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

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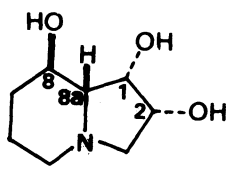
The title compound, one of the stereoisomers of physiologically interesting indolizidine alkaloid swainsonine, has been synthesized from the known methyl 3-azido-4,6-O-benzylidene-3-deoxy-α-D-altropyranoside.

(-)-Swainsonine (1), (1*S*,2*R*,8*R*,8a*R*)-octahydro-1,2,8-indolizinetriol, is a newly isolated indolizidine alkaloid which exhibits a physiological interest such as an α-D-mannosidase inhibitory activity and an immunoregulating activity.[1] The total synthesis of 1 was achieved recently in our laboratory and by other groups.[2] On the other hand, the synthesis of stereoisomers of 1, for an elucidation of the correlation of the structures and physiological activity, is a current interest.[3] Two stereoisomers of 1, 8-*epi*-swainsonine (2) and 1,8-di-*epi*-swainsonine (3) have been synthesized in our laboratory recently.[4] In this Letter, we wish to describe a synthesis of other stereoisomer, 8a-*epi*-swainsonine (4), by a different approach comparing the previous syntheses of 1, 2, and 3[2,4] using an azido-sugar as a starting material.



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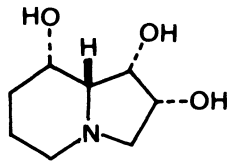

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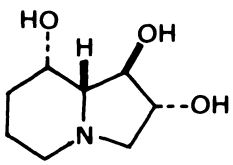

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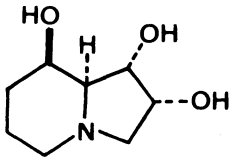

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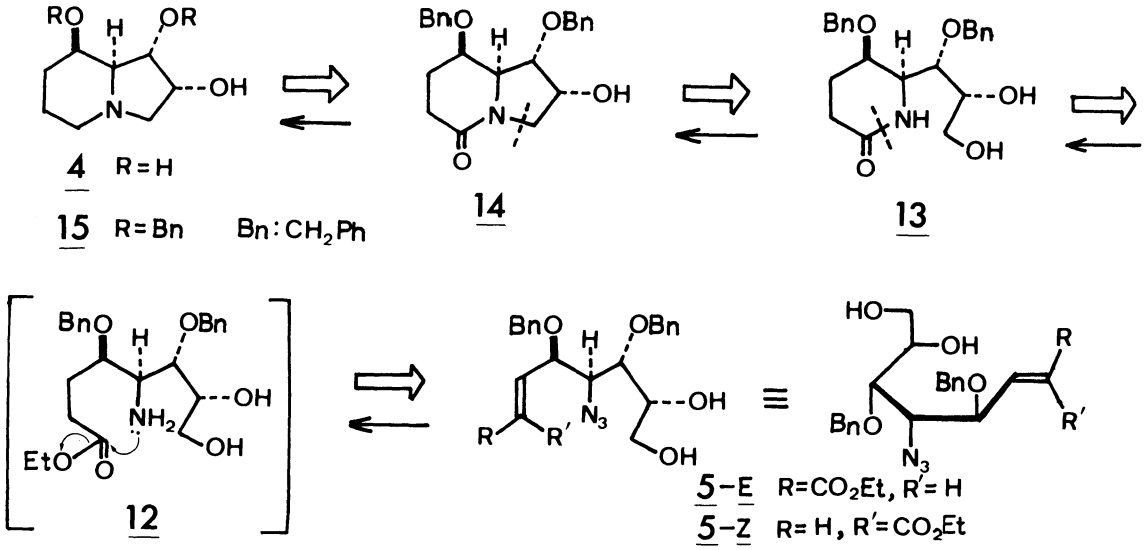
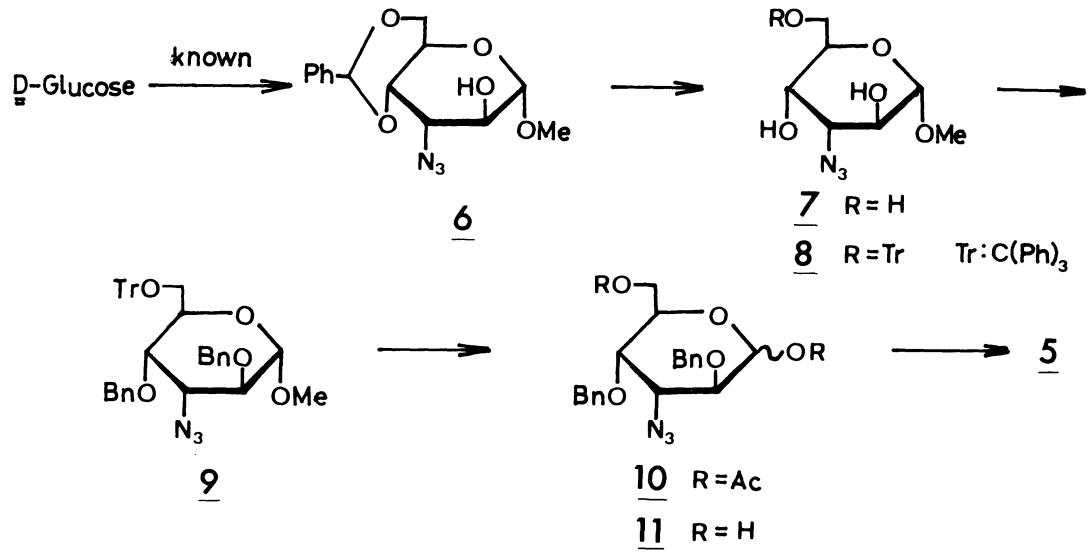
As shown in Scheme 1, the compound 4 was retro-synthesized to a compound (5), ethyl (*E*)- and /or (*Z*)-5-azido-4,6-di-O-benzyl-2,3,5-trideoxy-α-D-altro-oct-2-enonate, by the following C-N bond disconnection operation. A partially protected 4, that is a compound (15), would be obtained by reduction of the amido group in compound (14). The compound 14 is obtainable from a 5,6-di-substituted 2-piperidinone (13) by introduction of a suitable leaving group (for example, O-tosyl group) to the primary hydroxyl group in an intramolecular N-alkylation fashion. The compound 13, in turn, would be obtained



Scheme 1.



Scheme 2.

by hydrogenation of the compound 5 to a compound (12), which tends to a simultaneous intramolecular amide formation (a δ-lactam formation) providing the compound 13.

The configurations of the four continuous chiral centers in 5 are corresponding to those of C-2 to C-5 of 3-azido-3-deoxy-D-altrose. So, the synthesis of 5 was started from the known compound (6), which was readily prepared by regioselective epoxy ring opening of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside with an azido anion[5] (Scheme 2). Hydrolysis of 6 with 50% aqueous acetic acid at 100 °C provided a compound (7). The primary hydroxyl group in 7 was preferentially protected as a trityl ether to afford a compound (8)[6a,b] with trityl chloride in pyridine in the presence of DMAP in 82% yield from 6. O-Benzylation of 8 with benzyl bromide in DMF in the presence of sodium hydride furnished a compound (9)[6a] in 94% yield.

Acetolysis of 9 in acetic anhydride with a catalytic amount of sulfuric acid at 0 °C provided an anomeric mixture of a compound (10)[6a,b] in 80% yield. O-Deacetylation of 10 with sodium methoxide in methanol, followed by the Wittig olefination of a compound (11) with (carbethoxy)methylenetriphenylphosphorane in refluxing benzene afforded an approximately 1 to 1 mixture[6b] of (*E*)- and (*Z*)-5 in 54% combined yield. The pure (*E*)-5[6a] and (*Z*)-5[6a] were obtained by chromatographic separation on SiO_2, and the geometrical structure of each isomer 5 was established by the ^1H NMR spectrum. Hydrogenation of the each isomer 5 in the presence of Raney nickel afforded the compound 13[6a,b] in 67% yield from (*E*)-5 or in 73% yield from (*Z*)-5, respectively. The intramolecular cyclization of 13 to the 2-indolizinone compound 14[6a,b] was accomplished as follows. A solution of 13 in pyridine was stirred with 3.4 molar equivalents of *p*-tosyl chloride, which was added at 10 h interval in a five portion, at 70 to 100 °C in the presence of DMAP (0.4 mol). Under these conditions, the compound 14 was obtained in 60% yield without formation of a over-tosylated product (O-tosyl derivative of 14).[7] Although we could not detect an intermediate, the cyclization reaction was interpreted to proceed *via* a primary tosyloxy derivative, which cyclized readily to provide 14. The reduction of 14 with BH_3-Me_2S complex in THF at ambient temperature, followed by stirring the product in pyridine gave 1,8-di-O-benzyl-8a-*epi*-swainsonine 15[6a,b] in 84% yield. Deprotection of the compound 15[8] with iodotrimethylsilane[9] in chloroform and purification on PTLC (R_f 0.39, 1-butanol:chloroform:ethanol:aqueous ammonia= 4:4:4:1) furnished the desired 8a-*epi*-swainsonine[6a,b] as crystals in 75% yield.

A preliminary bioassay of the synthetic 4 for α-D-mannosidase inhibitory activity was performed. The compound 4 exhibited a 93% inhibition against a human α-D-mannosidase at 1 mM concentration and at pH 4 (optimal pH value). Under the same conditions, swainsonine 1, a potent α-D-mannosidase inhibitor, showed a 99% inhibition.

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6) a) All new compounds are fully characterized by the IR, ^{1}H NMR, and mass spectra, and b) gave satisfactory elemental analyses and/or high resolution mass spectra. The physical ($CHCl_3$ for $[\alpha]_D$) and spectral ($CDCl_3$ for ^{1}H NMR) data for the selected compounds are as follows. 8: $[\alpha]_D^{27}$+31.5° (*c* 1.35); 9: $[\alpha]_D^{28}$+28.4° (*c* 0.98); (*E*)-5: $[\alpha]_D^{20}$-14.7° (*c* 1.06), IR $\nu_{max}^{CHCl_3}$ 2100, 1720 cm^{-1}, ^{1}H NMR δ 1.27 (3H, t, *J*=7 Hz), 3.46-4.05 (8H, m), 4.22 (2H, q, *J*=7 Hz), 4.38-4.75 (4H, m), 6.12 (1H, d, *J*=18 Hz), 6.91 (1H, dd, *J*=18, 7 Hz), 7.34 (10H, s); (*Z*)-5: $[\alpha]_D^{20}$-64.1° (*c* 1.13), IR $\nu_{max}^{CHCl_3}$ 2110, 1710 cm^{-1}, ^{1}H NMR δ 1.27 (3H, t, *J*=7 Hz), 3.00-3.42 (2H, m), 3.58-4.38 (6H, m), 4.18 (2H, q, *J*=7 Hz), 4.40-4.74 (4H, m), 6.04 (1H, d, *J*=12 Hz), 6.33 (1H, dd, *J*=12, 8 Hz), 7.48 (10H, s); 13: mp 145-146 °C, $[\alpha]_D^{27}$-87.9° (*c* 1.00); 14: mp 88-90 °C, $[\alpha]_D^{19}$-78.4° (*c* 1.00); 15: $[\alpha]_D^{22}$-61.1° (*c* 0.97); 4: mp 122-124 °C (dec) (from $CHCl_3$), $[\alpha]_D^{19}$-64.5° (*c* 0.95, MeOH), ^{13}C NMR (CD_3OD, TMS) δ 20.87, 32.26, 54.10, 62.83, 64.71, 68.18, 70.91, 72.51. High resolution mass spectrum, calcd for $C_8H_{15}NO_3$: *m/z* 173.1050, found: M, 173.1050.

7) Among several conditions investigated for preparation of 14, good to best (60%) results were achieved when *p*-tosyl chloride was added portionwisely at several hours interval (10 to 15 h). When *p*-tosyl chloride (3.0 mol equiv.) was added to a pyridine solution of 13 all at once, and the mixture was stirred at ambient temperature for 24 h in the presence of DMAP (0.2 mol equiv.), the compound 14 was obtained in 41% yield along with the 2-O-tosyl derivative of 14 (30%). We have no rational explanation for this unexpected result.

8) By the hydrogenolysis in the presence of 10% Pd/C or by the treatment with cyclohexene in refluxing ethanol in the presence of 10% $Pd(OH)_2$/C, deprotection of the compound 15 did not proceed completely. A mono-O-benzyl derivative of 4 was a predominant product.

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