# Synthesis of (−)-8a-*epi*-Swainsonine, (1*S*,2*R*,8*R*,8a*S*)-Octahydro-1,2,8-indolizinetriol

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(−)-8a-*epi*-Swainsonine (**4**), one of the stereocongeners of physiologically interesting indolizidine alkaloid (−)-swainsonine (**1**), has been synthesized starting from known methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside. The α-D-mannosidase inhibitory activity of **4** was compared with natural **1**.

Swainsonine (**1**), which was isolated from some plants[1-3] and a microorganism,[4] is a novel indolizidine alkaloid. This alkaloid exhibits remarkable physiological effects such as an α-D-mannosidase inhibitory activity and immunoregulating activity.[5] The structure of **1** including absolute configuration was established by Harris and coworkers to be (1*S*, 2*R*, 8*R*, 8a*R*)-octahydro-1,2,8-indolizinetriol.[3] Owing to this structural novelty and the interesting physiological effects of **1**, extensive efforts have been made toward the total synthesis of **1**[6] and its stereocongeners.[7] After completion of the total synthesis of **1**,[6a] we have synthesized two stereocongeners of **1**, namely (−)-8-*epi*-(**2**) and (−)-1,8-di*epi*-swainsonine (**3**), from 3-amino-3-deoxy-D-glucose and -D-galactose derivatives.[8] Herein, we wish to describe a synthesis of another stereocongener, (−)-8a-*epi*-swainsonine (**4**), from readily available methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (**6**).[9]

Compound **4** was retro-synthesized to an azido group containing α,β-unsaturated ester (**5**-*E* and **5**-*Z*) by twice C-N bond disconnection as shown in Scheme 1. Hydrogenation of the both geometrical isomers **5** would give a disubstituted 2-piperidinone **13** via a 5-aminooctanoic acid ethyl ester **12**, which tends to cyclize simultaneously resulting a δ-lactam formation. The 2-indolizinone formation of **13** would be achieved by introduction of a suitable leaving group at the primary hydroxyl group in an intramolecular *N*-alkylation fashion. Reduction of the amido group in the resulting **14** would give 1,8-di-*O*-benzylated 8a-*epi*-swainsonine (**15**) and deprotection of **15** would furnish the desired **4**.

The configurations of the four continuous chiral centers in **5** are corresponding to those of C-2 to C-5 of 3-azido-3-deoxy-D-altrose. Therefore, our synthesis of

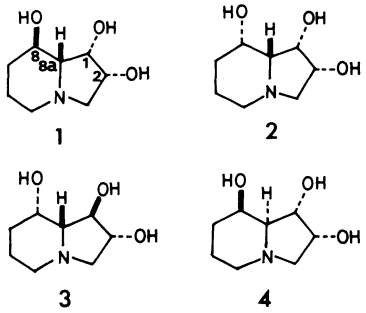
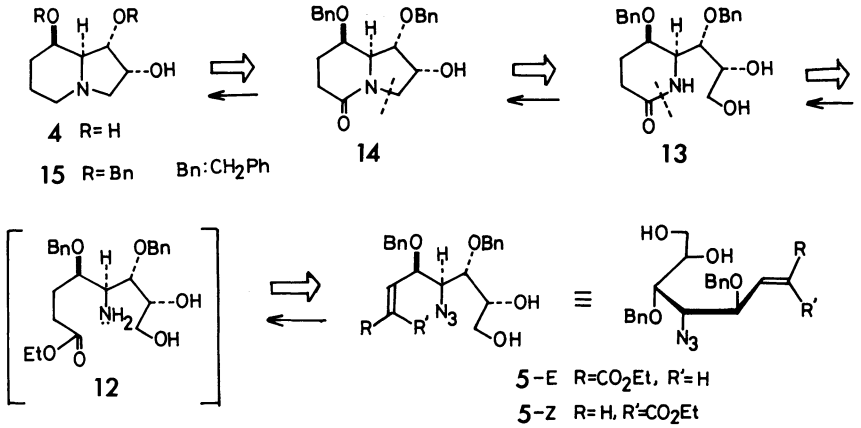



Fig. 1.




Scheme 1.

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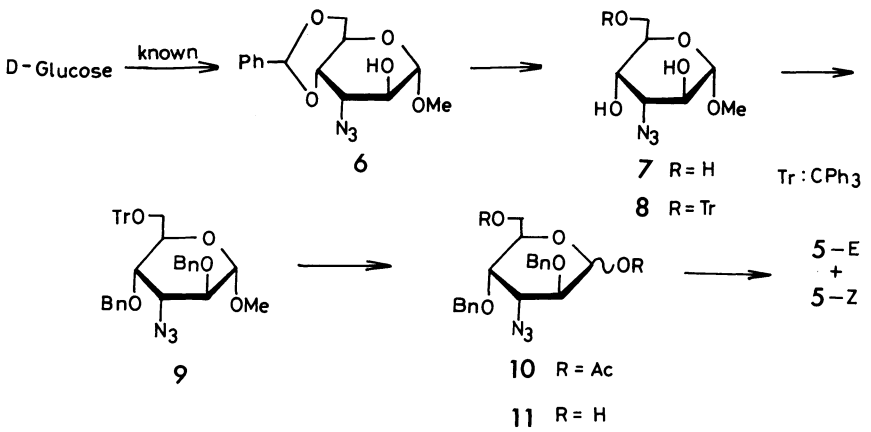


Scheme 2.

**4** was started from the known 3-azido sugar **6**, which was readily prepared by regioselective diaxial epoxy ring opening of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[10] (Scheme 2). Hydrolysis of **6** in 50% aqueous acetic acid at 100 °C gave *O*-debenzylidene derivative **7**, and the primary hydroxyl group in **7** was preferentially protected as a trityl ether by treatment with trityl chloride in pyridine in the presence of 4-(dimethylamino)pyridine to provide 6-*O*-trityl derivative **8** in 82% yield. *O*-Benzylation of **8** with excess benzyl bromide in the presence of sodium hydride gave 2,4-di-*O*-benzyl derivative **9** in 94% yield. Acetolysis of **9** in acetic anhydride in the presence of a catalytic amount of sulfuric acid at 0 °C gave an anomeric mixture of **10** in 80% combined yield. The anomeric mixture **10** was *O*-deacetylated with sodium methoxide to provide an anomeric mixture **11**, which was subjected to Wittig olefination for a two-carbon elongation. Treatment of the mixture **11** with (ethoxycarbonylmethylene)triphenylphosphorane in refluxing benzene gave a mixture of ***E***- and ***Z***-α,β-unsaturated esters **5-*E*** and **5-*Z***, which was separated by chromatography on silica gel, in 54% combined yield. The geometrical stereochemistry of each compound was determined by the $^1$H NMR spectrum. In the $^1$H NMR of **5-*E***, H-3 (α-olefinic proton of the α,β-unsaturated ester) appeared at δ 6.91 as a double doublet with $J_{2,3}$=18 Hz and $J_{3,4}$=7 Hz supporting a trans geometry of the double bond. On the other hand, H-3 of **5-*Z*** appeared at δ 6.33 as a double doublet with $J_{2,3}$=12 Hz and $J_{3,4}$=8 Hz. The ratio of **5-*E*** and **5-*Z*** was 10:8.5, and no preferential formation of the ***E***-isomer was observed in this Wittig olefination of **11** by stabilized ylide. As expected, hydrogenation of each **5-*E*** and **5-*Z*** in the presence of Raney nickel gave 2-piperidinone derivative **13** in 67 and 73% yields, respectively. No other products were detected in both reaction mixtures. Next, the intramolecular cyclization of **13** for trisubstituted indolizinone **14** was attempted under several conditions (TsCl in pyridine or MsCl in pyridine). The best result was obtained under *O*-tosylation conditions as follows. A solution of **13** in pyridine was stirred with 3.4 mol equivalent of *p*-toluenesulfonyl chloride, which was added in a five portion at 10 h interval, at 70 to 100 °C in the presence of 4-(dimethylamino)pyridine. Consequently, compound **14** was obtained in 60% yield. When *p*-toluenesulfonyl chloride (3.0 mol equiv) was added to a pyridine solution of **13** all at once, and the mixture was stirred at room temperature for 24 h, compound **14** was obtained in 41% yield along with a further *O*-tosylated product of **14** (30%). No intermediate of the reaction was detected, however, the cyclization seems to proceed via a *O*-tosyl derivative of **13** at the primary hydroxyl group. The *O*-tosyl derivative was attacked by amide nitrogen in **13** instantly. Reduction of **14** with borane-$Me_2S$ complex in THF at room temperature, followed by stirring the product in pyridine gave 1,8-dibenzylated 8a-*epi*-swainsonine **15** in 84% yield. For conversion of the initially formed amine-borane complex to **15**, the pyridine-treatment is essential. *O*-Debenzylation of **15** by hydrogenolysis in the presence of 10% Pd on charcoal, or by treatment with refluxing cyclohexene-ethanol in the presence of 20% $Pd(OH)_2$/C, gave a mono-*O*-benzyl derivative. The structure of the mono-*O*-benzyl derivative was not determined. The complete deprotection was achieved by treatment of **15** with iodotrimethylsilane,[11] and purification of the product by PTLC gave the desired **4** as crystals in 75% yield. The structure of **4** was supported by spectral means (IR, $^1$H and $^{13}$C NMR, and mass spectra). The overall yield from **6** to **4** was 9%.

A preliminary assay of **4** for α-D-mannosidase inhibitory activity was investigated. Against a human α-D-mannosidase, compound **4** exhibits a 93% inhibition at 1 mM concentration at pH 4 (optimal pH value). Under the same conditions, swainsonine **1** shows a 99% inhibition.

## Experimental

**General Procedures.** Reactions were carried out at room temperature unless otherwise stated. Reaction mixture, extract, and fraction of chromatography were concentrated under a reduced pressure below 40 °C with a bath by

an evaporator. Melting points were determined with a Mitamura Riken micro mp apparatus and are uncorrected. Specific rotations were measured in a 10 mm cell with a Jasco DIP-4 polarimeter. Column chromatography was performed on Kieselgel 60 (Merck), and thin-layer chromatography (TLC) was performed on a glass plate coated with Kieselgel 60 $GF_{254}$ (Merck), followed by detection by UV light and charring with sulfuric acid. Preparative TLC (PTLC) was performed on a glass plate (20×20 cm) coated with Kieselgel $PF_{254}$ (Merck). IR spectra were recorded with a Hitachi Model 225 (KBr) or with a Jasco Model A-202 ($CHCl_3$) spectrometer. $^1H$ NMR spectra were recorded with a Varian EM-390 (90 MHz) spectrometer in $CDCl_3$ solutions with internal tetramethylsilane. $^{13}C$ NMR spectra were recorded with a JEOL FX-200 spectrometer in $CD_3OD$ solution with internal tetramethylsilane. High-resolution mass spectra were obtained using a Hitachi M-80 mass spectrometer.

Pyridine was distilled over NaOH, *N*,*N*-dimethylformamide (DMF) was distilled over $CaH_2$, benzene was distilled over $LiAlH_4$, and tetrahydrofuran (THF) was distilled over $LiAlH_4$ and then over sodium-benzophenone.

**Methyl 3-Azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (6).** This compound was prepared according to the reported pocedure.[10] **6**: Mp 133—134 °C; lit,[10] mp 135—136 °C; $[\alpha]_D^{21}$ +34.2° (*c* 0.85, $CHCl_3$); lit,[10] $[\alpha]_D^{18}$ +37.9° (*c* 1.00, $CHCl_3$).

**Methyl 3-Azido-3-deoxy-6-*O*-trityl-α-D-altropyranoside (8).** A solution of **6** (2.02 g, 6.56 mmol) in 50% aqueous acetic acid (10 ml) was stirred at 100 °C for 90 min, and diluted with ethyl acetate (60 ml). The solution was extracted with water (50 ml×4), and the combined aqueous layers were concentrated with ethanol. The residue, which consisted of *O*-debenzylidene derivative **7**, was dissolved in pyridine (10 ml) and trityl chloride (4.58 g, 16.4 mmol) and 4-(dimethylamino)-pyridine (0.16 g, 1.31 mmol) were added. The mixture was stirred at 70 °C for 150 min and concentrated with toluene. The residue was partitioned between dichloromethane (60 ml) and water (60 ml). The aqueous layer was extracted with dichloromethane (60 ml×3). The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was chromatographed on silica gel (180 g, ethyl acetate-hexane=1 : 4 containing 1% triethylamine), and the fraction corresponding to $R_f$ 0.53 (ethanol-toluene=1 : 5) was concentrated to give **8** (2.48 g, 82%) as a colorless syrup. **8**: $[\alpha]_D^{27}$ +31.5° (*c* 1.35, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3760, 2950, 2130, 1460, 1270 $cm^{-1}$; $^1H$ NMR δ=2.32—2.63 (2H, m, 2×OH), 3.36—3.41 (2H, m, H-6, 6′), 3.43 (3H, s, $OCH_3$) 3.68—4.09 (4H, m, H-2,3,4,5), 4.56 (1H, d, *J*=2.5 Hz, H-1), 7.16—7.55 (15H, m, $C(C_6H_5)_3$). Found: C, 67.39; H, 5.92; N, 8.84%. Calcd for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10%.

**Methyl 3-Azido-2,4-di-*O*-benzyl-3-deoxy-6-*O*-trityl-α-D-altropyranoside (9).** Sodium hydride (60% emulsion in mineral oil, 967 mg, 24.2 mmol) was washed with hexane (2 ml×4), dried and suspended in DMF (8 ml). To the suspension was added a DMF solution (8 ml) of **8** (2.48 g, 5.37 mmol), and the mixture was stirred at 0 °C for 15 min. Benzyl bromide (2.88 ml, 24.2 mmol) was added to the mixture, and stirred for 19 h. The excess base was destroyed by addition of ethanol. After concentration of the mixture, the residue was partitioned between dichloromethane (80 ml) and water (80 ml). The aqueous layer was extracted with dichloromethane (80 ml×3). The combined extracts were dried over $Na_2SO_4$ and concentrated. The residue was chromatographed on silica gel (hexane containing 1% triethylamine), and the fraction corresponding to $R_f$ 0.74 (ethyl acetate-hexane=1 : 5) was concentrated to give **9** (3.24 g, 94%) as a colorless syrup. 9: $[\alpha]_D^{27.5}$ +28.4° (*c* 0.98, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3060, 3000, 2930, 2110, 1490, 1450, 1260 $cm^{-1}$; $^1H$ NMR δ=3.00—3.38 (2H, m, H-6,6′), 3.42 (3H, s, $OCH_3$), 3.57—4.28 (4H, m, H-2,3,4,5), 4.33—4.77 (5H, m, H-1, 2×$OC\underline{H}_2C_6H_5$), 6.98—7.67 (25H, m, 2×$OCH_2C_6\underline{H}_5$, $C(C_6H_5)_3$).

**Anomeric Mixture of 1,6-Di-*O*-acetyl-3-azido-2,4-di-*O*-benzyl-3-deoxy-D-altropyranose (10)** To a solution of **9** (1.91 g, 2.87 mmol) in acetic anhydride (16 ml) was added concd sulfuric acid (0.3 ml), and the solution was stirred for 2 h at 0 °C. The solution was diluted with water (90 ml) and extracted with dichloromethane (90 ml×3). The extract was washed with 10% aqueous $NaHCO_3$ (50 ml×2), dried over $Na_2SO_4$ and concentrated. The residue was acetylated with acetic anhydride (5 ml) in pyridine (10 ml) for 1 h. After concentration of the mixture with toluene, the residue was chromatographed on silica gel (150 g, ethyl acetate-hexane=1 : 8). The fractions corresponding to $R_f$ 0.40 and 0.31 (ethyl acetate-hexane=1 : 5) were combined and concentrated to give **10** (1.12 g, 80%) as a colorless syrup. IR $\nu_{max}^{CHCl_3}$ 3000, 2920, 2870, 2120, 1735 1450, 1370 $cm^{-1}$; $^1H$ NMR δ=1.98, 2.00, 2.06, 2.07 (total 6H, each s, 2×$OCOCH_3$), 3.60—4.85 (10H, m, H-2,3,4,5,6,6′, 2×$OC\underline{H}_2C_6H_5$), 6.00, 6.03 (total 1H, each d, *J*=2.5 Hz, H-1), 7.35 (10H, s, 2×$OCH_2C_6\underline{H}_5$). Found: C, 61.24; H, 5.87; N, 8.86%. Calcd for $C_{24}H_{27}N_3O_7$: C, 61.40; H, 5.80; N, 8.95%.

**Ethyl (*E*)- and (*Z*)-5-Azido-4,6-di-*O*-benzyl-2,3,5-trideoxy-altro-2-octenonate, (5-*E*) and (5-*Z*).** To a solution of **10** (1.94 g, 4.13 mmol) in dichloromethane (15 ml) was added sodium methoxide (1 mol $dm^{-3}$ in methanol, 9.08 ml, 9.08 mmol) at 0 °C with stirring. After stirring at 0 °C for 30 min, the solution was neutralized with Amberlite IR-120B ($H^+$). The resin was removed by filtration, washed with methanol, and the combined filtrate and washing were concentrated to give crude **11** ($R_f$ 0.03, ethyl acetate-hexane=1 : 3) as a syrup. To a benzene solution (14 ml) of the crude **11** was added (ethoxycarbonylmethylene)triphenylphosphorane (3.60 g, 10.5 mmol), and the mixture was refluxed for 2 h, and then concentrated. The residue was chromatographed on silica gel (120 g, ethyl acetate-hexane=1 : 4). The fraction corresponding to $R_f$ 0.23 (ethyl acetate-hexane=1 : 2) was concentrated to give **5-*Z*** (410 mg, 22%), and the fraction corresponding to $R_f$ 0.19 was concentrated to give **5-*E*** (511 mg, 27%). A mixture of **5-*Z*** and **5-*E*** was obtained (99 mg; total **5-*Z*** and **5-*E***, 1.02 g, 54%). **5-*E*** as a colorless syrup: $[\alpha]_D^{20}$ −14.7° (*c* 1.06, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2925, 2870, 2100, 1720, 1450, 1365, 1300, 1270, 1175 $cm^{-1}$; $^1H$ NMR δ=1.27 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.46—4.05 (8H, m, H-4,5,6,7,8,8′,2×OH), 4.22 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.38—4.75 (4H, m, 2×$OC\underline{H}_2C_6H_5$), 6.12 (1H, d, *J*=18 Hz, H-2), 6.91 (1H, dd, *J*=18 and 7 Hz, H-3), 7.34 (10H, s, 2×$OCH_2C_6\underline{H}_5$). **5-*Z*** as a colorless syrup: $[\alpha]_D^{20}$ −64.1° (*c* 1.13, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2930, 2110, 1710, 1455, 1410, 1385, 1190 $cm^{-1}$; $^1H$ NMR δ=1.27 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 3.00—3.42 (1H, br, OH), 3.58—4.38 (6H, m, H-5,6,7,8,8′, OH), 4.18 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.40—4.74 (4H, m, 2×$OC\underline{H}_2C_6H_5$), 5.40 (1H, dd, *J*=8 and 4 Hz, H-4), 6.04 (1H, d, *J*=12 Hz, H-2), 6.33 (1H, dd, *J*=12 and 8 Hz, H-3), 7.48 (10H, s, 2×$OCH_2C_6\underline{H}_5$). Found: C, 63.00; H, 6.61; N, 9.07%. Calcd for $C_{24}H_{29}N_3O_6$ (as a mixture of **5-*E*** and **5-*Z***): C, 63.28; H, 6.42; N, 9.23%.

**(5*R*,6*S*)-5-Benzyloxy-6-[(1*S*,2*R*)-1-benzyloxy-2,3-dihydroxypropyl]-2-piperidinone (13).** From compound **5-*E***. A solution of **5-*E*** (170 mg, 0.37 mmol) in ethanol (10 ml) was hydrogenated in the presence of Raney nickel T-4 under an atmospheric hydrogen pressure for 15 h. After removal of the catalyst with a Celite pad and washing with ethanol, the combined filtrate and washing were concentrated. The residue was chromatographed on silica gel (15 g, ethanol-toluene=1 : 10), and the fraction corresponding to $R_f$ 0.34 (ethanol-toluene=1 : 5) was concentrated to give **13** (96 mg, 67%) as crystals. **13**: Mp 145—146 °C; $[\alpha]_D^{27}$ −87.9° (*c* 1.00, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3400, 3290, 2910, 1640, 1620, 1470, 1450, 1390, 1325, 1295, 1270, 1210 $cm^{-1}$; $^1H$ NMR $\delta$=1.50—2.58 (4H, m, H-3,3′,4,4′), 3.48—4.30 (8H, m, H-5,6, H-1,2,3,3′ of the side chain, 2×OH), 4.32—4.82 (4H, m, 2×OC$\underline{H}_2$C$_6$H$_5$), 7.33 (10H, s, 2×OCH$_2$C$_6\underline{H}_5$), 8.04 (1H, s, NH). High-resolution mass spectrum, Found: *m/z* 385.1884, Calcd for $C_{22}H_{27}NO_5$: M, 385.1887. Found: C, 68.32; H, 7.03; N, 3.45%. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.68%. From compound **5-*Z***. Hydrogenation of **5-*Z*** (402 mg) and purification on silica gel as described in the case of **5-*E*** gave **13** (204 mg, 73%).

**(1*S*,2*R*,8*R*,8a*S*)-1,8-Bis(benzyloxy)-2-hydroxyoctahydro-5-indolizinone (14).** To a solution of **13** (68 mg, 0.16 mmol) in pyridine (3 ml) were added *p*-toluenesulfonyl chloride (24 mg) and 4-(dimethylamino)pyridine (4 mg). The mixture was stirred at 70 °C for 3 h, then at 100 °C. *p*-Toluenesulfonyl chloride was added after 25 h (18 mg), 40 h (30 mg), 50 h (15 mg), and 74 h (15 mg), successively. 4-(Dimethylamino)pyridine (4 mg) was added also after 44 h. The mixture was stirred at room temperature additional 41 h. The mixture was concentrated with toluene. The residue was partitioned between dichloromethane (20 ml) and water (20 ml), and the aqueous layer was extracted with dichloromethane (20 ml×2). The combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was chromatographed on silica gel (10 g, ethanol-toluene=1 : 40), and the fraction corresponding to $R_f$ 0.43 (ethanol-toluene=1 : 5) was concentrated to give **14** (37.5 mg, 60%) as crystals. **14**: Mp 88—90 °C; $[\alpha]_D^{22}$ −78.4° (*c* 1.01, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3540, 3000, 2875, 1630, 1455, 1370, 1355, 1325, 1295, 1090 $cm^{-1}$; $^1H$ NMR $\delta$=1.66—2.49 (4H, m, H-6,6′,7,7′), 2.53—2.84 (1H, OH), 3.38—3.82 (3H, m, H-3,3′, 8a), 3.84—4.29 (3H, m, H-1,2,8), 4.30—4.72 (4H, m, 2×OC$\underline{H}_2$C$_6$H$_5$), 7.10—7.58 (10H, m, 2×OCH$_2$C$_6\underline{H}_5$). High-resolution mass spectrum, Found: *m/z* 367.1776, Calcd for $C_{22}H_{25}NO_4$: M, 367.1781. Found: C, 68.38; H, 6.97; N, 3.48%. Calcd for $C_{22}H_{25}NO_4 \cdot H_2O$: C, 68.56; H, 7.06; N, 3.63%.

**(1*S*,2*R*,8*R*,8a*S*)-1,8-Di-*O*-benzyloctahydro-1,2,8-indolizinetriol (15).** To a solution of **14** (20.1 mg, 0.055 mmol) in THF (2 ml) was added borane-$Me_2S$ complex (10 mol $dm^{-3}$ in $BH_3$, 0.02 ml, 0.2 mmol) at 0 °C with stirring. The mixture was stirred at room temperature for 3 h, and then water (8 ml) was added. The aqueous solution was extracted with dichloromethane (15 ml×5), and the extract was washed with water (7 ml). The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was dissolved in pyridine (2 ml) and the solution was stirred for 17 h. After the mixture was concentrated, the residue was chromatographed on silica gel (ethyl acetate-hexane=1 : 2, then ethanol-toluene=1 : 20). The fraction corresponding to $R_f$ 0.45 (ethanol-toluene=1 : 3) was concentrated to give **15** (16.3 mg, 84%) as a colorless syrup. **15**: $[\alpha]_D^{22}$ −61.1° (*c* 0.97, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2875, 1480, 1435, 1340, 1305, 1220, 1195 $cm^{-1}$; $^1H$ NMR $\delta$=1.06—2.25 (7H, m, H-3,5,6,6′,7,7′,8a), 2.30—2.72 (1H, br s, OH), 2.87—3.21 (1H, m, H-5′), 3.48 (1H, dd, *J*=11 and 7 Hz, H-3′), 3.35—4.73 (7H, m, H-1,2,8,2×OC$\underline{H}_2$C$_6$H$_5$), 7.12—7.64 (10H, m, 2×OCH$_2$C$_6\underline{H}_5$). High-resolution mass spectrum, Found: *m/z* 353.1995, Calcd for $C_{22}H_{27}NO_3$: M, 353.1989.

**(1*S*,2*R*,8*R*,8a*S*)-Octahydro-1,2,8-indolizinetriol, 8a-*epi*-Swainsonine (4).** A solution of **15** (19.5 mg, 0.065 mmol) in chloroform (0.5 ml) in the presence of iodotrimethylsilane (0.09 ml, 0.65 mmol) was stirred in dark for 15 h. To the mixture was added methanol (2 ml), and the solution was stirred for 2 h and concentrated. The residue was partitioned between dichloromethane (10 ml) and water (10 ml), and the organic layer was extracted with water (10 ml). The combined aqueous layers were concentrated. The residue was purified on PTLC (aqueous ammonia-1-butanol-chloroform-ethanol=1 : 4 : 4 : 4), and a ninhydrin positive band ($R_f$ 0.39 on the same solvents) was extracted with methanol to give **4** as crystals (7.2 mg, 75%). Analytical sample was obtained by recrystallization from chloroform. **4**: Mp 122—124 °C (decomp); $[\alpha]_D^{19}$ −64.5° (*c* 0.95, MeOH); IR $\nu_{max}^{KBr}$ 3440, 3320, 2940, 2830, 2820, 1445, 1385, 1345, 1330, 1320, 1240, 1205, 1160, 1130, 1110 $cm^{-1}$; $^1H$ NMR ($D_2O$) $\delta$=1.31—2.40 (6H, m, H-5,6,6′,7,7′,8a), 2.81—3.17 (1H, br s, H-3), 3.22—3.60 (2H, m, H-3′,5′), 3.79—4.48 (3H, m, H-1,2,8). $^{13}C$ NMR $\delta$=20.87, 32.26, 54.10, 62.83, 64.71, 68.18, 70.91, 72.51, High-resolution mass spectrum, Found: *m/z* 173.1050, Calcd for $C_8H_{15}NO_3$: M, 173.1050.

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