Synthesis and Absolute Configuration of a New 3,4-Dihydro-β-carboline-Type Alkaloid, 3,4-Dehydro-5(*S*)-5-carboxystrictosidine, Isolated from Peruvian Uña de Gato (*Uncaria tomentosa*)

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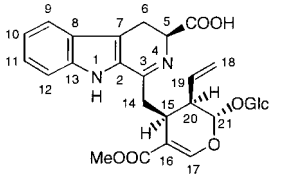
The structure including the absolute configuration of a new glucoalkaloid, 3,4-dehydro-5(*S*)-5-carboxystrictosidine, isolated from Peruvian Uña de Gato (Cat's Claw, original plant: *Uncaria tomentosa*), was confirmed by synthesis starting from secologanin and L-tryptophan.

Key words alkaloid; 3,4-dihydro-β-carboline; *Uncaria*

In continuation of our study on the chemical constituents of *Uncaria* plants (Rubiaceae), a new alkaloid, 3,4-dehydro-5(*S*)-5-carboxystrictosidine (**1**), was isolated from Peruvian Uña de Gato (Cat's Claw, original plant: *Uncaria tomentosa*) together with 5(*S*)-5-carboxystrictosidine (**2**) which is a main alkaloid of this herbal medicine.[1] Compound **1** was the first example of isolation from nature of a monoterpenoid glucoindole alkaloid having a 3,4-dihydro-β-carboline ring system. Its structure except for the absolute configuration was deduced from the spectroscopic analysis to be a 3,4-dehydro compound of 5(*S*)-5-carboxystrictosidine (**2**), which consists of secologanin (**3**) and L-tryptophan (**4**). This paper reports the synthesis of **1** from secologanin (**3**) and L-tryptophan (**4**) and determination of the structure of **1** including the absolute configuration.

In order to determine the absolute configuration of the secologanin part involving a sugar in **1**, acid hydrolysis of natural **1** was performed. Treatment of natural **1** with aqueous HCl in dioxane gave D-(+)-glucose, which was identified by HPLC analysis, revealing that the absolute configuration of the secologanin part in **1** was the same as that of common monoterpenoid indole alkaloids possessing a D-(+)-glucose. Although the absolute configuration at the C-5 position of **1** could not be clarified from the spectroscopic data, it was deduced to be *S* from the biosynthetic point of view that L-tryptophan (**4**) would be a biogenetic precursor.

To establish the structure of **1** including the absolute configuration, we planned synthesis of **1**. Some attempts at dehydrogenation between C-3 and N-4 in **2** were unsuccessful. Therefore, we adopted a synthesis of **1** from secologanin (**3**) and L-tryptophan (**4**). Acetylation of the hydroxy group in secologanin (**3**) followed by Jones oxidation of the aldehyde to carboxylic acid gave a known secoxyloganin tetraacetate (**5**).[2] First, L-tryptophan methyl ester (**6**) was used for the coupling with **5**. Compound **5** was condensed with **6** by using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBT) in dry CH_2Cl_2 to afford an amide (**7**) in 81% yield. The molecular formula of **7** was confirmed as $C_{37}H_{44}N_2O_{16}$ from the high resolution (HR)-FAB-MS spectrum. The *N*-H (δ 5.98) proton of the amide and the amide carbonyl carbon (δ 170.5) were observed in the ^{1}H- and ^{13}C-NMR spectra, respectively. The C ring of **8** was constructed by the Bishler–Napieralski reaction of **7** using $POCl_3$ in benzene to give two separable C-5 epimers of 3,4-dihydro-β-carboline derivative (**8a**, **b**). However, each compound, whose configuration at C-5 could not be determined, easily changed to a mixture of **8a** and **b**.



3,4-Dehydro-5(*S*)-5-carboxystrictosidine (**1**)
3,4-dihydro, 3*S* : 5(*S*)-5-carboxystrictosidine (**2**)

Fig. 1

Next L-tryptophan (**4**) itself was used as the starting material in place of L-tryptophan methyl ester (**6**) in order to avoid epimerization at the C-5 position after C-ring formation. Coupling of **5** with **4** was carried out by treatment with EDCI and HOBT in dry *N*,*N*-dimethylformamide (DMF) to afford amide (**9**) in 87% yield. The ^{1}H- and ^{13}C-NMR spectra showed the existence of an amide group (the amide *N*-H proton at δ 6.75 and the amide carbonyl carbon at δ 171.8). Next, the amide (**9**) was treated with dicyclohexylcarbodiimide (DCC) in dry CH_2Cl_2 and then with trifluoroacetic acid[3] to give 3,4-dihydro-β-carboline derivative (**10**) exhibiting the UV absorptions at 356, 230 nm, which were almost the same as those of natural **1**. Finally, deacetylation of **10** by NaOMe gave 3,4-dehydro-5(*S*)-5-carboxystrictosidine (**1**). Under the reaction conditions employed above (cyclization and deacetylation), epimerization at the C-5 position was not observed. As the spectroscopic data of the synthetic compound **1** (UV, ^{1}H- and ^{13}C-NMR, and MS) were identical with those of natural **1**, the structure and the absolute configuration of **1** were unambiguously determined.

In conclusion, the structure of 3,4-dehydro-5(*S*)-5-carboxystrictosidine (**1**), which was isolated from Peruvian Uña de Gato, including the absolute configuration was established by the synthesis from secologanin (**3**) and L-tryptophan (**4**) through a Bishler–Napieralski reaction.

Experimental

General Specific rotations: JASCO DIP-140. UV: JASCO V-560. IR: JASCO FT/IR-230. ^{1}H- and ^{13}C-NMR spectra: at 500 (^{1}H-NMR) and 125.65 (^{13}C-NMR) MHz, respectively. JEOL JNM A-500. FAB-MS and HR-FAB-MS: JEOL JMS-HX110. CD: JASCO J-720WI. TLC: Precoated Silica gel 60 F_{254} plates (Merck, 0.25 mm thick). Column Chromatography: Silica gel

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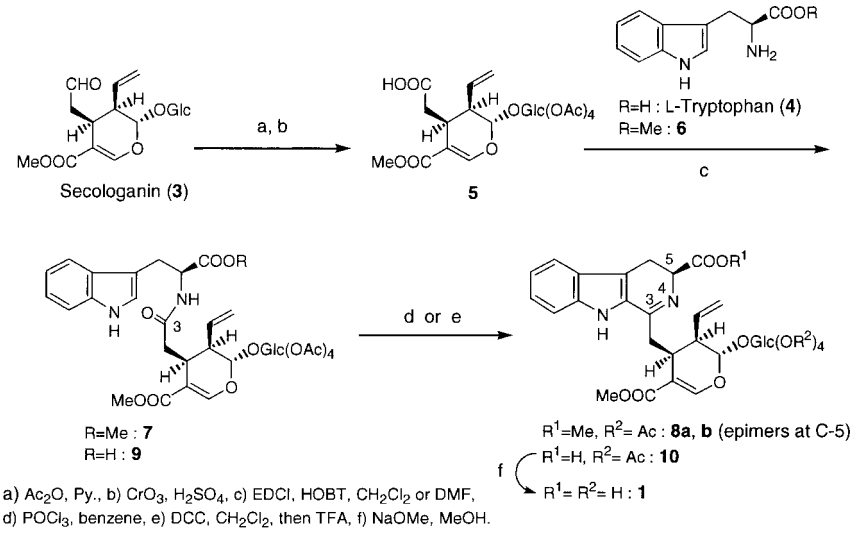

Chart 1

60 [Merck, 70—230 mesh], Amberlite IRA-93 [Organo]. medium pressure liquid chromatography (MPLC): C. I. G. prepacked column CPS-HS-221-05 (SiO_2) and CPO-HS-221-20 (ODS) [Kusano Kagakukikai], HPLC: Shodex RSpak DC-613 [Showa Denko].

Acid Hydrolysis of Natural 3,4-Dehydro-5(*S*)-5-carboxystrictosidine (1) A solution of natural **1** (6.6 mg) in 2 N HCl–dioxane (1 : 1, 1.0 ml) was heated at 100 °C for 2.5 h under Ar. Water was added to the reaction mixture and the solvent was slightly removed under reduced pressure. The whole was partitioned between water and AcOEt. The aqueous layer was neutralized by passage through Amberlite IRA-93 eluting with H_2O and evaporated *in vacuo* to give a sugar fraction. The identification and configuration of the sugar were determined by HPLC analysis by comparison with an authentic D-glucose (t_R, 10.8 min). HPLC conditions: column, Shodex RSpak DC-613 (6.0×150 mm i.d.); solvent, $CH_3CN : H_2O = 7 : 3$ (v/v); flow rate, 0.5 ml/min; temp., 70 °C; RI detection, Shodex RI-72 and chiral detection, JASCO OR-1590. The sugar fraction gave a peak of D-(+)-glucose (t_R, 10.8 min).

Preparation of Amide (7) from Secoxyloganin Tetraacetate (5) and L-Tryptophan Methyl Ester (6) To a solution of secoxyloganin tetraacetate (**5**, 104.3 mg, 0.182 mmol) in dry CH_2Cl_2 (3.0 ml) were added EDCI (41.9 mg, 0.219 mmol) and HOBT (33.5 mg, 0.219 mmol) at 0 °C and the mixture was stirred at room temperature for 15 min under Ar. After addition of L-tryptophan methyl ester (**6**, 47.7 mg, 0.219 mmol), the mixture was stirred at the same temperature for an additional 2 h. Cold 1% HCl aq. was added to the reaction mixture and the whole was extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ aq. and then brine, dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (SiO_2, 1% MeOH–$CHCl_3$) to afford amide (**7**, 113.2 mg, yield 81%).

7: Amorphous. $[\alpha]_D^{24}$ −69.8° (c=1.51, $CHCl_3$). UV λ_{max} (MeOH) nm: 282, 223. IR ($CHCl_3$) cm^{-1}: 3477, 3423, 3026, 2953, 1755, 1708, 1674, 1227. FAB-MS (NBA, positive) *m/z*: 773 $[M+H]^+$. HR-FAB-MS (NBA, positive) *m/z*: 773.2739 $[M+H]^+$ (Calcd for $C_{37}H_{45}N_2O_{16}$: 773.2769). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.59 (1H, br s, N_a-H), 7.59 (1H, d, J=7.5 Hz, H-9), 7.33 (1H, d, J=2.1 Hz, H-17), 7.33 (1H, d, J=7.5 Hz, H-12), 7.17 (1H, br dd, J=7.5, 7.5 Hz, H-11), 7.12 (1H, br dd, J=7.5, 7.5 Hz, H-10), 7.08 (1H, d, J=2.1 Hz, H-2), 5.98 (1H, d, J=7.6 Hz, N_b-H), 5.35 (1H, ddd, J=17.0, 10.1, 10.1 Hz, H-19), 5.26 (1H, dd, J=9.6, 9.6 Hz, H-3′), 5.17 (1H, dd, J=9.8, 9.8 Hz, H-4′), 5.14 (1H, d, J=2.7 Hz, H-21), 5.07 (1H, dd, J=9.6, 8.1 Hz, H-2′), 5.02 (1H, d, J=11.6 Hz, H-18), 4.93 (1H, overlapped, H-5), 4.92 (1H, d, J=8.2 Hz, H-1′), 4.71 (1H, d, J=17.0 Hz, H-18), 4.37 (1H, dd, J=12.4, 4.1 Hz, H-6′), 4.22 (1H, dd, J=12.5, 2.1 Hz, H-6′), 3.78 (1H, m, H-5′), 3.73 (3H, s, 5-CO_2CH_3), 3.66 (3H, s, 16-CO_2CH_3), 3.39 (1H, dd, J=14.8, 4.7 Hz, H-6), 3.18 (1H, dd, J=15.2, 7.9 Hz, H-6), 2.06, 2.05 and 2.03 (each 3H, s, 3′,4′,6′-OCOCH_3), 1.97 (1H, overlapped, H-14), 1.93 (3H, s, 2′-OCOCH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.6 (5-$\underline{C}O_2CH_3$), 170.7 (6′-O$\underline{C}$OCH$_3$), 170.5 (C-3), 170.2 (3′-O$\underline{C}$OCH$_3$), 169.3 (4′-O$\underline{C}$OCH$_3$), 169.1 (2′-O$\underline{C}$OCH$_3$), 166.7 (16-$\underline{C}O_2CH_3$), 150.9 (C-17), 136.3 (C-13), 131.3 (C-19), 127.1 (C-8), 123.3 (C-2), 122.2 (C-11), 121.4 (C-18), 119.6 (C-10), 118.7 (C-9), 111.1 (C-12), 110.1 (C-7), 109.7 (C-16), 96.3 (C-21), 95.9 (C-1′), 72.3 (C-3′, C-5′), 70.6 (C-2′), 67.9 (C-4′), 61.4 (C-6′), 52.3 (5-$CO_2\underline{C}H_3$), 52.1 (C-5), 51.3 (16-$CO_2\underline{C}H_3$), 42.3 (C-20), 35.1 (C-14), 27.9 (C-6), 27.2 (C-15), 20.7, 20.60 and 20.55 (3′,4′,6′-OCO$\underline{C}$H$_3$), 20.1 (2′-OCO$\underline{C}$H$_3$).

Bishler–Napieralski Reaction of 7 To a solution of amide (**7**, 10.0 mg, 0.013 mmol) in dry benzene (0.5 ml) was added $POCl_3$ (12.1 μl, 0.130 mmol) and the mixture was refluxed for 2 h under Ar. Cold saturated $NaHCO_3$ aq. was added to the reaction mixture and the whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (SiO_2, AcOEt–*n*-hexane–$CHCl_3$=2 : 1 : 1) to give 3,4-dihydro-β-carboline derivatives (**8a**, 4.3 mg, yield 45% and **8b**, 2.6 mg, yield 27%).

8a: Amorphous. $[\alpha]_D^{25}$ −68.8° (c=0.117, $CHCl_3$). UV λ_{max} (EtOH) nm: 318, 235 (By addition of diluted aqueous HCl solution to the EtOH solution of **8a**, the UV absorption shifted to 363 nm which was almost the same wavelength as that of natural **1**. These observations suggested that isolated **1** existed as a zwitter ionic form in the solution.[3]). IR ($CHCl_3$) cm^{-1}: 3312, 3028, 2954, 1755, 1686, 1228. FAB-MS (NBA, positive) *m/z*: 755 $[M+H]^+$. ^{1}H-NMR (500 MHz, $CDCl_3$, Selected data) δ: 10.24 (1H, br s, N_a-H), 7.59 (1H, d, J=7.7 Hz, H-9), 7.47 (1H, d, J=7.7 Hz, H-12), 7.46 (1H, d, J=1.2 Hz, H-17), 7.28 (1H, br dd, J=7.7, 7.7 Hz, H-11), 7.13 (1H, br dd, J=7.7, 7.7 Hz, H-10), 5.81 (1H, ddd, J=16.6, 10.0, 10.0 Hz, H-19), 5.44 (1H, d, J=5.5 Hz, H-21), 5.25 (2H, m, H_2-18), 4.53 (1H, dd, J=12.7, 7.5 Hz, H-5), 3.82 (3H, s, 16-CO_2CH_3), 3.79 (3H, s, 5-CO_2CH_3), 2.10 (3H, s, 6′-OCOCH_3), 2.02, 1.97 and 1.95 (each 3H, s, 2′,3′,4′-OCOCH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 173.8 (5-$\underline{C}O_2CH_3$), 170.7 (6′-O$\underline{C}$OCH$_3$), 170.2, 169.3 and 168.8 (2′,3′,4′-O$\underline{C}$OCH$_3$), 168.4 (16-$\underline{C}O_2CH_3$), 160.92 (C-3), 152.1 (C-17), 137.1 (C-13), 133.0 (C-19), 128.4 (C-2), 125.0 (C-8), 124.6 (C-11), 120.7 (C-18), 120.1 (C-10), 119.9 (C-9), 115.1 (C-7), 112.5 (C-12), 110.2 (C-16), 96.5 and 96.4 (C-1′, C-21), 72.4 (C-2′), 72.2 (C-5′), 70.8 (C-3′), 68.0 (C-4′), 61.6 (C-6′), 61.0 (C-5), 52.3 (5-$CO_2\underline{C}H_3$), 51.9 (16-$CO_2\underline{C}H_3$), 44.1 (C-20), 36.4 (C-14), 31.1 (C-15), 22.2 (C-6), 20.8 (6′-OCO$\underline{C}$H$_3$), 20.6 and 20.3 (2′,3′,4′-OCO$\underline{C}$H$_3$).

8b: Amorphous. UV λ_{max} (EtOH) nm: 318, 235. ^{1}H-NMR (500 MHz, $CDCl_3$, Selected data) δ: 10.33 (1H, br s, N_a-H), 7.60 (1H, d, J=7.6 Hz, H-9), 7.49 (1H, d, J=7.6 Hz, H-12), 7.48 (1H, d, J=1.2 Hz, H-17), 7.29 (1H, br dd, J=7.6, 7.6 Hz, H-11), 7.14 (1H, br dd, J=7.6, 7.6 Hz, H-10), 5.80 (1H, ddd, J=16.9, 10.0, 10.0 Hz, H-19), 5.38 (1H, d, J=5.8 Hz, H-21), 4.43 (1H, ddd, J=15.0, 7.2, 2.8 Hz, H-5), 3.85 and 3.84 (each 3H, s, 5, 16-$CO_2\underline{C}H_3$), 2.10, 2.01, 1.96 and 1.91 (each 3H, s, 2′,3′,4′,6′-OCOCH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 173.9 (5-$\underline{C}O_2CH_3$), 170.7 (6′-O$\underline{C}$OCH$_3$), 170.2 (3′-O$\underline{C}$OCH$_3$), 169.3 (4′-O$\underline{C}$OCH$_3$), 168.6 (2′-O$\underline{C}$OCH$_3$), 168.5 (16-CO_2CH_3), 160.85 (C-3), 152.2 (C-17), 137.1 (C-13), 132.8 (C-19), 127.9 (C-2), 125.1 (C-8), 124.5 (C-11), 121.0 (C-18), 120.1 (C-10), 119.9 (C-9), 115.2 (C-7), 112.5 (C-12), 110.2 (C-16), 96.4 (C-1′, C-21), 72.4 (C-3′), 72.2 (C-5′), 70.3 (C-2′), 68.0 (C-4′), 61.7 and 61.6 (C-5, C-6′), 52.4 and 51.9 (5,16-$CO_2\underline{C}H_3$), 44.2 (C-20), 36.9 (C-14), 30.8 (C-15), 22.1 (C-6), 20.8 (6′-OCO$\underline{C}$H$_3$), 20.6 (3′,4′-OCO$\underline{C}$H$_3$), 20.3 (2′-OCO$\underline{C}$H$_3$).

Preparation of Amide (9) from Secoxyloganin Tetraacetate (5) and L-Tryptophan (4) To a solution of secoxyloganin tetraacetate (**5**, 72.2 mg,

0.126 mmol) in dry DMF (2.0 ml) were added EDCI (26.6 mg, 0.139 mmol) and HOBT (21.3 mg, 0.139 mmol) at 0 °C and the mixture was stirred at room temperature for 14 h under Ar. After addition of L-tryptophan (**4**, 28.3 mg, 0.319 mmol), the mixture was stirred at the same temperature for an additional 3 h. Cold 1% HCl aq. was added to the reaction mixture and the whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (SiO_2, 2% MeOH–$CHCl_3$) to afford the amide (**9**, 83.5 mg, yield 87%).

9: Amorphous. $[\alpha]_D^{24}$ −103.3° (c=0.283, $CHCl_3$). UV λ_{max} (MeOH) nm: 291, 282, 223. IR ($CHCl_3$) cm^{-1}: 3419, 3027, 2953, 1756, 1711, 1670, 1227. FAB-MS (NBA, negative) m/z: 757 $[M-H]^-$. HR-FAB-MS (NBA, negative) m/z: 757.2493 $[M-H]^-$ (Calcd for $C_{36}H_{41}N_2O_{16}$: 757.2456). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.84 (1H, br s, N_a-H), 7.65 (1H, d, J=7.0 Hz, H-9), 7.30 (1H, s, H-17), 7.29 (1H, d, J=7.0 Hz, H-12), 7.16 (1H, dd, J=7.0, 7.0 Hz, H-11), 7.15 (1H, br s, H-2), 7.12 (1H, dd, J=7.0, 7.0 Hz, H-10), 6.75 (1H, br d, J=7.3 Hz, N_b-H), 5.29 (1H, dd, J=9.5, 9.5 Hz, H-3′), 5.25 (1H, overlapped, H-19), 5.21 (1H, dd, J=9.5, 9.5 Hz, H-4′), 5.15 (1H, dd, J=9.5, 7.9 Hz, H-2′), 5.06 (1H, d, J=2.7 Hz, H-21), 4.95 (1H, m, H-5), 4.94 (1H, d, J=7.9 Hz, H-1′), 4.87 (1H, d, J=11.6 Hz, H-18), 4.42 (1H, dd, J=12.5, 3.6 Hz, H-6′), 4.31 (1H, d, J=17.1 Hz, H-18), 4.26 (1H, dd, J=12.5, 2.2 Hz, H-6′), 3.84 (1H, ddd, J=9.5, 3.6, 2.2 Hz, H-5′), 3.65 (3H, s, 16-$CO_2C\underline{H}_3$), 3.48 (1H, dd, J=14.8, 4.1 Hz, H-6), 3.15 (1H, dd, J=14.8, 9.6 Hz, H-6), 3.01 (2H, m, H-14, 15), 2.06 (3H, s, 4′-OCOC$\underline{H}_3$), 2.05 (3H, s, 3′-OCOC$\underline{H}_3$), 2.03 (3H, s, 6′-OCOC$\underline{H}_3$), 1.95 (3H, s, 2′-OCOC$\underline{H}_3$), 1.88 (2H, m, H-14, 20). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.6 (5-$\underline{C}$OOH), 171.8 (C-3), 170.7 (6′-O$\underline{C}$OCH$_3$), 170.4 (2′-O$\underline{C}$OCH$_3$), 170.1 (3′-O$\underline{C}$OCH$_3$), 169.4 (4′-O$\underline{C}$OCH$_3$), 166.9 (16-$\underline{C}$O$_2$CH$_3$), 150.8 (C-17), 136.4 (C-13), 130.8 (C-19), 126.9 (C-8), 123.9 (C-2), 122.2 (C-11), 121.5 (C-18), 119.6 (C-10), 118.7 (C-9), 111.1 (C-12), 110.00 and 109.97 (C-7, C-16), 96.4 (C-21), 95.8 (C-1′), 72.3 (C-5′), 72.1 (C-3′), 70.9 (C-2′), 67.9 (C-4′), 61.3 (C-6′), 52.3 (C-5), 51.5 (16-$CO_2\underline{C}H_3$), 41.8 (C-20), 35.4 (C-14), 27.5 (C-6), 26.9 (C-15), 20.61 and 20.56 (3′,4′,6′-OCO$\underline{C}$H$_3$), 20.1 (2′-OCO$\underline{C}$H$_3$). CD (c=0.237 mmol/l, MeOH, 20 °C) $\Delta\varepsilon$ (λ nm): 0 (275), +1.51 (249), 0 (240), −3.58 (232).

Preparation of 3,4-Dihydro-β-carboline Derivative (10) from 9 To a solution of amide (**9**, 24.0 mg, 0.317 mmol) in dry CH_2Cl_2 (0.5 ml) was added a dry CH_2Cl_2 (0.5 ml) solution of DCC (7.8 mg, 0.380 mmol) and the mixture was stirred at room temperature for 3.5 h under Ar. TFA (1.0 ml) was added to the reaction mixture and the mixture was stirred at the same temperature for overnight under Ar. After concentration of the solvent under reduced pressure, the residue was purified by MPLC (SiO_2, 10% MeOH–$CHCl_3$) to give 3,4-dihydro-β-carboline derivative (**10**, 5.8 mg, yield 25%).

10: Amorphous. UV λ_{max} (MeOH) nm: 356, 230. FAB-MS (NBA, positive) m/z: 741 $[M+H]^+$.

Preparation of 3,4-Dehydro-5(*S*)-5-carboxystrictosidine (1) from 10 To a solution of **10** (11.5 mg, 0.015 mmol) in dry MeOH (0.7 ml) was added 1 N NaOMe in MeOH (23.3 μl, 0.023 mmol) and the mixture was stirred at room temperature for 3 h under Ar. After neutralization with 1 N HCl aq. (23.3 μl, 0.023 mmol), the reaction mixture was directly subjected to SiO_2 open column chromatography (MeOH–$CHCl_3$ gradient). The residue was purified by MPLC (ODS, 50% H_2O–MeOH) to give 3,4-dehydro-5(*S*)-5-carboxystrictosidine (**1**, 5.3 mg, yield 59%). The synthetic compound was identical with the natural product (UV, ^{1}H- and ^{13}C-NMR, and MS).

1: CD (c=0.787 mmol/l, MeOH, 20 °C) $\Delta\varepsilon$ (λ nm): 0 (438), +0.13 (408), 0 (375), −0.21 (348), 0 (316), −1.72 (245), −0.82 (232), −1.07 (226), 0 (219), +2.81 (206).

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