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TOTAL SYNTHESIS OF (−)-SWAINSONINE, AN α-D-MANNOSIDASE INHIBITOR ISOLATED FROM *Swainsona canescens*

TETSUO SUAMI*, KIN-ICHI TADANO, AND YOUICHI IIMURA
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223 (Japan)
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ABSTRACT

A newly isolated alkaloidal toxin, (−)-swainsonine [(1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyoctahydroindolizine], which exhibits an α-D-mannosidase inhibitory activity, has been synthesised stereoselectively in 15 steps starting from methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside.

INTRODUCTION

The alkaloidal toxin (−)-swainsonine (**1**), which was isolated[1] from *Swainsona canescens* (Benth.) A Lee, is a potent inhibitor of α-D-mannosidase, and ingestion of this plant by livestock induces a disease that is biochemically, morphologically, and clinically similar to mannosidosis, for example, depression of nervous, muscular non-coordination, *etc.* Also, **1** has been isolated from such other sources as *Astragalus lentiginosus*[2] and *Rhizoctonia leguminicola*[3]. Owing to its remarkable biological activity, **1** has attracted much attention in relation to structural determination and biosynthesis. Huxtable *et al.*[1] first proposed the relative stereochemistry of **1**, and this was developed by Harris *et al.*[3] to include the absolute stereochemistry, namely (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyoctahydroindolizine. Harris *et al.*[4] also investigated the biosynthesis of **1**, employing incorporation of deuteriopipecolic acid as an assumed precursor. Very recently, **1** has been synthesised chemically[5,6]. As part of our studies of the synthesis of biologically active natural products, employing carbohydrates as chiral synthons, an alternative total synthesis of **1** has been achieved from methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside[7] (**5**).

RESULTS AND DISCUSSION

One approach to the synthesis of **1** is the formation of a lactam in a pyrrolidine derivative (**3**) and successive conversion of an amide (**2**) into a tertiary amine. Prior to lactam formation, the formation of the pyrrolidine ring must be accomplished between C-6 and N-3 in 3-acetamido-2,4,5-tri-*O*-benzyl-3-deoxy-6-*O*-

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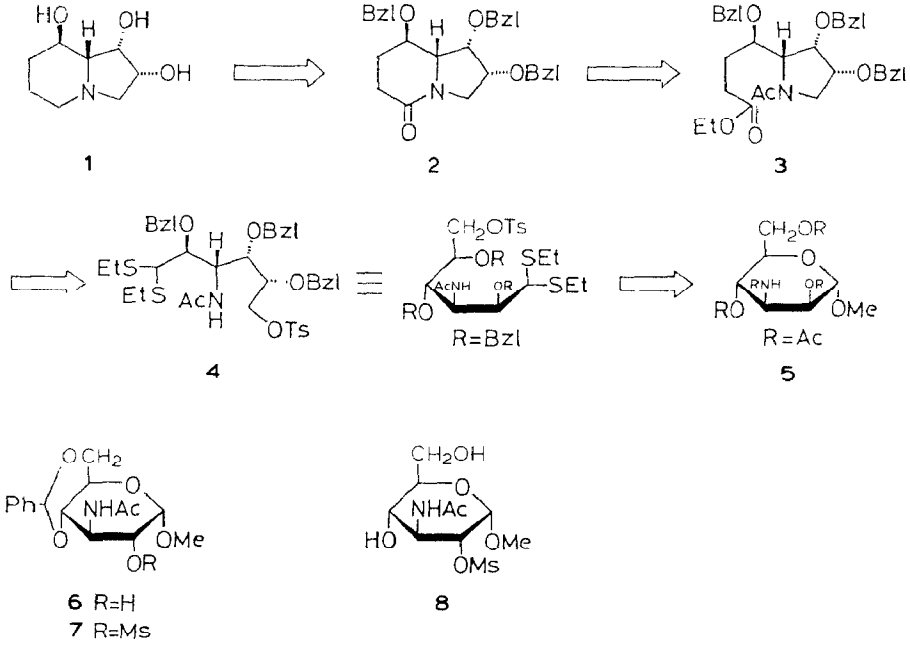
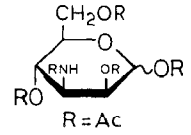


tosyl-D-mannose diethyl dithioacetal (**4**), which possesses all the necessary chiral carbons in **1**, by an intramolecular nucleophilic displacement, and an elongation of a two-carbon chain possessing a terminal ester on C-6 is necessary. Furthermore, **4** will be readily accessible from **5**.

Following this retrosynthetic approach, we have attempted the synthesis of **5** from the known methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (**6**). The mesylate (**7**) of **6** was converted into methyl 3-acetamido-3-deoxy-2-*O*-mesyl-α-D-glucopyranoside (**8**) by acid hydrolysis. Treatment of **8** with sodium acetate in boiling aqueous 2-methoxyethanol, followed by conventional acetylation of the product, afforded **5** in fairly good yield. The reaction **8**→**5** probably involves displacement of the mesyloxy group by participation of the vicinal acetamido group to yield an intermediary cyclic oxazolinium ion, which is attacked by water to give the *cis*-acetamido alcohol[9,10].

Hydrolysis of **5** in 2M HCl, followed by treatment with acetic anhydride in pyridine, afforded 3-acetamido-1,2,4,6-tetra-*O*-acetyl-3-deoxy-α,β-D-mannose (**9**, 98%). Zemplén deacetylation of **9**, reaction of the product with ethanethiol, followed by tritylation afforded 3-acetamido-3-deoxy-6-*O*-trityl-D-mannose diethyl dithioacetal (**10**, 55%). Treatment of **10** with benzyl bromide in the presence of sodium hydride, and removal of the trityl group from the product using toluene-*p*-sulfonic acid in methanol afforded the tri-*O*-benzyl derivative (**11**, 35%). Tosylation of **11** then gave 77% of the key intermediate **4**.

An intramolecular nucleophilic displacement of **4** in 1,4-dioxane containing aqueous sodium hydroxide afforded the pyrrolidine derivative **12** (93%), which



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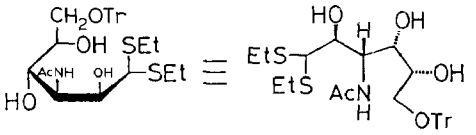

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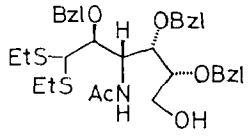

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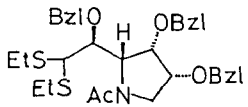

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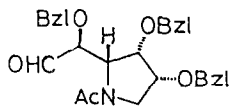

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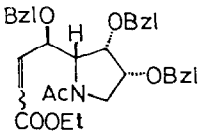
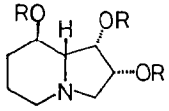


EZ-14



15 R=Bzl
16 R=Ac

comprised an inseparable mixture of two chiral amides (tertiary nitrogen atom). The ^{1}H-n.m.r. spectrum of **12** contained signals for NAc groups at δ 1.90 and 2.29, corresponding to a total of three protons. The diethyl dithioacetal **12** was converted into the aldehyde **13** by treatment with mercury(II) chloride and calcium carbonate[11]. Horner–Emmons reaction[12] of **13** with diethyl ethoxycarbonylmethylphosphonate then gave 77% of a mixture of two compounds (*E*- and *Z*-**14**), which was fractionated by column chromatography; *E*-*Z*-ratio ~40:1. The ^{1}H-n.m.r. spectra contained resonances for the α-vinyl protons of the α,β-unsaturated ester groups in *E*-**14** and *Z*-**14** at δ 6.06 (dd, *J* 2 and 15 Hz) and 6.26 (dd, *J* 2 and 11 Hz), respectively. Catalytic hydrogenation of *E*-**14** and *Z*-**14** gave the ester **3** in yields of 94 and 70%, respectively.

The intramolecular amide formation (**3**→**2**) was effected in fairly good yield (54%) by prolonged heating of **3** with aqueous ethanolic 15M potassium hydroxide in a sealed tube at 90°. The amide group in **2** was converted (74%) into the tertiary amine (**15**) by reaction with lithium aluminum hydride, and **15** was *O*-debenzylated[13] to give **1** (72%). The synthetic (−)-**1** was identical (i.r., ^{1}H-n.m.r., and mass spectra) with an authentic sample of the natural product. Acetylation[1] of **1** gave the triacetate **16**, the i.r., ^{1}H-n.m.r., and mass spectra of which were identical with those of an authentic sample.

Thus, the synthesis of the alkaloidal toxin (−)-swainsonine (**1**), starting from **5**, was effected in 4% overall yield.

EXPERIMENTAL

General procedures. — Evaporations were performed under diminished pressure at <40° (bath). Melting points were determined with a Mitamura Riken microapparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a JEOL DIP-4 polarimeter. Column chromatography was performed on Wakogel C-300, and t.l.c. on Kieselgel 60 F_{254} (Merck) with detection by u.v. light and charring with sulfuric acid. Preparative t.l.c. was performed on Kieselgel 60 PF_{254} (Merck). I.r. spectra were recorded with Hitachi Model 225 (KBr) and JEOL A-202 ($CHCl_3$) spectrometers. ^{1}H-N.m.r. spectra were recorded with a Varian EM-390 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). High-resolution mass spectra were obtained using an Hitachi M-80 mass spectrometer. Elemental analyses were performed by Mr. Saburo Nakada (Keio University).

*Methyl 3-acetamido-4,6-O-benzylidene-3-deoxy-2-O-mesyl-α-*D*-glucopyranoside* (**7**). — To a stirred suspension of methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside[8] (**6**; 5.0 g, 15.5 mmol) in pyridine (50 mL) was added mesyl chloride (1.80 mL, 23.2 mmol) with cooling (ice). After 2.5 h, the mixture was concentrated and the crystalline residue was washed with water (100 mL) to afford **7** (6.19 g) in a quantitative yield, m.p. 183–184°, $[\alpha]_D^{23}$ +60° (*c* 1, dimethyl sulfoxide), R_F 0.45 (ethanol–toluene, 1:5); ν_{max}^{KBr} 3420, 3280, 2910, 2850, 1645, 1545, 1360, and 1190 cm^{-1}. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.80 (s, 3 H, NAc), 3.15 (s, 3 H, OMs), 3.41 (s, 3 H, OMe), 3.53–4.67 (m, 6 H, H-2,3,4,5,6,6′), 4.93 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.54 (s, 1 H, C*H*Ph), 7.40 (s, 5 H, Ph), and 7.93 (d, 1 H, *J* 8 Hz, NH).

Anal. Calc. for $C_{17}H_{23}NO_8S$: C, 50.86; H, 5.77; N, 3.49; S, 7.99. Found: C, 51.08; H, 5.92; N, 3.51; S, 7.76.

*Methyl 3-acetamido-3-deoxy-2-O-mesyl-α-*D*-glucopyranoside* (**8**). — To a suspension of **7** (6.19 g, 15.4 mmol) in methanol (238 mL) was added aqueous 0.5% HCl (12.5 mL). The mixture was heated under reflux for 1 h and then concentrated. The residue was recrystallised from ethanol to give **8** (4.68 g, 97%), m.p. 195–199° (dec.), $[\alpha]_D^{23}$ +100° (*c* 1, methanol), R_F 0.33 (chloroform–ethanol, 3:1); ν_{max}^{KBr} 3490, 3280, 2940, 1655, 1560, 1350, and 1185 cm^{-1}. ^{1}H-N.m.r. data (CD_3OD): δ 1.97 (s, 3 H, NAc), 3.06 (s, 3 H, OMs), 3.47 (s, 3 H, OMe), 3.56–4.64 (m, 6 H, H-2,3,4,5,6,6′), and 4.97 (d, 1 H, $J_{1,2}$ 4 Hz, H-1).

Anal. Calc. for $C_{10}H_{19}NO_8S$: C, 38.33; H, 6.11; N, 4.47; S, 10.23. Found: C, 38.51; H, 5.92; N, 4.22; S, 9.98.

*Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-*D*-mannopyranoside* (**5**). — To a solution of **8** (4.56 g, 14.5 mmol) in 2-methoxyethanol (45 mL) and water (5 mL) was added sodium acetate (4.77 g, 58.2 mmol). The mixture was heated under reflux for 25 h, filtered, and concentrated, and the residue was acetylated conventionally with acetic anhydride (30 mL) in pyridine (30 mL) for 3 h. Recrystallisation of the product from ethanol gave **5** (3.21 g, 61%); from the mother liquor, a second crop of **5** (1.28 g) was obtained by column chromatography (ethyl acetate–hexane, 2:1). Compound **5** (4.49 g, 86%) had m.p. 151–152°, $[\alpha]_D^{23}$ +39° (*c* 1.75, water)

{lit.[7], m.p. 153°, $[\alpha]_D$ +41° (water)}; ν_{max}^{KBr} 3260, 3070, 2950, 1755, 1740, 1660, 1555, 1440, 1370, 1300, and 1255 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.92 (s, 3 H, NAc), 2.05, 2.10, and 2.19 (3 s, each 3 H, 3 OAc), 3.40 (s, 3 H, OMe), 3.90–5.19 (m, 7 H, H-1,2,3,4,5,6,6′), and 5.63 (d, 1 H, *J* 8 Hz, NH).

*3-Acetamido-1,2,4,6-tetra-*O*-acetyl-3-deoxy-α,β-*D*-mannopyranose* (**9**). — A suspension of **5** (3.0 g, 8.3 mmol) in 2M HCl (30 mL) was heated under reflux for 13 h and then concentrated, and the residue was acetylated with acetic anhydride (20 mL) in pyridine (30 mL) overnight. The crude product was purified by column chromatography (ethanol–toluene, 1:5) to give **9** (3.15 g, 98%); $\nu_{max}^{CHCl_3}$ 3430, 3000, 1740, 1680, 1500, and 1370 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.92 (s, 3 H, NAc), 2.06 (s, 6 H, 2 OAc), 2.15, 2.17, and 2.19 (3 s, 6 H, 2 OAc), 3.95–6.17 (m, 7 H, H-1,2,3,4,5,6,6′), and 5.80 (d, 1 H, *J* 8 Hz, NH).

Anal. Calc. for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60. Found: C, 49.62; H, 6.03; N, 3.37.

*3-Acetamido-3-deoxy-6-*O*-triphenylmethyl-*D*-mannose diethyl dithioacetal* (**10**). — To a stirred solution of **9** (3.04 g, 7.8 mmol) in methanol (15 mL) was added methanolic M sodium methoxide (37.5 mL, 37.5 mmol) with cooling (ice). After 2 h, the solution was neutralised with Amberlite IR-120 B (H^+) resin, filtered, and concentrated, and to a solution of the residue in conc. HCl (10 mL) at −15° was added ethanethiol (10 mL) with agitation. After 7 h, basic lead carbonate (60 g) was added, and the mixture was diluted with water (200 mL), filtered, and concentrated to dryness. The residue was dissolved in pyridine (30 mL) and 4-dimethylaminopyridine (0.15 g, 1.2 mmol) and chlorotriphenylmethane (2.57 g, 9.2 mmol) were added with stirring. After stirring at 70° for 3.5 h, the solution was concentrated, the residue was extracted with dichloromethane, and the extract was washed with water, dried (Na_2SO_4), and concentrated. The residual syrup was purified by column chromatography (ethanol–toluene, 1:15 containing 1% of Et_3N) to give **10** (2.46 g, 55%), m.p. 170–172°, $[\alpha]_D^{28}$ −32° (*c* 1, chloroform); ν_{max}^{KBr} 3400, 3050, 2920, 1620, 1450, and 1060 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.25 (t, 6 H, *J* 8 Hz, 2 SCH_2CH_3), 2.04 (s, 3 H, NAc), 2.68 (q, 4 H, *J* 8 Hz, 2 SCH_2CH_3), 3.27–4.70 (m, 10 H, H-1,2,3,4,5,6,6′ and 3 OH), 6.49 (d, 1 H, *J* 9 Hz, NH), and 7.18–7.58 (m, 15 H, OTr).

Anal. Calc. for $C_{31}H_{39}NO_5S_2$: C, 65.35; H, 6.90; N, 2.46; S, 11.25. Found: C, 65.64; H, 6.98; N, 2.43; S, 10.97.

*3-Acetamido-2,4,5-tri-*O*-benzyl-3-deoxy-*D*-mannose diethyl dithioacetal* (**11**). — To a stirred solution of **10** (387 mg, 0.7 mmol) in *N,N*-dimethylformamide (4 mL) was added a suspension of sodium hydride (60% emulsion in mineral oil; 84 mg, 2.1 mmol; washed with hexane) in *N,N*-dimethylformamide (1 mL). After 20 min, benzyl bromide (0.27 mL, 2.2 mmol) was added, and the mixture was stirred overnight in the dark and then concentrated. The residue was extracted with CH_2Cl_2, and the extract was washed with water, dried (Na_2SO_4), and concentrated. To a solution of the residue in methanol (6 mL) was added toluene-*p*-sulfonic acid monohydrate (259 mg, 1.4 mmol). After 2 h, the mixture was neutralised with

aqueous $NaHCO_3$, diluted with water (30 mL), and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (ethyl acetate–hexane, 1:5) to give **11** (142 mg, 35%) as a syrup, $[\alpha]_D^{24}$ −3° (*c* 1, chloroform); $\nu_{max}^{CHCl_3}$ 3560, 3420, 2960, 2870, 1670, 1400, and 1090 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.24 and 1.26 (2 t, each 3 H, *J* 8 Hz, 2 SCH_2CH_3), 1.86 (s, 3 H, NAc), 1.98–2.29 (m, 1 H, OH), 2.26 and 2.72 (2 q, each 2 H, *J* 8 Hz, 2 SCH_2CH_3), 3.32–5.11 (m, 13 H, H-1,2,3,4,5,6,6′, and 3 OCH_2Ph), 6.08 (d, 1 H, *J* 9 Hz, NH), 7.33, 7.35, and 7.37 (3 s, 15 H, OTr).

Anal. Calc. for $C_{33}H_{43}NO_5S_2$: *m/z* 597.2579 (M^+). Found: *m/z* 597.2560.

*3-Acetamido-2,4,5-tri-O-benzyl-3-deoxy-6-O-tosyl-*D*-mannose diethyl dithioacetal* (**4**). — To a stirred solution of **11** (120 mg, 0.2 mmol) in pyridine (2 mL) was added toluene-*p*-sulfonyl chloride (84 mg, 0.4 mmol). Stirring was continued for 16 h, the solution was then concentrated, and the residue was purified by column chromatography (ethyl acetate–hexane, 1:2) to give **4** (115 mg, 77%) as a syrup, $[\alpha]_D^{23}$ +5° (*c* 0.9, chloroform); $\nu_{max}^{CHCl_3}$ 3420, 2970, 2930, 2870, 1670, 1600, 1370, 1180, and 1100 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.20 and 1.22 (2 t, each 3 H, *J* 8 Hz, 2 SCH_2CH_3), 1.79 (s, 3 H, NAc), 2.39 (s, 3 H, $OSO_2C_6H_4CH_3$), 2.59 and 2.60 (2 q, each 2 H, *J* 8 Hz, 2 SCH_2CH_3), 3.45–5.08 (m, 13 H, H-1,2,3,4,5,6,6′ and 3 OCH_2Ph), 5.98 (d, 1 H, *J* 9 Hz, NH), 7.03–7.80 (m, 4 H, $OSO_2C_6H_4CH_3$), 7.29, and 7.31 (2 s, 15 H, 3 Ph).

Anal. Calc. for $C_{40}H_{50}NO_7S_3$: *m/z* 752.2746 $(M + H)^+$. Found: *m/z* 752.2750.

(2S,3S,4R)-1-Acetyl-3,4-dibenzyloxy-2-[(1S)-1-benzyloxy-2,2-bis(ethylthio)-ethyl]pyrrolidine (**12**). — A solution of **4** (100 mg, 0.1 mmol) in 1,4-dioxane (1.5 mL) and M sodium hydroxide (1.5 mL) was heated under reflux for 0.5 h, neutralised with M HCl, diluted with water (6 mL), and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated, and the residue was purified by preparative t.l.c. (ethyl acetate–hexane, 3:2) to give **12** (72 mg, 93%) as a syrup, $[\alpha]_D^{22}$ +28° (*c* 0.7, chloroform), R_F 0.30 (ethyl acetate–hexane, 1:1); $\nu_{max}^{CHCl_3}$ 3000, 2920, 2870, 1630, 1455, 1405, 1360, and 1140 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.07 and 1.20 (2 t, each 3 H, *J* 8 Hz, 2 SCH_2CH_3), 1.90 and 2.29 (2 s, total 3 H, NAc), 2.44–2.80 (m, 4 H, SCH_2CH_3), 3.17–5.19 (m, 13 H, H-2,3,4,5,5′, $(EtS)_2CHCH$, and 3 OCH_2Ph), 7.28, 7.30, and 7.37 (3 s, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{42}NO_4S_2$: *m/z* 580.2552 $(M + H)^+$. Found: *m/z* 580.2527.

(2R,3S,4R)-1-Acetyl-3,4-dibenzyloxy-2-[(1R,2E)-1-benzyloxy-3-ethoxycarbonyl-2-propenyl]pyrrolidine (E-**14**) *and (2R,3S,4R)-1-acetyl-3,4-dibenzyloxy-2-[(1R,2Z)-1-benzyloxy-3-ethoxycarbonyl-2-propenyl]pyrrolidine* (Z-**14**). — To a stirred solution of **12** (289 mg, 0.5 mmol) in water (1 mL) and acetonitrile (4 mL) were added mercury(II) chloride (297 mg, 1.1 mmol) and calcium carbonate (125 mg, 1.2 mmol). After 50 min, the mixture was filtered, diluted with CH_2Cl_2 (60 mL), and washed with M KI (20 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated to give **13** (264 mg) as a pale-yellow syrup, R_F 0.29 (ethyl acetate–hexane, 2:1), which was used for the next step without further purification.

To a stirred suspension of sodium hydride (60% emulsion in mineral oil; 70

mg, 1.7 mmol) in tetrahydrofuran (2 mL) was added diethyl ethoxycarbonylmethylphosphonate (0.35 mL, 1.7 mmol) under argon at 0°. After stirring for 10 min, a solution of **13** (264 mg) in tetrahydrofuran (4 mL) was added and stirring was continued for 4 h. The mixture was then diluted with water (30 mL) and extracted with CH_2Cl_2, and the crude product was purified by column chromatography and then preparative t.l.c. (ethyl acetate–toluene, 1:3) to give *E*-**14** (204 mg, 75%; syrup) and *Z*-**14** (5.1 mg, 2%; syrup).

Compound *E*-**14** had $[\alpha]_D^{24}$ +73° (*c* 1, chloroform), R_F 0.30 (ethyl acetate–toluene, 1:2; 4 developments); $\nu_{max}^{CHCl_3}$ 3000, 2930, 2860, 1720, 1640, 1455, 1405, 1360, 1300, 1275, and 1150 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.25 (t, 3 H, *J* 7 Hz, OCH_2CH_3), 1.89 and 2.06 (2 s, total 3 H, NAc), 3.35–5.17 (m, 14 H, H-2,3,4,5,5′, EtOOCCH=C*H*, OCH_2CH_3, and 3 OCH_2Ph), 6.06 (dd, 1 H, *J* 2 and 15 Hz, CH=C*H*COOEt), 6.72–7.08 (m, 1 H, C*H*=CHCOOEt), 7.28, 7.32, and 7.36 (3 s, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{37}NO_6$: *m/z* 543.2618 (M^+). Found: *m/z* 543.2633.

Compound *Z*-**14** had $[\alpha]_D^{22}$ +88° (*c* 0.4, chloroform), R_F 0.41 (ethyl acetate–toluene, 1:2; 4 developments); $\nu_{max}^{CHCl_3}$ 3000, 2930, 2850, 1740, 1640, 1455, 1410, 1360, 1185, and 1140 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.13 and 1.16 (2 t, total 3 H, *J* 7 Hz, OCH_2CH_3), 1.90 and 2.13 (2 s, total 3 H, NAc), 3.46–5.00 (m, 13 H, H-2,3,4,5,5′, OCH_2CH_3, 3 OCH_2Ph), 5.68–6.05 (m, 2 H, EtOOCCH=C*H*C*H*), 6.26 (dd, 1 H, *J* 2 and 11 Hz, CH=C*H*COO), 7.22, 7.26, and 7.32 (3 s, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{37}NO_6$: *m/z* 543.2618 (M^+). Found: *m/z* 543.2600.

*(2*R*,3*S*,4*R*)-1-Acetyl-3,4-dibenzyloxy-2-[(1*R*)-1-benzyloxy-3-ethoxycarbonylpropyl]pyrrolidine* (**3**). — *(a) From* E-**14**. A solution of *E*-**14** (400 mg, 0.74 mmol) in ethanol (5 mL) was hydrogenated in the presence of Raney nickel under atmospheric hydrogen pressure for 2 h. The mixture was then filtered and concentrated, and the residue was purified by preparative t.l.c. (ethyl acetate–toluene, 1:2) to give **3** (375 mg, 94%) as a syrup, $[\alpha]_D^{26}$ +27.5° (*c* 0.9, chloroform), R_F 0.39 (ethyl acetate–toluene, 1:1; 4 developments); $\nu_{max}^{CHCl_3}$ 3000, 2940, 2860, 1730, 1630, 1455, 1410, 1360, 1260, and 1140 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.14 and 1.16 (2 t, total 3 H, *J* 7 Hz, OCH_2CH_3), 1.60–2.47 (m, 2 H, $EtOOCCH_2CH_2$), 1.98 and 2.16 (2 s, total 3 H, NAc), 3.40–4.70 (m, 16 H, H-2,3,4,5,5′, $EtOOCCH_2CH_2CH$, OCH_2CH_3, and 3 OCH_2Ph), 7.27, 7.32, and 7.35 (3 s, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{39}NO_9$: *m/z* 545.2774 (M^+). Found: *m/z* 545.2766.

(b) From Z-**14**. Compound *Z*-**14** (6.8 mg, 0.01 mmol) was hydrogenated as in *(a)*, to give **3** (4.8 mg, 70%).

*(1*S*,2*R*,8*R*,8a*R*)-1,2,8-Tribenzyloxy-5-oxo-octahydroindolizine* (**2**). — A solution of **3** (126 mg, 0.24 mmol) in ethanol (3 mL) and 15M KOH (1 mL) in a sealed tube was heated at 90° for 6 days. The ethanolic layer was separated and concentrated, and the residue was diluted with water (15 mL), neutralised with acetic acid, and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated, and the residue was purified by preparative t.l.c. (ethyl acetate–toluene, 2:1). The u.v.-absorbing fraction was extracted with $CHCl_3$ to afford **2** (60

mg, 54%), m.p. 87–89°, $[\alpha]_D^{25}$ −46° (*c* 0.6, chloroform); ν_{max}^{KBr} 3440, 2920, 2870, 1630, 1460, 1410, 1270, 1150, and 1120 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.50–2.60 (m, 4 H, H-6,6′,7,7′), 3.40–5.06 (m, 12 H, H-1,2,3,3′,8,8a and 3 OCH_2Ph), 7.31, and 7.33 (2 s, 15 H, 3 Ph).

Anal. Calc. for $C_{29}H_{31}NO_4$: C, 76.12, H, 6.83; N, 3.06. Found: C, 76.33; H, 6.91; N, 3.25.

(1S,2R,8R,8aR)-1,2,8-Tribenzyloxyoctahydroindolizine (swainsonine tribenzylate, **15***).* — To a solution of **2** (58.6 mg, 0.13 mmol) in tetrahydrofuran (2 mL) was added $LiAlH_4$ (9.7 mg, 0.26 mmol). The mixture was heated under reflux for 5 h and ethyl acetate (1 mL) was added. Insoluble matter was removed, the filtrate was concentrated, and the residue was purified by preparative t.l.c. (ethyl acetate–toluene, 2:1). The u.v.-absorbing fraction was extracted with $CHCl_3$ to afford **15** (42.2 mg, 74%) as a pale-yellow syrup, $[\alpha]_D^{24}$ −89° (*c* 0.8, chloroform), R_F 0.48 (ethyl acetate–toluene, 2:1); $\nu_{max}^{CHCl_3}$ 3020, 2940, 2800, 1455, 1220, 1205, 1140, and 1110 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.05–2.55 (m, 7 H, H-3,5,6,6′,7,7′,8a), 2.80–3.35 (m, 2 H, H-3′,5′), 3.65–4.35 (m, 3 H, H-1,2,8), 4.42–5.00 (m, 6 H, 3 OCH_2Ph), 7.29, and 7.32 (2 s, 15 H, 3 Ph).

Anal. Calc. for $C_{29}H_{33}NO_3$: *m/z* 443.2458 (M^+). Found: *m/z* 443.2449.

(1S,2R,8R,8aR)-1,2,8-Trihydroxyoctahydroindolizine (swainsonine, **1***).* — To a solution of **15** (33 mg, 0.07 mmol) in ethanol (1 mL) were added 20% $Pd(OH)_2/C$ (15 mg) and cyclohexene (1 mL). The mixture was heated under reflux for 44 h, filtered, and concentrated, and the residue was purified[3] by preparative t.l.c. (acetone–chloroform–water–conc. ammonia, 30:5:4:1). The fraction having R_F 0.28 (the edge of which was detected with ninhydrin) was extracted with methanol, and the extract was concentrated to afford **1** (9.3 mg, 72%). Recrystallisation from chloroform gave material having m.p. 142–143°, $[\alpha]_D^{23}$ −82° (*c* 0.6, methanol); {lit.[1,3], m.p. 144–145°, $[\alpha]_D^{20}$ −78.9° (methanol), $[\alpha]_D^{25}$ −87.2° (methanol)}; ν_{max}^{KBr} 3500, 3200, 2940, 2800, and 1070 cm^{-1}. ^{1}H-N.m.r. data (D_2O): δ 0.98–2.15 (m, 6 H, H-5,6,6″,7,7′,8a), 2.50 (dd, 1 H, $J_{2,3}$ 6, $J_{3,3'}$ 11 Hz, H-3), 2.74–3.01 (m, 2 H, H-3′,5′), 3.76 (ddd, 1 H, $J_{7,8}$ 5, $J_{7',8}$ 10, $J_{8,8'}$ 10 Hz, H-8), 4.17–4.44 (m, 2 H, H-1,2); mass spectrum (l.r.-m.s.): *m/z* 173 (M^+), 155, 138, 113, and 96.

Anal. Calc. for $C_8H_{15}NO_3$: *m/z* 173.1051 (M^+). Found: *m/z* 173.1058.

(1S,2R,8R,8aR)-1,2,8-Triacetoxyoctahydroindolizine (swainsonine triacetate, **16***).* — Synthetic **1** (4.0 mg, 0.02 mmol) was acetylated[1] to give **16** (6.9 mg) as a pale-yellow syrup, $[\alpha]_D^{24}$ +1.3° (*c* 0.3, methanol) {lit.[3] $[\alpha]_D^{26}$ +7° (methanol)}, R_F 0.53 (ethanol–toluene, 1:5); $\nu_{max}^{CHCl_3}$ 3020, 2950, 2800, 1745, 1375, 1260, 1210, and 1045 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.05–2.20 (m, 6 H, H-5,6,6′,7,7′,8a), 1.98, 2.04, and 2.09 (3 s, each 3 H, 3 OAc), 2.55 (dd, 1 H, *J* 8 and 11 Hz, H-3′), 2.90–3.07 (m, 1 H, H-5′), 3.19 (dd, 1 H, *J* 2 and 11 Hz, H-3), 4.96 (ddd, 1 H, *J* 5, 10, and 10 Hz, H-8), 5.24 (ddd, 1 H, *J* 2, 6, and 8 Hz, H-2), and 5.51 (dd, 1 H, *J* 4 and 6 Hz, H-1); mass spectrum (l.r.-m.s.): *m/z* 239, 180, 137, and 120.

Anal. Calc. for $C_{14}H_{22}NO_6$: *m/z* 300.1445 $(M + H)^+$. Found: *m/z* 300.1433.

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