# Lupin Alkaloids from Chinese *Maackia amurensis*

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**Two new alkaloids were isolated together with 16 known lupin alkaloids from the leaves and stems of Chinese *Maackia amurensis*. Their structures were determined by spectroscopic methods to be (−)-6α-methoxylupanine and (−)-5α-(12-cytisinylmethyl)-6α-hydroxylupanine and identified by comparison with synthetic samples. The structures of lupin alkaloids were also related to the geographical distributions of the *Maackia* plants.**

**Key words** *Maackia amurensis*; Leguminosae; (−)-6α-methoxylupanine; (−)-5α-(12-cytisinylmethyl)-6α-hydroxylupanine; (−)-6α-hydroxylupanine; chemotaxonomy

In our recent phytochemical study of *Maackia* (*M.*) (Leguminosae) plants native in Japan, we discovered that the structural types of lupin alkaloids are related to geographical distribution of the plants. *M. amurensis* is found in northern Japan and contains sparteine-type lupin alkaloids but not lupinine-type alkaloids. *M. tashiroi*, *M. floribunda* and *M. floribunda f. pubescens*, all of which grow in southern Japan, produce lupinine-type alkaloids, and sparteine-type alkaloids are not found.[1] *Maackia* plants produce alkaloids having a >N–$CH_2$–Y moiety such as (−)-*N*-(2-oxopyrrolidinomethyl)cytisine and (−)-*N*-(*N*-acetylaminomethyl)-cytisine.[2] The above phenomena are interesting when the chemotaxonomy of leguminous plants and biosynthesis of lupin alkaloids are considered. This report describes the isolation and structural determination of 18 alkaloids from Chinese *M. amurensis*, which also occurs in northern China. (−)-6α-Hydroxylupanine (**1**) was isolated for the first time from *Maackia* plants. (−)-6α-Methoxylupanine (**2**) and (−)-5α-(12-cytisinylmethyl)-6α-hydroxylupanine (**3**) are new alkaloids. The relations between the geographical distributions and the structural types of lupin alkaloids, and a comparison of alkaloidal constituents of Chinese *Maackia* plants with Japanese ones are also discussed.

## Results and Discussion

The total alkaloid mixture (11.0 g) obtained from 75% methanol extracts of air-dried stems (2.0 kg) of *M. amurensis* was separated repeatedly by silica gel column chromatography to yield 18 lupin alkaloids: **1**, **2**, **3**, (−)-*N*-methylcytisine (**4**), (+)-5,6-dehydrolupanine (**5**), (−)-lupanine (**6**), (−)-anagyrine, (−)-epibaptifoline, (−)-cytisine, (−)-12,12′-methylenedicytisine, (−)-*N*-formylcytisine, (−)-*N*-(3-oxobutyl)cytisine, (−)-lusitanine, (−)-tenuamine, (−)-rhombifoline, (−)-camoensidine, (+)-ammodendrine and (+)-maackiamine. Compounds **2** and **3** are new alkaloids (Chart 1). The known alkaloids were identified by direct comparison with authentic samples (co-TLC, mp, $[\alpha]_D$, IR, $^1$H-NMR, $^{13}$C-NMR and mass spectrometry) as described in our previous reports.[2—4]

The total base (11.7 g) obtained from the *M. amurensis* leaves (3.5 kg) was treated similarly to yield 16 alkaloids, which are the same as the constituents of the stems except (−)-*N*-(3-oxobutyl)cytisine and (−)-rhombifoline. It is characteristic of *Maackia* species that unusual lupin alkaloids containing a pyrrolidine or an indolizidine ring and common lupin alkaloids with a piperidine or quinolizidine ring coexist in the plants.[2,3] It is surprising that three couples of unusual and common lupin alkaloids, namely (−)-camoensidine and (−)-lupanine, (−)-tenuamine and (−)-lusitanine, and (+)-maackiamine and (+)-ammodendrine, were isolated together from Chinese *M. amurensis* (Chart 1).

The molecular formula of alkaloid **1** was determined to be $C_{15}H_{24}N_2O_2$ by $^{13}$C-NMR and high resolution electron impact MS (HR-EI-MS) spectrometry. The presence of a hydroxy group was indicated by the absorption at 3280 $cm^{-1}$ in the IR spectrum and by fragment ions at *m/z* 247 ($M^+-OH$) and 246 ($M^+-H_2O$) in the EI-MS spectrum. The down-field signal at $\delta$ 85.7 (s) in the $^{13}$C-NMR spectrum suggested the presence of a >N–C–OH group in the molecule (Table 1). When the acidic solution of **1** in $CH_2Cl_2$ was stirred for 8 h at room temperature, a dehydrated product, **5**,[4] was obtained. This indicates the presence of a hydroxy group at position 6 in **6**. The $[\alpha]_D^{23}$, mp, IR, $^1$H-NMR, $^{13}$C-NMR and MS data for alkaloid **1** coincided with the reported values for (−)-6α-hydroxylupanine;[5] therefore the structure of **1** was determined to be (−)-6α-hydroxylupanine.

The HR-EI-MS and $^{13}$C-NMR spectra of alkaloid **2** yielded the molecular formula $C_{16}H_{26}N_2O_2$. The presence of a –$OCH_3$ group was indicated by the signal at $\delta$ 3.48 (3H, s) in the $^1$H-NMR spectrum and the signal at $\delta$ 49.3 (q) in the $^{13}$C-NMR spectrum. The signal at $\delta$ 89.5 in the $^{13}$C-NMR spectrum suggested the presence of a >N–C–O group in the structure of **2**. All of the $^{13}$C signals, except for C-6 (+3.8 ppm), C-7 (−2.2 ppm) and C-4 signals (+1.3 ppm) effected by –$OCH_3$ group, agreed with those of **1** (Table 1), indicating that **2** is 6-methoxylupanine, which has the same relative stereochemistry as that of **1**. When **2** was stirred in $CH_2Cl_2$ solution at room temperature for 48 h, it was transformed into **5**, whose absolute configuration is known.[4] The spectroscopic data and the results of transformation into **5** suggested that **1** and **2** have the same absolute stereochemistry. Thus, alkaloid **2** was determined to be (−)-6α-methoxylupanine that had the absolute configuration 6*R*, 7*R*, 9*R*, 11*R*, which is the same as that of **1**.

The IR spectrum of alkaloid **3**, colorless oil and $[\alpha]_D^{23}$ −31.5° (*c*=0.26, EtOH), showed absorptions at 3400 $cm^{-1}$

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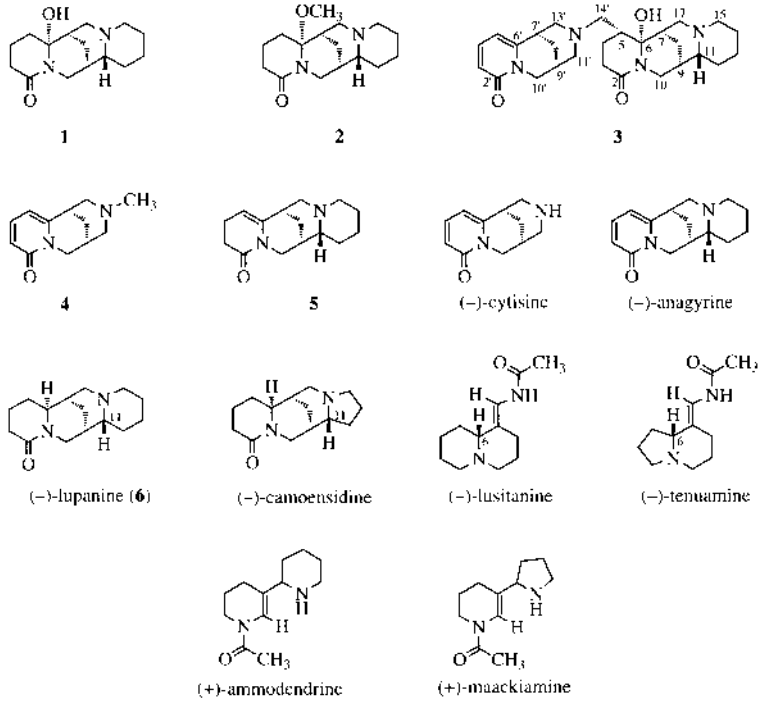



Chart 1

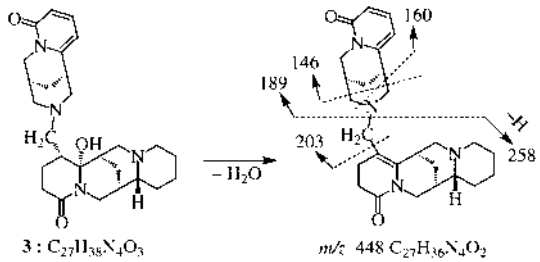



Fig. 1. Diagnostic EI-MS Fragment Ions (*m/z*) of **3**

(OH) and 1640 $cm^{-1}$ (C=O). The $^{13}$C-NMR spectrum of **3** revealed the presence of 27 carbons. The EI-MS spectrum showed the highest MS ion at *m/z* 448 ($C_{27}H_{37}N_4O_2$) and the next MS ion at *m/z* 258 ($C_{16}H_{22}N_2O$) (Fig. 1), suggesting that **3** might consist of two alkaloid units. The characteristic fragment ions at *m/z* 203, 189, 160 and 146 indicated the presence of an *N*-alkylcytisine moiety in the structure of **3** such as (−)-rhombifoline and (−)-*N*-(3-oxobutyl)cytisine.[2,7] The signal at $\delta$ 87.1 (s) in the $^{13}$C-NMR spectrum and the characteristic signal at $\delta$ 4.20 (1H, dd, $J$=13.0, 2.0 Hz, 10-H$\beta$) in the $^1$H-NMR spectrum suggested the presence of a lupanine moiety having a >N–C–OH group. Subtraction of the 11 peaks corresponding to (−)-cytisine from the 27 $^{13}$C-NMR signals of **3** left the 15 peaks that were very similar to those of **1** except for signals due to 4-C—7-C and one methylene carbon signal at $\delta$ 58.0 which was presumed to be adjacent to a nitrogen (Table 1). The above results suggest that alkaloid **3** contains a cytisine and a 6$\alpha$-hydroxylupanine, which are linked by a methylene group. Differences in the chemical shifts of 4-C—7-C between **1** and **3** indicated that the 12-cytisinylmethyl group is located in position 5 of **1** and oriented equatorially ($\alpha$-configuration). Compared with shifts in alkaloid **1**, down-field shifts of C-4 (+4.7 ppm), C-5 (+5.6 ppm) and C-6 signals (+1.4 ppm) are explained by a substitution effect through a bond, and an up-field shift of the C-7 signal (−5.7 ppm) occurs through a $\gamma$-effect through space. Both effects are caused by the equatorial alkyl group at position 5. Therefore, alkaloid **3** was presumed to be 5$\alpha$-(12-cytisinylmethyl)-6$\alpha$-hydroxylupanine. The structure was confirmed by comparison with a synthetic sample, which was

Table 1. $^{13}$C-NMR Spectral Data for Alkaloids **1**—**4** and **6** (in $CDCl_3$)[6]

| C | **1** | (**1**−**6**) | **2** | (**2**−**1**) | **3** | (**3**−**1**) | **4** | **6** |
|---|---|---|---|---|---|---|---|---|
| 2 | 171.6 | (+0.1) | 172.3 | (+0.7) | 171.2 | (−0.4) | | 171.5 |
| 3 | 33.1 | (+0.1) | 32.8 | (−0.3) | 33.0 | (−0.1) | | 33.0 |
| 4 | 15.9 | (−3.7) | 17.2 | (+1.3) | 20.6 | (+4.7) | | 19.6 |
| 5 | 32.5 | (+5.8) | 32.0 | (−0.5) | 38.1 | (+5.6) | | 26.7 |
| 6 | 85.7 | (+24.0) | 89.5 | (+3.8) | 87.1 | (+1.4) | | 61.7 |
| 7 | 38.0 | (+3.1) | 35.8 | (−2.2) | 32.3 | (−5.7) | | 34.9 |
| 8 | 19.4 | (−7.9) | 19.8 | (+0.4) | 19.4 | (0.0) | | 27.3 |
| 9 | 34.2 | (+1.8) | 34.3 | (+0.1) | 35.1 | (+0.9) | | 32.4 |
| 10 | 42.8 | (−3.8) | 42.9 | (+0.1) | 42.9 | (+0.1) | | 46.6 |
| 11 | 63.9 | (+0.1) | 63.6 | (−0.3) | 63.8 | (−0.1) | | 63.8 |
| 12 | 34.1 | (+0.6) | 34.1 | (0.0) | 34.3 | (+0.2) | | 33.5 |
| 13 | 24.5 | (0.0) | 24.2 | (−0.3) | 24.4 | (−0.1) | | 24.5 |
| 14 | 24.6 | (−0.7) | 24.6 | (0.0) | 24.7 | (+0.1) | | 25.3 |
| 15 | 55.2 | (−0.1) | 55.1 | (−0.1) | 55.2 | (0.0) | | 55.3 |
| 17 | 54.4 | (+1.6) | 53.6 | (−0.8) | 54.4 | (0.0) | | 52.8 |
| –$OCH_3$ | — | | 49.3 | | — | | | — |
| 2′ | | | | | 162.9 | | 163.3 | |
| 3′ | | | | | 116.9 | | 116.6 | |
| 4′ | | | | | 138.8 | | 138.4 | |
| 5′ | | | | | 104.6 | | 104.4 | |
| 6′ | | | | | 150.5 | | 151.3 | |
| 7′ | | | | | 35.3 | | 35.3 | |
| 8′ | | | | | 25.7 | | 25.8 | |
| 9′ | | | | | 28.3 | | 27.9 | |
| 10′ | | | | | 49.9 | | 49.8 | |
| 11′ | | | | | 62.1 | | 62.4 | |
| 13′ | | | | | 61.0 | | 62.1 | |
| 14′ | | | | | 58.0 | | 46.1 | |

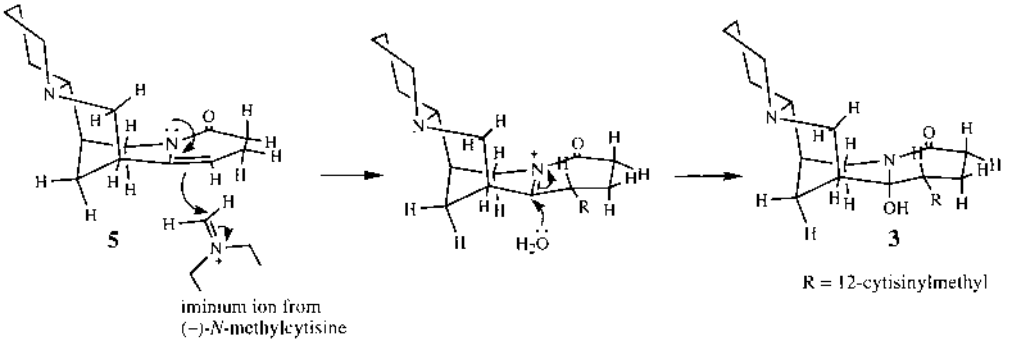



Chart 2

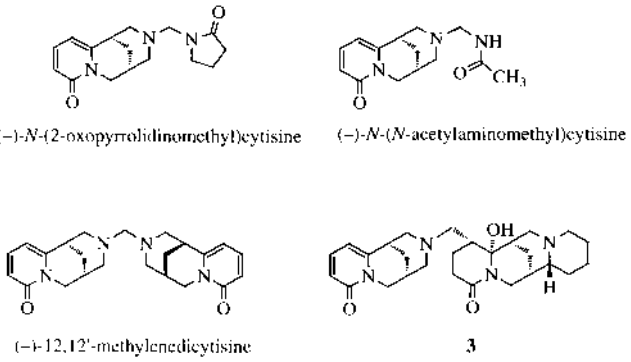



Chart 3

synthesized in a 12% yield by stirring a solution of (−)-cytisine, **5** and HCHO in $H_2O$ for 12 h. Consideration of the reaction mechanism suggested $\alpha$-configuration of the cytisinylmethyl group of the product (Chart 2). The molecular formula of alkaloid **3** should be $C_{27}H_{38}N_4O_3$, but in high resolution chemical ionization MS (HR-CI-MS), the highest MS ion at *m/z* 449.2906 suggested the formula $C_{27}H_{37}N_4O_2$ (Calcd for 449.2916, base peak), which corresponds to $[(M+H)^+-H_2O]$ (Fig. 1). We consider this to be attributable to dehydration of **3** during MS measurement process because **3** is a large molecule and contains a tertiary hydroxy group. The structure of **3** was confirmed to be (−)-5$\alpha$-(12-cytisinylmethyl)-6$\alpha$-hydroxylupanine.

Compound **5** is considered to be an important intermediate in the metabolic pathway from **6** to (−)-anagyrine.[4] In this report, two unstable alkaloids, **1** and **2**, were identified. These may be biosynthetic intermediates between **5** and **6**.

The conjugate of (−)-cytisine and **1**, **3**, also contains a >N–$CH_2$–Y (Y=C) moiety in its structure. Four alkaloids including **3**, (−)-*N*-(2-oxopyrrolidinomethyl)cytisine,[2] (−)-*N*-(*N*-acetylaminomethyl)cytisine[2] and (−)-12,12′-methylenedicytisine,[8] have so far been isolated from *Maackia* species (Chart 3). The alkaloids having a >N–$CH_2$–Y moiety in their structures are rarely found in plants, at least in lupin alkaloids, though the berberine bridge in the alkaloid berberine is well known as an example of such a group.[9] The methylene bridge of the above lupin alkaloids is presumed to be formed by Mannich-like reaction *via* an oxidative process in which the *N*-methyl group of **4** is oxidized to a iminium ion analogous with the formation of the berberine bridge in the biosynthesis of berberine from reticuline. The lupin alkaloids containing the methylene bridge consist of two molecules, one of which is (−)-cytisine. Thus, *Maackia* plants are characterized by production of these alkaloids.

In our phytochemical study of Chinese *Maackia* plants, the components of three species (*M. hupehensis*, *M. tenuifolia* and *M. amurensis*) were investigated. *M. hupehensis* and *M. tenuifolia*, which are native to southern China, produce lupinine-type alkaloids such as (−)-lupinine and (+)-epilupinine but not sparteine-type alkaloids. *M. amurensis*, which grows in northern China, produces sparteine-type alkaloids but not lupinine-type alkaloids. The anagyrine-type, cytisine-type alkaloids and lusitanine alkaloid are common in the plants of the above two groups. (−)-Lusitanine[10] is similar to (−)-lupinine. However, (−)-lupinine[11] comes directly from lysine. (−)-Lusitanine is thought to come from the C, D-ring of tetracyclic lupin alkaloids because its configuration at position 6 agrees with that of position 11 in (−)-lupanine and (−)-anagyrine (Chart 1). The absolute configuration of (−)-tenuamine[2] is not clear; (−)-tenuamine may also come from the C, D-ring of camoensidine in analogy with (−)-lusitanine.

Unusual alkaloids with a pyrrolidine or an indolizidine ring and common alkaloids with a piperidine or quinolizidine ring such as (−)-camoensidine and (−)-lupanine, and (−)-tenuamine and (−)-lusitanine, occur in pairs and coexist in all *Maackia* plants (Chart 1). This is characterized for *Maackia* species and suggests that *Maackia* plants might have the biosynthetic ability to use ornithine instead of lysine as the precursor amino acid for the alkaloids.

The above phenomena of Chinese *Maackia* plants are the same as those for Japanese *Maackia* species (Table 2). This is interesting from the perspectives of both the chemotaxonomy of *Maackia* plants and the biosynthesis of lupin alkaloids.

## Experimental

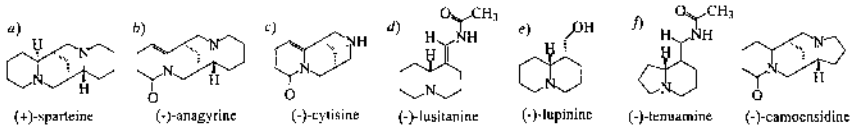
Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-200 fourier transform infrared spectrometer. High and low resolution MS were measured at 70 eV using a direct inlet system with a JEOL JMS-600W spectrometer. The NMR ($^1$H, 500 MHz, $^{13}$C, 125 MHz) spectra were recorded using tetramethylsilane (TMS) as an internal standard with a JEOL NMR instruments. TLC were conducted on precoated silica gel plates (Merck 60 $F_{254}$). Column chromatography was performed on silica gel with the following solvent systems: A, $Et_2O$–$CH_2Cl_2$–MeOH–25%$NH_4OH$ (4 : 4 : 6 6 : 0.1) for separation of alkaloids **1**, **2** and **3**; B, $CH_2Cl_2$–MeOH–25% $NH_4OH$ (90 : 9 : 1) for anagyrine, 5,6-dehydrolupanine, lupanine and ammodendrine; and C, $CH_2Cl_2$–MeOH (4 : 1) for cytisine, epibaptifoline and lusitanine.

**Plant Material** The leaves and stems of *M. amurensis* were collected in

Table 2. Components of the Chinese and Japanese *Maackia* Plants

| Country | Plants | Sparteine-type[a] | Anagyrine-type[b] | Cytisine-type[c] | Lusitanine[d] | Lupinine-type[e] | Unusual-type[f] |
|---|---|---|---|---|---|---|---|
| Japan | *M. tashioi* | | + | +++ | ++ | ++ | + |
| | *M. floribunda* | | + | ++ | + | + | + |
| | *M. floribunda f. pubescens* | | + | +++ | ++ | +++ | + |
| | *M. amurensis* | +++ | + | +++ | + | | + |
| China | *M. hupehensis* | | ++ | +++ | + | ++ | + |
| | *M. tenuifolia* | | + | +++ | + | + | + |
| | *M. amurensis* | ++ | ++ | +++ | ++ | | ++ |

(+++, <30%; ++, <20%; +, <10%)




Liaoning province, northern China, during July 1998 and identified by Prof. Ze-Rong Jiang, Department of Pharmacognosy, Shenyang Pharmaceutical University. A voucher specimen (No. 1269358) is deposited in the Herbarium Institute of Botany, Chinese Academy of Sciences, Xiangshan.

**Extraction and Isolation** The air-dried stems of *M. amurensis* (2.0 kg) were extracted with 75% MeOH for 24 h at room temperature (3 times). The combined extracts were concentrated and acidified with 10% HCl to pH 3. The acidic phase was washed quickly with $Et_2O$ (3 times), basified with 25% $NH_4OH$ to pH 11 and then extracted with $CH_2Cl_2$ (3 times). The basic phase was saturated with $K_2CO_3$ and then extracted with $CH_2Cl_2$ repeatedly until it became negative to Dragendorff's reagent. The $CH_2Cl_2$ extracts were combined, dried over $Na_2SO_4$ and evaporated to dryness. The crude alkaloid (11.0 g, 0.55%) obtained was subjected to silica gel column chromatography (230—400 mesh, 550 g) with $CH_2Cl_2$–MeOH–25%$NH_4OH$ (30 : 1.5 : 0.1), monitoring with TLC, to give 15 frs., which were further separated to give (−)-anagyrine (0.7 g), (−)-*N*-(3-oxobutyl)cytisine (85 mg), (−)-rhombifoline (76 mg), (−)-*N*-methylcytisine (**4**, 0.4 g), (−)-*N*-formylcytisine (0.3 g), (+)-5,6-dehydrolupanine (**5**, 0.6 g), (−)-6$\alpha$-methoxylupanine (**2**, 98 mg), (−)-lupanine (1.0 g), (−)-6$\alpha$-hydroxylupanine (**1**, 74 mg), (−)-cytisine (1.6 g), (−)-5$\alpha$-(12-cytisinylmethyl)-6$\alpha$-hydroxylupanine (**3**, 52 mg), (−)-12,12′-methylenedicytisine (0.6 g), (−)-epibaptifoline (0.6 g), (+)-ammodendrine (0.2 g), (+)-maackiamine (0.1 g), (−)-lusitanine (0.4 g), (−)-tenuamine (0.2 g), and (−)-camoensidine (0.5 g).

The crude alkaloid (11.7 g) from the *M. amurensis* leaves was treated in the similar manner as described above to yield (−)-anagyrine (0.8 g), (−)-*N*-methylcytisine (**4**, 0.45 g), (−)-*N*-formylcytisine (0.4 g), (+)-5,6-dehydrolupanine (**5**, 0.8 g), (−)-6$\alpha$-methoxylupanine (**2**, 0.11 g), (−)-lupanine (1.0 g), (−)-6$\alpha$-hydroxylupanine (**1**, 86 mg), (−)-cytisine (2.0 g), (−)-5$\alpha$-(12-cytisinylmethyl)-6$\alpha$-hydroxylupanine (**3**, 46 mg), (−)-12,12′-methylenedicytisine (0.7 g), (−)-epibaptifoline (1.0 g), (+)-ammodendrine (0.2 g), (+)-maackiamine (0.2 g), (−)-lusitanine (0.6 g), (−)-tenuamine (0.4 g), and (−)-camoensidine (0.7 g) in order of elution.

**1**: Colorless crystals, mp 115—117 °C, $[\alpha]_D^{23}$ −69.2° ($c$=0.34, EtOH). IR (KBr) $cm^{-1}$: 3280 (OH), 2850, 2800, 2750 (Bohlmann bands), 1640 (lactam C=O). HR-EI-MS: 264.1821 ($M^+$, Calcd for $C_{15}H_{24}N_2O_2$: 264.1828). EI-MS *m/z* (ret. int. %): 264 (35), 247 (30), 246 (100), 217 (8), 203 (10), 189 (9), 163 (10), 150 (25), 136 (45), 110 (45). $^1$H-NMR ($CDCl_3$) $\delta$: 4.22 (1H, dd, $J$=13.2, 2.1 Hz, 10-H$\beta$), 2.95 (1H, d, $J$=13.2 Hz, 10-H$\alpha$), 2.92 (1H, dd, $J$=11.8, 7.8 Hz, 17-H$\alpha$), 2.76 (1H, m, 15-H$\alpha$), 2.48 (1H, ddd, $J$=13.1, 6.8, 5.4 Hz, 3-H$\alpha$), 2.35 (1H, ddd, $J$=13.1, 2.5, 2.5 Hz, 3-H$\beta$), 2.09 (1H, m, 7-H). $^{13}$C-NMR: see Table 1.

**Dehydration of 1** (−)-6$\alpha$-Hydroxylupanine (**1**, 30 mg) was dissolved in 3 ml of $CH_2Cl_2$, and 30 $\mu$l of 0.1% HCl–MeOH was added to the solution. The acidic solution was stirred at room temperature for 8 h. The reaction mixture was concentrated, basified with 25% $NH_4OH$ and then extracted with $CH_2Cl_2$ (3 times). The $CH_2Cl_2$ extract was evaporated to dryness, and the residue was purified by silica gel column chromatography (20 g) with solvent B to give an oily substance (16 mg) that was identified as (+)-5,6-dehydrolupanine (**5**), $[\alpha]_D^{23}$ +35.4° ($c$=0.12, EtOH). HR-EI-MS: 246.1731 ($M^+$, Calcd for $C_{15}H_{22}N_2O$: 246.1733). $^1$H-NMR ($CDCl_3$) $\delta$: 4.90 (1H, dd, $J$=5.6, 3.6 Hz, 5-H), 3.97 (1H, d, $J$=13.2 Hz, 10-H$\beta$). $^{13}$C-NMR ($CDCl_3$) $\delta$: 19.2 (t, 4-C), 21.4 (t, 13-C), 22.8 (t, 14-C), 25.1 (t, 8-C), 27.4 (t, 12-C), 31.8 (t, 3-C), 33.2 (d, 9-C), 34.2 (d, 7-C), 48.2 (t, 10-C), 54.7 (t, 17-C), 56.5 (t, 15-C), 63.3 (d, 11-C), 102.2 (d, 5-C), 143.0 (s, 6-C), 170.8 (s, 2-C).

**2**: Colorless oil, $[\alpha]_D^{23}$ −16.5° ($c$=0.42, EtOH). HR-EI-MS: 278.2002 ($M^+$, Calcd for $C_{16}H_{26}N_2O_2$: 278.1994), 263.1751 (Calcd for $C_{15}H_{23}N_2O_2$: 263.1759), 246.1725 (Calcd for $C_{15}H_{22}N_2O$: 246.1732). EI-MS *m/z* (ret. int. %): 278 (20), 263 (100), 246 (30), 150 (16), 136 (15), 122 (8), 98 (75). $^1$H-NMR ($CDCl_3$) $\delta$: 4.30 (1H, dd, $J$=12.8, 2.0 Hz, 10-H$\beta$), 3.48 (3H, s, –$OCH_3$), 2.95 (1H, dd, $J$=12.8, 2.3 Hz, 10-H$\alpha$), 2.82 (1H, ddd, $J$=13.2, 7.4, 2.9 Hz, 17-H$\alpha$), 2.75 (1H, d, $J$=11.5 Hz, 15-H$\alpha$), 2.46 (1H, m, 3-H$\alpha$), 2.38 (1H, m, 3-H$\beta$), 2.20 (1H, m, 7-H). $^{13}$C-NMR: see Table 1.

**Conversion of 2 to 5** (−)-6$\alpha$-Methoxylupanine (**2**, 40 mg) was stirred in $CH_2Cl_2$ (5.0 ml) at room temperature for 48 h. The solution was evaporated, and the residue was separated by silica gel column chromatography (30 g) with solvent A to give **5** (15 mg) and recovered **2** (20 mg).

**3**: Colorless oil, $[\alpha]_D^{23}$ −31.5° ($c$=0.26, EtOH). IR (KBr) $cm^{-1}$: 3400 (OH), 1640 (C=O). HR-CI-MS: 449.2906 {[(M+H)$^+$−$H_2O$], Calcd for $C_{27}H_{37}N_4O_2$: 449.2916}. HR-EI-MS: 258.1739 (Calcd for $C_{16}H_{22}N_2O$: 258.1732). EI-MS *m/z* (ret. int. %): 448 (8), 258 (100), 203 (15), 189 (20), 160 (33), 146 (80), 134 (40). $^1$H-NMR ($CDCl_3$) $\delta$: 7.29 (1H, dd, $J$=9.1, 6.9 Hz, 4′-H), 6.41 (1H, dd, $J$=9.1, 1.3 Hz, 3′-H), 5.99 (1H, dd, $J$=6.9, 1.3 Hz, 5′-H), 4.20 (1H, dd, $J$=13.0, 2.0 Hz, 10-H$\beta$), 4.05 (1H, d, $J$=15.5 Hz, 10′-H$\beta$), 3.85 (1H, dd, $J$=15.5, 6.3 Hz, 10′-H$\alpha$). $^{13}$C-NMR: see Table 1.

**Synthesis of 3** To a stirred solution of **5** (130 mg, 0.51 mmol) in 10 ml of $H_2O$ was added 2 ml of 37% HCHO (0.52 mmol) and (−)-cytisine (100 mg, 0.55 mmol). After it was stirred at room temperature for 12 h, the solution was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extract was evaporated to dryness and then purified by silica gel column chromatography (25 g) with $CH_2Cl_2$–MeOH–25% $NH_4OH$ (65 : 5 : 0.8) to yield **3** (30 mg, 0.06 mmol).

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**References and Notes**

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sider our assignment appropriate because it reflects properly the substituent effects of the hydroxy group at position 6.

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