evaporation to give 33.9 mg (76%) of a mixture (1:3, 200-MHz ^{1}H NMR) of dimethyl jaconate and its epimer.

L-Selectride Reduction of Ketone 24. Ketone **24** (30 mg, 0.12 mmol) was dissolved in 2 mL of dry THF and cooled under nitrogen to −78 °C. L-Selectride (nAldrich; 0.2 mL, 1 M in THF, 0.2 mmol) was slowly added via syringe, and the mixture was stirred under nitrogen at −78 °C for 0.5 h. The reaction was then quenched by the slow addition of 2 mL of saturated ammonium chloride and water. The resulting mixture was extracted three times with ether, and then the ether was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a crude oil. This material was purified with the Chromatotron (1-mm plate, ether) to give 3 mg (10%) of a mixture (1:1.5, 200-MHz ^{1}H NMR) of dimethyl jaconate and its epimer.

K-Selectride Reduction of Ketone 24. Ketone **24** was dissolved in 3 mL of dry THF and cooled under nitrogen to −78 °C. K-Selectride (Aldrich; 0.44 mL, 1 M in THF, 0.44 mmol) was added via syringe, and the solution was stirred at −78 °C for 1 h. The reaction was then warmed to 0 °C and quenched by the addition of 0.33 mL of 1.6 M NaOH followed by the slow addition of 0.14 mL of 30% hydrogen peroxide. The mixture was allowed to warm to room temperature, made acidic with 3 N HCl, and extracted three times with ether. The ether was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give a yellow oil. This oil was purified with the Chromatotron (1-mm plate, ether) to give 35 mg (61%) of a mixture (1:1.8, 200-MHz ^{1}H NMR) of dimethyl jaconate and its epimer.

Sodium Borohydride Reduction of Ketone 25. Ketone **25** (321 mg, 1.22 mmol) was reduced as described for ketone **24** to give 287 mg (89%) of a clear oil. The ozonolysis and Raney Nickel desulfurization of this material gave a mixture (4:1, 200-MHz ^{1}H NMR, GC–MS) of dimethyl jaconate and its epimer: ^{13}C NMR of major isomer (50.31 MHz, $CDCl_3$) δ 174.42, 172.73, 90.31, 86.45, 67.80, 52.50, 39.92, 34.01, 19.97, 16.97, 14.14.

L-Selectride Reduction of Ketone 25. Ketone **25** was reduced with L-Selectride (0.62 mL, 1 M in THF, 0.62 mmol) as for ketone **24**. The crude oil was purified with the Chromatotron (1-mm plate, ether–hexane (1:1)) to give 80 mg (63%) of a solid (mp 85–90 °C). The ozonolysis and Raney nickel desulfurization of this material gave a mixture (5:1, 200-MHz ^{1}H NMR, GC–MS) of dimethyl jaconate and its epimer.

Zinc Borohydride Reduction of Ketone 25. An ether solution of zinc borohydride (8 mL, 0.18 M, 1.44 mmol) was used to reduce ketone **25** (199 mg, 0.75 mmol) as for ketone **24** to give 162 mg (81%) of a solid (mp 83–90 °C). The ozonolysis and Raney nickel desulfurization or this material gave a mixture (1.5:1, 200-MHz ^{1}H NMR, GC–MS) of dimethyl jaconate and its epimer.

K-Selectride Reduction of Ketone 25. Ketone **25** (199 mg, 0.75 mmol) was reduced described as for ketone **24**. The crude oil was purified with the Chromatotron (1-mm plate, ether–hexane (1:1)) to give 57 mg (30%) of a 1:2 mixture (200-MHz ^{1}H NMR) of the tricyclic alcohols leading to dimethyl jaconate and its epimer. A second less polar component (44 mg) was isolated and found to be the product of reduction of the double bond.

Jaconecic Acid (3a). A 5:1 mixture of synthetic dimethyl jaconate and its epimer (22 mg), from the L-Selectride reduction of **25** was dissolved in about 4 mL of 80% ethanol containing 0.4 g of KOH. This solution was heated at reflux for 2 h, the ethanol was removed, and the slurry was dissolved in water. This aqueous solution was extracted with ether and made acidic with 3 N HCl. The water was removed by high-vacuum rotary evaporation. The salts were extracted with hot ethyl acetate three times, and the solvent was removed by rotary evaporation to give 13.4 mg (66%) of a light yellow solid. Recrystallization gave pure (±)-jaconecic acid (mp 170–175 °C, ethyl acetate/hexane): ^{1}H NMR (200 MHz, acetone-d_6) δ 1.07 (d, J = 6.42 Hz, 3 H, CH_3CH), 1.24 (d, J = 6.44 Hz, 3 H, CH_3CH(OH)), 1.32 (s, 3 H, CH_3), 1.70–1.80 (m, 1 H, CH), 2.25–2.50 (m, 2 H, CH_2), 4.05 (q, J = 6.44 Hz, 1 H, HCOH). The 200-MHz ^{1}H NMR spectrum is identical with that of an authentic sample of jaconecic acid.[13]

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Syntheses of (−)-2,8a- and (−)-8,8a-Di-*epi*-swainsonine and Evaluation of Their Inhibitory Activity against Several Glycosidases[1]

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Two stereoisomers of the potent α-D-mannosidase inhibitor, swainsonine (**1**), namely, (−)-2,8a- (**5**) and (−)-8,8a-di-*epi*-swainsonine (**6**), have been synthesized from the known azido alcohol **7**. The synthesis of **5** was accomplished via a configurational inversion at C-2 of (1*S*,2*R*,8*R*,8a*S*)-1,8-bis(benzyloxy)-2-[(methylsulfonyl)-oxy]octahydro-5-indolizinone (**10**), which in turn was prepared from the previously reported disubstituted 2-piperidone **8**. The synthesis of **6** involved (1) 2-piperidone (δ-lactam) formation from both of the geometrical isomers of ethyl (4*R*,5*S*,6*S*,7*R*)-5-azido-4-(benzyloxy)-8-[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedi-oxy)-2-octenoate (**19**-*E* and **19**-*Z*) by reduction of the azido group and the double bond followed by desilylation accompanied with cyclization for construction of the 2-piperidone skeleton and (2) stereochemical inversion at C-8 of (1*S*,2*R*,8*R*,8a*R*)-1,2-(isopropylidenedioxy)-8-[(methylsulfonyl)oxy]octahydro-5-indolizinone (**23**). Preliminary bioassays of (−)-2,8a- (**5**) and (−)-8,8a-di-*epi*-swainsonine (**6**) for the glycosidase inhibitory activity reveal that **6** is a potent inhibitor of human lysosomal α-D-mannosidase.

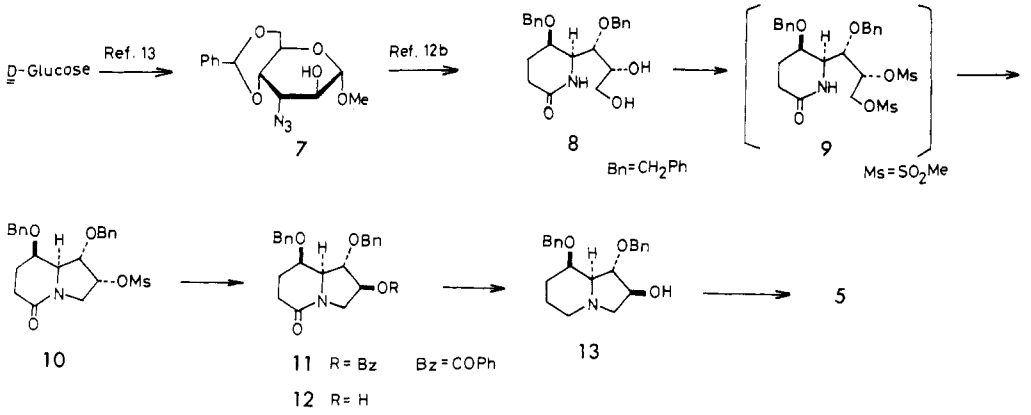
(−)-Swainsonine (**1**), (1*S*,2*R*,8*R*,8a*R*)-octahydro-1,2,8-indolizinetriol, was first isolated from the fungus *Rhizoctonia leguminicola* by Broquist et al. in 1973.[2] This novel indolizidine alkaloid 1 has also been isolated from several

(1) The present work was presented at the 54th National Meeting of the Japan Chemical Society in Tokyo, April 1–4, 1987.

(2) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055.

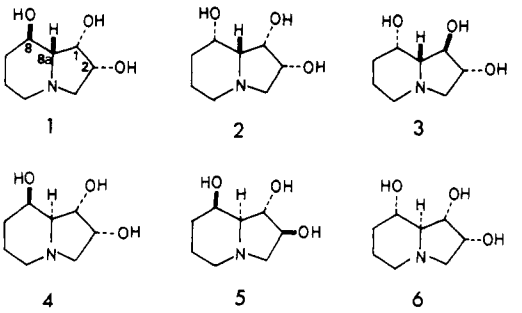
0022-3263/88/1953-5209$01.50/0

Scheme I



other sources such as *Swainsona canescens*,[3] *Astragalus lentiginosus*,[4] and *Metarhizium anisopliae* F-3622.[5] Swainsonine has aroused much interest owing to its potent α-D-mannosidase inhibitory activity[3,4,6] and immunomodulating activity.[7] The latter activity may be sufficient to consider **1** as a possible candidate for cancer chemotherapy. The relative stereochemistry of **1** was determined by spectral means,[3] and the absolute configuration of **1** was established by Harris et al. in 1983.[8] Enantioselective total syntheses of (−)-**1**[9] have confirmed the absolute configuration of **1** to be 1*S*,2*R*,8*R*,8a*R*. Very recently, Harris et al. have reported the biosynthesis of (−)-**1** from L-lysine via L-pipecolic acid, and its biosynthetic correlation to the related indolizidine alkaloid, slaframine, was demonstrated.[10]

Synthetic studies on the stereoisomers of **1** are of current interest to elucidate the structure–bioactivity relationship of the inhibition of glycosidases by unnatural indolizidine alkaloids.[11] Recently, we reported syntheses and α-D-mannosidase inhibitory activity for three swainsonine stereoisomers, namely, (−)-8-*epi*-(**2**),[12a] (+)-1,8-di-*epi*-swainsonine (**3**),[12a] and (−)-8a-*epi*-swainsonine (**4**).[12b] The



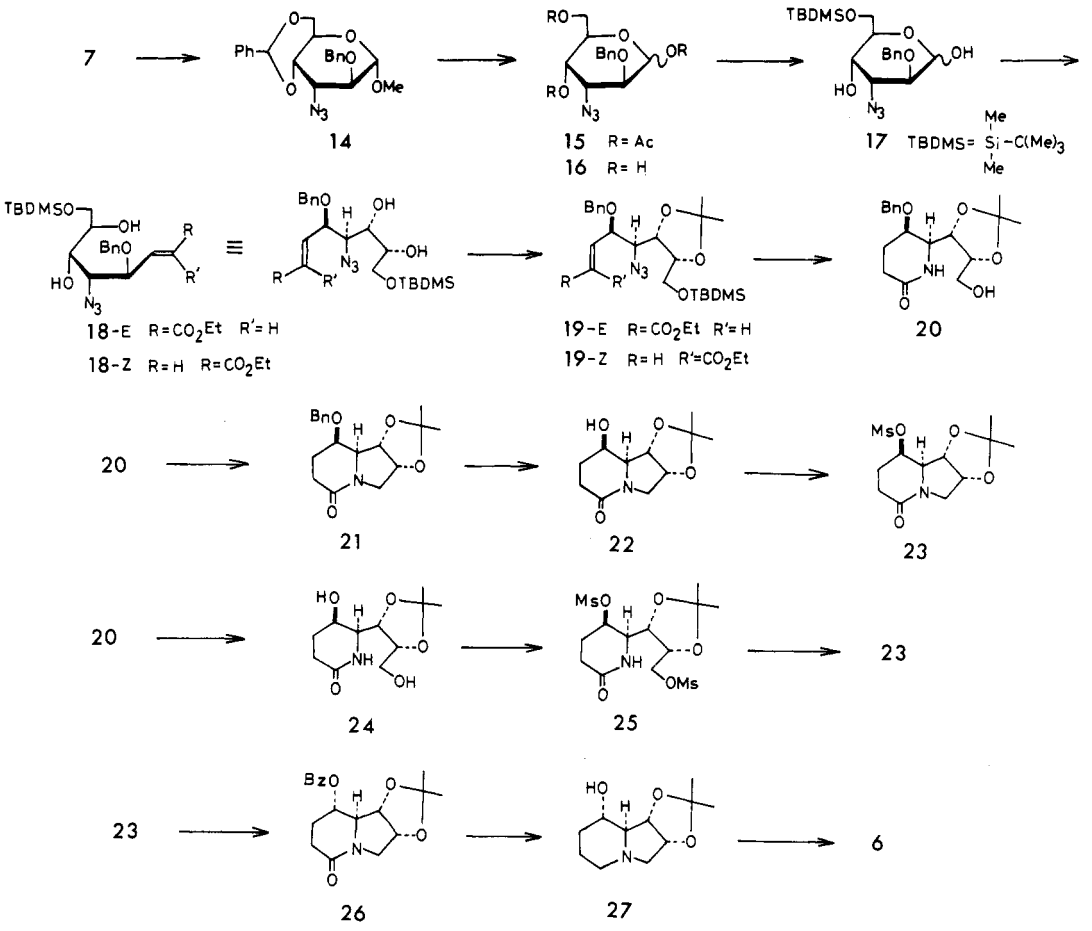
syntheses of **2**–**4** were achieved by conceptually analogous routes to our previous synthesis of (−)-**1**,[9a] and two 3-amino-3-deoxy-D-aldohexose derivatives and a 3-azido-3-deoxy-D-altrose derivative were efficiently transformed into **2**–**4**. Furthermore, compound **4** exhibited potent α-D-mannosidase inhibitory activity. This fact prompted us to extend the synthetic work to other stereoisomers of **1**.

In this paper, we describe syntheses of two new swainsonine stereoisomers, namely, (−)-2,8a- (**5**) and (−)-8,8a-di-*epi*-swainsonine (**6**), from the readily available methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (**7**).[13] The syntheses of **5** and **6** from **7** involve (1) our previously developed[12b] intramolecular δ-lactam formation (2-piperidone formation) and (2) stereoinversion of the 2- or 8-hydroxy group in the constructed 5-oxoindolizinetriol derivatives. The inhibitory activity of synthetic **5** and **6** against glycosidases was also investigated.

Synthesis of (−)-2,8a-Di-*epi*-swainsonine (5) (Scheme I). Azido sugar **7**[13] was converted into (5*R*,6*S*)-5-(benzyloxy)-6-[(1*S*,2*R*)-[1-(benzyloxy)-2,3-dihydroxy]propyl]-2-piperidone (**8**) as previously described.[12b] O-Sulfonylation of **8** with excess methanesulfonyl chloride gave 2-*O*-mesyl derivative **10** of octahydro-5-oxoindolizine-1,2,8-triol in 64% yield. This reaction most likely proceeds via dimesylate **9**, which could

(3) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257. Skeleton, B. W.; White, A. H. *Ibid.* **1980**, *33*, 435.
(4) Molyneux, R. J.; James, L. F. *Science (Washington, D.C.)* **1982**, *216*, 190.
(5) Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926.
(6) Dorling, P. R.; Huxtable, C. R.; Colegate, S. M. *Biochem. J.* **1980**, *181*, 649. Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7393. Tulsiani, D. R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936.
(7) Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 936. Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1752. Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131.
(8) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29.
(9) (a) Suami, T.; Tadano, K.; Iimura, Y. *Chem. Lett.* **1984**, 513; *Carbohydr. Res.* **1985**, *136*, 67. (b) Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447; *Carbohydr. Res.* **1985**, *136*, 225. (c) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853. (d) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1984**, 1201. (e) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420. (f) Setoi, H.; Takano, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948. (g) Bashyal, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083. (h) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140.
(10) Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940 and references cited therein for the preceding works on biosynthesis of **1** and slaframine.
(11) (a) Syntheses of (−)-8-*epi*- (**2**) and (+)-2,8-di-*epi*-swainsonine: Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1985**, 31. (b) Another synthesis of (−)-**2**: Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095. (c) Syntheses of (−)-1-*epi*- and (+)-1,8-di-*epi*-swainsonine (**3**): Ikota, N.; Hanaki, A. *Heterocycles* **1987**, *26*, 2369. (d) Glycosidase activity of (−)-2-*epi*- and (−)-2,8-di-*epi*-swainsonine: Elbein, A. D.; Szumilo, T.; Sanford, B. A.; Sharpless, K. B.; Adams, C. *Biochemistry* **1987**, *26*, 2502. (e) Syntheses of (6*R*,7*S*,8a*R*)-dihydroxyindolizidine and (6*R*,7*R*,8*S*,8a*R*)- and (6*S*,7*R*,8*R*,8a*R*)-trihydroxyindolizidine: Hendry, D.; Hough, L.; Richardson, A. C. *Tetrahedron Lett.* **1987**, *28*, 4597 and 4601.
(12) (a) Iimura, Y.; Hotta, Y.; Fukabori, C.; Tadano, K.; Suami, T. *J. Carbohydr. Chem.* **1986**, *5*, 147; *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3885. In these articles, we regretfully misread the $[\alpha]_D$ of **3**. The correct value of it was shown in ref 11c. We are grateful to Dr. Ikota (National Institute of Radiological Sciences, Japan) for the indication and valuable discussion in this matter of the specific rotation of **3**. The α-D-mannosidase inhibitory activity of (−)-**2** and (+)-**3** are approximately 15% and 20% of (−)-**1**, respectively. (b) Tadano, K.; Hotta, Y.; Morita, M.; Suami, T.; Winchester, B.; Cenci di Bello, I. *Chem. Lett.* **1986**, 2105; *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2667. The α-D-mannosidase inhibitory activity of (−)-**4** is 93% of (−)-**1**.
(13) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1963**, 5288.

Scheme II



not be isolated, and successive intramolecular N-alkylation affording the octahydro-5-indolizinone skeleton. Displacement of the mesyloxy group in **10** by benzoate anion in S_N2 fashion was achieved smoothly by refluxing **10** in DMF in the presence of sodium benzoate. Compound **11** was obtained in 86% yield. Debenzoylation of **11** with sodium methoxide in methanol gave the 2-hydroxy derivative **12** in 62% yield. Reduction of **12** with excess of BH_3–Me_2S complex at 0 °C afforded partially benzylated (1*S*,2*S*,8*R*,8a*S*)-octahydro-1,2,8-indolizinetriol **13** in 76% yield. Final deprotection of the benzyl ethers in **13** was achieved by treatment of **13** in $CHCl_3$ with iodotrimethylsilane.[14] Under these conditions, the desired **5** was obtained in 88% yield as white crystals after purification using preparative TLC. Comparison of the ^{13}C NMR spectrum of **5** with that of (−)-8a-*epi*-swainsonine (**4**)[12b] demonstrated that the two compounds are different and that configurational inversion had occurred at C-2.

Synthesis of (−)-8,8a-Di-*epi*-swainsonine (6) (Scheme II). The hydroxy group at C-2 in **7**, which corresponds to C-8 of **6**, was first protected as a benzyl ether by a standard benzylation procedure to afford **14** as crystals in 94% yield. Debenzylidenation of **14** with aqueous acetic acid followed by acetolysis with acetic anhydride in the presence of sulfuric acid provided the triacetate **15** as an anomeric mixture. This anomeric mixture **15**, without separation, was then deacetylated with sodium methoxide to give an anomeric mixture **16** as crystals in 82% yield. Selective silylation of the primary hydroxyl group in **16** with *tert*-butylchlorodimethylsilane in a DMF solution in the presence of triethylamine gave 6-O-silylated derivative **17** in 85% yield as an anomeric mixture. Wittig olefination of the mixture **17** with (carbethoxymethylene)triphenylphosphorane (3 molar equiv) in refluxing benzene provided the *E* isomer of α,β-unsaturated ester **18**-*E* and the *Z* isomer, **18**-*Z*, in an approximately 1:1 ratio (60% combined yield). The inseparable mixture **18**-*E* and **18**-*Z* was then converted into the isopropylidene derivatives under standard conditions. The resulting mixture **19**-*E* and **19**-*Z* was partially separable, and pure **19**-*E* and **19**-*Z* were obtained in 35% and 40% yields, respectively (9% of the 1:1 mixture of **19**-*E* and **19**-*Z* was also obtained). The geometries of **19**-*E* and **19**-*Z* were determined by their ^1H NMR spectra (a doublet at δ 6.09 with J = 16 Hz for the α-vinyl proton in **19**-*E* and a doublet at δ 5.93 with J = 12 Hz for the α-vinyl proton in **19**-*Z*). Reduction of the azido group and hydrogenation of the double bond in both **19**-*E* and **19**-*Z* by catalytic hydrogenation in the presence of Raney nickel, followed by desilylation with tetrabutylammonium fluoride, furnished 2-piperidone derivative **20** in 82% yield from **19**-*E* and in 77% yield from **19**-*Z*. The cyclization of the reduced product to the 2-piperidone was possible after desilylation.[15] Then, under O-sulfonylation conditions (methanesulfonyl chloride in pyridine at 40 °C), compound **20** was converted into crystalline 5-indolizinone derivative **21** in 77% yield. Next,

(14) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(15) The preparation of **20** was also examined starting from 3-azido-2-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-α,β-D-allose, which was prepared by silylation of **16** with *tert*-butylchlorodiphenylsilane (64%), by the analogous reaction sequence for the preparation of **20** from **16**. The overall yield of the series of reactions was 25% (60% for *E* and *Z* mixture by the Wittig olefination, 88% for the isopropylidenation, and 48% for reduction of the *E* and *Z* mixture followed by desilylation). Therefore, the route from **17** to **20** was more practical than that from the 6-*O*-(*tert*-butyldiphenylsilyl) derivative of **16**.

introduction of a leaving group at C-8 in **21** was investigated. Debenzylation of **21** under the Hanessian conditions[16] provided **22** in 64% yield (17% of **21** was recovered). Sulfonylation of **22** with methanesulfonyl chloride gave the 8-*O*-mesyl derivative **23** in 83% yield. At this stage, we pursued a more practical route to **23** from **20**. Prior to cyclization to the 5-indolizinone skeleton, the benzyl group in **20** was deblocked by the Hanessian conditions[16] to provide **24**. Compound **24** was then treated with excess of methanesulfonyl chloride in pyridine at room temperature. As a result, the dimesylate **25** was obtained, which was directly treated with potassium carbonate in an aqueous dioxane solution at 90 °C. Compound **23** was isolated in 67% yield from **20** after silica gel chromatographic purification. Thus, compound **23** was obtained in improved yield by the latter route. S_N2 displacement of the mesyloxy group in **23** by benzoate in hot DMF afforded **26** in 84% yield. BH_3–Me_2S complex reduction of **26** followed by potassium carbonate treatment in methanol at 75 °C afforded an octahydro-1,2,8-indolizinetriol derivative **27** in 76% yield. Finally, deisopropylidenation of **27** with 1 M aqueous HCl gave **6** in 84% yield after purification by passage through an Amberlite column. The spectral (^1H and ^{13}C NMR) data for the product are consistent with structure **6**.

Inhibitory Activity of 2,8a-Di-*epi*-swainsonine (5) and 8,8a-Di-*epi*-swainsonine (6) against Glycosidases.[17] 8,8a-Di-*epi*-swainsonine (**6**) is a powerful competitive inhibitor of human acidic (lysosomal) α-D-mannosidase, with a value of K_i of 2×10^{-6} M at pH 4.0, the optimum pH for this enzyme. This compares with a value of K_i of 7×10^{-8} M for swainsonine acting on the same enzyme under identical conditions.[18] This compound was also a very weak inhibitor (24% at 1 mM) of β-D-mannosidase. All the other glycosidases were inhibited or activated by less than 15% at this high concentration of inhibitor.

In contrast, 2,8a-di-*epi*-swainsonine (**5**) did not inhibit α-D-mannosidase but caused slight activation (+15%) as it did for β-D-mannosidase, α-D-galactosidase, and α-D-glucosidase. It was however a weak inhibitor of β-D-galactosidase (−30%), α-L-arabinosidase (−21%) and β-D-xylosidase (−13%), suggesting that it inhibits the broad specificity cytosolic β-D-galactosidase in human liver. It had no effect on the other glycosidases.

We have shown previously that alteration of the configuration at the bridge carbon atom (8a) does not abolish the inhibitory activity of swainsonine toward α-D-mannosidase.[12b] However, additional change of the configuration at carbons 2 or 8 abolished and enhanced inhibition of α-D-mannosidase, respectively. Elbein et al. have demonstrated that alteration of the configuration of swainsonine at either C-2 or C-8 separately abolishes inhibitory activity toward α-D-mannosidase.[11d]

The small activation of glycosidases by these compounds is often observed with sugar analogues and is attributable to general stabilization of the enzymes by such compounds.

Experimental Section

General Procedures. Reactions were carried out at room temperature unless otherwise described. The reaction mixtures and the combined extracts were concentrated in vacuo by an evaporator at 30–40 °C. Melting points are uncorrected. Specific rotations were measured on a Jasco DIP-4 polarimeter in $CDCl_3$ solutions with a 10-mm cell. Column chromatography was performed with a silica gel (Katayama Chemicals, K070) and thin-layer chromatography (TLC) with a glass plate coated with Kieselgel 60 GF_{254} (Merck), followed by UV light detection and charring with sulfuric acid. Preparative TLC (PTLC) was performed on a glass plate (20 × 20 cm) coated with Kieselgel PF_{254} (Merck). ^1H NMR spectra were recorded at 90 MHz in $CDCl_3$ solution. ^{13}C NMR spectra were recorded at 100 MHz in CD_3OD solution.

Acetone was distilled over K_2CO_3. Benzene, dichloromethane (CH_2Cl_2), and *N*,*N*-dimethylformamide (DMF) were dried over CaH_2 and then distilled. Pyridine was distilled over NaOH. Tetrahydrofuran (THF) was distilled over $LiAlH_4$ and then over Na/benzophenone.

(1*S*,2*R*,8*R*,8a*S*)-1,8-Bis(benzyloxy)-2-[(methylsulfonyl)oxy]octahydro-5-indolizinone (10). To a stirred solution of **8**[12b] (213 mg, 0.55 mmol) in pyridine (20 mL) was added methanesulfonyl chloride (0.13 mL, 1.66 mmol). The mixture was stirred for 24 h, while methanesulfonyl chloride was added after 2.5 h (0.13 mL) and 6.5 h (0.06 mL). The mixture was concentrated and the residue was partitioned between CH_2Cl_2 (40 mL) and water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL × 2), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The resulting white crystals were purified by PTLC (EtOH/toluene 1:5, three developments; $CHCl_3$ extraction) to give **10** (158 mg, 64%) as white needles, mp 167–168 °C. **10**: TLC R_f 0.61 (EtOH/toluene 1:5); $[\alpha]^{24}_D$ −116.2° (*c* 1.02); IR ν_{max}^{KBr} 3020, 2960, 2890, 1620, 1450, 1370, 1350, 1270 cm^{-1}; ^1H NMR δ 2.14–2.57 (4 H, m H-6,6′,7,7′), 2.98 (3 H, s, OSO_2CH_3), 3.60–4.88 (9 H, m, H-1,3,3′,8,8a, 2 × $OCH_2C_6H_5$), 5.27–5.46 (1 H, m, H-2), 7.32, 7.35 (total 10 H, each s, 2 × $OCH_2C_6H_5$). Anal. Found: C, 61.90; H, 6.09; N, 3.03. Calcd for $C_{23}H_{27}NO_6S$: C, 62.00; H, 6.11; N, 3.14.

(1*S*,2*S*,8*R*,8a*S*)-2-(Benzoyloxy)-1,8-bis(benzyloxy)octahydro-5-indolizinone (11). A solution of **10** (158 mg, 0.35 mmol) in DMF (6 mL) containing dried sodium benzoate (78 mg, 0.53 mmol) was refluxed for 3.5 h and then concentrated. The residue was partitioned between AcOEt (100 mL) and water (100 mL). The aqueous layer was extracted with AcOEt (100 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (20 g, EtOH/toluene 1:30). Fractions corresponding to R_f 0.68 (EtOH/toluene 1:5) were concentrated to give **11** (144 mg, 86%) as a pale yellow syrup. **11**: $[\alpha]^{25}_D$ −31.1° (*c* 0.77); IR ν_{max}^{neat} 3000, 2980, 2870, 1720, 1640, 1450, 1360, 1270 cm^{-1}; ^1H NMR δ 2.13–2.57 (4 H, m, H-6,6′,7,7′), 3.48–4.04 (5 H, m, H-1,3,3′,8,8a), 4.18–4.47 (4 H, m, 2 × $OCH_2C_6H_5$), 5.26–5.54 (1 H, m, H-2), 7.25, 7.30 (total 10 H, each s, 2 × $OCH_2C_6H_5$), 7.36–7.60, 7.88–8.12 (total 5 H, each m, $OCOC_6H_5$).

(1*S*,2*S*,8*R*,8a*S*)-1,8-Bis(benzyloxy)-2-hydroxyoctahydro-5-indolizinone (12). A solution of **11** (144 mg, 0.305 mmol) in CH_2Cl_2 (8 mL) containing sodium methoxide (1 M in methanol, 0.92 mL, 0.92 mmol) was stirred at 0 °C for 5 h and then at room temperature for 4 h. The mixture was neutralized by addition of acetic acid, diluted with water (80 mL), and extracted with AcOEt (80 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (15 g, EtOH/toluene 1:40). Fractions corresponding to R_f 0.51 (EtOH/toluene 1:5) were concentrated to give **12** (69 mg, 62%) as a colorless foam. **12**: $[\alpha]^{24}_D$ −81.4° (*c* 0.97); IR ν_{max}^{KBr} 3260, 2950, 2900, 1630, 1480, 1450, 1350, 1210 cm^{-1}; ^1H NMR δ 2.05–2.57 (4 H, m, H-6,6′,7,7′), 3.00–4.23 (7 H, m, H-1,2,3,3′,8,8a, OH), 4.26–4.82 (4 H, m, 2 × $OCH_2C_6H_5$), 7.32, 7.34 (total 10 H, each s, 2 × $OCH_2C_6H_5$). Anal. Found: C, 71.89; H, 6.91; N, 3.70. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81.

(1*S*,2*S*,8*R*,8a*S*)-1,8-Di-*O*-benzyloctahydro-1,2,8-indolizinetriol (13). To a stirred solution of **12** (67 mg, 0.18 mmol) in THF (3 mL) was added BH_3–Me_2S complex (10 M, neat, 0.06 mL, 0.6 mmol) at 0 °C under argon atmosphere. After being stirred for 2 h, the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (20 mL × 4). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in EtOH (6 mL), and the solution was refluxed for 2 h and then concentrated. The residue was chromatographed on silica gel (6 g, EtOH/toluene 1:40). Fractions corresponding to

(16) Hanessian, S.; Liak, T.; Vanasse, B. *Synthesis* **1981**, 396.

(17) The results on the glycosidase inhibitory activity of **5** and **6** were presented by one of us (B.W.) at the Swainsonine and Related Glycosidase Inhibitors Workshop in Logan, Utah, August 10–14, 1987.

(18) Chotai, K.; Jennings, C.; Winchester, B.; Dorling, P. *J. Cell. Biochem.* **1983**, *21*, 107.

R_f 0.73 (EtOH/toluene 1:4) were concentrated to give **13** (48.5 mg, 76%) as a colorless syrup. **13**: $[\alpha]^{25}_D$ −100.8° (*c* 0.95); IR ν^{neat}_{max} 3500, 3000, 2950, 2800, 1450, 1360, 1260 cm^{-1}; ^{1}H NMR δ 1.12–2.25 (6 H, m, H-5,6,6′,7,7′,8a), 2.45 (1 H, dd, *J* = 6 and 10 Hz, H-3), 2.60–3.14 (3 H, m, H-3′,5′, OH), 3.63–4.13 (3 H, m, H-1,2,8), 4.18–4.72 (4 H, m, 2 × OCH_2C$_6$H$_5$), 7.32 (10 H, s, 2 × OCH$_2$C$_6$H$_5$); high-resolution mass spectrum, calcd for $C_{22}H_{27}NO_3$ *m*/*z* 353.1989, found (M) 353.1988.

(1*S*,2*S*,8*R*,8a*S*)-Octahydro-1,2,8-indolizinetriol (2,8a-Di-*epi*-swainsonine, 5). A solution of **13** (39 mg, 0.11 mmol) in $CHCl_3$ (2 mL) containing iodotrimethylsilane (0.15 mL, 1.05 mmol) was stirred in dark for 15 h. Then MeOH (1 mL) was added to the mixture, which was stirred for 2 h. The solution was concentrated. The residue was partitioned between CH_2Cl_2 (15 mL) and water (15 mL). The organic layer was extracted with water (15 mL × 2). The combined aqueous layers were concentrated. The residue was purified by PTLC (ammonia–water/butanol/$CHCl_3$/EtOH 1:4:4:4, six developments, the edge of the plate was visualized by spraying with ninhydrin for detection of **5**). Compound **5** was extracted with MeOH to give 17 mg (88%) as white crystals, mp 138–142 °C dec. **5**: TLC R_f 0.66 (ammonia–water/butanol/$CHCl_3$/EtOH 1:4:4:4); $[\alpha]^{26}_D$ −24.0° (*c* 1.14, MeOH); IR ν^{KBr}_{max} 3410, 3260, 2920, 2820, 1335, 1240, 1210 cm^{-1}; ^{1}H NMR (D_2O) δ 1.35–2.25 (6 H, m, H-5,6,6′,7,7′,8a), 2.60 (1 H, dd, *J* = 6 and 10 Hz, H-3), 2.77–3.08 (2 H, m, H-3′,5′), 3.87–4.20 (3 H, m, H-1,2,8); ^{13}C NMR δ 20.46, 32.26, 54.15, 62.81, 64.71, 75.09, 77.96, 80.30; high-resolution mass spectrum, calcd for $C_8H_{15}NO_3$ *m*/*z* 173.1051, found (M) 173.1055.

Methyl 3-Azido-2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (14). Sodium hydride (60% emulsion in mineral oil, 547 mg, 13.7 mmol) was washed with hexane (4 mL × 3), dried, and suspended in DMF (15 mL). To the suspension was added a DMF solution (25 mL) of **7**[13] (3.50 g, 11.4 mmol). After being stirred for 5 min at 0 °C, benzyl bromide (1.63 mL, 13.7 mmol) was added. After being stirred for 1 h at room temperature, EtOH (5 mL) and water (5 mL) were added to the mixture. The mixture was concentrated, and the residue was partitioned between CH_2Cl_2 (150 mL) and water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (150 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was crystallized from AcOEt–hexane to give crystals of **14** (3.72 g). The mother liquor was concentrated and the residue was chromatographed on silica gel (30 g, AcOEt/hexane 1:20) to give additional crystals of **14** (0.52 g, total 4.24 g, 94%). **14**: as white needles, mp 91–92 °C; TLC R_f 0.52 (AcOEt/hexane 1:4); $[\alpha]^{25}_D$ +8.7° (*c* 1.00); IR ν^{KBr}_{max} 3030, 2940, 2900, 2120, 1460, 1430, 1390, 1280, 1260 cm^{-1}; ^{1}H NMR δ 3.38 (3 H, s, OCH_3), 3.58–4.43 (7 H, m, H-1,2,3,4,5,6,6′), 4.63 (2 H, s, OCH_2C$_6$H$_5$), 5.57 (1 H, s, CHC$_6$H$_5$), 7.10–7.80 (5 H, m, CHC$_6$H$_5$), 7.38 (5 H, s, OCH$_2$C$_6$H$_5$). Anal. Found: C, 63.40; H, 5.86; N, 10.56. Calcd for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57.

3-Azido-2-*O*-benzyl-3-deoxy-α,β-D-altrose (16). A solution of **14** (4.24 g, 10.7 mmol) in 80% aqueous acetic acid (40 mL) was stirred at 100 °C for 4 h and then concentrated. The residue was chromatographed on silica gel (50 g, EtOH/toluene 1:10). Fractions corresponding to R_f 0.45 (EtOH/toluene 1:6) were concentrated. The residue was dissolved in acetic anhydride (24 mL) and concentrated sulfuric acid (0.02 mL) was added at 0 °C. After being stirred at room temperature for 4 h, water (2 mL) was added. The solution was neutralized by addition of saturated aqueous $NaHCO_3$ solution and diluted with water (300 mL). This was extracted with CH_2Cl_2 (200 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to give **15** (5.08 g, TLC R_f 0.42 and 0.47, AcOEt/hexane 1:3) as an anomeric mixture. A solution of this mixture **15** (5.08 g) in methanol (40 mL) containing sodium methoxide (1 M MeOH solution, 10.7 mL, 10.7 mmol) was stirred for 5 min. This mixture was then neutralized with Amberlite IR-120 (H^+). The resin was removed by filtration and washed with MeOH. The filtrate and washings were combined and concentrated. The residue was crystallized from AcOEt–hexane to give crude **16**, which was recrystallized from AcOEt, giving **16** (1.96 g) as colorless cubics, mp 94–97 °C. The mother liquor was concentrated, and the residue was chromatographed on silica gel (20 g, EtOH/toluene 1:20). Fractions corresponding to R_f 0.36 (EtOH/toluene 1:6) were concentrated to give additional **16** (0.62 g, total 2.58 g, 82%). **16**: IR ν^{KBr}_{max} 3540, 3200, 2930, 2120, 1460, 1360, 1260 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.23–4.10 (6 H, m H-2,3,4,5,6,6′), 4.63 (2 H, s, OCH_2C$_6$H$_5$), 5.13–5.34 (1 H, m, H-1), 7.35 (5 H, s, OCH$_2$C$_6$H$_5$). Anal. Found: C, 52.83; H, 5.77; N, 13.94. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.87; H, 5.80; N, 14.23.

3-Azido-2-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α,β-D-altrose (17). To a solution of **16** (1.40 g, 4.74 mmol) in pyridine (30 mL) were added *tert*-butylchlorodimethylsilane (1.07 g, 7.11 mmol) and triethylamine (1.32 mL, 9.48 mmol). After being stirred for 3 h, the silylating reagent (0.36 g, 2.37 mmol) and triethylamine (0.33 mL, 2.37 mmol) were added. After being stirred more 3 h, the mixture was concentrated. The residue was partitioned between CH_2Cl_2 (100 mL) and water (150 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (50 g, AcOEt/hexane 1:10). Fractions corresponding to R_f 0.37 (AcOEt/hexane 1:3) were concentrated to give **17** (1.65 g, 85%) as a colorless syrup. **17**: IR ν^{neat}_{max} 3600, 3450, 2960, 2930, 2830, 2110, 1460, 1260, 1210 cm^{-1}; ^{1}H NMR δ 0.08 (6 H, s, OSi(CH_3)$_2$), 0.90 (9 H, s, OSiC(CH_3)$_3$), 2.54–3.22 (2 H, br, 2 × OH), 3.52–4.28 (6 H, m, H-2,3,4,5,6,6′), 4.52–4.70 (2 H, m, OCH_2C$_6$H$_5$), 5.13–5.38 (1 H, m, H-1), 7.28, 7.32 (total 5 H, each s, OCH$_2$C$_6$H$_5$). Anal. Found: C, 57.70; H, 7.69; N, 8.48. Calcd for $C_{19}H_{31}N_3O_5Si$: C, 57.59; H, 7.78; N, 8.76.

E* and *Z* Mixture of Ethyl (4*R*,5*S*,6*S*,7*R*)-5-Azido-4-(benzyloxy)-8-[(*tert*-butyldimethylsilyl)oxy]-6,7-dihydroxy-2-octenoate (18-*E* and 18-*Z*).** A mixture of **17** (1.58 g, 3.86 mmol) and [(ethoxycarbonyl)methylene]triphenylphosphorane (4.03 g, 11.6 mmol) in benzene (30 mL) was refluxed for 3 h and concentrated. The residue was chromatographed on silica gel (100 g, AcOEt/hexane 1:10). Fractions corresponding to R_f 0.49 and 0.57 (AcOEt/hexane 1:3) were combined and concentrated to give a mixture of **18-*E and **18-*Z*** (1.11 g, 60%) as a colorless syrup: IR ν^{neat}_{max} 3570, 3400, 2960, 2930, 2860, 2110, 1720, 1460, 1260 cm^{-1}; ^{1}H NMR δ 0.08 (6 H, s, OSi(CH_3)$_2$), 0.91 (9 H, s, OSiC(CH_3)$_3$), 1.06–1.42 (3 H, m, COOCH$_2$CH_3), 2.53–3.45 (2 H, m, 2 × OH), 3.22–4.75 (9.5 H, m, H-4 for **18-*E***, H-5,6,7,8,8′, COOCH_2CH$_3$, OCH_2C$_6$H$_5$), 5.45–5.62 (0.5 H, m, H-4 for **18-*Z***), 5.87–7.10 (2 H, m, H-2,3), 7.38 (5 H, s, OCH$_2$C$_6$H$_5$). Anal. Found: C, 57.70; H, 7.69; N, 8.48. Calcd for $C_{23}H_{37}N_3O_5Si$: C, 57.59; H, 7.78; N, 8.76.

(*E*)- and (*Z*)-Ethyl (4*R*,5*S*,6*S*,7*R*)-5-Azido-4-(benzyloxy)-8-[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-2-octenoate (19-*E* and 19-*Z*). A mixture of the mixture **18-*E*** and **18-*Z*** (900 mg, 1.88 mmol) and 2,2-dimethoxypropane (2.31 mL, 18.8 mmol) in acetone (20 mL) in the presence of camphorsulfonic acid (31 mg, 0.13 mmol) was stirred for 2 h, and then water (10 mL) was added. The mixture was neutralized by addition of saturated aqueous $NaHCO_3$ solution and concentrated. The residue was partitioned between CH_2Cl_2 (80 mL) and water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (80 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (40 g, AcOEt/hexane 1:40). Fractions corresponding to R_f 0.75 (AcOEt/hexane 1:8) were concentrated to give **19-*Z*** (386 mg, 40%) as a colorless syrup. Fractions corresponding to R_f 0.56 were concentrated to give **19-*E*** (340 mg, 35%) as a colorless syrup. An approximately 1:1 mixture of **19-*E*** and **19-*Z*** was also obtained (92 mg, total amount of the mixture, 818 mg, 84%). **19-*Z***: $[\alpha]^{25}_D$ −9.0° (*c* 1.22); IR ν^{neat}_{max} 2930, 2860, 2110, 1710, 1460, 1380, 1250 cm^{-1}; ^{1}H NMR δ 0.07 (6 H, s, OSi(CH_3)$_2$), 0.88 (9 H, s, OSiC(CH_3)$_3$), 1.24 (3 H, t, *J* = 7 Hz, COOCH$_2$CH_3), 1.33, 1.45 (3 H × 2, each s, C(CH_3)$_2$), 3.58 (1 H, dd, *J* = 3 and 9 Hz, H-5), 3.72–3.88 (2 H, m, H-8,8′), 4.13 (2 H, q, *J* = 7 Hz, COOCH_2CH$_3$), 3.95–4.63 (4 H, m, H-6,7, OCH_2C$_6$H$_5$), 5.44 (1 H, dd, *J* = 3 and 8 Hz, H-4), 5.93 (1 H, d, *J* = 12 Hz, H-2), 6.40 (1 H, dd, *J* = 8 and 12 Hz, H-3), 7.28 (5 H, s, OCH$_2$C$_6$H$_5$). Anal. Found: C, 60.30, H, 7.84; N, 7.91. Calcd for $C_{26}H_{41}N_3O_6Si$: C, 60.08; H, 7.95; N, 8.09. **19-*E***: $[\alpha]^{25}_D$ −20.1° (*c* 1.34); IR ν^{neat}_{max} 2930, 2860, 2110, 1710, 1460, 1380, 1370, 1250 cm^{-1}; ^{1}H NMR δ 0.07 (6 H, s, OSi(CH_3)$_2$), 0.88 (9 H, s, OSiC(CH_3)$_3$), 1.29 (3 H, t, *J* = 7 Hz, COOCH$_2$CH_3), 1.29, 1.38 (3 H × 2, each s, C(CH_3)$_2$), 3.38 (1 H, dd, *J* = 3 and 9 Hz, H-5), 3.68–3.84 (2 H, m, H-8,8′), 4.17 (2 H, q, *J* = 7 Hz, COOCH_2CH$_3$), 4.06–4.74 (5 H, m, H-4,6,7, OCH_2C$_6$H$_5$), 6.09 (1 H, d, *J* = 16 Hz, H-2), 6.90 (1 H, dd, *J* = 6 and 16 Hz, H-3), 7.26 (5 H, s,

$OCH_2C_6H_5$). Anal. Found: C, 60.26; H, 7.91; N, 8.08. Calcd for $C_{26}H_{41}N_3O_6Si$: C, 60.08; H, 7.95; N, 8.09.

(5*R*,6*S*)-5-(Benzyloxy)-6-[(1*S*,2*R*)-3-hydroxy-1,2-(isopropylidenedioxy)propyl]-2-piperidone (20). From 19-*E*. A solution of **19-*E*** (330 mg, 0.64 mmol) in EtOH (15 mL) was hydrogenated in the presence of Raney nickel W-4 under atmospheric hydrogen pressure for 36 h. The catalyst was removed by using a Celite pad, and the filtrate was concentrated. The residue (R_f 0.48 and 0.18, AcOEt/hexane 1:3) was dissolved in THF (15 mL), and tetrabutylammonium fluoride (1 M in THF, 1.59 mL, 1.59 mmol) was added. After being stirred for 4 h, the solution was concentrated. The residue was partitioned between CH_2Cl_2 (50 mL) and water (80 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (10 g, EtOH/toluene 1:25). Fractions corresponding to R_f 0.53 (EtOH/toluene 1:5) were concentrated to give **20** (175 mg, 82%) as colorless cubics, mp 139–140 °C. **20**: $[\alpha]^{23}_D$ −65.9° (*c* 0.99); IR ν^{KBr}_{max} 3400, 3150, 2930, 2910, 1660, 1470, 1400, 1370, 1320, 1240, 1220 cm^{-1}; ^1H NMR δ 1.34 (6 H, s, $C(CH_3)_2$), 1.52–2.68 (4 H, m, H-3,3′,4,4′), 3.44–3.92 (3 H, m, H-6, H-3,3′ of the side chain at C-6), 3.94–4.12 (1 H, m, H-5), 4.18–4.68 (2 H, m, H-1,2 of the side chain at C-6), 4.60 (2 H, s, $OCH_2C_6H_5$), 5.66–6.03 (1 H, br, OH), 7.33 (5 H, s, $OCH_2C_6H_5$), 7.73 (1 H, br s, NH). Anal. Found: C, 64.29; H, 7.50; N, 3.94. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18.

From 19-*Z*. Compound **19-*Z*** (368 mg, 0.71 mmol) was converted into **20** (184 mg, 77%) by the same procedure and workup as described above.

From the Mixture of 19-*E* and 19-*Z*. The mixture (66 mg) was also converted into 17 mg (48%) of **20**.

(1*S*,2*R*,8*R*,8a*S*)-8-(Benzyloxy)-1,2-(isopropylidenedioxy)octahydro-5-indolizinone (21). To a stirred solution of **20** (100 mg, 0.30 mmol) in pyridine (6 mL) was added methanesulfonyl chloride (0.09 mL, 1.2 mmol). After being stirred at 40 °C for 3 h, the mixture was concentrated. The residue was partitioned between AcOEt (20 mL) and water (25 mL). The aqueous layer was extracted with AcOEt (20 mL × 2). The combined organic layers were concentrated. The residue was dissolved in a mixture of dioxane (4 mL) and water (1 mL), and potassium carbonate (41 mg, 0.3 mmol) was added. After being stirred at 90 °C for 2 h, the mixture was concentrated to ca. 2 mL volume and water (25 mL) was added. This aqueous solution was extracted with AcOEt (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (2 g, EtOH/toluene 1:30). Fractions corresponding to R_f 0.62 (EtOH/toluene 1:5) were concentrated to give **21** (73 mg, 77%) as white needles, mp 146–148 °C. **21**: $[\alpha]^{22}_D$ −50.6° (*c* 0.96); IR ν^{KBr}_{max} 2960, 2890, 1640, 1440, 1420, 1380, 1330, 1250 cm^{-1}; ^1H NMR δ 1.35, 1.51 (3 H × 2, each s, $C(CH_3)_2$), 1.60–2.25 (4 H, m, H-6,6′,7,7′), 3.28–3.65 (2 H, m, H-3,8a), 3.94–4.34 (2 H, m, H-3′,8), 4.37–4.93 (4 H, m, H-1,2, $OCH_2C_6H_5$), 7.33 (5 H, s, $OCH_2C_6H_5$). Anal. Found: C, 67.90; H, 7.36; N, 4.13. Calcd for $C_{18}H_{23}NO_4$: C, 68.12, H, 7.30; N, 4.41.

(1*S*,2*R*,8*R*,8a*S*)-8-Hydroxy-1,2-(isopropylidenedioxy)-octahydro-5-indolizinone (22). A solution of **21** (36 mg, 0.11 mmol) and freshly distilled cyclohexene (2 mL) in EtOH (2 mL) was refluxed for 14 h in the presence of 20% $Pd(OH)_2$ on charcoal (20 mg). The catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in cyclohexene (2 mL), and the solution was refluxed for 12 h in the presence of 20% $Pd(OH)_2$ on charcoal (20 mg). The catalyst was removed, and the filtrate was concentrated. The residue was chromatographed on silica gel (2 g, EtOH/toluene 1:12). Fractions corresponding to R_f 0.34 (EtOH/toluene 1:4) were concentrated to give **22** (17 mg, 64%) as crystals, mp 132–135 °C. From the fractions corresponding to R_f 0.62, 6 mg (17%) of **21** was recovered. **22**: $[\alpha]^{22}_D$ −90.5° (*c* 0.26); IR ν^{KBr}_{max} 3400, 3150, 2930, 1610, 1480, 1370, 1230 cm^{-1}; ^1H NMR δ 1.36, 1.52 (3 H × 2, each s, $C(CH_3)_2$), 1.17–2.67 (4 H, m, H-6,6′,7,7′), 3.20–4.45 (5 H, m, H-3,3′,8,8a, OH), 4.46–4.97 (2 H, m, H-1,2); high-resolution mass spectrum, calcd for $C_{11}H_{17}NO_4$ *m/z* 227.1156, found (M) 227.1146.

(1*S*,2*R*,8*R*,8a*R*)-1,2-(Isopropylidenedioxy)-8-[(methylsulfonyl)oxy]octahydro-5-indolizinone (23). From 22. To a stirred solution of **22** (17 mg, 0.07 mmol) in pyridine (2 mL) was added methanesulfonyl chloride (0.023 mL, 0.29 mmol). After being stirred for 4 h, the mixture was concentrated. The residue was partitioned between AcOEt (10 mL) and water (10 mL). The aqueous layer was extracted with AcOEt (10 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (1.5 g, EtOH/toluene 1:15). Fractions corresponding to R_f 0.46 (EtOH/toluene 1:4) were concentrated to give **23** (18.5 mg, 83%) as a colorless syrup. **23**: $[\alpha]^{22}_D$ −51.5° (*c* 1.24); IR ν^{neat}_{max} 2990, 2930, 1640, 1460, 1410, 1370, 1340, 1230 cm^{-1}; ^1H NMR δ 1.36, 1.53 (3 H × 2, each s, $C(CH_3)_2$), 1.75–2.64 (4 H, m, H-6,6′,7,7′), 3.12 (3 H, s, OSO_2CH_3), 3.32–3.76 (2 H, m, H-3,8a), 4.15 (1 H, dd, *J* = 5 and 13 Hz, H-3′), 4.48–4.83 (2 H, m, H-1,2), 5.18–5.37 (1 H, m, H-8); high-resolution mass spectrum, calcd for $C_{11}H_{16}NO_6S$ *m/z* 290.0697, found (M − CH_3) 290.0697.

From 20 via 24 and 25. A solution of **20** (250 mg, 0.75 mmol) in a mixture of EtOH (6 mL) and cyclohexene (6 mL) was refluxed in the presence of 20% $Pd(OH)_2$ on charcoal (80 mg). Each 2 mL of cyclohexene was added after 6 h and 9 h, and the mixture was refluxed for total 12 h. The catalyst was removed by filtration, and the filtrate was concentrated to give (5*R*,6*S*)-5-hydroxy-6-[(1*S*,2*R*)-3-hydroxy-1,2-(isopropylidenedioxy)propyl]-2-piperidone (**24**) (R_f 0.30, EtOH/toluene 1:4) as a colorless syrup (204 mg). To a stirred solution of **24** (204 mg) in pyridine (10 mL) was added methanesulfonyl chloride (0.29 mL, 3.7 mmol). After being stirred at 35 °C for 5 h, the mixture was concentrated. The residue was partitioned between AcOEt (20 mL) and water (25 mL), and the aqueous layer was extracted with AcOEt (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give (5*R*,6*R*)-6-[(1*S*,2*R*)-1,2-(isopropylidenedioxy)-3-[(methylsulfonyl)oxy]propyl]-5-[(methylsulfonyl)oxy]-2-piperidone (**25**) (R_f 0.42, EtOH/toluene 1:4) as a pale yellow syrup which was used in the next step directly. A solution of **25** in a mixture of dioxane (8 mL) and water (2 mL) was heated at 90 °C for 2 h in the presence of potassium carbonate (309 mg, 2.24 mmol). The mixture was then concentrated. The residue was partitioned between AcOEt (30 mL) and water (40 mL), and the aqueous layer was extracted with AcOEt (30 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (6 g, EtOH/toluene 1:15) to give **23** (153 mg, 67% from **20**), which was identical with an authentic sample prepared from **22** (TLC, IR, and ^1H NMR).

(1*S*,2*R*,8*S*,8a*S*)-8-(Benzoyloxy)-1,2-(isopropylidenedioxy)octahydro-5-indolizinone (26). A suspension of **23** (113 mg, 0.37 mmol) and dried sodium benzoate (213 mg, 1.48 mmol) in DMF (6 mL) was heated at 140 °C with vigorous stirring for 30 min. The mixture was diluted with water (20 mL) and extracted with AcOEt (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (6 g, EtOH/toluene 1:40). Fractions corresponding to R_f 0.62 (EtOH/toluene 1:4) were concentrated to give **26** (103 mg, 84%) as a colorless syrup. **26**: $[\alpha]^{23}_D$ −13.5° (*c* 0.80); IR ν^{KBr}_{max} 3000, 2960, 1720, 1640, 1450, 1380, 1270 cm^{-1}; ^1H NMR δ 1.32, 1.52 (3 H × 2, each s, $C(CH_3)_2$), 1.68–2.68 (4 H, m, H-6,6′,7,7′), 3.24–3.83 (2 H, m, H-3,8a), 4.22 (1 H, dd, *J* = 6 and 13 Hz, H-3′), 4.39–4.82 (2 H, m, H-1,2), 4.97–5.30 (1 H, m, H-8), 7.28–7.66, 7.80–8.17 (total 5 H, each m, $OCOC_6H_5$); high-resolution mass spectrum, calcd for $C_{18}H_{22}NO_5$ *m/z* 332.1496, found (M + H) 332.1487.

(1*S*,2*R*,8*S*,8a*S*)-1,2-*O*-Isopropylideneoctahydro-1,2,8-indolizinetriol (27). To a stirred solution of **26** (87 mg, 0.26 mmol) in THF (4 mL) was added BH_3–Me_2S complex (10 M, neat, 0.16 mL, 1.6 mmol) at 0 °C under argon atmosphere. After being stirred at room temperature for 2 h, 10% aqueous $NaHCO_3$ solution (4 drops) was added to the mixture. This was diluted with water (20 mL) and extracted with CH_2Cl_2 (15 mL × 4). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in MeOH (3 mL) and potassium carbonate (72 mg, 0.52 mmol) was added. The mixture was heated at 65 °C for 2 h and neutralized by addition of 1 M HCl solution. The mixture was concentrated to give a white solid, which was chromatographed on silica gel (3 g, EtOH/toluene 1:12 containing 1% triethylamine). Fractions corresponding to R_f 0.30 (EtOH/toluene 1:3) were concentrated to give **27** (42.5 mg, 76%) as a colorless syrup. **27**: $[\alpha]^{22}_D$ −29.6° (*c* 1.14); IR ν^{neat}_{max} 3580, 2980, 2800, 1450, 1370, 1250 cm^{-1}; ^1H NMR δ 1.33, 1.52 (3 H × 2, each

s, $C(CH_3)_2$), 1.08–2.28 (6 H, m, H-5,6,6′,7,7′,8a), 2.38 (1 H, dd, J = 5 and 9 Hz, H-3), 2.77 (1 H, dt, J = 3 and 10 Hz, H-5′), 3.28–3.58 (2 H, m, H-3′,8), 3.67 (1 H, s, OH), 4.34–4.82 (2 H, m, H-1,2); high-resolution mass spectrum, calcd for $C_{11}H_{19}NO_3$ m/z 213.1364, found (M) 213.1369.

(1*S*,2*R*,8*S*,8a*S*)-Octahydro-1,2,8-indolizinetriol (8,8a-Di-*epi*-swainsonine, 6). A solution of **27** (35 mg, 0.16 mmol) in a 1 M aqueous HCl solution (1.5 mL) was refluxed for 30 min and concentrated. The residue was dissolved in a small amount of water and charged on a column of Amberlite IRA-400 (OH^-). The column was eluted with water, and the ninhydrin-positive fractions were concentrated. The residual solid was recrystallized from $CHCl_3$–hexane to give white crystals of **6** (24 mg, 84%), mp 130–131 °C dec. **6**: TLC R_f 0.32 (ammonia–water/butanol/CH_2Cl_2/EtOH 1:3:3:3, ninhydrin coloring); $[\alpha]^{22}_D$ −21.2° (c 0.78, MeOH); IR ν^{KBr}_{max} 3500–3200 (br), 2930, 2830, 2800, 1360, 1250 cm^{-1}; ^1H NMR (D_2O) δ 1.60–2.40 (6 H, m, H-5,6,6′,7,7′,8a), 2.22 (1 H, dd, J = 6 and 10 Hz, H-3), 2.73–3.02 (1 H, m, H-5′), 3.22–3.66 (2 H, m, H-3′,8), 3.72–4.34 (2 H, m, H-1,2); ^{13}C NMR δ 24.86, 34.67, 52.83, 61.94, 68.47, 72.63, 74.55, 75.26; high-resolution mass spectrum, calcd for $C_8H_{15}NO_3$ m/z 173.1050, found (M) 173.1042.

Enzyme Assays and Inhibition Experiments. Eleven glycosidase activities in a water-soluble extract of human liver were assayed at their pH-optima in the presence and absence of 1 mM (−)-2,8a- (**5**) and (−)-8,8a-di-*epi*-swainsonine (**6**) by using the appropriate fluorigenic (4-methylumbelliferyl) substrate (Koch-Light Ltd., Haverhill, Suffolk, U. K.) at a concentration of 0.5 mM as described previously.[19] The enzymes were α- and β-D-mannosidase, α- and β-D-glucosidase, α- and β-D-galactosidase, *N*-acetyl-β-D-hexosaminidase, α-L-fucosidase, β-D-xylosidase, α-L-arabinosidase, and β-D-glucunonidase. The percent activation or inhibition was calculated by comparing the activities in the presence and absence of the swainsonine analogues. The nature and the value of K_i for the inhibition of α-D-mannosidase by the (−)-8,8a-di-*epi*-swainsonine (**6**) were determined by the Dixon graphical procedure using a computer program to get the lines of best fit.

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Microbiological Reduction of Acyclic β-Diketones†

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Regio- and enantiospecificities of the biological reduction of various acyclic β-diketones by lower fungi were studied in order to obtain ketols of *R* configuration. Only 2-hydroxy compounds were obtained from 2,4-diketones as already observed for *S* ketols formed with bakers' yeast. Both 3-hydroxy and 5-hydroxy ketols were produced from 3,5-diones. All but 4-hydroxy-3-methylpentan-2-one had the *R* configuration expected.

Introduction

In previous work[1] we showed that bakers' yeast (*Saccharomyces cerevisiae*) reduces 2,4-diones to the corresponding ketols bearing a 2-hydroxy group of configuration 2*S* with high enantiomeric excess. The microbiological reduction of 2,4-diones by *S. cerevisiae* is both enantio- and regioselective, as confirmed in recent work by Ohta et al.[2] Such optically active ketols are of great interest in the chemistry of naturally occurring substances since this grouping is present in biologically active compounds[3] and chiral ketols make excellent synthons for the stereospecific synthesis of antibiotics[4] and pheromones.[5]

Having available a method for readily obtaining β-ketols of absolute configuration 2S, we set out to find biological systems that would enable us to obtain enantiomeric 2*R* ketols.

In the course of work on the synthesis of the two enantiomers of the pheromone sulcatol (6-methylhept-5-en-2-ol),[6] we found that certain microorganisms such as *Geotrichum candidum* and *Aspergillus niger* reduced a monoketone to the corresponding alcohol of *R* configuration. We report here the results obtained with these two fungi on a variety of 2,4-diones and 3,5-diones and, when not previously published, results obtained with bakers' yeast.

Results and Discussion

1. Reduction of 2,4-Diones. The 2,4-diones shown in Figure 1 were studied.

The microbiological reductions were carried out with washed resting cells suspended in water or glucose solution (see Experimental Section). The glucose was used not for fermentation or as a reducing agent, but simply to avoid metabolism of the reduced product, particularly by *G. candidum*. The results are collected in Table I. For comparison with our previous work,[1] the results obtained with bakers' yeast are also displayed in Table I.

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