# Aporphine Glycosides from *Stephania cepharantha* Seeds

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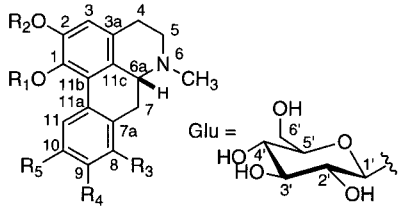
Two new aporphine glycosides, stesakine-9-*O*-*β*-D-glucopyranoside (**1**) and *N*-methylasimilobine-2-*O*-*β*-D-glucopyranoside (**2**), were isolated from the seeds of *Stephania cepharantha* cultivated in Japan, together with 16 known alkaloids. The structures of **1** and **2** were spectroscopically determined by comparison of their $^1$H and $^{13}$C NMR data with those of stesakine (**11**) and *N*-methylasimilobine (**12**), respectively.

The alkaloid constituents from the root tubers,[1] leaves,[2] and stems[3] of *Stephania cepharantha* Hayata (Menispermaceae) cultivated in Japan were reported in previous papers. The alkaloid constituents of the seeds have been investigated by Kunitomo et al., who isolated eight alkaloids: six aporphines and two bisbenzylisoquinolines.[4] In our investigation, two new aporphine glycosides, stesakine-9-*O*-*β*-D-glucopyranoside (**1**) and *N*-methylasimilobine-2-*O*-*β*-D-glucopyranoside (**2**), were obtained, together with 16 known alkaloids.[5] This paper describes the isolation and structure elucidation of **1** and **2**.

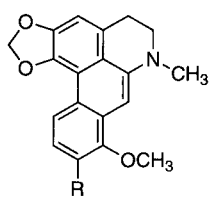
## Results and Discussion

Seeds of *S. cepharantha* were successively extracted with *n*-hexane and MeOH. The *n*-hexane extract was repeatedly subjected to a combination of column chromatography, preparative TLC, and crystallization, to afford 10 known aporphine alkaloids: dehydrostephanine (**3**),[4] dehydrocrebanine (**4**),[6] stephanine (**5**),[7] crebanine (**6**),[7] (−)-dicentrine (**7**),[8] (−)-roemerine (**8**),[9] (−)-isolaureline (**9**),[10] nuciferine (**10**),[11] stesakine (**11**),[6] and *N*-methylasimilobine (**12**).[11] The MeOH extract was fractionated, and the alkaloid-containing fraction was purified using the same methods as for the fractionation of the *n*-hexane extract, to give stesakine-9-*O*-*β*-D-glucopyranoside (**1**) and *N*-methylasimilobine-2-*O*-*β*-D-glucopyranoside (**2**), as well as nine known alkaloids: four aporphines, **6**, **11**, **12**, and (−)-cassythicine (**13**);[12] one proaporphine, pronuciferine (**14**);[13] and four bisbenzylisoquinolines, cepharanthine,[14] cepharanoline,[15] isotetrandrine,[16] and berbamine.[17]

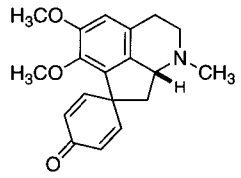
Glycoside **1** was obtained as an amorphous powder. The molecular formula of $C_{25}H_{29}NO_9$ was deduced by FABMS. The EIMS showed a molecular ion peak at *m*/*z* 487 and strong ion peaks at *m*/*z* 325 $[M - 162]^+$ and 324 $[M - 163]^+$, indicating that **1** was probably an alkaloid glycoside.[18,19] The $^1$H NMR spectrum showed signals of one *N*-methyl group (*δ* 2.48), one methoxy group (*δ* 4.01), methylenedioxy protons (*δ* 5.98, 6.11), one singlet aromatic proton (*δ* 6.60), and a set of coupled aromatic protons (*δ* 7.71, 8.01); the spectrum was similar to that of stesakine (**11**), except for signals assigned to the sugar moiety. The $^{13}$C NMR spectrum showed 25 signals, of which five methines and one methylene were assigned to the *β*-glucopyranose moiety; the other 19 signals were similar to those of **11**. These data suggested that **1** was an aporphine glycoside, with **11** as the aglycon and *β*-glucopyranose as the sugar moiety. The sugar linkage was determined as follows: $^1$H NMR signals of the C-8 methoxy group (*δ* 4.01) and H-10 (*δ* 7.71) were shifted downfield compared with those of **11** (*δ* 3.89, 7.30), suggesting that the sugar moiety was linked to C-9. This assignment was supported by the results of COLOC and NOESY experiments. The optical rotation was levorotatory ($[\alpha]^{27}_D$ −74.5°), indicating that the absolute configuration of C-6a is *R* (*β*-H).[20] Therefore, **1** was identified as stesakine-9-*O*-*β*-D-glucopyranoside.




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| **1** | – $CH_2$ – | | $OCH_3$ | OGlu | H |
| **2** | $CH_3$ | Glu | H | H | H |
| **5** | – $CH_2$ – | | $OCH_3$ | H | H |
| **6** | – $CH_2$ – | | $OCH_3$ | $OCH_3$ | H |
| **7** | – $CH_2$ – | | H | $OCH_3$ | $OCH_3$ |
| **8** | – $CH_2$ – | | H | H | H |
| **9** | – $CH_2$ – | | H | $OCH_3$ | H |
| **10** | $CH_3$ | $CH_3$ | H | H | H |
| **11** | – $CH_2$ – | | $OCH_3$ | OH | H |
| **12** | $CH_3$ | H | H | H | H |
| **13** | – $CH_2$ – | | H | OH | $OCH_3$ |




**3** R = H, **4** R = $OCH_3$




**14**

Glycoside **2** was isolated as an amorphous powder, and the molecular formula was assigned as $C_{24}H_{29}NO_7$ by FABMS. In the EIMS, the molecular ion peak at *m*/*z* 443 and strong ion peaks at *m*/*z* 281 $[M - 162]^+$ and 280 $[M - 163]^+$ suggested that **2** should be also an alkaloid glycoside.[17,18] The $^1$H NMR spectrum exhibited signals of one *N*-methyl group (*δ* 2.41), one methoxy group (*δ* 3.93), four overlapping aromatic protons (*δ* 7.30−7.44), one separate aromatic proton at *δ* 8.70, and signals assigned to the sugar moiety. The $^{13}$C NMR spectrum showed 24 signals, including six signals assignable to *β*-glucopyranose. The $^1$H and $^{13}$C NMR spectra, except for signals of the sugar

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moiety, were closely related to those of *N*-methylasimilobine (**12**), indicating that **2** was a *β*-glucopyranoside of **12**. The sugar moiety was placed at C-2, because $^1$H NMR signals of the C-1 methoxy group (*δ* 3.93) and H-3 (*δ* 7.39) were shifted downfield compared with those of **12** (*δ* 3.73, 7.01). The HMBC and NOESY experiments also supported placement of the sugar moiety at C-2. The absolute configuration was C-6a*R* (*β*-H) as deduced from the optical rotation ($[\alpha]^{27}_D$ −116.1°).[20] Thus, **2** was assigned as *N*-methylasimilobine-2-*O*-*β*-D-glucopyranoside.

The structures of known alkaloids **3**−**14** were confirmed by comparison of the spectroscopic data with published values and from the results of 2D NMR experiments; the other known alkaloids were identified by direct comparison of the spectroscopic data with those of authentic samples isolated previously.[1] The aporphine alkaloids, including a dehydroaporphine and aporphine glycoside, were major constituents in the seeds of *S. cepharantha*. However, aporphines **1**−**13** were not detectable in the root tubers, leaves, and stems.

To date, only four aporphine glycosides have been reported: (−)-asimilobine-2-*O*-*β*-D-glucoside,[18] kamaline,[19] floripavidine,[21] and tuberosinone-*N*-*β*-D-glucoside.[22] The aglycons of these glycosides were asimilobine derivatives and tuberosinone, respectively. Therefore, stesakine-9-*O*-*β*-D-glucopyranoside (**1**) represents the first aporphine glycoside having stesakine (**11**) as the aglycon. *N*-Methylasimilobine-2-*O*-*β*-D-glucopyranoside (**2**) was a fourth asimilobine derivative glycoside.

## Experimental Section

**General Experimental Procedures.** Melting points were determined on a Yanagimoto hot-stage melting point apparatus without correction. Optical rotations ($[\alpha]_D$) were determined on a DIP-1000 (JASCO) polarimeter. IR spectra were obtained on an FT/IR-5000 (JASCO) spectrometer using KBr disks. NMR spectra were recorded on a JNM-α500 (JEOL) (500 MHz for $^1$H and 125 MHz for $^{13}$C) spectrometer with tetramethylsilane as internal standard. MS were recorded on a JMS-HX110A (JEOL) spectrometer for EIMS and FABMS, and a JMS-D300 (JEOL) spectrometer was used for HRMS. EIMS were measured at 60 eV. Column chromatography was performed on Wakogel C-200 (Wako Pure Chemical Industries, Ltd.). Preparative TLC was performed on precoated Si gel 60 $F_{254}$ (0.25 mm thickness) plates (Merck).

**Plant Material.** *S. cepharantha* was cultivated at Yasato-machi, Ibaraki Prefecture, in Japan, and the seeds were collected in October 1980. A voucher specimen was deposited at the research laboratory of Kaken Shoyaku Co., Ltd.

**Extraction and Isolation.** Dried and crushed seeds of *S. cepharantha* (1.07 kg) were extracted exhaustively with hot *n*-hexane (15 L), then with hot MeOH (15 L). After concentration in vacuo, the residue from *n*-hexane was 252 g, and the MeOH residue was 60 g. The *n*-hexane residue was subjected to column chromatography using *n*-hexane−benzene (1:1), benzene, and MeOH−$CHCl_3$ (1:1) as eluents, to afford fractions of 165 g, 45 g, and 42 g, respectively. The 45-g fraction was subjected to a combination of column chromatography and crystallization to afford dehydrostephanine (**3**, 1.1 g).[4] The 42-g fraction was subjected to a combination of column chromatography, preparative TLC, and crystallization, to give dehydrocrebanine (**4**, 28 mg),[6] stephanine (**5**, 382 mg),[7] crebanine (**6**, 535 mg),[7] (−)-dicentrine (**7**, 56 mg),[8] (−)-roemerine (**8**, 6 mg),[9] (−)-isolaureline (**9**, 10 mg),[10] nuciferine (**10**, 2 mg),[11] stesakine (**11**, 14 mg),[6] and *N*-methylasimilobine (**12**, 42 mg).[11] The MeOH residue was dissolved in 5% HCl. After filtration of insoluble materials, the solution was washed with $Et_2O$. The aqueous layer was then adjusted to pH 10 with $NH_4OH$ and extracted successively with $Et_2O$ and $CHCl_3$, to afford fractions **A** (142 mg) and **B** (144 mg), respectively. Fraction **A** was subjected to column chromatography using 1%, 5%, and 20% MeOH−$CHCl_3$ as eluents to give fractions of 55 mg, 51 mg, and 38 mg, respectively. The first fraction (55 mg) was separated by preparative TLC to yield **6** (8 mg), **11** (18 mg), cepharanthine (4 mg),[14] and isotetrandrine (5 mg).[16] The 51-mg fraction was also purified by preparative TLC to afford **12** (18 mg), (−)-cassythicine (**13**, 4 mg),[12] pronuciferine (**14**, 2 mg),[13] cepharanoline (3 mg),[15] and berbamine (12 mg).[17] The final fraction (38 mg) was separated by preparative TLC [with EtOAc−MeOH (1:2)] to afford stesakine-9-*O*-*β*-D-glucopyranoside (**1**, 5 mg) and *N*-methylasimilobine-2-*O*-*β*-D-glucopyranoside (**2**, 10 mg). Fraction **B** was subjected to column chromatography using 3%, 20%, and 50% MeOH−$CHCl_3$ and final purification by preparative TLC [with EtOAc−MeOH (1:2)] to afford **1** (25 mg) and **2** (30 mg).

The structures of known alkaloids **3**−**14** were confirmed by comparison of the spectroscopic data with published values and from the results of 2D NMR experiments; the other known alkaloids were identified by direct comparison of the spectroscopic data with those of authentic samples isolated previously.[1]

**Stesakine-9-*O*-*β*-D-glucopyranoside** (**1**): amorphous powder; $[\alpha]^{27}_D$ −74.5° (*c* 0.20, MeOH); IR (KBr) $\nu_{max}$ 3400, 1604, 1577, 1493, 1408, 1389, 1236, 1076, 1036 cm$^{-1}$; $^1$H NMR (pyridine-$d_5$, 500 MHz) *δ* 6.60 (s, H-3), 2.51 (ddd, *J* = 16.2, 3.7, 1.2 Hz, H-4), 3.12 (ddd, *J* = 16.2, 10.7, 5.5 Hz, H-4), 2.39 (ddd, *J* = 11.6, 10.7, 3.7 Hz, H-5), 2.94 (ddd, *J* = 11.6, 5.5, 1.2 Hz, H-5), 3.08 (dd, *J* = 13.7, 4.3 Hz, H-6a), 2.48 (dd, *J* = 13.7, 13.7 Hz, H-7), 3.91 (dd, *J* = 13.7, 4.3 Hz, H-7), 7.71 (d, *J* = 8.6 Hz, H-10), 8.01 (d, *J* = 8.6 Hz, H-11), 5.98 (d, *J* = 1.2 Hz, $OCH_2O$), 6.11 (d, *J* = 1.2 Hz, $OCH_2O$), 2.48 (s, *N*-$CH_3$), 4.01 (s, 8-$OCH_3$), 5.71 (d, *J* = 7.3 Hz, H-1′), 4.38 (m, H-2′), 4.38 (m, H-3′), 4.35 (m, H-4′), 4.19 (ddd, *J* = 8.9, 5.5, 2.1 Hz, H-5′), 4.42 (dd, *J* = 11.9, 5.5 Hz, H-6′), 4.60 (dd, *J* = 11.9, 2.1 Hz, H-6′); $^{13}$C NMR (pyridine-$d_5$, 125 MHz) *δ* 142.7 (s, C-1), 147.12 (s, C-2), 107.4 (d, C-3), 127.32 (s, C-3a), 29.6 (t, C-4), 53.9 (t, C-5), 62.47 (d, C-6a), 27.5 (t, C-7), 130.3 (s, C-7a), 147.07 (s, C-8), 151.2 (s, C-9), 115.4 (d, C-10), 123.8 (d, C-11), 126.3 (s, C-11a), 116.9 (s, C-11b), 127.25 (s, C-11c), 101.1 (t, $OCH_2O$), 44.0 (q, *N*-$CH_3$), 61.0 (q, 8-$OCH_3$), 102.7 (d, C-1′), 75.0 (t, C-2′), 78.8 (t, C-3′), 71.3 (t, C-4′), 79.1 (t, C-5′), 62.45 (t, C-6′); NOESY H-3−H-4; *N*-$CH_3$−H-5, -6a, -7; H-7−8-$OCH_3$; H-1′−H-10, -3′, -5′; COLOC H-3 → C-1, -4, -11c; H-5 → C-3a, -6a; H-7 → C-8, -11a, -11c; H-10 → C-8, -11a; H-11 → C-7a, -9; $OCH_2O$ → C-1, -2, *N*-$CH_3$ → C-5, -6a; 8-$OCH_3$ → C-8; H-1′ → C-9; EIMS *m*/*z* 487 $[M]^+$ (7), 485 (8), 325 (64), 324 (100), 308 (19), 282 (34), 280 (10), 267 (6), 264 (7), 251(7); positive FABMS *m*/*z* 488 $[M + H]^+$; positive HRFABMS *m*/*z* 488.1935 $[M + H]^+$ (calcd for $C_{25}H_{30}NO_9$, 488.1920).

***N*-Methylasimilobine-2-*O*-*β*-D-glucopyranoside** (**2**): amorphous powder; $[\alpha]^{27}_D$ −116.1° (*c* 0.60, MeOH); IR (KBr) $\nu_{max}$ 3400, 1595, 1573, 1496, 1425, 1371, 1254, 1074, 1045 cm$^{-1}$; $^1$H NMR (pyridine-$d_5$, 500 MHz) *δ* 7.39 (s, H-3), 2.50 (dd, *J* = 17.7, 3.4 Hz, H-4), 3.11 (ddd, *J* = 17.7, 11.9, 5.5 Hz, H-4), 2.23 (ddd, *J* = 11.9, 11.6, 3.4 Hz, H-5), 2.84 (dd, *J* = 11.6, 5.5 Hz, H-5), 2.96 (dd, *J* = 13.7, 4.0 Hz, H-6a), 2.75 (dd, *J* = 13.7, 13.7 Hz, H-7), 3.21 (dd, *J* = 13.7, 4.0 Hz, H-7), 7.38 (d, *J* = 7.6 Hz, H-8), 7.31 (dd, *J* = 7.6, 7.6 Hz, H-9), 7.42 (dd, *J* = 7.9, 7.6 Hz, H-10), 8.70 (d, *J* = 7.9 Hz, H-11), 2.41 (s, *N*-$CH_3$), 3.93 (s, 1-$OCH_3$), 5.64 (d, *J* = 7.0 Hz, H-1′), 4.38 (m, H-2′), 4.37 (m, H-3′), 4.31 (m, H-4′), 4.16 (ddd, *J* = 7.6, 5.5, 2.1 Hz, H-5′), 4.40 (dd, *J* = 11.9, 5.5 Hz, H-6′), 4.62 (dd, *J* = 11.9, 2.1 Hz, H-6′); $^{13}$C NMR (pyridine-$d_5$, 125 MHz) *δ* 146.1 (s, C-1), 151.2 (s, C-2), 116.1 (d, C-3), 129.6 (s, C-3a), 29.6 (t, C-4), 53.5 (t, C-5), 62.9 (d, C-6a), 35.4 (t, C-7), 137.3 (s, C-7a), 128.6 (s, C-8), 127.8 (s, C-9), 127.3 (d, C-10), 128.8 (d, C-11), 132.9 (s, C-11a), 127.2 (s, C-11b), 129.9 (s, C-11c), 44.0 (q, *N*-$CH_3$), 60.7 (q, 1-$OCH_3$), 102.4 (d, C-1′), 75.0 (t, C-2′), 78.9 (t, C-3′), 71.4 (t, C-4′), 79.1 (t, C-5′), 62.6 (t, C-6′); NOESY H-3−H-4; *N*-$CH_3$−H-5, -6a, -7; H-7−H-8, H-10−H-11; H-11−1-$OCH_3$; H-1′−H-3, -3′, -5′; HMBC H-3 → C-1, -4, -11c; H-5 → C-3a, -6a; H-7 → C-11a, -11c; H-8 → C-7, C-10, -11a; H-9 → C-7a, -11; H-10 → C-8, -11a; H-11 → C-7a, -9; 1-$OCH_3$ → C-1; *N*-$CH_3$ → C-5, -6a; H-1′ → C-2, -5′; EIMS *m*/*z* 443 $[M]^+$ (36), 281 (73), 280 (100), 266 (50), 250 (31), 249 (29), 238 (25), 178 (18), 165 (20); positive FABMS *m*/*z* 444

$[M + H]^+$; positive HRFABMS *m/z* 444.2010 $[M + H]^+$ (calcd for $C_{24}H_{30}NO_7$, 444.2022).

**Stesakine** (**11**): mp 160−161° (MeOH); $[\alpha]^{27}_D$ −89.8° (*c* 0.60, $CHCl_3$); IR (KBr) $\nu_{max}$ 3400, 1604, 1583, 1496, 1388, 1296, 1234, 1039 $cm^{-1}$; $^1H$ NMR (pyridine-$d_5$, 500 MHz) $\delta$ 6.60 (s, H-3), 2.52 (m, H-4), 3.12 (m, H-4), 2.40 (ddd, $J$ = 12.1, 11.9, 4.0 Hz, H-5), 2.94 (ddd, $J$ = 11.9, 5.8, 1.2 Hz, H-5), 3.11 (dd, $J$ = 13.7, 4.3 Hz, H-6a), 2.54 (dd, $J$ = 14.3, 13.7 Hz, H-7), 3.91 (dd, $J$ = 13.4, 4.3 Hz, H-7), 7.30 (d, $J$ = 8.6 Hz, H-10), 8.07 (d, $J$ = 8.6 Hz, H-11), 6.00 (d, $J$ = 1.2 Hz, $OCH_2O$), 6.11 (d, $J$ = 1.2 Hz, $OCH_2O$), 2.50 (s, *N*-$CH_3$), 3.89 (s, 8-$OCH_3$), 11.69 (br s, 9-OH); $^{13}C$ NMR (pyridine-$d_5$, 125 MHz) $\delta$ 142.4 (s, C-1), 147.1 (s, C-2), 106.9 (d, C-3), 127.3 (s, C-3a), 29.7 (t, C-4), 53.9 (t, C-5), 62.6 (d, C-6a), 27.8 (t, C-7), 130.4 (s, C-7a), 145.8 (s, C-8), 151.3 (s, C-9), 115.8 (d, C-10), 124.40 (d, C-11), 124.40 (s, C-11a), 117.6 (s, C-11b), 127.6 (s, C-11c), 101.0 (t, $OCH_2O$), 44.1 (q, *N*-$CH_3$), 60.5 (q, 8-$OCH_3$); EIMS *m/z* 325 $[M]^+$ (67), 324 (100), 308 (68), 282 (30), 280 (34), 267 (12), 264 (17), 251 (15), 222 (14); HRMS *m/z* 325.1313 (calcd for $C_{19}H_{19}NO_4$, 325.1313).

***N*-Methylasimilobine** (**12**): mp 195−197° (EtOAc); $[\alpha]^{27}_D$ −211.2° (*c* 0.66, $CHCl_3$); IR 3400, 1610, 1589, 1570, 1496, 1471, 1452, 1423, 1373, 1298, 1273, 1242, 1173, 1142 $cm^{-1}$; $^1H$ NMR (pyridine-$d_5$, 500 MHz) $\delta$ 7.01 (s, H-3), 2.57 (dd, $J$ = 17.1, 3.4 Hz, H-4), 3.14 (ddd, $J$ = 17.1, 11.9, 4.9 Hz, H-4), 2.36 (ddd, $J$ = 11.9, 11.6, 3.4 Hz, H-5), 2.90 (dd, $J$ = 11.6, 4.9 Hz, H-5), 3.01 (dd, $J$ = 13.7, 3.7 Hz, H-6a), 2.78 (dd, $J$ = 13.7, 13.7 Hz, H-7), 3.22 (dd, $J$ = 13.7, 3.7 Hz, H-7), 7.40 (d, $J$ = 7.3 Hz, H-8), 7.32 (dd, $J$ = 7.6, 7.3 Hz, H-9), 7.43 (dd, $J$ = 8.2, 7.6 Hz, H-10), 8.72 (d, $J$ = 8.2 Hz, H-11), 2.43 (s, *N*-$CH_3$), 3.73 (s, 1-$OCH_3$), 11.18 (br s, 2-OH); $^{13}C$ NMR (pyridine-$d_5$, 75 MHz) $\delta$ 145.0 (s, C-1), 150.9 (s, C-2), 116.6 (d, C-3), 130.1 (s, C-3a), 29.5 (t, C-4), 53.7 (t, C-5), 63.0 (d, C-6a), 35.6 (t, C-7), 137.3 (s, C-7a), 128.7 (d, C-8), 127.7 (d, C-9), 127.4 (d, C-10), 128.3 (d, C-11), 133.2 (s, C-11a), 126.9 (s, C-11b), 127.5 (s, C-11c), 44.1 (q, *N*-$CH_3$), 60.00 (q, 1-$OCH_3$); EIMS *m/z* 281 $[M]^+$ (100), 280 (69), 266 (37), 265 (37), 264 (29), 250 (39), 248 (22), 238 (19), 223 (14), 220 (14), 178 (29), 165 (19); HRMS *m/z* 281.1398 (calcd for $C_{18}H_{19}NO_2$, 281.1413).

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