladine C (**26**) was assigned as 5-*O*-acetyl form of lycopladine B (**25**).

Lycopladine D (**27**) showed the pseudomolecular ion peak at *m*/*z* 278 $(M+H)^+$ in the ESI-MS, and the molecular formula, $C_{16}H_{23}NO_3$, was established by HRESIMS [*m*/*z* 278.1773, $(M+H)^+$, Δ +1.7 mmu].

IR absorptions implied the presence of hydroxy (3380 cm^{-1}) and lactone carbonyl (1780 cm^{-1}) functionalities. ^{13}C NMR data of **27** revealed 16 carbon signals due to one ester carbonyl carbon, two sp^3 quaternary carbons, four sp^3 methines, and nine sp^3 methylenes.

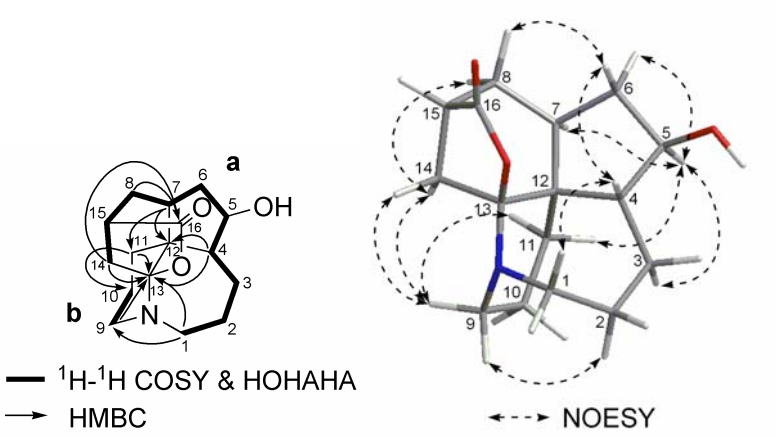


Figure 9. Selected 2D NMR correlations for lycopladine D (**27**).

The gross structure of **27** was elucidated by analyses of 2D NMR data including the ^1H–^1H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Figure 9). The ^1H–^1H COSY and HOHAHA spectra of **3** revealed two structural units **a** (C-1 to C-8, C-14 to C-15, and C-8 to C-15) and **b** (C-9 to C-10). In unit **a**, C-5 was deduced to be connected to a hydroxy group from the ^1H and ^{13}C NMR data (δ_H 3.43, δ_C 74.0). HMBC cross-peaks of H-1a (δ_H 3.46) to C-9 (δ_C 46.6), and H-1b (δ_H 2.62) and H-9b (δ_H 3.05) to C-13 (δ_C 101.3) suggested connections of C-1 to C-9, C-1 to C-13, and C-9 to C-13 through a nitrogen atom. The δ_C value (101.3 ppm) suggested that C-13 was ascribed to aminoacetal carbon. HMBC correlations of H-8a (δ_H 2.09) and H-14a (δ_H 2.62) to C-16 (δ_C 179.0) revealed that the ester carbonyl group was connected to C-15. The connection of C-10 to C-11 was suggested by the HMBC cross-peak of H-11a (δ_H 1.91) to C-10 (δ_C 21.2). HMBC correlations of H-7 (δ_H 1.70) to C-11 (δ_C 34.1) and C-12 (δ_C 46.1) indicated that C-7 was connected to C-11 through C-12. HMBC cross-peaks of H-4 (δ_H 2.19) to C-12 (δ_C 46.1) and C-13 (δ_C 101.3), and H-14b (δ_H 2.00) to C-13 (δ_C 101.3) revealed that C-4 was connected to C-14 through C-12 and C-13. Thus, the gross structure of lycopladine D was elucidated to be **27**.

The NOESY spectrum of **27** showed cross-peaks as shown in computer-generated 3D drawing (Figure 9). The relative stereochemistry of H-4 was deduced to be a β-configuration from NOESY correlations of H-1b/H-4, H-4/H-6b, and H-6b/H-8b, while the relative stereochemistry of H-5 and H-7 was deduced to be both β-configurations from NOESY correlations of H-3b/H-5, H-5/H-6a, H-5/H-7, and H-5/H-11a. A chair-like conformation of the piperidine ring (N-1 and C-9 to C-13) and the cyclohexane ring (C-7 to C-8 and C-12 to C-15) and relative stereochemistry of H-15 were suggested by NOESY correlations of H-8b/H-6b H-8a/H-14a, H-9a/H-11a, and H-9a/H_2-14. Thus, the relative stereochemistry of lycopladine

D (**27**) was elucidated as shown in Figure 9.

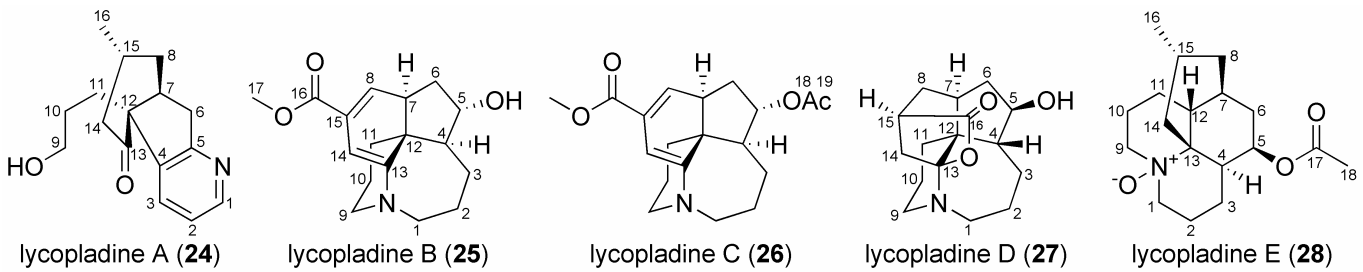
The absolute configuration of lycopladine D (**27**) was elucidated by the modified Mosher's method for the MTPA ester of **27**. The values of Δδ[δ(*S*-MTPA ester)–δ(*R*-MTPA ester)] for H_2-6, H_2-8, and H-15 were positive, while the values of Δδ for H_2-1, H_2-2, H_2-3, H-4, H_2-9, H_2-10, and H-14a were negative, suggesting that the absolute configuration at C-5 was *R*. Thus, the absolute configuration of **27** was assigned as shown.

Lycopladine E (**28**) was a new $C_{16}N$-type alkaloid having a lycopodane-skeleton with *N*-oxide and acetoxy group at C-5. The relative and absolute stereochemistry were confirmed by 2D NMR technique and chemical correlation.

Table 6. ^{13}C NMR Data of Lycopladines A (**24**), B (**25**), C (**26**), D (**27**), and E (**28**).

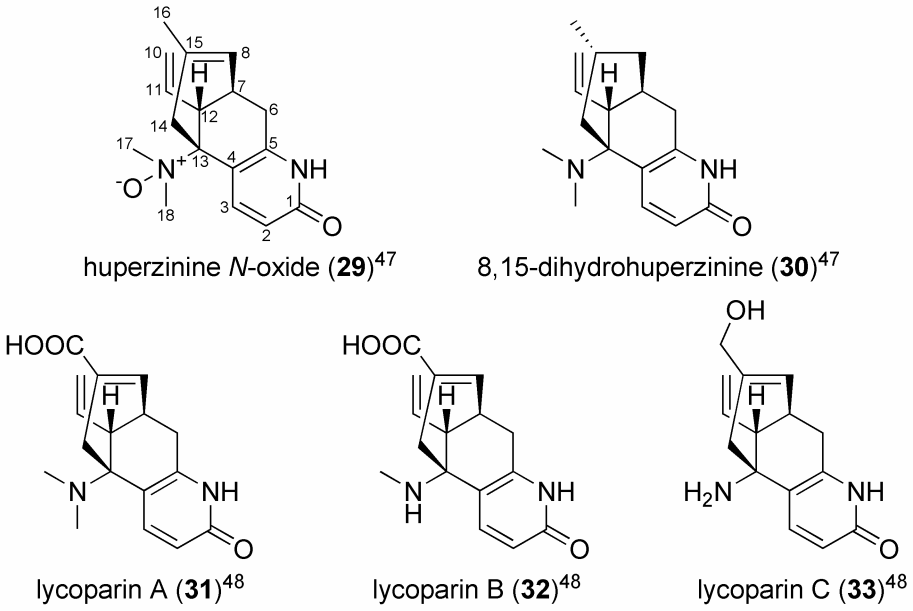
	24[a]	**25**[b]	**26**[b]	**27**[b]	**28**[a]
1	148.8	62.8	61.4	48.8	64.6
2	123.0	30.2	31.2	26.8	22.9
3	136.1	32.1	36.9	21.0	21.9
4	140.0	59.9	55.7	48.5	36.7
5	164.3	80.8	81.1	74.0	70.4
6	38.6	40.3	36.9	43.9	30.9
7	43.5	47.4	46.3	41.2	36.7
8	34.8	139.7	135.8	27.8	41.9
9	62.8	53.5	51.7	46.6	60.6
10	29.1	23.0	22.6	21.2	20.9
11	33.4	42.1	41.0	34.1	23.1
12	62.7	48.2	47.2	46.1	39.2
13	214.6	147.9	145.2	101.3	75.0
14	47.7	114.9	113.2	37.7	33.5
15	29.5	127.6	127.3	41.4	24.9
16	22.0	167.1	166.0	179.0	24.4
17		52.3	51.7		170.6
18			170.8		21.1
19			21.2		

[a] Solution in CD_3OD referenced to CD_3OD at 49.0.
[b] Solution in CD_3OD referenced to CD_3OD at 49.5.



lycopladine A (**24**) lycopladine B (**25**) lycopladine C (**26**) lycopladine D (**27**) lycopladine E (**28**)

G. HUPERZININE RELATED ALKALOIDS



Two new *Lycopodium* alkaloids, huperzinine *N*-oxide (**29**) and 8,15-dihydrohuperzinine (**30**) were isolated from *Lycopodium casuarinoides*.[47] Their relative and absolute stereochemistries were analyzed by spectroscopic data including CD spectra and chemical correlations.

In our search for bioactive *Lycopodium* alkaloids, lycoparins A−C (**31**-**33**), new alkaloids were isolated from the club moss *L. casuarinoides*.[48]

The club moss *L. casuarinoides* was extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted to pH 10 with sat. Na_2CO_3, were extracted with $CHCl_3$, and then *n*-BuOH. The aqueous layer was subjected to an HP-20 column (H_2O/MeOH, 1:0 → 0:1), and then an ODS column (10% MeOH → MeOH), in which a fraction eluted with 30% MeOH was purified by an amino silica gel column ($CHCl_3$/MeOH, 10:1) and then an ODS HPLC (13% CH_3CN/0.1% TFA) to afford lycoparins A (**31**, 3.0 mg, 0.0002% yield), B (**32**, 3.0 mg, 0.0002% yield), and C (**33**, 7.6 mg, 0.0005%) together with huperzines B[13], C[73], and D[73].

Lycoparin A {**31**, $[\alpha]_D^{27}$ +1° (*c* 1.0, MeOH)} was revealed to have the molecular formula $C_{17}H_{20}N_2O_3$, by HRESITOFMS [*m/z* 301.1541 $(M+H)^+$, Δ −1.2 mmu]. UV absorptions at 230 nm and 310 nm indicated the presence of α-pyridone ring. IR absorption implied the presence of α,β-unsaturated ketone (1660 cm^{-1}) and a hydroxyl (3440 cm^{-1}) group.

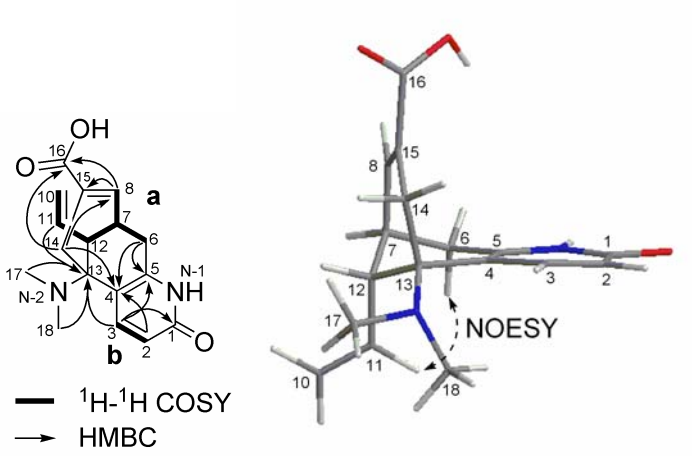


Figure 10. Selected 2D NMR correlations for lycoparin A (**31**).

The gross structure of lycoparin A was deduced from detailed analyses of 2D NMR spectra of **31** (Figure 10). And the relative stereochemistry of **31** was elucidated by NOESY correlations as shown in computer-generated 3D drawing (Figure 10). The vinyl group at C-12 was elucidated to be α-configuration by the NOESY correlation of H-6a/H-11. Thus, the relative stereochemistry of **31** was assigned as shown in Figure 10. The absolute structure was deduced to be in Figure 11 by use of Flack parameter[74] of the X-ray crystal structure of lycoparin A (**31**) TFA salt.

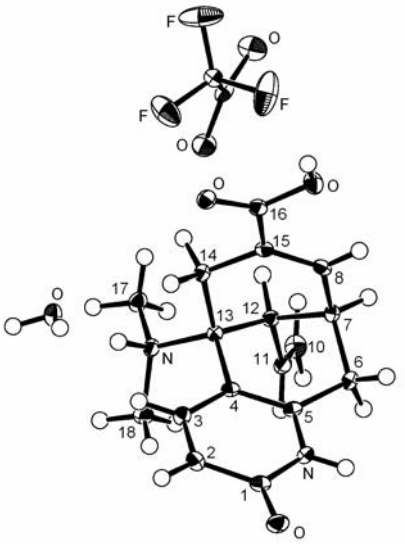


Figure 11. X-Ray structure of lycoparin A (**31**) with one H_2O and one TFA molecules.

The relative stereochemistry of lycoparin B (**32**) was assigned to be an *N*-demethyl form of lycoparin A (**31**) by detailed analyses of 2D NMR data.

Lycoparin C (**33**), colorless amorphous solid, $[\alpha]_D^{27}$ −12 (*c* 1.0, MeOH), was shown to have the molecular formula of $C_{15}H_{18}N_2O_2$ by HRESITOFMS [m/z 259.1429, $(M+H)^+$, Δ −1.7 mmu], which was smaller than that of huperzine D by 28 mmu. ^{1}H and ^{13}C NMR data of **33** were analogous to those of

huperzine D, although two *N*-methyl signals lacking for **33** was observed for huperzine D. The gross structure of **33** was elucidated by 2D NMR (^{1}H–^{1}H COSY, HMQC, HMBC) data, and relative stereochemistry of **33** was assigned as des-*N*-methyl form of huperzine D by NOESY correlation of H-6b and H-11 (Figure 12).

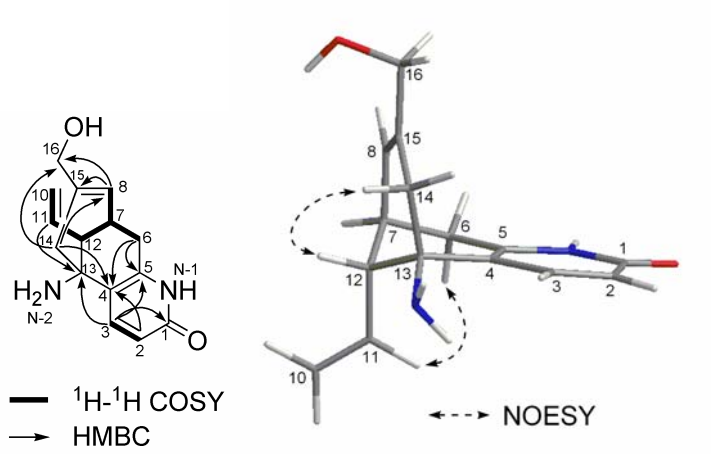


Figure 12. Selected 2D NMR correlations for lycoparin C (**33**).

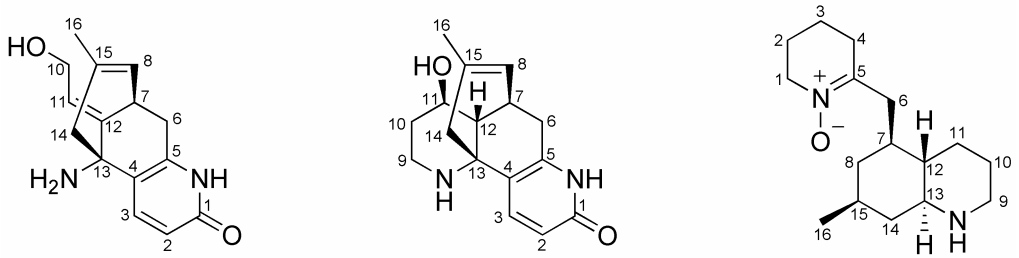
Lycoparin C (**33**) inhibited acetylcholinesterase (from bovine erythrocyte) with IC_{50} 25 μM, whereas lycoparins A (**31**) and B (**32**) possessing a carboxylic acid at C-15 and one or two *N*-methyl groups did not show such activity (IC_{50}>200 μM).[75]

Table 7. ^{13}C NMR Data of Huperzinine *N*-oxide (**29**), 8,15-Dihydrohuperzinine (**30**), and Lycoparins A (**31**), B (**32**), and C (**33**).

	29[a]	**30**[a]	**31**[b]	**32**[b]	**33**[b]
1	165.2	165.6	164.9	165.0	164.4
2	117.6	118.6	120.8	120.5	118.5
3	143.9	143.7	139.7	139.0	142.6
4	114.3	120.7	111.8	113.4	122.2
5	143.3	146.6	146.3	145.4	143.3
6	29.0	31.0	28.5	28.6	30.0
7	39.5	39.8	39.5	37.9	37.1
8	123.4	43.9	141.7	141.8	126.7
10	118.7	116.6	122.2	123.5	120.1
11	138.0	143.1	136.5	134.5	137.7
12	46.8	49.0	43.7	43.2	51.1
13	77.6	63.0	69.4	61.4	52.1
14	40.3	49.0	37.4	35.7	44.0
15	134.0	29.0	129.5	129.1	138.4
16	22.8	22.8	168.5	169.1	66.0
17	57.1	40.4	41.0	28.3	
18	55.3	40.4	41.0		

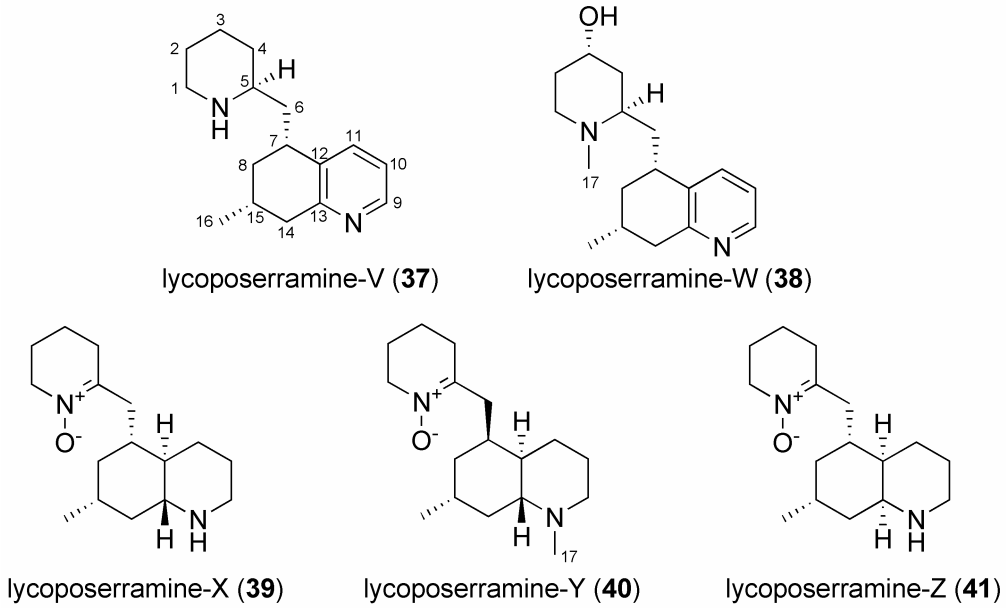
[a] Solution in $CDCl_3$.
[b] Solution in CD_3OD referenced to CD_3OD at 49.0.

H. CARINATUMINS



Three new *Lycopodium* alkaloids, carinatumins A−C (**34-36**), have isolated from the club moss *Lycopodium carinatum*.[49] Relative stereochemistry of carinatumins A (**34**) and B (**35**) were assigned as 10-hydroxyhuperzine A and 11-hydroxyhuperzine B, respectively. On the other hands, carinatumin C (**36**) was the same structure as lycoposerramine-X, isolated from *Lycopodium serratum*.[51] Carinatumins A (**34**) and B (**35**) inhibited acetylcholinesterase with IC_{50} 4.6 and 7.0 μM, respectively, whereas carinatumin C (**36**) did not show such activity (IC_{50} > 100 μM).

I. LYCOPOSERRAMINES



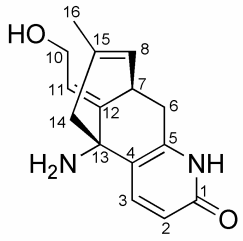
Takayama and co-workers are energetically studying *Lycopodium* alklaoids and many fawcettimane-type and fawcettidane-type alkaloids, a series of lycoposerramines were isolated from *L. serratum* in Japan.[76-80]

Recently, they isolated five new alkaloids, lycoposeramines-V (**37**), -W (**38**), -X (**39**), -Y (**40**), and -Z (**41**), having phlegmarine-related structures, from the club moss *Lycopodium serratum* and their structures were elucidated on the basis of spectroscopic analysis.[50,51] Among them, the absolute configuration of lycoposerramines-V (**37**) and -W (**38**) were established by asymmetric total synthesis by themselves.[50]

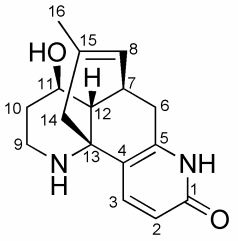
Table 8. ^{13}C NMR Data of Carinatumins A (**34**) and B (**35**), and Lycoposerramine-V (**37**), -W (**38**), -X (**39**), -Y (**40**), and -Z (**41**).

	34[a]	**35**[a]	**37**[b]	**38**[b]	**39**[b]	**40**[b]	**41**[b]
1	165.4	165.3	44.8	49.5	58.3	58.3	58.3
2	119.5	120.4	22.6[c]	31.0	23.2	23.3	23.2
3	138.5	138.4	22.3[c]	65.0	18.9	19.0	18.8
4	116.8	112.2	30.3	37.7	30.5[c]	29.9	30.0
5	146.1	147.0	54.8	55.7	148.5	148.5	149.0
6	36.4	29.6	41.1	40.0	35.6	35.8	35.9
7	34.2	30.0	33.3	35.9	37.4	33.0	29.6
8	125.2	126.6	37.9	39.0	41.0	37.7	41.1
9		40.7	146.8	146.6	46.3[d]	57.7	47.4
10	58.2	32.8	121.1	121.1	26.0	25.4	20.3
11	120.5	65.0	135.0	134.6	28.1	28.5	26.4[c]
12	137.2	45.8	133.9	135.7	46.6[d]	47.0	40.6
13	57.8	60.7	157.3	157.6	60.7	63.4	56.6
14	45.9	44.7	41.7	42.0	41.2	35.7	40.6
15	133.3	131.8	28.6	29.2	30.6[c]	27.3	26.5[c]
16	22.3	22.5	22.2	22.3	22.4	19.5	22.5
17				41.1		42.8	

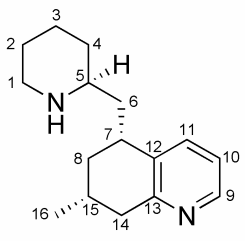
[a] Solution in CD_3OD referenced to CD_3OD at 49.0.
[b] Solution in $CDCl_3$ refferenced to $Si(CH_3)_4$.
[c,d] Interchangeable.



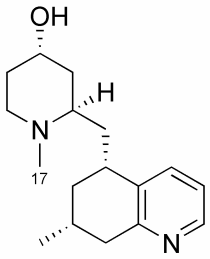
carinatumin A (**34**)



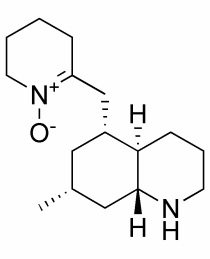
carinatumin B (**35**)



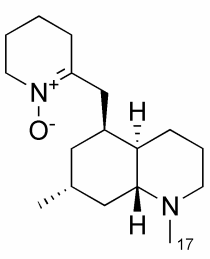
lycoposerramine-V (**37**)



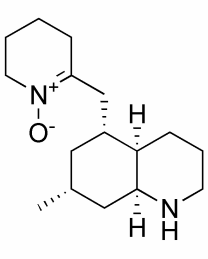
lycoposerramine-W (**38**)



lycoposerramine-X (**39**)



lycoposerramine-Y (**40**)



lycoposerramine-Z (**41**)

J. NANKAKURINES

New *Lycopodium* alkaloids, nankakurine A (**42**) and B (**43**) were isolated from the club moss *Lycopodium hamiltonii*.[52,53] Nankakurine A {**42**, $[\alpha]^{21}_{D}$ +16° (*c* 0.4, MeOH)} showed the pseudomolecular ion peak at *m*/*z* 263 $(M + H)^+$ in the FABMS spectrum, and the molecular formula, $C_{17}H_{30}N_2$, was established by HRFABMS [*m*/*z* 263.2497, $(M + H)^+$, Δ +1.0 mmu].

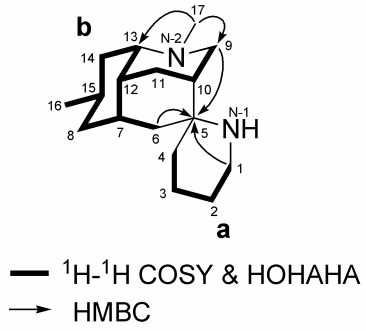


Figure 13. Selected 2D NMR correlations for nankakurine A (**42**).

The gross structure of **42** was deduced from extensive analyses of the two-dimensional NMR data, including the ^{1}H−^{1}H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Figure 13). The ^{1}H-^{1}H COSY and HOHAHA spectra in CD_3OD revealed connectivities of two partial structures **a** (C-1−C-4) and **b** (C-6 to C-8, C-9−C-16, C-7 to C-12, and C-8 to C-15) as shown in Figure 13. HMBC correlations were observed for H-1 and H-4 to C-5 (δ_C 56.1), suggesting that C-1 and C-4 were connected to each other through C-5 and a nitrogen atom to form a piperidine ring. The connectivities of C-17 to C-9 and C-13 through a nitrogen atom were implied by HMBC correlations for H_3-17 to C-9 (δ_C 58.5) and C-13 (δ_C 65.1). HMBC cross-peaks for H-9b and H-6a to C-5 (δ_C 56.1) indicated that a 3-aza-bicyclo[3.3.1]nonane ring was connected to a piperidine ring through a spiro carbon (C-5). ^{1}H-^{1}H correlations observed in the ^{1}H-^{1}H COSY and HOHAHA spectra indicated that a cyclohexane ring with a methyl at C-15 was connected to the 3-aza-bicyclo[3.3.1]nonane ring at C-7, C-12, and C-13. Thus, the gross structure of nankakurine A was elucidated to be **42** possessing an unprecedented caged skeleton consisting of a cyclohexane ring (C-7−C-8 and C-12−C-15) with a methyl group at C-15 and a 3-aza-bicyclo[3.3.1]nonane ring (C-5−C-7, C-9−C-13, and N-2) with a *N*-methyl group (C-17) connected to a piperidine ring (N-1 and C-1−C-5) through a spiro carbon at C-5.

Nankakurine B {**43**, $[\alpha]_D^{19}$ +12° (*c* 1.0, MeOH)} showed the pseudomolecular ion peak at *m/z* 277 $(M+H)^+$ in the FABMS, and the molecularformula, $C_{18}H_{32}N_2$, was established by HRFABMS [*m/z* 277.2653 $(M+H)^+$, Δ +0.9 mmu]. IR absorptions implied the presence of an amine (3300 cm^{-1}) functionality. ^{13}C NMR data resembled that of nankakurine A except for the excess of a signal for an *N*-methyl group. The gross structure of **43** was assigned as *N*-methyl form of nankakurine A by 2D NMR data.

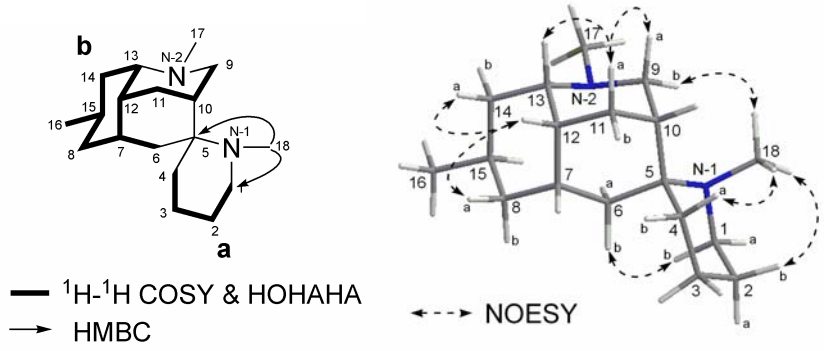


Figure 14. Selected 2D NMR correlations for nankakurine B (**43**).

The relative stereochemistry of **43** was elucidated by NOESY correlations and $^3J_{H-H}$ couplings as shown in gomputer-generated 3D drawing (Figure 14). Conformations of the piperidine ring (N-1, C-1−C-5), the bicyclo[3.3.1]nonane ring (C-5−C-7, C-9−C-13, and N-2), and the cyclohexane ring (C-7, C-8, and C-12−C-15), in which all of the 6-membered rings took chair forms, were deduced from NOESY correlations such as H_3-18/H-2b and H-4a, H-11a/H-9a and H-13, and H-12/H-8a and H-14a as shown in Figure 14. The ^{13}C high field shift at C-2 (δ_C 17.9) by its γ-gauche effect indicated that the *N*-methyl at C-18 took an axial orientation. Stereochemistry of the spiro carbon at C-5 was elucidated to be *R** by the clear NOESY correlations of H-1b/H-6b, and H_3-18/H-9b. Thus, the relative stereochemistry of **43** was assigned as shown in Figure 14. Treatment of nankakurine A (**42**) with HCOOH and HCHO, nankakurine B (**43**) was obtained, so nankakurine A is demethyl form of nankakurine B.

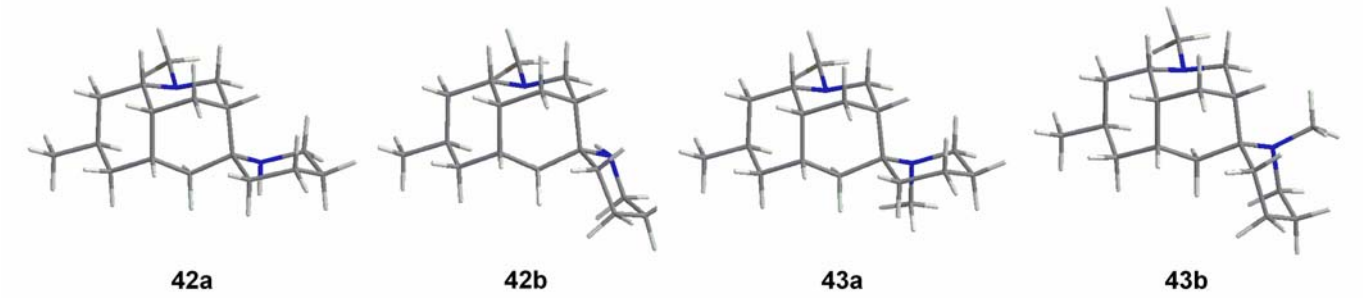
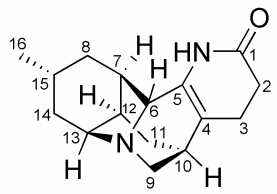


Figure 15. Each two representative stable conformers (**42a** and **42b**; **43a** and **43b**) analyzed by conformational analysis.

There are two possible conformational states for the piperidine ring of **42** and **43** in solution as shown in Figure 15. The conformational space was searched using MMFF force field[81] implemented in the Macromodel program.[82] Each of the lowest energy conformers belonging to two separate clusters are represented as **42a**, **42b**, **43a**, and **43b**. Each conformer possessed a chair conformation in the piperidine part, while the bicyclo[3.3.1]nonane ring and the cyclohexane ring adopted the same chair conformation. In the case of nankakurine B, **43b** was abundant from the populations calculated for these two clusters (**43a** and **43b**). On the other hand, **42a** and **42b** took a similar energy. These results of the simulations were consistent with the relative stereochemistry of **43** and the equilibrium to the more stable conformer **43b** in CD_3OD inferred on basis of the NMR data.

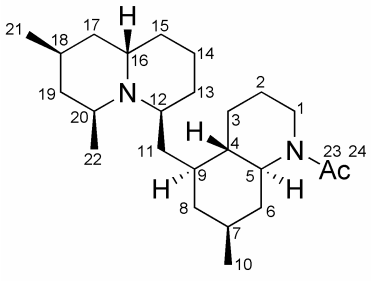
K. LYCONADIN B



lyconadin B (**44**)

Lyconadin B (**44**) isolated from *L. complanatum*,[45] was assigned as 2,3-dihydro form of lyconadin A.[72] Lyconadin B elevated NGF mRNA expression in 1321N1 human astrocytoma cells.

L. SENEPODINE F



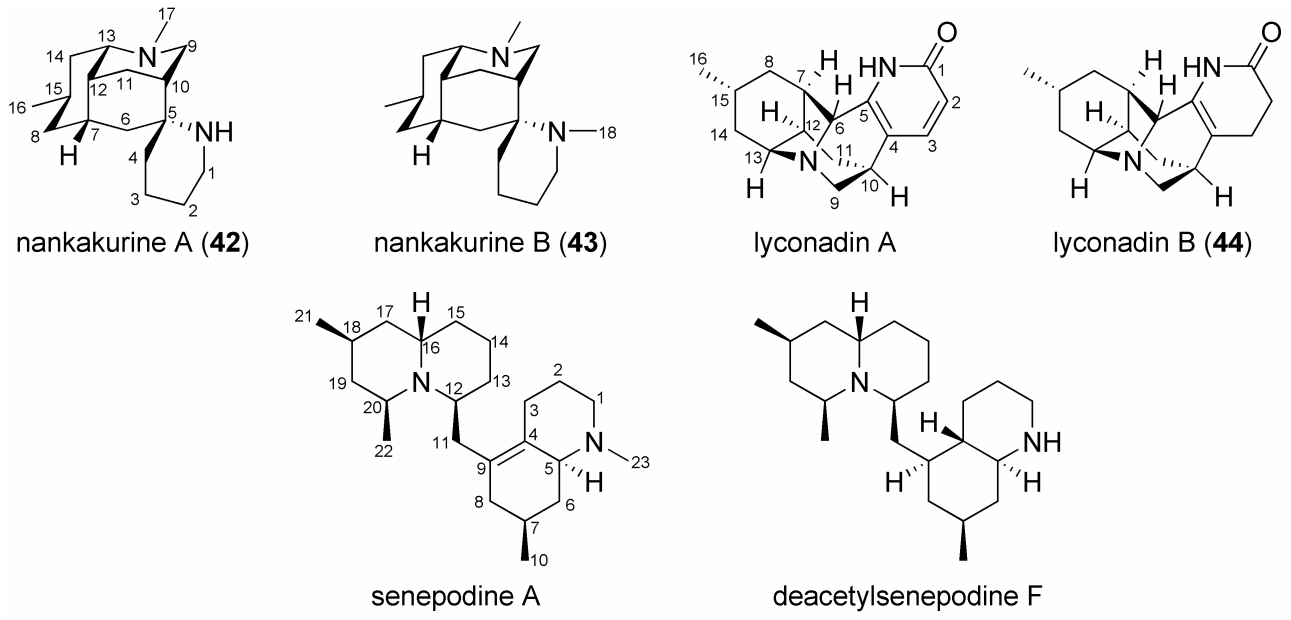
senepodine F (**45**)

A new class of $C_{22}N_2$-type *Lycopodium* alkaloids consisting of a decahydroquinoline and a quinolizidine ring, senepodine F (**45**, 0.01%) was isolated from the club moss *Lycopodium chinense*,[54] together with known related alkaloids, senepodines A[83] and E.[84] The relative stereochemistry of **45** was determined by NOESY correlations for a deacetylated derivative.

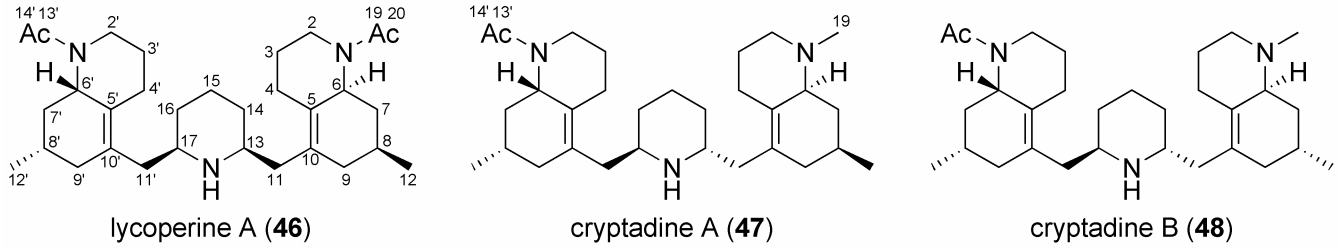
Table 10. ^{13}C NMR Data of Nankakurines A (**42**) and B (**43**), Lyconadins A, and B (**44**), Senepodine A, and Deacetylsenepodine F.

	42[a,b]	**43**[a,c]	Lyconadin A[a]	**44**[a]	Senepodine A[a]	Deacetylsenepodine F[a]
1	41.0	50.4	165.3	173.3	58.2	45.5
2	26.3	17.9	116.6	31.5	26.5	23.7
3	20.9	25.5	141.6	24.0	29.2	27.3
4	34.6	17.7	126.2	120.7	131.7	45.2
5	56.1	67.0	148.8	135.8	66.0	60.7
6	40.0	31.5	64.6	63.6	39.0	39.0
7	34.5	32.0	50.4	49.9	29.0	31.5
8	41.9	39.0	40.2	40.9	40.5	42.3
9	58.5	55.8	61.4	61.9	130.9	40.2
10	37.4	35.9	33.6	34.6	22.4	22.2
11	32.5	28.4	34.0	33.4	35.4	33.5
12	36.9	33.3	48.1	48.2	53.9	57.3
13	65.1	65.5	73.1	72.5	19.2	21.7
14	40.0	35.3	40.2	41.2	20.1	18.1
15	22.0	21.6	26.1	26.2	24.5	24.3
16	23.0	22.2	21.9	22.1	52.9	55.2
17	43.4	45.3			39.9	37.8
18		34.5			26.1	25.0
19					44.1	41.6
20					50.1	52.9
21					22.4	21.6
22					20.3	17.9
23					43.3	

[a] Solution in CD_3OD referenced to CD_3OD at 49.0.
[b] Free base.
[c] TFA salt.



M. LYCOPERINE A AND CRYPTADINES



Three novel $C_{27}N_3$-type pentacyclic *Lycopodium* alkaloids, lycoperine A (**46**) and cryptadines A (**47**) and B (**48**) consisting of two octahydroquinoline rings and a piperidine ring were isolated from the club moss *Lycopodium hamiltonii*[55] and *L. cryptomerinum*,[56] respectively.

Lycoperine A (**46**) was shown to have the molecular formula $C_{31}H_{49}N_3O_2$ by HRFABMS [*m*/*z* 496.3907, $(M + H)^+$, Δ +0.4 mmu]. The IR spectrum was indicative of amide carbonyl (1629 cm^{-1}) and amine (3440 cm^{-1}) functionalities. ^1H and ^{13}C NMR spectra showed broad signals because of rotation of its *N*-acetyl moiety. Treatment of **46** with $LiAlH_4$ afforded tetrahydrodeoxylycoperine A (**52**), which provided sharp signals on the ^1H and ^{13}C NMR spectra.

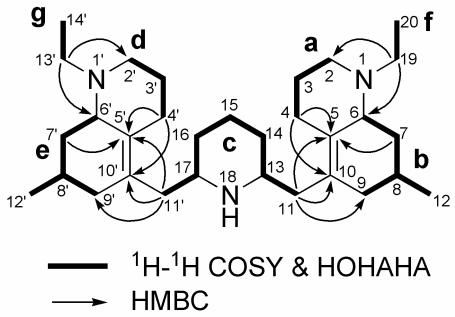


Figure 16. Selected 2D NMR correlations for tetrahydrodeoxylycoperine A (**52**).

Tetrahydrodeoxylycoperine A (**52**) showed the pseudomolecular ion peak at *m*/*z* 468 $(M + H)^+$. Analysis of the ^1H and ^{13}C NMR data and the HMQC spectrum of **52** revealed the presence of six sp^3 methines, seventeen sp^3 methylenes, four sp^2 quaternary carbons, and four methyl groups. Among them, four sp^3 methylenes (δ_C 52.5, δ_H 2.17 and 2.91; δ_C 52.4, δ_H 2.13 and 2.85; δ_C 47.3, δ_H 2.42 and 2.83; δ_C 47.2, δ_H 2.43 and 2.78) and four sp^3 methines (δ_C 61.7, δ_H 2.84; δ_C 61.6, δ_H 2.75; δ_C 56.6, δ_H 2.70; δ_C 55.6, δ_H 2.69) were ascribed to those bearing a nitrogen atom.

The gross structure of **52** was deduced from extensive analyses of the 2D NMR data, including the $^1H-^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in C_6D_6 (Figure 16). The $^1H-^1H$ COSY and HOHAHA spectra in C_6D_6 revealed connectivities of seven partial structures, **a** (C-2−C-4), **b** (C-6−C-9, C-12), **c** (C-11, C-13−C-17, C-11'), **d** (C-2'−C-4'), **e** (C-6'−C-9', C-12'), **f** (C-19−C-20), and **g** (C-13'−C-14'), as shown in Figure 16.

In the octahydroquinoline moiety, the connectivity of partial structures **a** and **b** revealed by the $^{1}H–^{1}H$ COSY and HOHAHA spectra was analyzed by the HMBC spectrum. HMBC correlations from H_2-19 to C-2 (δ_C 52.5) and C-6 (δ_C 61.7) established the connection among C-2, C-6, and C-19 through a nitrogen atom. HMBC cross-peaks of H-4, H-7, and H-11 to C-5, of H-4 and H-11 to C-10, and of H-11 to C-9 indicated the connection among partial structures **a**, **b**, **c**, and four-substituted olefinic carbons assigned to C-5 and C-10, constructing the octahydroquinoline ring (C-2−C-10 and N-1) with a methyl group (C-12) at C-8. Another octahydroquinoline moiety (C-2'−C-10' and N-1') was analyzed in the same way as that metioned above. Thus, the gross structure of tetrahydrodeoxylycoperine A was assigned as **52**.

The relative stereochemistry of **52** was elucidated by NOESY correlations and by comparison of chemical shifts with known piperidine derivatives. The NOESY correlation of H-6 to H-8 suggested that H-6 and H-8 were oriented to the same side (Figure 17). A similar incident was observed for another octahydroquinoline moiety (C-2'−C-10' and N-1'). The relative stereochemistry of the piperidine moiety (C-13−C-17 and N-18) was deduced from comparison of chemical shifts with andrachamine (**53**)[85] and its analogue (**54**).[85]

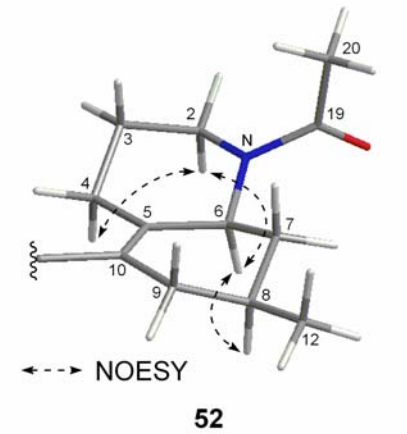


Figure 17. Selected NOESY correlations and relative configurations for an octahydroquinoline ring of tetrahydrodeoxylycoperine A (**52**).

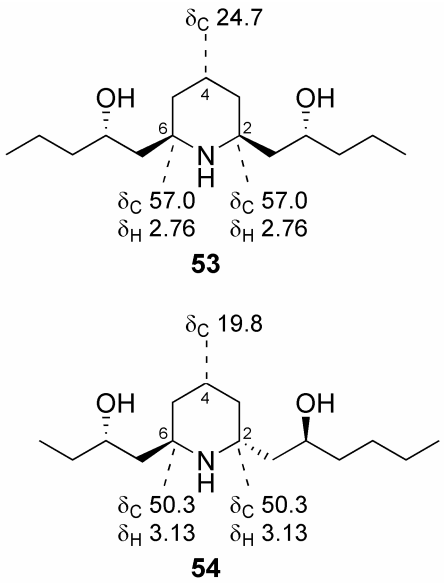


Figure 18. Partial NMR chemical shifts of andrachamine (**53**) and its analogue (**54**).

The ^{1}H signals assigned to the piperidine ring of **52** were observed at δ 2.70 (H-13) and δ 2.69 (H-17), and the ^{13}C signals were observed at δ 56.6 (C-13), δ 25.6 (C-15), and δ 55.6 (C-17). The ^{13}C signals of the trans-substituted piperidine analogue (**54**) of andrachamine were observed at higher fields than those of **52** and **53** (see Figure 18). On the other hand, andrachamine (**53**) with a cis-substituted piperidine ring showed ^{1}H and ^{13}C chemical shifts similar to those of **52**. Thus, the piperidine ring (C-13−C-17 and N-18) of tetrahydrodeoxylycoperine A (**52**) was assigned as cis configuration. The gross relative stereochemistry of **52** was deduced from the ^{13}C NMR spectrum. Because **52** is not a symmetrical

structure (26 signals were observed in the ^{13}C NMR spectrum of **52**), the absolute configurations of the two octahydroquinoline moieties were elucidated to be the same. Consequently, the relative stereochemistry of lycoperine A consisting of the two octahydroquinoline rings with the same absolute stereochemistry and a piperdine ring was assigned as **46**.

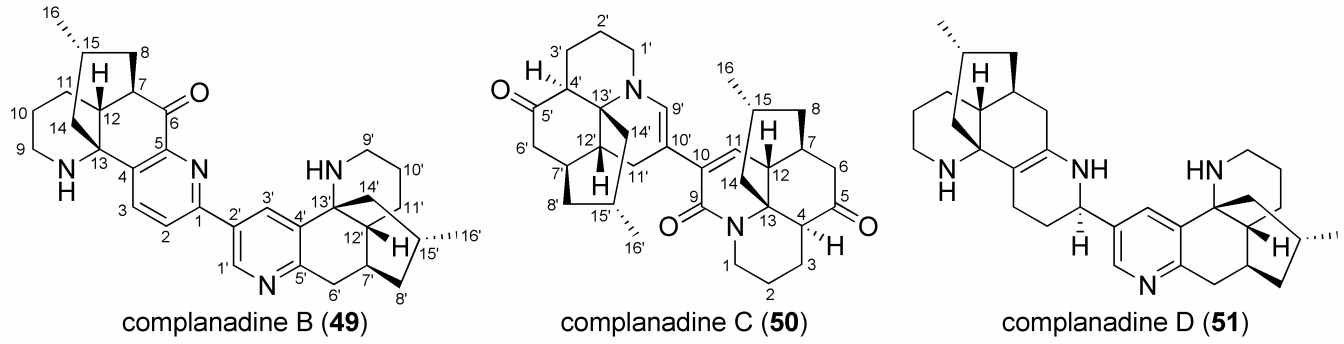
Relative stereochemistry for cryptadines A (**47**) and B (**48**) from *L. cryptomerinum* was elucidated on the basis of spectroscopic data, chemical transformations, and computational methods.
Lycoperine A (**46**) and cryptadines A (**47**) and B (**48**) exhibited an inhibitory activity against acetylcholinesterase at IC_{50} 60.9, 106.3, and 18.5 μM, respectively.

Table 11. ^{13}C NMR Data of Tetrahydrodeoxylycoperine A (**52**), and Dihydrodeoxycryptadines A and B.

	52[a]	Dihydrodeoxy cryptadine A[a]	Dihydrodeoxy cryptadine B[a]
2	52.5	57.9	58.8
3	26.3	26.6	26.8
4	28.8	29.2	29.7
5	128.3	128.6	128.6
6	61.7	65.1	63.6
7	38.4	39.0	35.0
8	28.5	28.5	25.1
9	39.9	40.4	39.5
10	132.0	131.9	132.2
11	41.1	39.4	40.6
12	22.5	22.4	21.1
13	56.6	50.6	49.6
14	32.5	31.5	32.8
15	25.6	20.7	20.8
16	33.5	31.5	30.8
17	55.6	50.5	50.9
19	47.3	43.7	43.1
20	10.1		
2’	52.4	52.6	52.6
3’	26.5	26.6	28.0
4’	28.6	28.9	29.0
5’	128.3	128.8	128.7
6’	61.6	61.7	61.6
7’	38.2	38.7	38.6
8’	28.3	28.3	28.4
9’	39.7	40.4	39.8
10’	132.3	131.5	131.9
11’	41.7	39.4	37.8
12’	22.4	22.5	22.5
13’	47.2	47.3	47.3
14’	9.7	10.5	10.2

[a] Solution in C_6D_6 referenced to C_6D_6 at 128.0.

N. COMPLANADINES



In 2000, we isolated a first dimeric alkaloid containing a lycodine-type $C_{16}N_2$ skeleton,[86] complanadine A from *Lycopodium complanatum*.[87] Further investigation of the extracts of *L. complanatum* resulted in the isolation of three new dimeric alkaloids, complanadines B (**49**),[39] C (**50**),[57] and D (**51**).[57]

Complanadine B (**49**), $[\alpha]_D^{23}$ −13° (*c* 0.5, MeOH) showed the pseudomolecular ion peak at *m/z* 497 $(M+H)^+$ in the FABMS, and the molecular formula, $C_{32}H_{40}N_4O$, was established by HRFABMS (*m/z* 497.3259, $[M+H]^+$, Δ −2.1 mmu). IR absorptions implied the presence of amine and conjugated ketone (3322 and 1697 cm^{-1}, respectively) functionalities. ^{13}C NMR data of **49** was analogous to those of complanadine A, although a carbonyl carbon instead of one sp^3 methylene was observed for complanadine A. The gross structure of **49** was assigned as a new alkaloid consisting of lycodine[86] and 6-oxolycodine units, in which C-1 in 6-oxolycodine was connected to C-2' in lycodine.

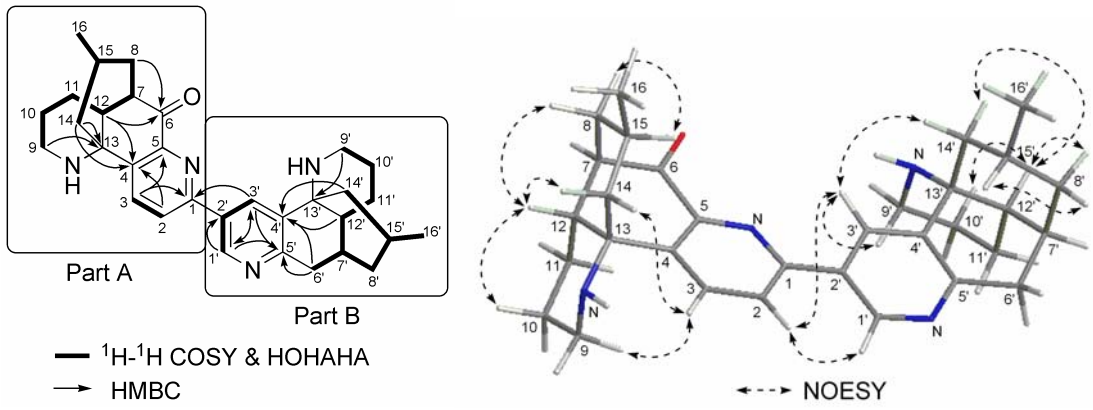


Figure 19. Selected 2D NMR correlations for complanadine B (**49**).

The phase sensitive NOESY spectrum of **49** showed cross-peaks as shown in computer-generated 3D drawing (Figure 19). The relative configurations at C-7, C-12, C-13, and C-15 in part A were based on NOESY correlations of H-12/Hb-10, H-3/Hb-14, Ha-8/H-15, and Hb-8/H-12, while the piperidine and cyclohexane (C-7, C-8, and C-12−C-15) rings adopted both chair conformations. On the other hand, a

NOESY correlation of H′-15/H′a-8 was also observed in addition of the corresponding NOESY correlations for part B. Thus, the relative stereostructure of complanadine B (**49**) was assigned as shown in Figure 19. The CD spectrum [λ_{max} 230 (θ −9200), 260 (4000), 290 (3300), 315 (2300), and 350 (−2000) nm] of **49** in MeOH was similar to those [complanadine A: λ_{max} 260 (θ 4500), 285 (1500), 295 (2000), and 315 (3000) nm; lycodine: λ_{max} 250 (θ 5000), 280 (3000), and 325 (3000) nm] of complanadine A and lycodine except for a negative CD curve at 350 nm. According to the anti-octant sector rule[88] applied to aromatic conjugated ketones, absolute configurations of the 6-oxolycodine part were assigned as 7*R*, 12*R*, 13*R*, and 15*R*.

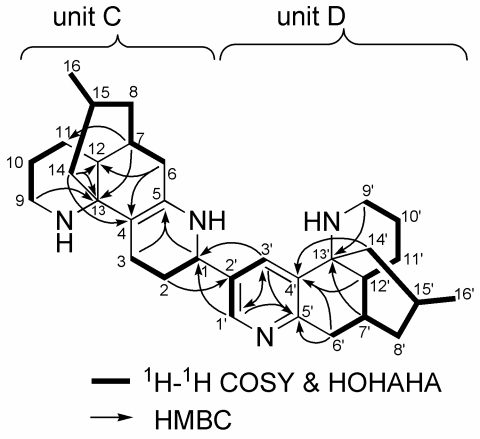


Figure 20. Selected 2D NMR correlations for complanadine D (**51**).

Complanadine D (**51**) showed the pseudomolecular ion peak at *m/z* 487 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{32}H_{46}N_4$, was established by HRESIMS [*m/z* 487.3801, $(M+H)^+$, Δ +1.6 mmu]. Most of ^{1}H and ^{13}C NMR signals of **51** seemed to be due to each half moiety [units C (C-1−C-16) and D (C-1′−C-16′)] of a dimeric compound, of which the ^{1}H and ^{13}C NMR spectra were similar to those of complanadine A, except for lacking NMR signals for one of two trisubstituted pyridine rings in complanadine A. The ^{1}H−^{1}H COSY and HOHAHA spectra of **51** revealed the connection of C-1−C-3 and HMBC correlations of H-1 (δ_H 4.44) and H_2-3 (δ_H 1.96 and 1.57) to C-5 (δ_C 140.0), and H_2-6 (δ_H 2.50 and 1.77) to C-4 (δ_C 98.6) and C-5, indicated the existence of a trisubstituted tetrahydropyridine ring in unit C. The connection between the tetrahydropyridine ring in unit C and a pyridine ring in unit D was provided by HMBC correlations of H_2-2 (δ_H 2.14 and 1.96) to C-2′ (δ_C 140.2), and H-1′ (δ_H 8.24) and H-3′ (δ_H 7.89) to C-1 (δ_C 52.9) (Figure 20). Thus, the gross structure of complanadine D (**51**) was assigned as *N*-1,1,2,3-tetrahydro form of complanadine A.

The NOESY spectrum of **51** was similar to that of complanadine A, suggesting that the relative stereochemistry was the same as that of complanadine A except for the tetrahydropyridine ring in unit C. Analysis of the NOESY spectrum of **51** revealed a pseudochair form of the tetrahydropyridine ring (N-1 and C-1−C-5) and an α-configuration of H-1 (Figure 21).

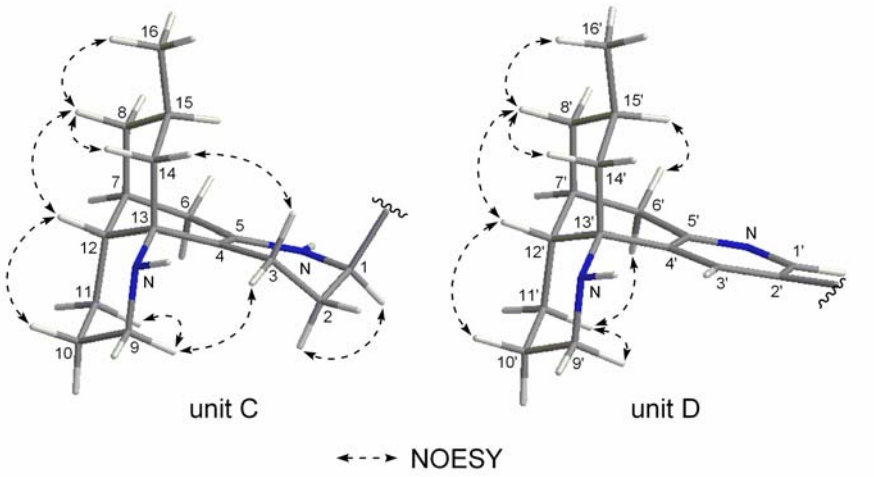


Figure 21. Selected NOESY correlations for complanadine D (**51**).

Complanadine C (**50**) showed the pseudomolecular ion peak at *m*/*z* 503 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{32}H_{42}N_2O_3$, was established by HRESIMS [*m*/*z* 503.3270, $(M+H)^+$, Δ −0.4 mmu].

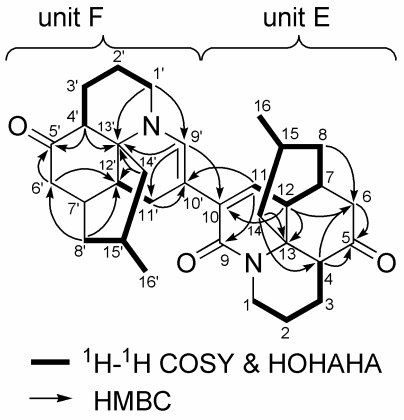


Figure 22. Selected 2D NMR correlations for complanadine C (**50**).

The gross structure of **50** was elucidated by analyses of 2D NMR data including the ^{1}H–^{1}H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Figure 22). Most of ^{1}H and ^{13}C NMR signals appeared to be due to each half moiety (units A and B) of a dimeric compound. In unit A (C-1−C-16), ^{1}H-^{1}H COSY and HOHAHA spectra revealed connectivities of C-1−C-4, C-7−C-8, C-7−C-12, C-8−C-15, C-11−C-12, and C-14−C-16. HMBC correlations of H-4 (δ_H 2.70) to C-5 (δ_C 209.9) and C-6 (δ_C 43.3), H-6b (δ_H 2.29) to C-5, and H-8b (δ_H 1.38) and H-12 (δ_H 2.73) to C-6 suggested connections of C-4 to C-6 through C-5 and C-6 to C-8 through C-7. Connections of C-4 to C-12, C-4 to C-14, and C-12 to C-14 through C-13 were deduced from HMBC cross-peaks of H-12 to C-13 (δ_C 61.7), H-14b (δ_H 1.16) to C-4 (δ_C 50.0) and C-13. HMBC cross-peaks of H-1b (δ_H 3.08) to C-9 (δ_C 166.5), H-11 (δ_H 5.96) to C-9, and H-12 (δ_H 2.73) to C-10 (δ_C 135.1) indicated connections of C-1 to C-9 through a nitrogen atom and C-9 to C-11 through C-10. In unit B (C-1′−C-16′), the ^{1}H-^{1}H COSY and HOHAHA spectra of **1** revealed three

partial structures C-1′−C-4′, C-8′−C-15′ and C-14′−C-16′, and C-11′−C-12′. HMBC correlations of H-4′ (δ_H 2.62) and H-6′b (δ_H 2.23) to C-5′ (δ_C 211.7) suggested the connection of C-4′ to C-6′ through C-5′. Connections of C-6′ to C-12′, C-6′ to C-8′, and C-8′ to C-12′ through C-7′ were deduced from HMBC cross-peaks of H-6′b to C-12′ (δ_C 40.5), and H-8′b (δ_H 1.30) to C-6′ (δ_C 42.4) and C-12′. HMBC cross-peaks of H-4′ to C-13′ (δ_C 57.3) and H-14′a (δ_H 2.56) to C-12′ and C-13′ indicated connections of C-4′ to C-12′, C-4′ to C-14′, and C-12′ to C-14′ through C-13′. Connections of C-1′ to C-9′, C-1′ to C-13′, and C-9′ to C-13′ through a nitrogen atom were suggested from HMBC cross-peaks of H-1′b (δ_H 2.92) to C-9′ (δ_C 137.2) and C-13′, and H-9′ (δ_H 7.22) to C-13′. HMBC cross-peaks of H-9′ to C-11′ (δ_C 25.9) and H-11′a (δ_H 2.55) to C-10′ (δ_C 103.4) revealed the connection of C-9′ to C-11′ through C-10′. The connection of units A and B was provided from HMBC correlations of H-11 to C-10′ and H-9′ to C-10. Thus, the gross structure of complanadine C was elucidated to be **50**.

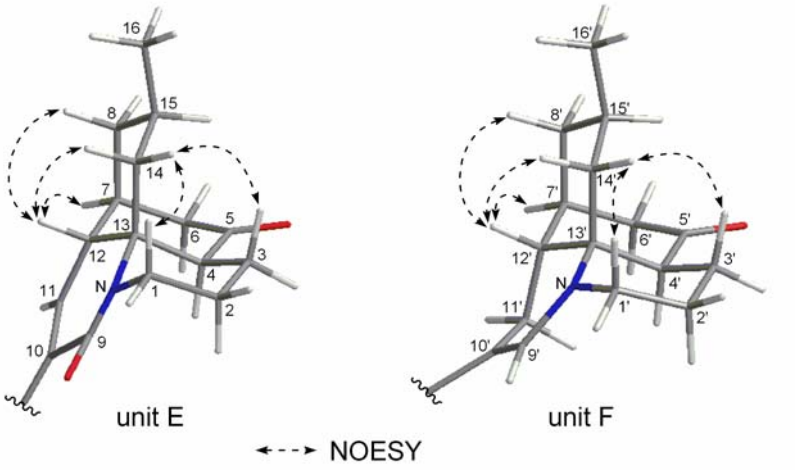


Figure 23. Selected NOESY correlations for complanadine C (**50**).

The NOESY spectrum of **50** showed cross-peaks as shown in computer-generated 3D drawing (Figure 23). In unit A, a chair-like conformation of a piperidine ring (N-1, C-1−C-4, and C-13) was suggested from NOESY correlations of H-14a to H-1b and H-3b. NOESY cross-peaks and $^3J_{H\text{-}14/H\text{-}15}$ (12.6 Hz) indicated a chair conformation of a cyclohexane ring (C-7−C-8 and C-12−C-15). In unit B, NOESY correlations of H-14′a to H-1′ and H-3′b suggested a chair-like conformation of a piperidine ring (N-1′, C-1′−C-4′, and C-13′). A chair conformation of a cyclohexane ring (C-7′−C-8′ and C-12′−C-15′) was deduced from NOESY correlations of H-8′ to H-16′, and H-12′ to H-8′b and H-14′b. Thus, the partial relative stereochemistry of complanadine C (**50**) was elucidated as shown in Figure 23.

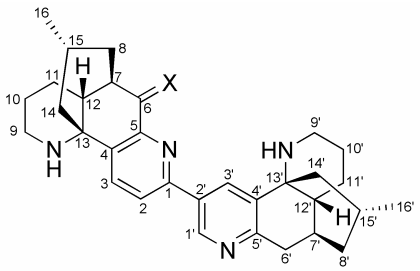
Complanadine C (**50**) is the first dimeric *Lycopodium* alkaloid containing a lycopodane-type $C_{16}N$ skeleton, while complanadine B (**49**) and D (**51**) are structure analogue of complanadine A. Effects of complanadine D (**51**) on neurotrophic factor biosynthesis in 1321N1 human astrocytoma cells were examined by a semiquantitative RT-PCR method, and it was found that the mRNA expressions for NGF

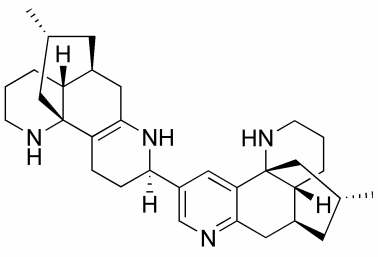
were enhanced by **51**. Complanadine D (**51**) exhibited cytotoxicity against murine leukemia L1210 cells (IC_{50}, 7 μg/ml) in vitro, while **50** did not show such activity (IC_{50} > 10 μg/ml). Complanadines C (**50**) and D (**51**) showed antimicrobial activity against *Cryptococcus neoformans* (MIC, 0.52 and 0.26 μg/ml, respectively) and *Aspergillus niger* (MIC, 2.05 and 4.16 μg/ml, respectively).

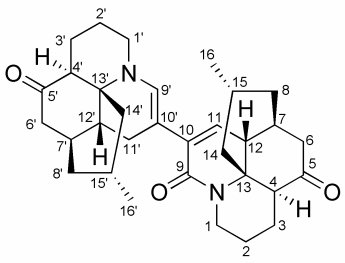
Table 12. ^{13}C NMR Data of Complanadines A, B (**49**), D (**51**), and C (**50**).

	Complanadine A[a]	**49**[a]	**51**[b]	**50**[b]
1	154.2	155.0	52.9	37.7
2	120.5	126.6	30.3	24.3
3	135.3	138.3	18.5	18.6
4	132.7	143.6	98.6	50.0
5	160.3	150.5	140.0	209.9
6	36.0	202.5	32.0	43.3
7	34.4	52.7	34.8	36.8
8	43.6	39.7	44.3	41.0
9	42.1	42.0	42.6	166.5
10	27.1	27.3	26.3	135.1
11	26.1	27.1	27.8	127.9
12	43.8	48.1	44.6	42.6
13	60.2	58.2	60.2	61.7
14	50.0	49.0	45.5	42.2
15	25.7	27.6	28.0	25.2
16	22.1	22.1	22.4	22.7
1’	147.2	146.0	146.0	47.3
2’	134.8	133.8	140.2	24.9
3’	133.1	133.8	133.5	19.2
4’	134.2	138.0	137.3	48.0
5’	160.1	160.9	157.8	211.7
6’	35.5	35.8	35.4	42.4
7’	34.5	34.7	34.6	35.7
8’	43.8	44.7	44.8	42.5
9’	42.1	42.1	42.3	137.2
10’	27.1	27.3	25.6	103.4
11’	26.2	27.3	27.2	25.9
12’	43.6	44.2	44.8	40.5
13’	60.5	58.0	57.7	57.3
14’	50.1	51.6	51.8	41.1
15’	25.9	27.0	27.1	24.9
16’	22.1	22.4	22.2	22.5

[a] Solution in CD_3OD referenced to CD_3OD at 49.0.
[b] Solution in CD_3OD referenced to CD_3OD at 49.5.



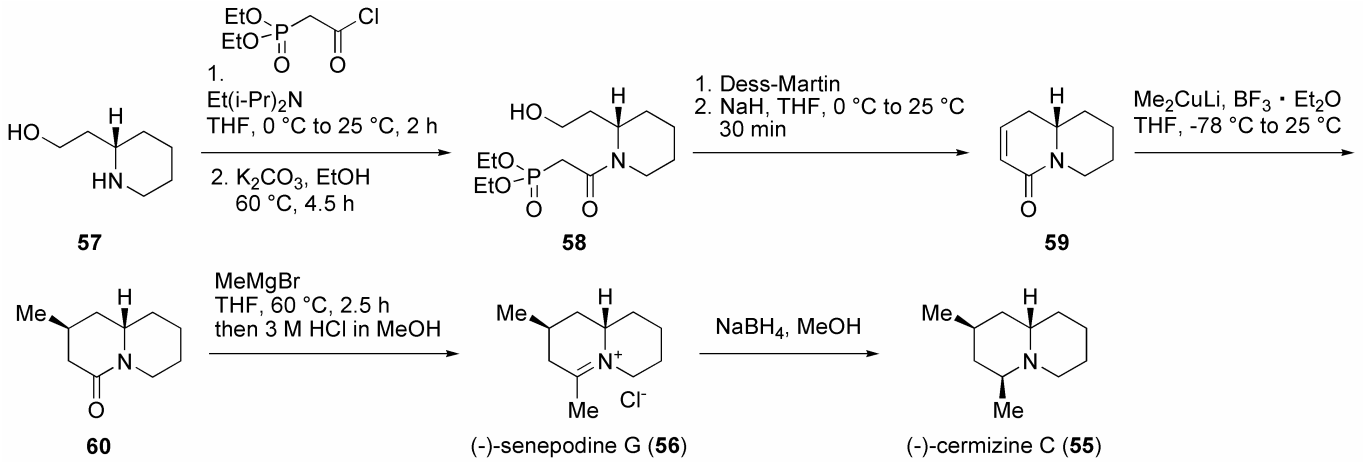




TOTAL SYNTHESIS

CERMIZINE C AND SENEPODINE G

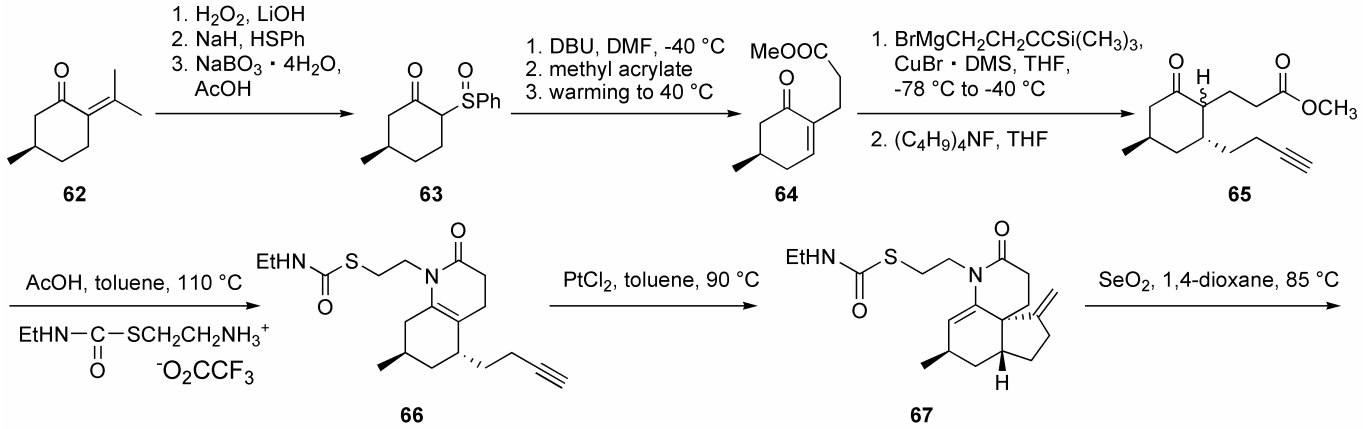
Cermizine C (**55**)[89] and senepodine G (**56**)[89] are new class of $C_{11}N$ *Lycopodium* alkaloids, consisting of a quinolizidine ring, isolated from *Lycopodium cernuum* and *L. chinense*, respectively. An efficient, stereospecific synthesis of these alkaloids has been completed by Snider and Grabowski using the conjugate addition of Me_2CuLi to α,β-unsaturated lactam **59** to provide lactam **60** to senepodine G (**56**, 6 steps, 40% overall yield), and $NaBH_4$ reduction of **56** to give cermizine C (**55**, 7 steps, 40% overall yield).[90]

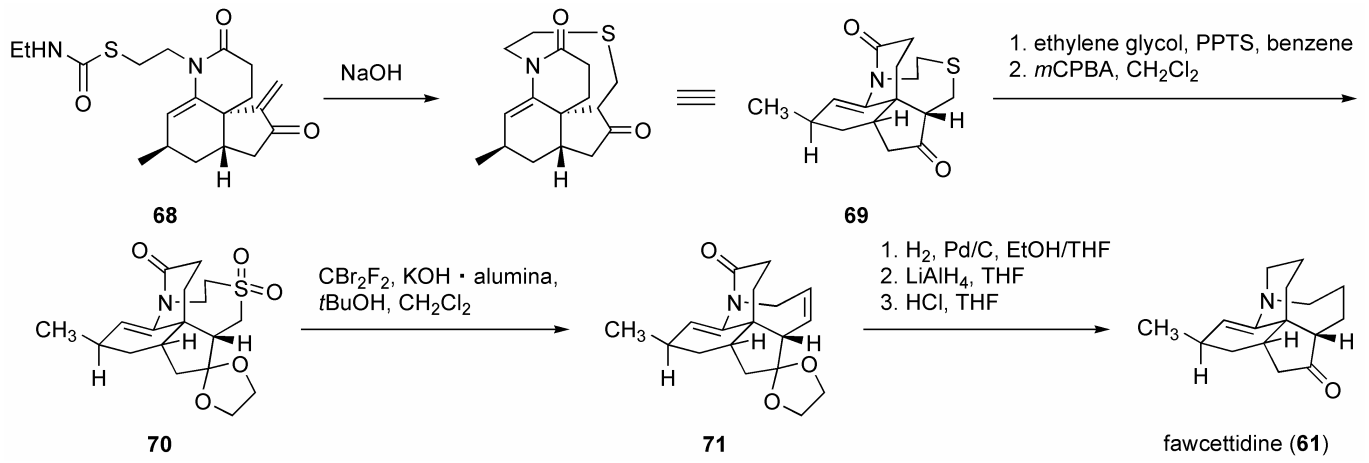


Scheme 1. Synthesis of cermizine C (**55**) and senepodine G (**56**).

(+)-FAWCETTIDINE

Fawcettidine (**61**)[91,92] was isolated by Burnell and co-workers from *Lycopodium fawcetti* in the late 1950s. Recently, Dake and Kozak reported first total synthesis of this alkaloids by 16 steps in 1% overall yield.[93] They used (*R*)-(+)-pulegone (**62**) as a starting material and employed platinum(II)-catalyzed annulation and a one-pot Ramberg-Bäcklund reaction for the key steps.

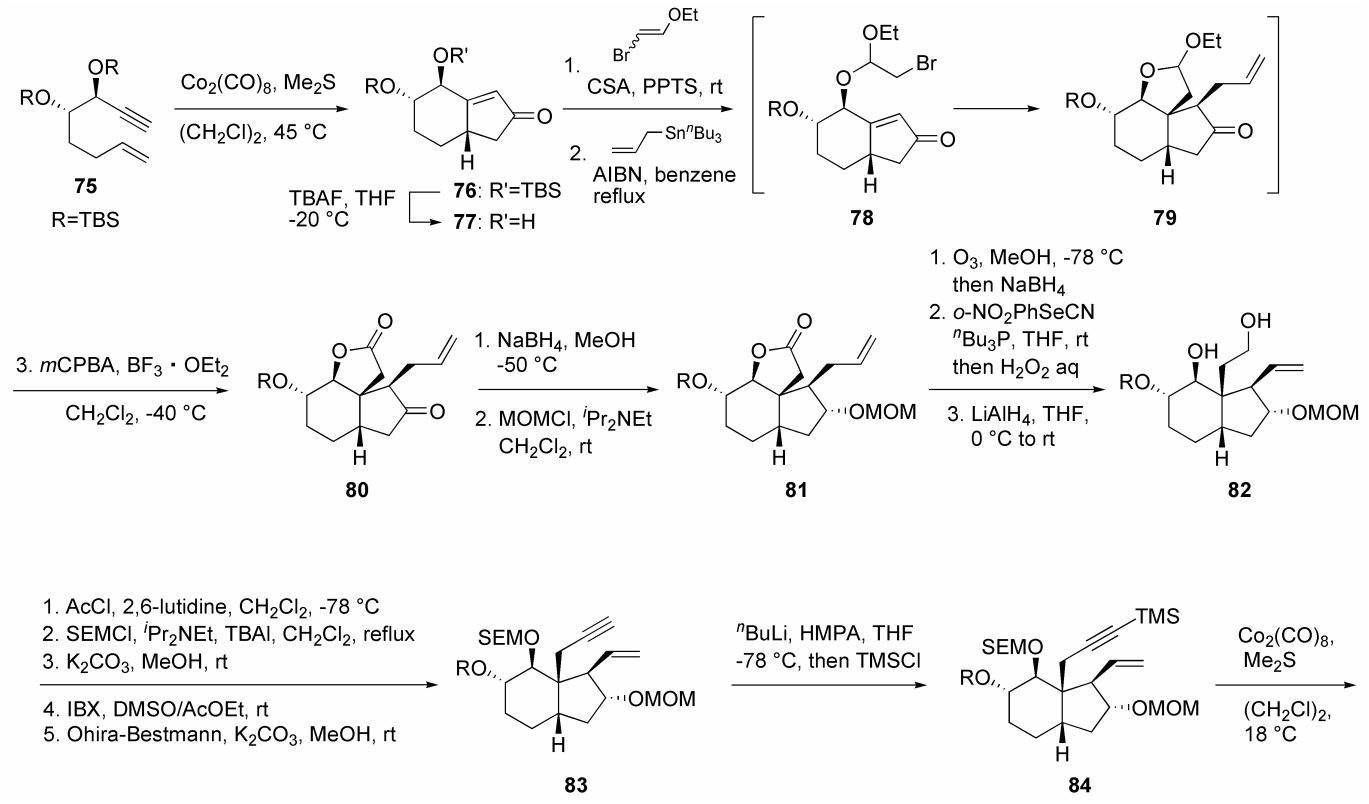


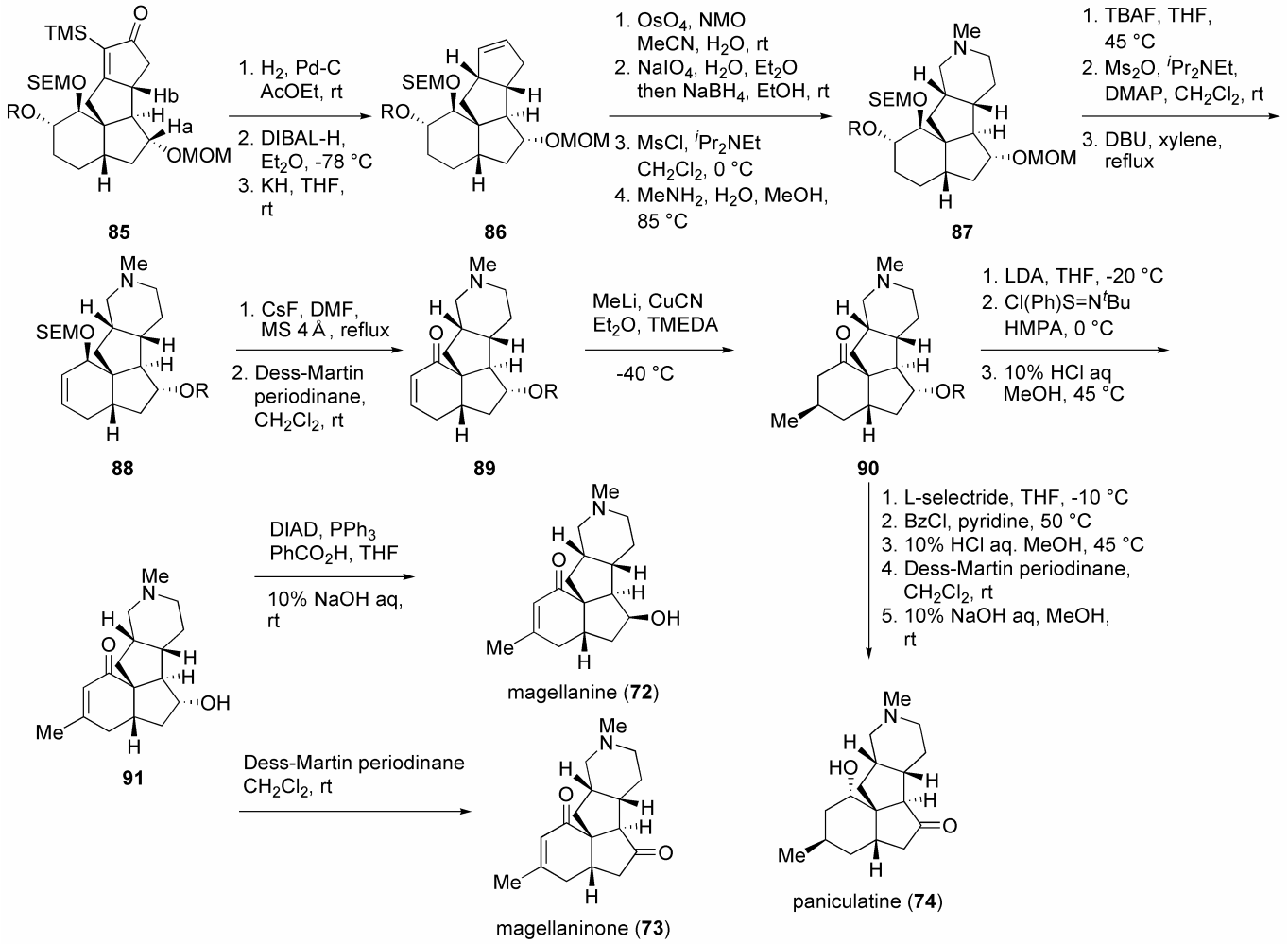


Scheme 2. Synthesis of fawcettidine (**61**).

(−)-MAGELLANINE, (+)-MAGELLANINONE, AND (+)-PANICULATINE

Three alkaloids, magellanine (**72**),[94] magellaninone (**73**),[95] and paniculatine (**74**),[96,97] which possess a highly condensed tetracyclic nucleus with five to seven stereogenic cneters. Unique and challenging structures of magellanine skeleton has evoked a great of attention from the synthetic community, and several studies have been directed toward its total synthesis.[98-104] Stereoselective total synthesis of (−)-magellanine (**72**), (+)-magellaninone (**73**), and (+)-paniculatine (**74**), from diethyl L-tartrate (**72**, 43 steps, 1.7% overall yield; **73**, 43 steps, 1.9% overall yield; **74**, 45 steps, 2.8% overall yield).[105] The key reactions in these syntheses involved two intramolecular Pauson-Khand reactions of enynes.

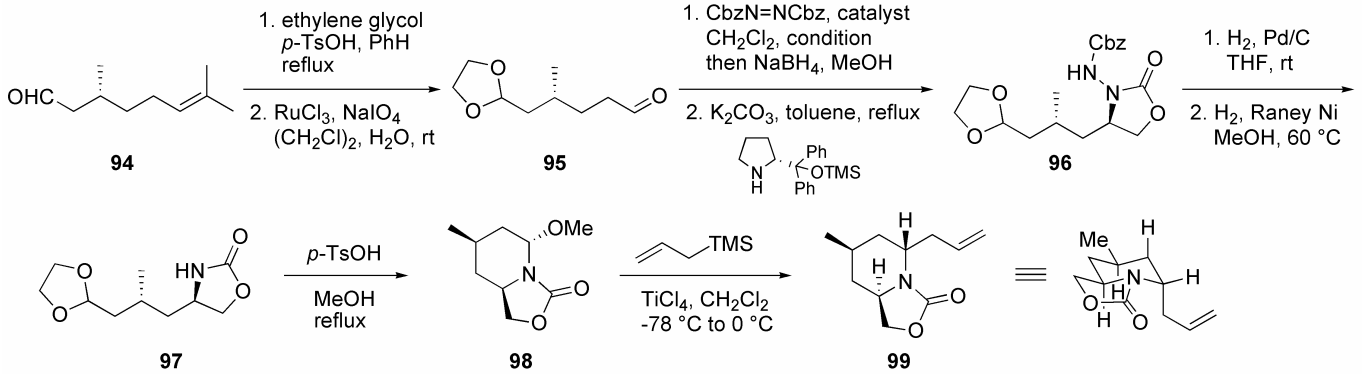


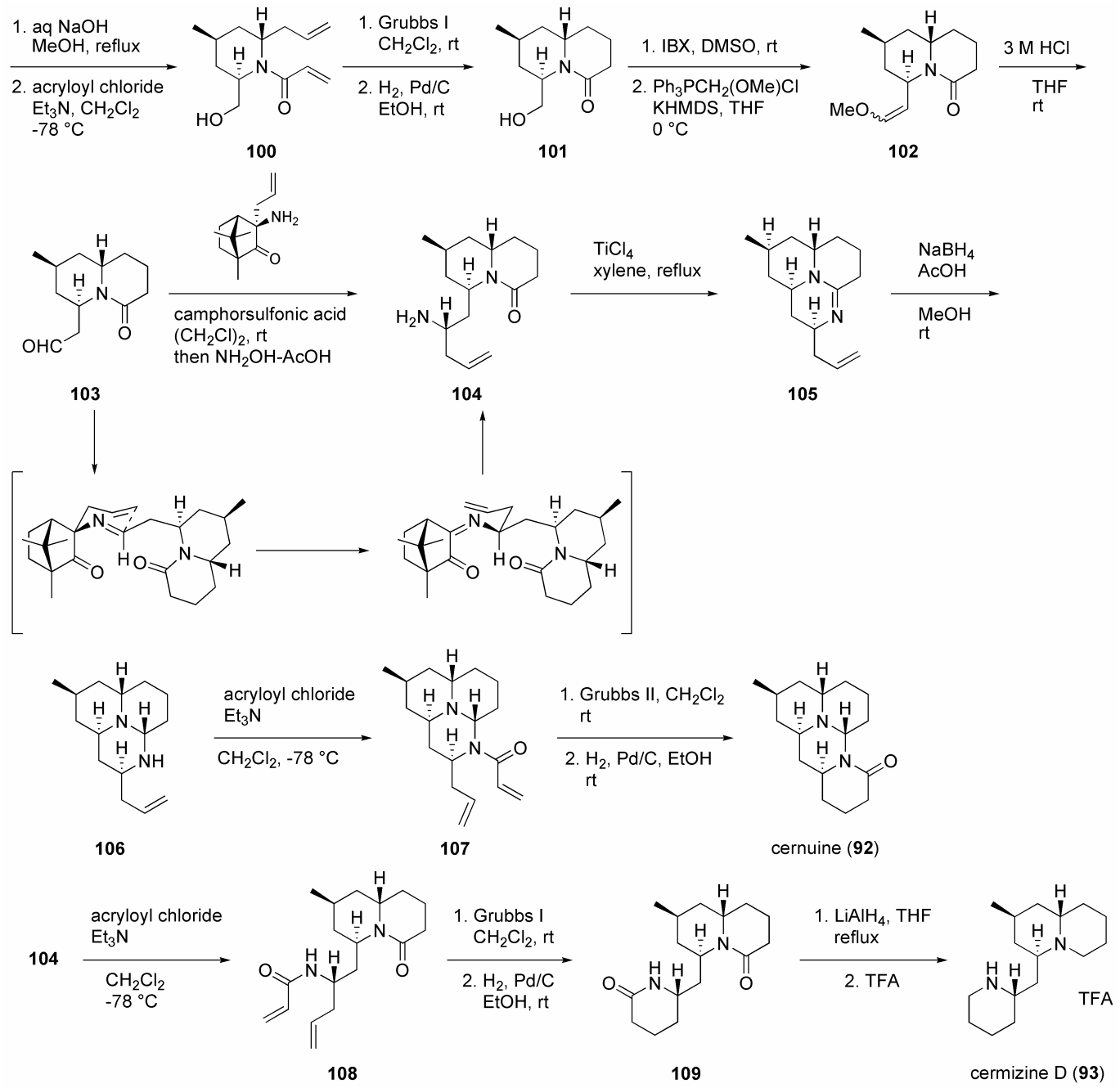


Scheme 3. Synthesis of magellanine (**72**), magellaninone (**73**), and paniculatine (**74**).

CERNUINE AND CERMIZINE D

The first total syntheses of two cernuane-type lycopodium alkaloids, (−)-cernuine (**92**)[106-110] and (+)-cermizine D (**93**),[89] were accomplished by Takayama and co-workers.[111] They used (+)-citronellal (**94**) as a starting material and achieved syntheses of them via an organocatalytic α-amination and a transter aminoallylation (**92**, 19 steps, 11.0% overall yield; **93**, 18 steps, 13.9% overall yield).

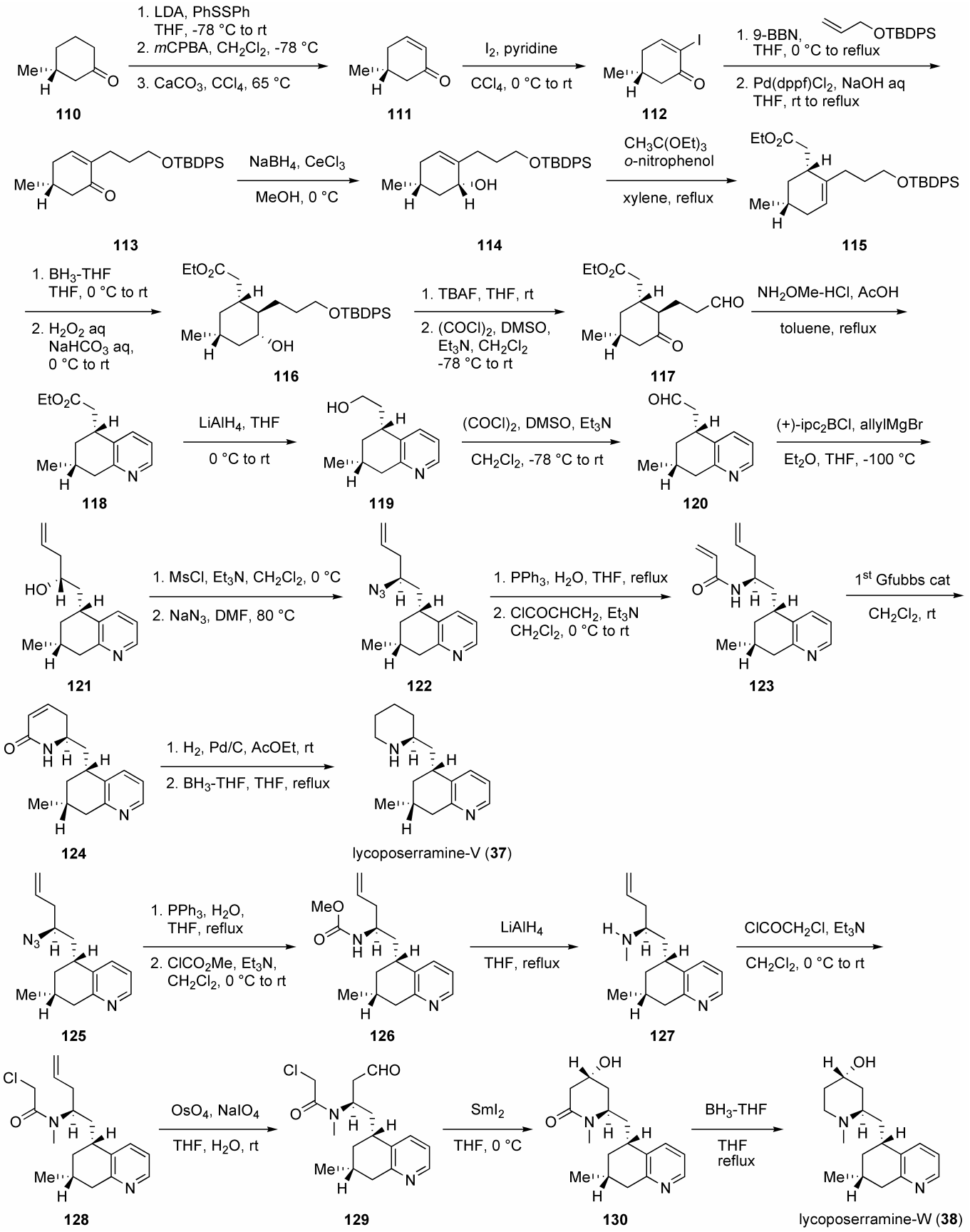




Scheme 4. Synthesis of cernuine (**92**) and cermizineD (**93**).

LYCOPOSERRAMINES-V AND -W

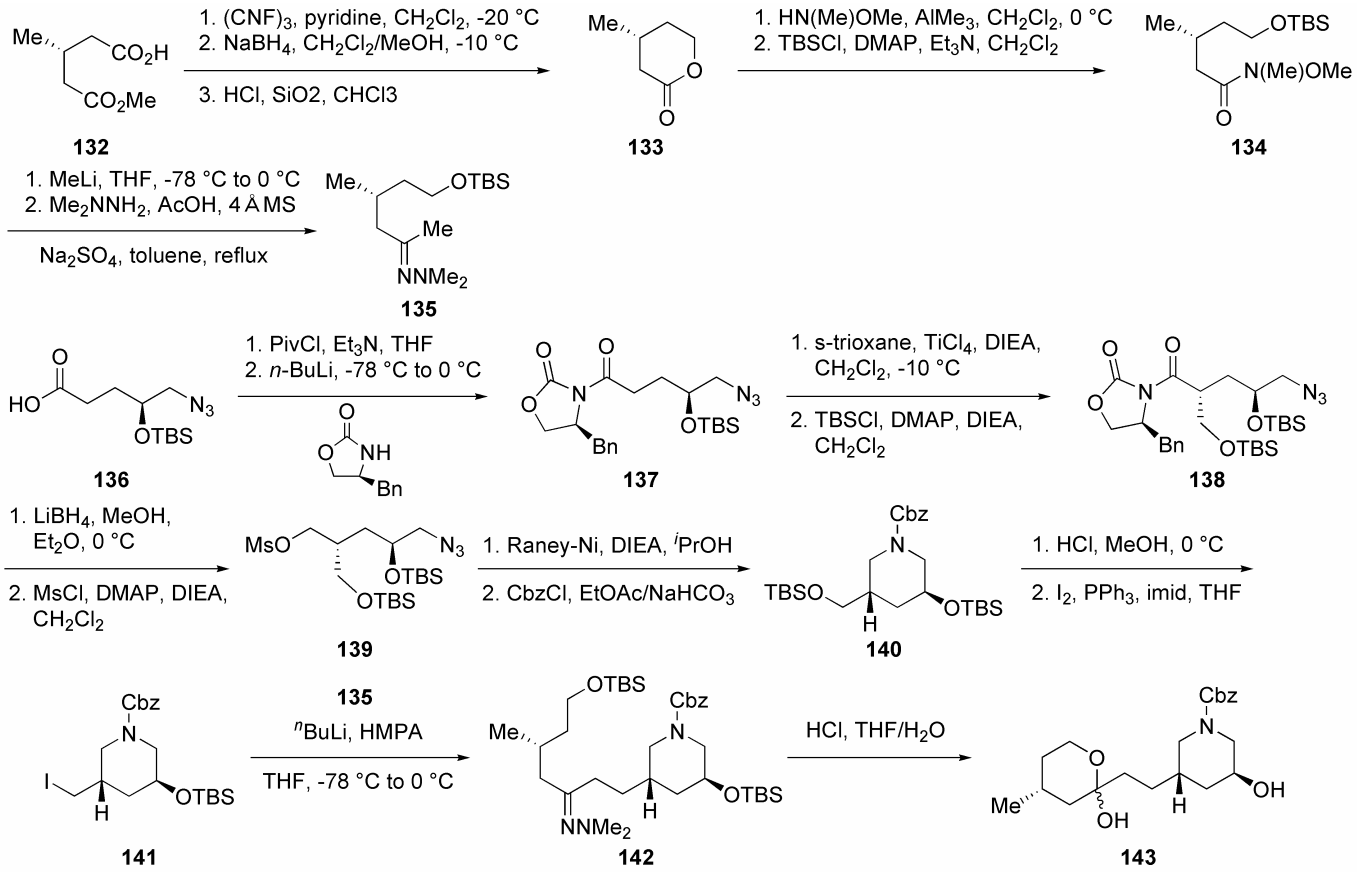
Lycoposerramines-V (**37**) and -W (**38**) were isolated from *Lycopodium serratum* by Takayama and co-workers.[50] These alkaloids possess partially aromatized phlegmarane skeleton[21] and their structures including the absolute configuration were established by asymmetric total synthesis involving Johnson-Claisen rearrangement and ring-closing metathesis or SmI_2-mediated stereoselective piperidine ring construction (**37**, 22 steps, 4.3% overall yield; **38**, 23 steps, 1.4% overall yield).[50]

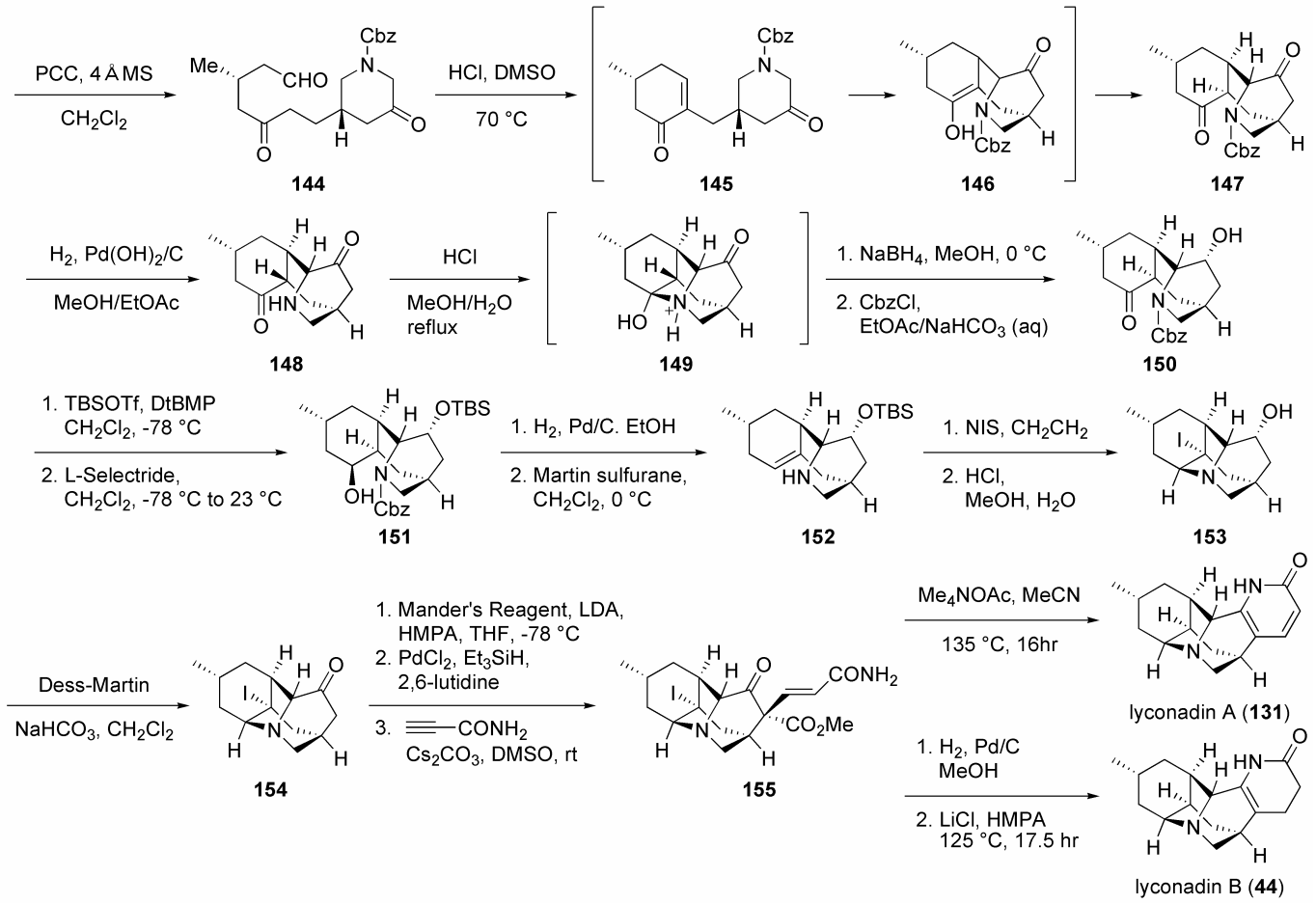


Scheme 5. Synthesis of lycoposerramine-V (**37**) and lycoposerramine-W (**38**).

LYCONADINS A AND B

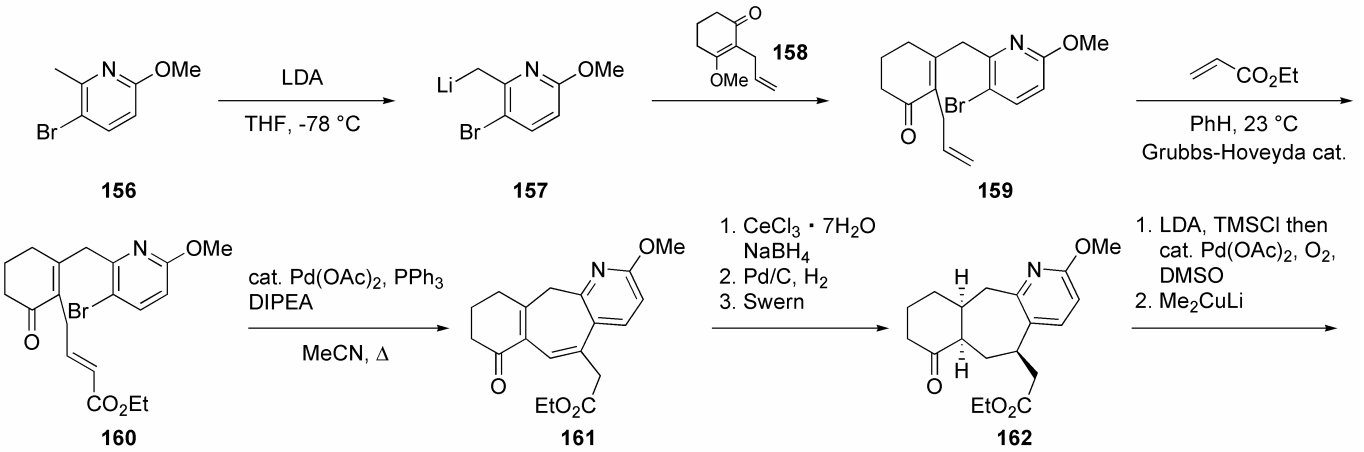
We isolated two novel alkaloids (+)-lyconadin A (**131**)[72] and (−)-lyconadin B (**44**)[45] from *Lycopodium complanatum* in 2001 and 2006, respectively. These alkaloids contains unprecedented pentacyclic ring system, with either an α-pyridone or 3,4-dihydro-α-pyridinone ring and attracted great interest from biogenetic, synthetic, and biological points of view. Recently, the first total synthesis of (+)-lyconadin A (**131**) and (−)-lyconadin B (**44**) were accomplished by Smith's group.[112] They chose (−)-methyl (*R*)-3-methylglutarate (**132**) and (−)-carboxylic acid (**136**) as starting materials. **142** was obtained from hydrazone **135** and iodide **141** in the presence of ^{n}BuLi and HMPA. Intramolecular aldol/conjugate addition of **144** led to tricyclic ketone **147**, after removal of Cbz group and reflux in water/methanol/HCl induced epimerization at C-12. Aminoiodination of alkene **152** with *N*-iodosuccinimide (NIS) furnished crystalline iodide **153**, followed by construction of β-ketoester and Michael addition of propiolamide provided **155**. Application of novel one-pot protocol involving decarboxylation, mediated by Me_4NOAc, olefin isomerization, and cyclocondensation, total synthesis of lyconadin A was achieved (**131**, 22 steps, 4.3% overall yield). Hydrogenation of **155** followed by a similar one-pot protocol, lyconadin B was generated (**44**, 22 steps, 4.3% overall yield).

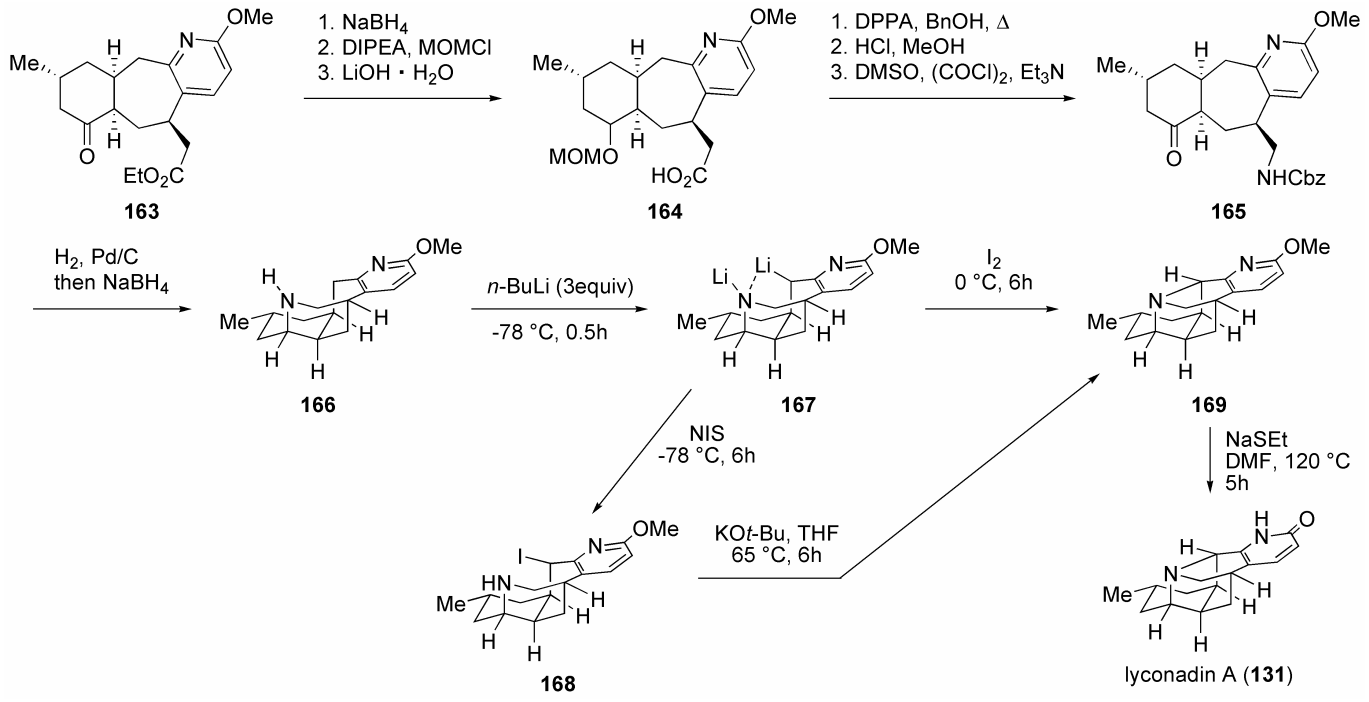




Scheme 6. Synthesis of lyconadins A (**131**) and B (**44**).

The second total synthesis of lyconadin A was achieved by Sarpong and co-workers.[113] They selected readily available picoline derivative **156** and vinylogous ester **158** as a starting materials, and utilized unique proximity-driven oxidative C−N bond-forming reaction for constructing the caged pentacycle **169**. The total synthesis of lyconadin A (**131**) was accomplshed by 18 steps in 10% overall yield.





Scheme 7. Synthesis of lyconadin A (**131**).

CONCLUSIONS

Studies on the *Lycopodium* alkaloids from 2004 to July in 2008 have been reviewed, particularly focusing on recent developments in the synthesis of these alkaloids, the structures of the new types of alkaloids, such as the lycopodatines, lycovatine A, lannotinidines, lycopladines, lycoparins, carinatumins, lycoposerramines, nankakurines, lyconadins, senepodines, lycoperine A, cryptadines, and complanadines. There are currently more than 250 *Lycopodium* alkaloids of known structure. Huperzine A, a representative *Lycopodium* alkaloid, is a highly specific and potent inhibitor of acetylcholinesterase, and the inherent inhibition of acetylcholinesterase has poromoted the pursuit of the total synthesis and SAR studies of this alkaloid. Further phytochemical investigations will bring increasing structural variation to this alkaloid group. Although the total syntheses of some of the $C_{16}N$ and $C_{16}N_2$ type skeletons have been accomplished, the other skeletal variants remain attractive targets.

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