Syntheses of (−)-8-*epi*-Swainsonine and (−)-1,8-Di-*epi*-swainsonine, Stereoisomers of Physiologically Interesting Indolizidine Alkaloid, Swainsonine

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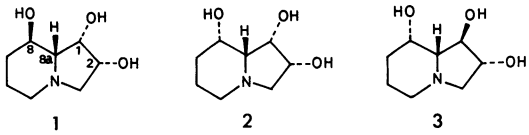
Two stereoisomers of the indolizidine alkaloid swainsonine, (−)-8-*epi*-swainsonine (**2**) and (−)-1,8-di-*epi*-swainsonine (**3**), have been synthesized from the known methyl 3-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside and methyl 3-acetamido-2-*O*-acetyl-3-deoxy-4,6-di-*O*-mesyl-α-D-glucopyranoside (**14**), respectively. The key pyrrolidine ring formation was achieved by intramolecular cyclization of a 6-*O*-tosyl derivative or a di-*O*-mesyl derivative **14** efficiently. The α-mannosidase inhibitory activity of the synthetic **2** and **3** was also evaluated.

(−)-Swainsonine (**1**), (1*S*, 2*R*, 8*R*, 8a*R*)-octahydro-1,2,8-indolizinetriol, is one of the indolizidine alkaloids isolated from *Swainsona canescens*,[1] *Astragalus lentiginosus*,[2] *Rhizoctonia leguminicola*,[3] and *Metarhizium anisopline*[4] (Fig. 1). The structure of **1** was established by chemical and spectral means,[1,3] and the rarely known trihydroxylated octahydroindolizine structure of **1** prompted us to achieve the total synthesis. We have completed the total synthesis of **1** in the natural form from 3-amino-3-deoxy-D-mannose derivative.[5] The total synthesis of **1** has also been achieved by Richardson et al.,[6] Fleet et al.,[7] Takaya et al.,[8] Sharpless et al.,[9] and Hashimoto et al.[10] Meanwhile, the alkaloid **1** was found to exhibit a remarkable physiological effects such as an α-mannosidase inhibitory activity[3] and an immunoregulating activity.[4,11] In order to elucidate a relationship between structure and physiological activity, the synthesis of stereoisomers of **1** is another interesting problem.[12] Recently, we have finished the syntheses of 8-*epi*-swainsonine **2** and 1,8-di-*epi*-swainsonine **3** from readily available 3-amino-3-deoxy-D-glucose derivatives.[13] Herein, we wish to describe details of these syntheses, and the α-mannosidase inhibitory activity of **2** and **3** is also reported.



1 2 3

Fig. 1.

Results and Discussion

The synthesis of **2** was commenced with the known methyl 3-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (**4**)[14] (Fig. 2). The compound **4** possesses all the chiral centers in **2** with correct configurations (the configurations at C-2, 3, 4, and 5 in **4** are corresponding to C-8, 8a, 1, and 2 in **2**, respectively). Hydrolysis of **4** in 50% aqueous acetic acid under reflux, and successive preferential *O*-tosylation of the primary hydroxyl group provided a compound **5** in 83% yield. Intramolecular *N*-alkylation at *N*-3 in **5** (a pyrrolidine ring formation) was achieved smoothly by treatment of **5** with sodium hydride in DMF at 100 °C, and the product was acetylated in the usual manner to afford a bicyclic compound, methyl 2,4-di-*O*-acetyl-3,6-acetylimino-3,6-dideoxy-α-D-glucopyranoside (**6**) in 68% yield. *O*-Deacetylation of **6** with sodium methoxide in methanol, dithioacetal formation with ethanethiol in concd HCl, and successive *O*-benzylation of the diethyl dithioacetal with benzyl bromide in the presence of sodium hydride, furnished a trisubstituted pyrrolidine (**7**) in 59% yield. A two-carbon elongation of **7** for construction of the octahydroindolizine skeleton was accomplished as follows. Dethioacetalization of **7** with mercury(II) chloride in aqueous acetonitrile followed by the Horner-Emmons olefination of the resulting aldehyde with diethyl ethoxycarbonylmethylphosphonate in the presence of sodium hydride provided an (*E*)-α,β-unsaturated ester (**8**) in 82% yield. The (*E*) geometry of the double bond in **8** was established by the ^{1}H NMR spectrum, in which the α-vinyl proton of the α,β-unsaturated ester appeared at δ 6.10 as a double-doublet with J=2 and 15 Hz. No (*Z*)-isomer was detected in the reaction mixture. In the ^{1}H NMR spectrum of **8**, two singlets with totally three protons appeared at δ 1.95 and 2.10 (approximately 3 to 1 ratio) and these signals are attributable to methyl protons of the *N*-acetyl group. This spectral phenomenon is explained by the exsistence of both endo and exo stereoisomers on the trisubstituted nitrogen atom. Some of other trisubstituted pyrrolidine derivatives exhibited the same property in the ^{1}H NMR spectra (see the spectral data of each compound in the Experimental). Catalytic hydrogenation of **8** in the presence of Raney nickel T-4 in ethanol gave a saturated ester (**9**) in 86% yield. Intramolecular cyclization (δ-lactam formation) of the compound **9** to an octahydro-5-indolizinone (**10**) was best accomplished by heating **9** in a mixture of 15 mol dm^{-3} aqueous KOH and ethanol at 120 °C (sealed tube) for 14 d. Under these conditions, the compound **10** was obtained in 40% yield along with an uncyclized carboxylic acid (**11**) in 51% yield. Although a pro-

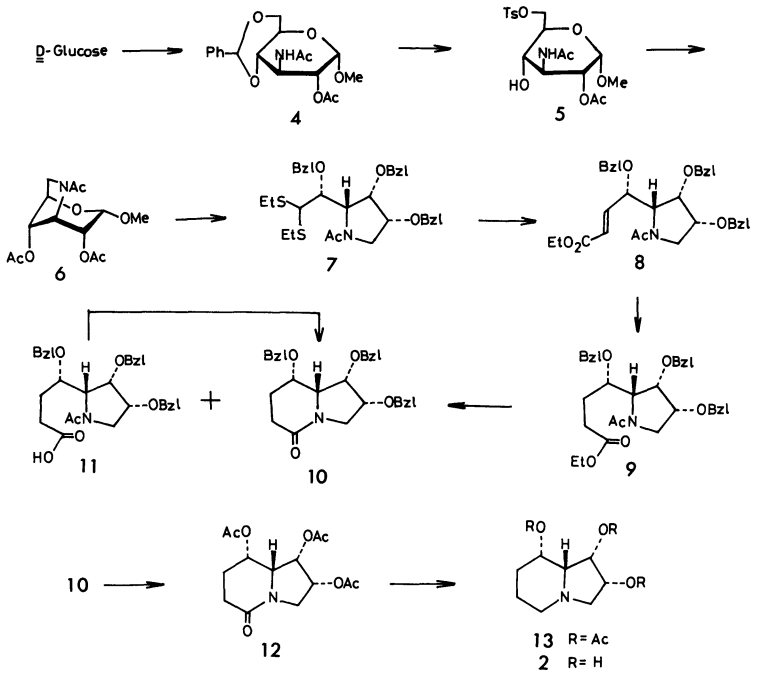


Fig. 2.

longed heating of **9** in the basic solution decreased the yield **10**, the isolated carboxylic acid **11** was converted to **10** in 43% yield by the same conditions. Reduction of the compound **10** to the corresponding octahydroindolizine was a troublesome step. In the case of swainsonine synthesis,[5] the corresponding octahydro-5-indolizinone derivative was smoothly converted to tribenzyloxyswainsonine by lithium aluminium hydride reduction in a high yield. On the contrary, lithium aluminium hydride reduction of **10** in THF gave a complex mixture. The other conditions (BH_3-THF and $NaBH_4$-pyridine-reflux) gave the same disappointing results. We have no rational explanation for this complex reaction. Next, reduction of the *O*-acetyl derivative (**12**) was examined. The compound **12** was prepared by *O*-debenzylation of **10** with cyclohexene in refluxing ethanol in the presence of 20% $Pd(OH)_2$ on charcoal[15] followed by acetylation in 84% yield. Reduction of **12** with borane-dimethyl sulfide complex in THF followed by aqueous $NaHCO_3$ treatment provided 8-*epi*-swainsonine triacetate (**13**) in 64% yield. To convert an intermediate amine-borane complex to **13**, the work-up with $NaHCO_3$ solution was necessary. Deprotection of **13** with K_2CO_3 in methanol, the same conditions employed for *O*-deacetylation of swainsonine triacetate,[5] gave an uncharacterized complex mixture. On the contrary, hydrolysis of **13** in refluxing 1 mol dm^{-3} aqueous HCl followed by deionization with Amberlite IRA-400 (OH^-) afforded 8-*epi*-swainsonine **2** as crystals in 86% yield. The synthetic **2** was fully characterized by the correlation of the ^1H and ^{13}C NMR spectra with those of swainsonine **1**. The optical rotation value of **2** ($[\alpha]_D^{21}=-24.8°$) was somewhat different from the reported value ($[\alpha]_D^{21}=-3.4°$).[12] The $[\alpha]_D^{21}$ of our synthetic compound was determined with a pure crystalline sample, while the reported value[12] was taken with a syrupy compound. Therefore, we believe that our measurement gave the correct $[\alpha]_D^{21}$ value of the compound **2**.

The synthesis of the other stereoisomer **3** was started from the known methyl 3-acetamido-2-*O*-acetyl-3-deoxy-4,6-di-*O*-mesyl-α-D-glucopyranoside (**14**)[16] (Fig. 3). Solvolysis of the compound **14** in refluxing 90% aqueous 2-methoxyethanol in the presence of sodium acetate followed by acetylation, according to the literature,[16] furnished methyl 2,4-di-*O*-acetyl-3,6-acetylimino-3,6-dideoxy-α-D-galactopyranoside (**15**, 68%) accompanied by methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-galactopyranoside (**16**, 27%), which was readily separated by silica-gel chromatography. In contrast to our result, Guthrie and Mutter[16] did not show the isolation of the 3,6-imino compound **15** in their literature. After acetolysis of the solvolytic product, *O*-deacetylation and successive acid hydrolysis, they isolated 3-amino-3-deoxy-D-galactose hydrochloride as a sole product (no yield was given). In our opinions, they would miss accidentally the presence of the compound **15** in the reaction mixture. The D-galacto configuration of **16** was confirmed in the following way. Hydrolysis of **16** in refluxing 2 mol dm^{-3} HCl followed by acetylation gave an anomeric mixture of 3-acetamido-1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-galactopyranose (**17**-α) and (**17**-β), which were readily separated by silica-gel chromatography (**17**-α, 41%; **17**-β, 43%). The α-anomer **17**-α was the known compound,[17] and the melting point and $[\alpha]_D$ value of **17**-α were in accordance with the reported ones. The 3,6-imino structure of the bicyclic compound **15** pos-

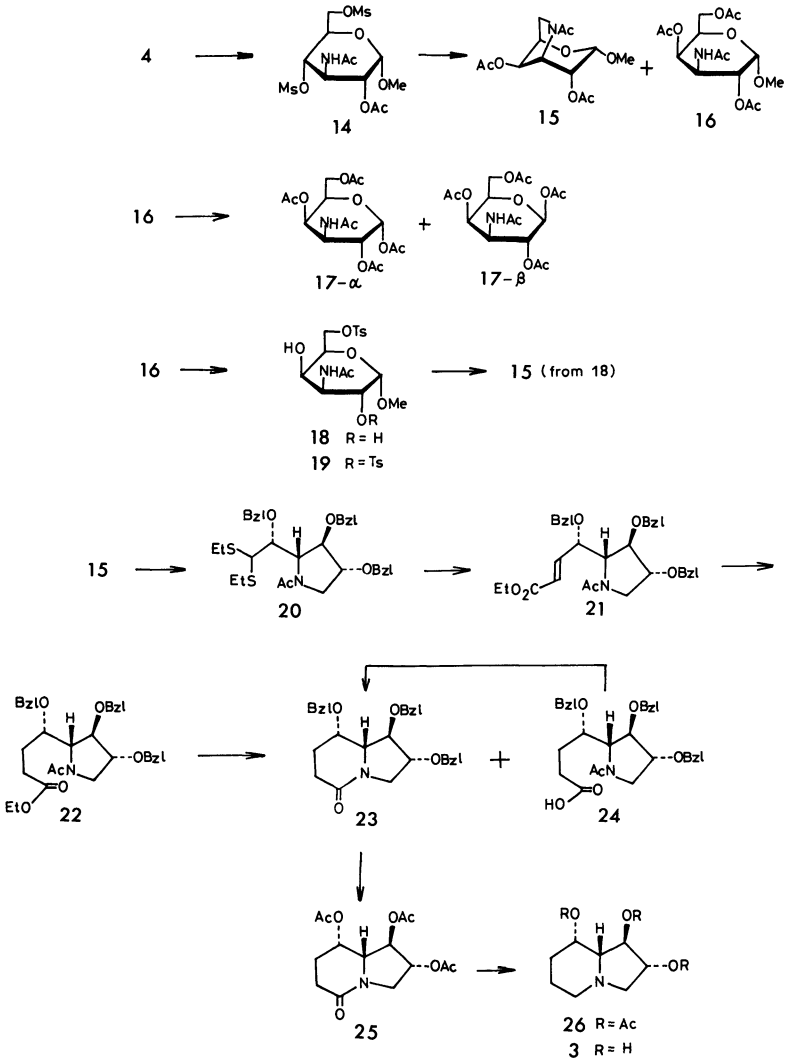


Fig. 3.

sessing D-galacto configuration was established as follows. *O*-Deacetylation of **16** with sodium methoxide in methanol and preferential *O*-tosylation of the primary hydroxyl group in the 2,4,6-triol afforded a 6-*O*-tosyl derivative (**18**) in 32% yield [a 2,6-di-*O*-tosyl derivative (**19**, 12% yield) was accompanied, and 28% of the 2,4,6-triol was recovered]. Treatment of the compound **18** with sodium hydride in DMF at 100 °C for 3,6-imino formation and successive acetylation provided the compound **15** in 56% yield as a sole product. The compound **15** is equipped with the correct configuration of all chiral centers in **3**, and the route from **15** to **3** was virtually the same as in the synthesis of **2** from **6**. *O*-Deacetylation of the compound **15** with sodium methoxide in methanol, diethyl dithioacetal formation with ethanethiol in concd HCl and successive *O*-benzylation afforded a trisubstituted pyrrolidine (**20**) in 56% yield. Dethioacetalization of **20** with mercury(II) chloride in aqueous acetonitrile followed by Horner-Emmons reaction of the aldehyde with diethyl ethoxycarbonylmethylphosphonate gave an (*E*)-α,β-unsaturated ester (**21**) as a sole product in 52% yield. Hydrogenation of **21** in the presence of Raney nickel T-4 provided a saturated ester (**22**) in 86% yield. Intramolecular cyclization of **22** by the treatment with a mixture of 15 mol dm^{-3} aqueous KOH and ethanol in a sealed tube at 120 °C for 10 d furnished a compound (**23**, 34%) and an uncyclized carboxylic acid (**24**, 62%). The compound **24** was converted to **23** in 75% yield by the same base treatment. *O*-Debenzylation of **23** by the Hanessian's condition[15] and successive acetylation afforded compound (**25**) in 83% yield. Reduction of **25** with borane-dimethyl sulfide complex, aqueous $NaHCO_3$ treatment and successive acetylation gave 1,8-di-*epi*-swainsonine triacetate (**26**) in 67% yield. Finally, deprotection of **26** with potassium carbonate in methanol afforded 1,8-di-*epi*-swainsonine **3** in 98% yield. In this case, methanolysis of the *O*-acetyl groups proceeded cleanly under the basic conditions. This newly synthesized compound **3** was fully characterized by the spectral methods (^{13}C and ^{1}H NMR spectra).

The α-mannosidase inhibitory effect of the compounds **2** and **3** was examined at pH 4. Under the conditions, in which swainsonine **1** exhibits a 92%

inhibition, the compounds **2** and **3** exhibit 15 and 20% inhibition, respectively. So the inhibitory effect of **2** and **3** against the enzyme is approximately one-fifth of that of swainsonine.

Experimental

General. Evaporations were performed under diminished pressure at below 40 °C (bath). Melting points were determined with a Mitamura Riken micro apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Jasco DIP-4 polarimeter. Column chromatography was performed on Kieselgel 60 (Merck), and TLC was performed on Kieselgel 60 GF_{254} (Merck) with detection by UV light and charring with sulfuric acid. Preparative TLC was performed on Kieselgel 60 PF_{254} (Merck). IR spectra were recorded with Hitachi Model 225 (KBr) and Jasco A-202 ($CHCl_3$) spectrometers. ^1H NMR spectra were recorded with a Varian EM-390 spectrometer for solutions in $CDCl_3$ (internal standard Me_4Si). ^{13}C NMR spectra were recorded with a JEOL FX-200 spectrometer for solutions in CD_3OD (internal standard Me_4Si). High resolution mass spectra were obtained using a Hitachi M-80 mass spectrometer. Elemental analyses were performed by Mr. Saburo Nakada to whom our thanks are due.

Methyl 3-Acetamido-2-*O*-acetyl-3-deoxy-6-*O*-tosyl-α-D-glucopyranoside (5). A suspension of methyl 3-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (**4**)[14] (10.20 g, 27.9 mmol) in 50% aqueous acetic acid (250 ml) was heated under reflux for 30 min and evaporated. The residue was dissolved in water (400 ml) and the aqueous solution was washed with ethyl acetate (300 ml). After evaporation of the aqueous layer, the residual white solid was dissolved in pyridine (70 ml). To the solution was added *p*-toluenesulfonyl chloride (10.66 g, 55.9 mmol), and the mixture was stirred at 0 °C for 18 h. After evaporation of the mixture, the residue was partitioned between chloroform (200 ml) and water (200 ml). The aqueous layer was extracted with chloroform (200 ml×2), and the combined extracts were dried (Na_2SO_4). After evaporation of the extracts, the residue was chromatographed on SiO_2 (300 g, ethanol: toluene=1 : 20). Fractions corresponding to R_f 0.58 (ethanol: toluene=1 : 3) were evaporated to afford **5** (9.93 g, 83%) as a colorless foam, $[\alpha]_D^{24}$+88.7° (*c* 1.10, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3010, 1740, 1660, 1520, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.97 (3H, s, $NCOCH_3$), 2.10 (3H, s, $OCOCH_3$), 2.47 (3H, s, $OSO_2C_6H_4C\underline{H}_3$), 3.36 (3H, s, OCH_3), 3.40—5.00 (8H, m, H-1, 2, 3, 4, 5, 6, 6′, OH), 6.60 (1H, d, *J*=8 Hz, NH), 7.59 (4H, ABq, *J*=10 Hz, $SO_2C_6\underline{H}_4CH_3$). Found: C, 50.14; H, 5.82; N, 3.09; S, 7.31%. Calcd for $C_{18}H_{25}NO_9S_2$: C, 50.11; H, 5.84; N, 3.25; S, 7.43%.

Methyl 2,4-Di-*O*-acetyl-3,6-acetylimino-3,6-dideoxy-α-D-glucopyranoside (6). To a stirred suspension of sodium hydride (60% emulsion in mineral oil, 1.88 g, 47.0 mmol, washed with hexane; 10 ml×3) in DMF (25 ml) was added a DMF (60 ml) solution of **5** (5.80 g, 13.4 mmol). The mixture was heated at 100 °C for 30 min with stirring, and ethanol (10 ml) was added. After evaporation of the resulting solution, the residue was triturated with methanol (50 ml). The resulting insoluble materials were removed by filtration, and the filtrate was evaporated. The residue was acetylated with acetic anhydride (50 ml) in pyridine (60 ml) for 12 h and the solution was evaporated. The residue was partitioned between chloroform (250 ml) and water (400 ml), and the aqueous layer was extracted with chloroform (250 ml×1, 100 ml×1). The combined extracts were washed with saturated aqueous NaCl (300 ml), dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (100 g, ethyl acetate: toluene=1 : 1), and fractions corresponding to R_f 0.50 (ethanol : toluene=1 : 3) were evaporated to afford **6** (2.75 g, 68%), mp 166—168 °C; $[\alpha]_D^{22}$+89.0° (*c* 1.00, $CHCl_3$); IR ν_{max}^{KBr} 2940, 1750, 1650, 1410, 1390, 1300 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.10 (3H, s, $NCOCH_3$), 2.20, 2.21 (3H×2, each s, 2×$OCOCH_3$), 3.56 (3H, s, OCH_3), 3.40—3.91 (2H, m, H-6, 6′), 4.42—5.32 (5H, m, H-1, 2, 3, 4, 5). Found: C, 52.10; H, 6.25; N, 4.38%. Calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.36; N, 4.65%.

(2*S*,3*S*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*R*)-1-benzyloxy-2,2-bis(ethylthio)ethyl]pyrrolidine (7). To a stirred solution of **6** (4.30 g, 14.3 mmol) in dichloromethane (15 ml) was added sodium methoxide in methanol (1 mol dm^{-3}, 34.3 ml, 34.3 mmol). After stirring for 30 min, the solution was neutralized with Amberlite IR-120 B (H^+). The resin was removed by filtration and the filtrate was evaporated. The residue was dissolved in concd HCl (10.0 ml) and ethanethiol (10.0 ml) was added at 0 °C. After stirring for 18 h at the temperature, the mixture was diluted with water (50 ml) and neutralized with lead(II) carbonate hydroxide. The resulting insoluble materials were removed through Celite-pad, and the filtrate was evaporated. The residue was triturated with methanol (70 ml) and insoluble materials were removed. After evaporation of the filtrate, the residue was benzylated without purification. To a suspension of sodium hydride (60%, 2.05 g, 51.4 mmol, washed with hexane; 10 ml×3) in DMF (15 ml) was added a DMF (40 ml) solution of the above residue. After stirring for 20 min at ambient temperature, benzyl bromide (6.1 ml, 51.4 mmol) was added to the mixture. The mixture was stirred for 1.5 h and ethanol (15 ml) was added. The solution was evaporated and the residue was partitioned between dichloromethane (300 ml) and water (400 ml). After extraction of the aqueous layer with dichloromethane (300 ml×2), the combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (200 g, ethyl acetate: hexane=1 : 1), and fractions corresponding to R_f 0.52 (ethanol: toluene=1 : 6) were evaporated to afford **7** (4.88 g, 59%) as a colorless syrup, $[\alpha]_D^{22}$+8.5° (*c* 1.10, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3000, 2920, 1630, 1450, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.98, 1.18 (3H×2, each t, *J*=8 Hz, 2×$SCH_2C\underline{H}_3$), 2.10 (3H, s, $NCOCH_3$), 2.38, 2.70 (2H×2, each q, *J*=8 Hz, 2×$SC\underline{H}_2CH_3$), 3.40—4.75 (13H, m, H-2,3,4,5,5′, H-1,2 of the side chain, 3×$OC\underline{H}_2C_6H_5$), 7.26, 7.33, 7.34 (total 15H, each s, 3×$OCH_2C_6\underline{H}_5$). High resolution mass spectrum, calcd for $C_{33}H_{42}NO_4S_2$: *m/z* 580.2553, found: M+H, 580.2563.

(2*R*,3*S*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*S*,2*E*)-1-benzyloxy-3-ethoxycarbonyl-2-propenyl]pyrrolidine (8). To a stirred solution of **7** (1.00 g, 1.72 mmol) in a mixture of acetonitrile (8 ml) and water (2 ml) were added mercury(II) chloride (2.34 g, 8.62 mmol) and calcium carbonate (0.95 g, 9.49 mmol). After stirring for 4 h, an insoluble material was removed through Celite-pad. The filtrate was diluted with dichloromethane (200 ml), washed with 1 mol dm^{-3} aqueous KI (100 ml×3), dried (Na_2SO_2), and evaporated. The residue was subjected to the Horner-Emmons reaction directly. To a suspension of sodium hydride (60%, 0.24 g, 6.04 mmol, washed with hexane; 2 ml×3) in THF (5 ml) was added diethyl ethoxycarbonylmethylphosphonate (1.20 ml, 6.04

mmol) at 0 °C. After stirring for 20 min, a solution of the above residue in THF (10 ml) was added. The mixture was stirred for 3 h at ambient temperature and diluted with water (100 ml). The aqueous solution was extracted with dichloromethane (150 ml×2, 100 ml×1), and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (60 g, ethyl acetate : hexane=2 : 5), and fractions corresponding to R_f 0.28 (ethyl acetate : hexane=1 : 2) were evaporated to afford **8** (0.77 g, 82%) as a colorless syrup, $[\alpha]_D^{23}$+71.5° (*c* 1.10, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2990, 2930, 2860, 1730, 1630, 1450, 1420, 1360, 1260, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.24 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.95, 2.10 (total 3H, each s, $NCOCH_3$), 3.36 (1H, d, *J*=13 Hz, H-5), 3.72 (1H, d, *J*=7 Hz, H-5′), 3.76—5.00 (12H, m, H-2, 3, 4, H-1 of the side chain, $COOC\underline{H}_2CH_3$, 3×$OC\underline{H}_2C_6H_5$), 6.10 (1H, dd, *J*=2 and 15 Hz, H-3 of the side chain), 7.00—7.05 (16H, m, H-2 of the side chain, 3×$OCH_2C_6\underline{H}_5$). High resolution mass spectrum, calcd for $C_{33}H_{38}NO_6$: *m/z* 544.2696, found: M+H, 544.2677.

(2*R*,3*S*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*S*)-1-benzyloxy-3-(ethoxycarbonyl)propyl]pyrrolidine (9). A solution of **8** (2.45 g, 4.51 mmol) in ethanol (20 ml) was hydrogenated in the presence of Raney nickel T-4 under atmospheric hydrogen pressure for 5 h. After removal of the catalyst through Celite-pad, the filtrate was evaporated. The residue was chromatographed on SiO_2 (200 g, ethyl acetate : hexane =1 : 1), and fractions corresponding to R_f 0.19 (ethyl acetate : hexane=2 : 1) were evaporated to afford **9** (2.11 g, 86%) as a colorless syrup, $[\alpha]_D^{22}$+0.9° (*c* 1.10, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2990, 2930, 2860, 1730, 1630, 1450, 1420, 1360, 1260, 1150, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13, 1.16 (total 3H, each t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.50—2.50 (7H, m, $C\underline{H}_2C\underline{H}_2COOEt$, $NCOCH_3$), 3.45—4.80 (14H, m, H-2, 3, 4, 5, 5′, H-1 of the side chain, $COOC\underline{H}_2CH_3$, 3×$OC\underline{H}_2C_6H_5$), 7.23, 7.33 (total 15H, each s, 3×$OCH_2C_6\underline{H}_5$). High resolution mass spectrum, calcd for $C_{33}H_{40}NO_6$: *m/z* 546.2853, found: M+H, 546.2853.

(1*S*,2*R*,8*S*,8*aR*)-1,2,8-Tris(benzyloxy)-octahydro-5-indolizinone (10) and (2*R*,3*S*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*S*)-1-benzyloxy-3-carboxypropyl]pyrrolidine (11). A solution of **9** (240 mg, 0.44 mmol) in a mixture of ethanol (8 ml) and 15 mol dm^{-3} aqueous KOH (2 ml) was heated at 120 °C (Pyrex-glass sealed tube) for 14 d. After neutralization with 1 mol dm^{-3} aqueous HCl, the resulting solution was evaporated. The residue was diluted with water (25 ml) and extracted with dichloromethane (20 ml×3). The extracts were dried (Na_2SO_4) and evaporated. The residual brown syrup was chromatographed on SiO_2 (20 g, ethanol : toluene =1 : 30). Fractions corresponding to R_f 0.46 (ethanol : toluene =1 : 5) were evaporated to afford **10** (80 mg, 40%), and fractions corresponding to R_f 0.43 were evaporated to afford **11** (115 mg, 51%) as a colorless syrup. **10**: Mp 98—99 °C; $[\alpha]_D^{22}$—28.2 (*c* 1.00, $CHCl_3$); IR ν_{max}^{KBr} 3420, 2920, 2860, 1640, 1450, 1410, 1370, 1200, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.56—2.68 (4H, m, H-6,6′,7,7′), 3.30—4.84 (12H, m, H-1, 2, 3, 3′, 8, 8a, 3×$OC\underline{H}_2C_6H_5$), 7.27, 7.29 (total 15H, each s, 3×$OCH_2C_6\underline{H}_5$). Found: C, 76.27; H, 6.85; N, 3.08%. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06%. **11**: $[\alpha]_D^{23}$—4.0° (*c* 1.05, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3670, 3500, 3020, 2400, 1710, 1630, 1450, 1420, 1360, 1260, 1210, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.57—2.60 (7H, m, H-2, 2′, 3, 3′ of the side chain, $NCOCH_3$), 3.43—4.76 (12H, m, H-2, 3, 4, 5, 5′, H-1 of the side chain, 3×$OC\underline{H}_2C_6H_5$), 7.00—7.50 (15H, m, 3×$OCH_2C_6\underline{H}_5$).

Conversion of 11 to 10. A solution of **11** (219 mg, 0.42 mmol) in a mixture of ethanol (4 ml) and 15 mol dm^{-3} aqueous KOH (1 ml) was heated at 120 °C for 14 d. After the analogous work-up described above, the crude mixture was chromatographed on SiO_2 to afford **10** (80 mg, 43%) [95 mg (46%) of **11** was recovered].

(1*S*,2*R*,8*S*,8*aR*)-1,2,8-Triacetoxyoctahydro-5-indolizinone (12). To a solution of **10** (80 mg, 0.175 mmol) in ethanol (1.5 ml) were added cyclohexene (1.5 ml) and 20% $Pd(OH)_2$ on charcoal (40 mg). The mixture was heated under reflux for 4 h, and the catalyst was removed through Celite-pad. The filtrate was evaporated, and the residue was acetylated with acetic anhydride (1 ml) in pyridine (1 ml) for 4 h. After evaporation of the mixture, the residue was chromatographed on SiO_2 (5 g, ethanol : toluene=1 : 20). Fractions corresponding to R_f 0.51 (ethanol : toluene=1 : 3) were evaporated to afford **12** (46 mg, 84%), mp 126—127 °C; $[\alpha]_D^{21}$ −21.8° (*c* 0.90, $CHCl_3$); IR ν_{max}^{KBr} 3450, 2960, 1730, 1640, 1470, 1420, 1380, 1270, 1230, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47—2.83 (13H, m, H-6, 6′, 7, 7′, 3×$OCOCH_3$), 3.50—4.30 (3H, m, H-3, 3′, 8a), 5.20—5.77 (3H, m, H-1, 2, 8). Found: C, 53.52; H, 6.05; N, 4.47%. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47%.

(1*S*,2*R*,8*S*,8*aR*)-1,2,8-Triacetoxyoctahydroindolizine, 8-*epi*-Swainsonine Triacetate (13). To a stirred solution of **12** (26 mg, 0.08 mmol) in THF (1 ml) was added borane-dimethyl sulfide complex (Aldrich, 10.0 mol dm^{-3} in BH_3, 0.04 ml, 0.42 mmol) at 0 °C under argon atmosphere. After stirring at ambient temperature for 2 h, the mixture was diluted with water (10 ml) and stirred for 15 min. The aqueous solution was extracted with dichloromethane (10 ml×3). The extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in dioxane (1.5 ml) and saturated aqueous $NaHCO_3$ solution (0.5 ml) was added. After stirring for 5 h at ambient temperature, the solution was diluted with water (10 ml), extracted with dichloromethane (10 ml×3). The extracts were dried (Na_2SO_4) and evaporated. The residue was purified by PTLC (ethanol : toluene=1 : 15) to afford **13** (R_f= 0.44; ethanol : toluene=1 : 5) (16 mg, 64%), mp 79—80 °C; $[\alpha]_D^{19}$—17.1° (*c* 0.35, $CHCl_3$); IR ν_{max}^{KBr} 3450, 2940, 1730, 1380, 1270, 1250, 1160, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.14—2.30 (6H, m, H-5, 6, 6′, 7, 7′, 8a), 2.00, 2.03, 2.11 (3H×3, each s, 3×$OCOCH_3$), 2.42 (1H, dd, *J*=7 and 12 Hz, H-3), 3.10—3.35 (2H, m, H-3′, 5′), 5.13—5.50 (3H, m, H-1, 2, 8). High resolution mass spectrum, calcd for $C_{14}H_{22}NO_6$: *m/z* 300.1446, found: M+H, 300.1447.

(1*S*,2*R*,8*S*,8*aR*)-Octahydro-1,2,8-indolizinetriol, 8-*epi*-Swainsonine (2). A solution of **13** (27.0 mg, 0.09 mmol) in 1 mol dm^{-3} aqueous HCl (1 ml) was heated under reflux for 3 h and evaporated. The residue was dissolved in a minimum volume of water and charged on a column of Amberlite IRA-400 (OH^-) (2 ml). The column was eluted with water, and the ninhydrin-positive fractions (R_f 0.35, aqueous ammonia : 1-butanol : chloroform : ethanol=1 : 4 : 4 : 4) were evaporated to afford **2** (13.4 mg, 86%), mp 93—95 °C; $[\alpha]_D^{21}$—24.8° (*c* 0.67, MeOH); IR ν_{max}^{KBr} 3600—3000 (br), 2940, 2850, 2820, 1440, 1150, 1100 cm^{-1}; ^1H NMR (D_2O) δ=1.40—2.30 (6H, m, H-5, 6, 6′, 7, 7′, 8a), 2.50 (1H, dd, *J*=7 and 11 Hz, H-3), 2.86—3.20 (2H, m, H-3′, 5′), 4.20—4.46 (3H, m, H-1,2,8); ^{13}C NMR (CD_3OD) δ=20.63, 32.09, 54.27, 62.98, 67.53, 69.40, 69.96, 74.29. High resolution mass spectrum, calcd for $C_8H_{15}NO_3$: *m/z* 173.1051, found: M, 173.1056.

Methyl 2,4-Di-*O*-acetyl-3,6-acetylimino-3,6-dideoxy-α-D-

galactopyranoside (15) and Methyl 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-galactopyranoside (16). A solution of methyl 3-acetamido-2-*O*-acetyl-3-deoxy-4,6-di-*O*-mesyl-α-D-glucopyranoside (**14**)[16] (7.80 g, 18.0 mmol) in a mixture of 2-methoxyethanol (180 ml) and water (20 ml) containing sodium acetate (7.82 g, 95.0 mmol) was heated under reflux for 6 h, and evaporated. The residue was triturated with boiling acetone (400 ml) and insoluble materials were removed by filtration. After evaporation of the filtrate, the residue was acetylated with acetic anhydride (65 ml) in pyridine (65 ml) for 14 h. The mixture was evaporated with toluene and the residue was chromatographed on SiO_2 (300 g, ethanol : toluene=1 : 30). Fractions corresponding to R_f 0.32 (ethanol : toluene=1 : 5) were evaporated to afford **15** (3.67 g, 68%) as a foam, and fractions corresponding to R_f 0.27 were evaporated to afford **16** (1.72 g, 27%) as crystals. **15**: $[\alpha]_D^{26}$+25.3° (*c* 1.36, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3660, 3020, 2400, 1750, 1650, 1410, 1370, 1260, 1220, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.03 (3H, s, $NCOCH_3$), 2.09, 2.12, 2.15, 2.19 (total 6H, each s, 2×$OCOCH_3$), 3.45, 3.49 (total 3H, each s, OCH_3), 3.60—3.76 (2H, m, H-6, 6′), 4.23—4.68 (2H, m, H-3, 5), 4.71, 4.73 (total 1H, each d, *J*=2 Hz, H-1), 5.02—5.49 (2H, m, H-2, 4). High resolution mass spectrum, calcd for $C_{13}H_{19}NO_7$: *m/z* 301.1160, found: M, 301.1133. **16**: Mp 107—108 °C; $[\alpha]_D^{21}$+117.8° (*c* 1.48, $CHCl_3$); IR ν_{max}^{KBr} 3340, 3240, 2930, 1735, 1655, 1540, 1440, 1370, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.90 (3H, s, $NCOCH_3$), 2.06, 2.10, 2.17 (3H×3, each s, 3×$OCOCH_3$), 3.45 (3H, s, OCH_3), 3.95—4.32 (3H, m, H-5, 6, 6′), 4.66 (1H, ddd, *J*=3, 8, and 12 Hz, H-3), 4.84 (1H, d, *J*=4 Hz, H-1), 5.10 (1H, dd, *J*=4 and 12 Hz, H-2), 5.40 (1H, dd, *J*=1 and 3 Hz, H-4), 5.72 (1H, d, *J*=8 Hz, NH). Found: C, 50.14; H, 6.50; N, 3.93%. Calcd for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.41; N, 3.88%.

3-Acetamido-1,2,4,6-tetra-*O*-acetyl-3-deoxy-α- and -β-D-galactopyranose (17-α and 17-β). A solution of **16** (45 mg, 0.12 mmol) in 2 mol dm^{-3} aqueous HCl (2 ml) was heated under reflux for 13 h and evaporated. The residue was acetylated with acetic anhydride (0.5 ml) in pyridine (0.5 ml) for 4 h. After evaporation of the mixture, the residue was chromatographed on SiO_2 (5 g, ethanol : toluene=1 : 20). Fractions corresponding to R_f 0.49 (ethanol : toluene=1 : 5) were evaporated to afford **17-β** (21 mg, 43%), and fractions corresponding to R_f 0.45 were evaporated to afford **17-α** (20 mg, 41%). **17-α**: Mp 178—179 °C, lit,[17] mp 181—182 °C; $[\alpha]_D^{26}$+123.8° (*c* 1.00, $CHCl_3$), lit,[17] $[\alpha]_D^{23}$+119° (*c* 1.00, $CHCl_3$); IR ν_{max}^{KBr} 3440, 1760, 1740, 1680, 1530, 1435, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.93 (3H, s, $NCOCH_3$), 2.03, 2.19 (6H×2, each s, 4×$OCOCH_3$), 3.85—4.25 (2H, m, H-6, 6′), 4.38 (1H, dt, *J*=1 and 7 Hz, H-5), 4.68 (1H, ddd, *J*=3, 9, and 11 Hz, H-3), 5.25 (1H, dd, *J*=4 and 11 Hz, H-2), 5.48 (1H, dd, *J*=1 and 3 Hz, H-4), 6.01 (1H, d, *J*=9 Hz, NH), 6.31 (1H, d, *J*=4 Hz, H-1). **17-β**: Mp 117—118 °C; $[\alpha]_D^{24}$+36.0° (*c*, 1.06, $CHCl_3$); IR ν_{max}^{KBr} 3370, 1740, 1650, 1520, 1370, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.89 (3H, s, $NCOCH_3$), 2.02, 2.04, 2.10, 2.15 (3H×4, each s, 4×$OCOCH_3$), 3.97—4.23 (3H, m, H-5, 6, 6′), 4.44 (1H, ddd, *J*=4, 8, and 9 Hz, H-3), 5.06 (1H, dd, *J*=9 and 12 Hz, H-2), *5.40 (1H, d, J=4Hz, H-4), 5.80 (1H, d, J=9 Hz, H-1), 6.04* (1H, d, *J*=8 Hz, NH). Found: C, 49.09; H, 5.91; N, 3.66%. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60%.

Methyl 3-Acetamido-3-deoxy-6-*O*-tosyl-α-D-galactopyranoside (18) and Methyl 3-Acetamido-3-deoxy-2,6-di-*O*-tosyl-α-D-galactopyranoside (19). To a stirred solution of **16** (350 mg, 0.97 mmol) in methanol (3 ml) was added sodium methoxide in methanol (1 mol dm^{-3} solution, 3.8 ml, 3.8 mmol) at 0 °C. After stirring at the temperature for 30 min, the solution was neutralized with Amberlite 120B (H^+). The resin was removed by filtration and the filtrate was evaporated to afford a colorless syrup. To a solution of the syrup in pyridine (4 ml) was added *p*-toluenesulfonyl chloride (184 mg, 0.97 mmol). The mixture was stirred for 10 h at −17 to −10 °C and evaporated. The residue was chromatographed on SiO_2 (60 g, chloroform : methanol=40 : 1). Fractions corresponding to R_f 0.58 (ethanol : toluene=1 : 3) were evaporated to afford **19** (64 mg, 12%), fractions corresponding to R_f 0.31 were evaporated to afford **18** (120 mg, 32%), and fractions corresponding to R_f 0.10 were evaporated to recover the 2,4,6-triol (64 mg, 28%). **18**: Mp 146—147 °C; $[\alpha]_D^{23}$+136.1° (*c* 1.09, MeOH); IR ν_{max}^{KBr} 3340, 2920, 1630, 1600, 1570, 1445, 1370, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.04 (3H, s, $NCOCH_3$), 2.45 (3H, s, $OSO_2C_6H_4C\underline{H}_3$), 2.56—2.98 (2H, m, 2×OH), 3.36 (3H, s, OCH_3), 3.62—4.33 (6H, m, H-2, 3, 4, 5, 6, 6′), 4.71 (1H, d, *J*=4 Hz, H-1), 6.54 (1H, d, *J*=8 Hz, NH), 7.58 (4H, ABq, $OSO_2C_6\underline{H}_4CH_3$). High resolution mass spectrum, calcd for $C_{16}H_{24}NO_8S$: *m/z* 390.1220, found: M+H, 390.1214. **19**: Mp 194—195 °C; $[\alpha]_D^{24}$+75.2° (*c* 1.00, DMF); IR ν_{max}^{KBr} 3330, 3200, 1640, 1590, 1540, 1360, 1190, 1175 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.69 (3H, s, $NCOCH_3$), 2.42 (6H, s, 2×$OSO_2C_6H_4C\underline{H}_3$), 3.12 (3H, s, OCH_3), 3.53—4.62 (7H, m, H-1, 2, 3, 4, 5, 6, 6′), 5.34 (1H, d, *J*=6 Hz, NH), 7.61, 7.63 (total 8H, 2×$OSO_2C_6\underline{H}_4CH_3$). Found: C, 51.08; H, 5.43; N, 2.77; S, 11.50%. Calcd for $C_{23}H_{29}NO_{10}S_2$: C, 50.82; H, 5.38; N, 2.58; S, 11.80%.

Compound 15 from Compound 18. To a suspension of sodium hydride (60%, 31 mg, 1.28 mmol, washed with hexane; 1 ml×3) in DMF (0.5 ml) was added a solution of **18** (86 mg, 0.22 mmol) in DMF (1 ml). The mixture was heated at 100 °C for 3 h and ethanol (0.5 ml) was added. After evaporation of the mixture, the residue was acetylated with acetic anhydride (2 ml) in pyridine (2 ml) for 16 h. The mixture was evaporated and the residue was partitioned between chloroform (30 ml) and water (30 ml). The aqueous layer was extracted with chloroform (30 ml). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (5 g, ethanol : toluene=1 : 10), and fractions corresponding to R_f 0.32 (ethanol : toluene=1 : 5) were evaporated to afford **15** (37 mg, 56%) which was identical in all respects with that prepared by the solvolysis of **14**.

(2*S*,3*R*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*R*)-1-benzyloxy-2,2-bis(ethylthio)ethyl]pyrrolidine (20). Compound **15** (1.43 g, 4.75 mmol) was *O*-deacetylated with 1 mol dm^{-3} sodium methoxide in methanol (14.2 ml) at 0 °C for 30 min. After neutralization of the mixture with Amberlite IR-120B (H^+), the crude product was treated with ethanethiol (5 ml) in concd HCl (3 ml) at 0 °C for 1 h. Work-up as described in preparation of **7** gave the dithioacetal derivative (R_f=0.51, ethanol : toluene=1 : 2) which was directly benzylated with benzyl bromide (1.72 ml) in DMF (25 ml) in the presence of sodium hydride (580 mg) for 12 h. Extractive work-up *($CHCl_3$) and chromatography of the product on SiO_2 (100* g, ethyl acetate : toluene=1 : 10) afforded **20** (R_f=0.36, ethyl acetate : hexane=1 : 1) (1.55 g, 56%) as a colorless syrup; $[\alpha]_D^{27}$+9.6° (*c* 1.17, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3000, 1620, 1450, 1420, 1360, 1260, 1210, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13, 1.20 (3H×2, each t, *J*=8 Hz, 2×$SCH_2C\underline{H}_3$), 2.09 (3H, s, $NCOCH_3$), 2.50, 2.66 (2H×2, each q, *J*=8 Hz, 2×$SC\underline{H}_2CH_3$),

3.20—4.70 (13H, m, H-2, 3, 4, 5, 5′, H-1, 2 of the side chain, 3×OCH$_2$C$_6$H$_5$), 7.25, 7.30, 7.35 (total 15H, each s, 3×OCH$_2$C$_6$H$_5$). High resolution mass spectrum, calcd for $C_{33}H_{41}NO_4S_2$: *m/z* 579.2475, found: M, 579.2503.

(2*R*,3*R*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*S*,2*E*)-1-benzyloxy-3-ethoxycarbonyl-2-propenyl]pyrrolidine (21). Compound **20** (2.66 g, 4.6 mmol) in a mixture of acetonitrile (40 ml) and water (10 ml) was treated with mercury(II) chloride (3.99 g) and calcium carbonate (1.61 g). Work-up as described in preparation of **8** gave the dethioacetal derivative (R_f 0.54, ethyl acetate : hexane=1 : 2), which was subjected to Horner-Emmons reaction with diethyl ethoxycarbonylmethylphosphonate (3.19 ml) in THF in the presence of sodium hydride (0.64 g) for 90 min at ambient temperature. Extractive work-up (CH_2Cl_2) and repeated chromatography on SiO_2 (2-butanone : toluene=1 : 14, then ethyl acetate : toluene=1 : 2) of the reaction mixture afforded **21** (R_f 0.47, ethyl acetate : toluene=1 : 2) (1.29 g, 52%) as a colorless syrup, $[\alpha]_D^{27}$+9.9° (*c* 0.91, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 2990, 2960, 2930, 1710, 1630, 1450, 1410, 1370, 1300, 1270, 1175, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.22, 1.31 (total 3H, each t, *J*=7 Hz, COOCH$_2$CH$_3$), 2.00, 2.05 (total 3H, each s, NCOCH$_3$), 3.06—4.90 (14H, m, H-2, 3, 4, 5, 5′, H-1 of the side chain, COOCH$_2$CH$_3$, 3×OCH$_2$C$_6$H$_5$), 5.91, 6.01 (total 1H, d and dd, *J*=15 Hz and *J*=2 and 15 Hz, CH=CHCOOEt), 6.60—7.02 (1H, m, CH=CHCOOEt), 7.30, 7.34 (total 15H, each s, 3×OCH$_2$C$_6$H$_5$). High resolution mass spectrum, calcd for $C_{33}H_{37}NO_6$: *m/z* 543.2618, found: *m/z* 543.2589.

(2*R*,3*R*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*S*)-1-benzyloxy-3-(ethoxycarbonyl)propyl]pyrrolidine (22). Compound **21** (668 mg, 1.23 mmol) in ethanol (9 ml) was hydrogenated in the presence of Raney nickel T-4 for 3 h. Work-up as described in preparation of **9** and chromatography of the product on SiO_2 (2-butanone : toluene=1 : 10) afforded **22** (R_f=0.46, ethyl acetate : toluene1=1 : 1) (577 mg, 86%) as a colorless syrup, $[\alpha]_D^{20}$−28.1° (*c* 1.34, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3660, 3570, 3480, 3010, 1725, 1630, 1420, 1270, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.18, 1.20 (total 3H, each t, *J*=7 Hz, COOCH$_2$CH$_3$), 1.57—1.93 (2H, m, H-2, 2′ of the side chain), 2.00, 2.04 (total 3H, each s, NCOCH$_3$), 2.30, 2.32 (total 2H, each t, *J*=7 Hz, H-3, 3′ of the side chain), 3.27—4.73 (13H, m, H-2, 3, 4, 5, 5′, COOCH$_2$CH$_3$, 3×OCH$_2$C$_6$H$_5$), 7.27, 7.30 (total 15H, each s, 3×OCH$_2$C$_6$H$_5$). High resolution mass spectrum, calcd for $C_{33}H_{39}NO_6$: *m/z* 545.2775, found: M, 545.2786.

(1*R*,2*R*,8*S*,8*aR*)-1,2,8-Tris(benzyloxy)-octahydro-5-indolizinone (23) and (2*R*,3*R*,4*R*)-1-Acetyl-3,4-bis(benzyloxy)-2-[(1*S*)-1-benzyloxy-3-carboxypropyl]pyrrolidine (24). A solution of **22** (577 mg, 1.1 mmol) in a mixture of ethanol (20 ml) and 15 mol dm^{-3} aqueous KOH (20 ml) in sealed tubes (100—120 mg of **22**/tube) was heated at 120 °C for 10 d. The soluble part was collected, and the unsoluble material was washed with ethanol several times. The ethanolic soluble part and washing were combined, diluted with water (20 ml), neutralized with acetic acid and evaporated. The residue was partitioned between chloroform (50 ml) and water (50 ml), and the aqueous layer was extracted with chloroform (50 ml×2). The extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (50 g, ethanol : toluene=1 : 35). Fractions corresponding to R_f 0.38 (ethanol : toluene=1 : 10, acidified with acetic acid) were evaporated to afford **23** (166 mg, 34%) as a colorless syrup which crystallized gradually from ether and petroleum ether. Fractions corresponding to R_f 0.35 were evaporated to afford **24** (340 mg, 62%) as a colorless syrup. **23**: Mp 52—54 °C; $[\alpha]_D^{20}$+15.1° (*c* 1.18, $CHCl_3$); IR ν_{max}^{KBr} 3420, 3020, 2880, 1640, 1490, 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.43—2.54 (4H, m, H-6, 6′, 7, 7′), 3.40—4.85 (12H, m, H-1, 2, 3, 3′, 8, 8a, 3×OCH$_2$C$_6$H$_5$), 7.27, 7.29, 7.33 (total 15H, each s, 3×OCH$_2$C$_6$H$_5$). High resolution mass spectrum, calcd for $C_{29}H_{31}NO_4$: *m/z* 457.2251, found: M, 457.2226. **24**: $[\alpha]_D^{20}$−21.5° (*c* 0.93, $CHCl_3$); IR ν_{max}^{KBr} 3660, 3020, 2880, 1720, 1650, 1450, 1420, 1360, 1260, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.42—1.92 (2H, m, H-2, 2′ of the side chain), 1.98, 2.03 (total 3H, each s, NCOCH$_3$), 2.13—2.58 (2H, m, H-3, 3′ of the side chain), 3.23—4.70 (12H, m, H-2, 3, 4, 5, 5′, H-1 of the side chain, 3×OCH$_2$C$_6$H$_5$), 7.27, 7.29, 7.32 (total 15H, each s, 3×OCH$_2$C$_6$H$_5$).

Compound 23 from 24. Compound **24** (66 mg) was cyclized under the same conditions employed above. After SiO_2 chromatography, 44 mg (75%) of **23** was obtained and 13 mg (20%) of **24** was recovered.

(1*R*,2*R*,8*S*,8*aR*)-1,2,8-Triacetoxy-octahydro-5-indolizinone (25). *O*-Debenzylation of **23** (103 mg, 0.23 mmol) and successive acetylation under the same conditions and work-up described in preparation of **12** provided **25** (59 mg, 83%) after SiO_2 chromatography (ethanol : toluene=1 : 20, **25**: R_f=0.39, ethanol : toluene=1 : 8). **25**: Mp 118—119 °C; $[\alpha]_D^{24}$−20.9° (*c* 1.04, $CHCl_3$); IR ν_{max}^{KBr} 3440, 1740, 1635, 1460, 1380, 1260, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.58—2.75 (4H, m, H-6, 6′, 7, 7′), 2.09, 2.10, 2.13 (3H×3, each s, 3×OCOCH$_3$), 3.60—4.04 (3H, m, H-3, 3′, 8a), 5.10—5.53 (3H, m, H-1, 2, 8). Found: C, 53.38; H, 5.90; N, 4.43%. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47%.

(1*R*,2*R*,8*S*,8*aR*)-1,2,8-Triacetoxyoctahydroindolizine (26). Reduction of compound **25** (33 mg, 0.11 mmol) with borane-dimethyl sulfide (0.03 ml) at 0 °C, extractive work-up, saturated aqueous $NaHCO_3$ treatment, and successive acetylation as described in preparation of **13** afforded **26** (21 mg, 67%) after PTLC purification (ethanol : toluene=1 : 10). **26** (R_f=0.38, ethanol : toluene=1 : 10): Mp 124—125 °C; $[\alpha]_D^{20}$ −20.8° (*c* 1.00, $CHCl_3$), IR ν_{max}^{KBr} 3440, 2950, 2800, 1730, 1240, 1170 cm^{-1}; ^{1}H NMR δ=1.20—2.32 (6H, m, H-5, 6, 6′, 7, 7′, 8a), 2.07, 2.10, 2.17 (3H×3, each s, 3×OCOCH$_3$), 2.64 (1H, dd, *J*=8 and 11 Hz, H-3), 2.99—3.23 (2H, m, H-3′, 5′), 4.96—5.25 (3H, m, H-1, 2, 8). High resolution mass spectrum, calcd for $C_{14}H_{21}NO_6$: *m/z* 299.1367, found: M, 299.1344.

(1*R*,2*R*,8*S*,8*aR*)-Octahydro-1,2,8-indolizinetriol, 1,8-Di-*epi*-swainsonine (3). To a stirred solution of **26** (21 mg, 0.07 mmol) in methanol (1.5 ml) was added potassium carbonate (29 mg, 0.21 mmol). After stirring for 3 h at ambient temperature, the mixture was evaporated. The residue was purified by PTLC (aqueous ammonia : acetone : chloroform : water=1 : 30 : 5 : 4, the edge of the plate was colorized with ninhydrin and iodine) to afford a crystalline **3** (12 mg, 98%, R_f=0.28), which was recrystallized from chloroform, mp 138—140 °C (decomp); $[\alpha]_D^{21}$−35.6° (*c* 0.59, MeOH); IR ν_{max}^{KBr} 3600—3000 (br), 2920, 2810, 1330, 1240, 1210, 1150, 1135, 1100 cm^{-1}; ^{1}H NMR (D_2O) δ=1.22—2.27 (6H, m, H-5, 6, 6′, 7, 7′, 8a), 2.60 (1H, dd, *J*=6 and 11 Hz, H-3), 2.75—3.10 (2H, m, H-3′, 5′), 3.83—4.30 (3H, m, H-1, 2, 8); ^{13}C NMR (CD_3OD) δ=20.39, 32.19, 54.08, 62.74, 64.66, 75.05, 77.89, 80.23. High resolution mass spectrum, calcd for $C_8H_{15}NO_3$: *m/z* 173.1051, found: M, 173.1052.

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References

1) S. M. Colegate, P. R. Dorling, and C. R. Huxtable, *Aust. J. Chem.*, **32**, 2257 (1979).

2) R. J. Molyneux and L. F. James, *Science*, **216**, 190 (1982).

3) M. J. Schneider, F. S. Ungemach, H. P. Broquist, and T. M. Harris, *Tetrahedron*, **39**, 29 (1983).

4) M. Hino, O. Nakayama, Y. Tsurumi, K. Adachi, T. Shibata, H. Terano, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, **38**, 926 (1985).

5) T. Suami, K. Tadano, and Y. Iimura, *Chem. Lett.*, **1984**, 513; *Carbohydr. Res.*, **136**, 67 (1985).

6) M. H. Ali, L. Hough, and A. C. Richardson, *J. Chem. Soc., Chem. Commun.*, **1984**, 447; *Carbohydr. Res.*, **136**, 225 (1985).

7) G. W. J. Fleet, M. J. Gough, and P. W. Smith, *Tetrahedron Lett.*, **25**, 1853 (1984).

8) N. Yasuda, H. Tsutsumi, and T. Takaya, *Chem. Lett.*, **1984**, 1201.

9) C. E. Adams, F. J. Walker, and K. B. Sharpless, *J. Org. Chem.*, **50**, 422 (1985).

10) H. Setoi, H. Takeno, and M. Hashimoto, *J. Org. Chem.*, **50**, 3948 (1985)

11) T. Kino, N. Inamura, K. Nakahara, S. Kiyoto, T. Goto, H. Terana, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, **38**, 936 (1985).

12) The syntheses of 8-*epi*-swainsonine and 2,8-di-*epi*-swainsonine were reported recently: N. Yasuda, H. Tsutsumi, and T. Takaya, *Chem. Lett.*, **1985**, 31. The overall yield of 8-*epi*-swainsonine in the literature seems to be unpractical.

13) The preliminary communication of the synthesis: Y. Iimura, Y. Hotta, C. Fukabori, K. Tadano, and T. Suami, *J. Carbohydr. Chem.*, **5**, 147 (1986).

14) R. D. Guthrie and L. F. Johnson, *J. Chem. Soc.*, **1961**, 4166.

15) S. Hanessian, T. J. Liak, and B. Vanasse, *Synthesis*, **1981**, 398.

16) R. D. Guthrie and G. P. B. Mutter, *J. Chem. Soc.*, **1964**, 1614.

17) F. W. Lichtenthaler, G. Bambach, and U. Scheidegger, *Chem. Ber.*, **102**, 986 (1969).