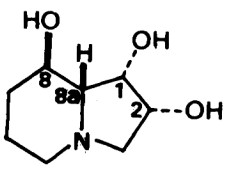
CHEMISTRY LETTERS, pp. 2105-2108, 1986.

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

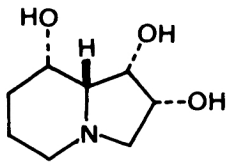
Kin-ichi TADANO,* Yukinori HOTTA, Masahiro MORITA, Tetsuo SUAMI,*
Bryan WINCHESTER,† and Isabelle Cenci di BELLO†
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223
†Department of Biochemistry, King's College London, University of London, Campden Hill Road, Kensington, London W8 7AH, U. K.

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.

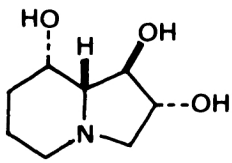
(-)-Swainsonine (1), (1*S*,2*R*,8*R*,8a*R*)-octahydro-1,2,8-indolizinetriol, is a newly isolated indolizidine alkaloid which exhibits a physiological interest such as an α-D-mannosidase inhibitory activity and an immunoregulating activity.[1] The total synthesis of 1 was achieved recently in our laboratory 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.



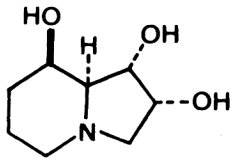
1



2

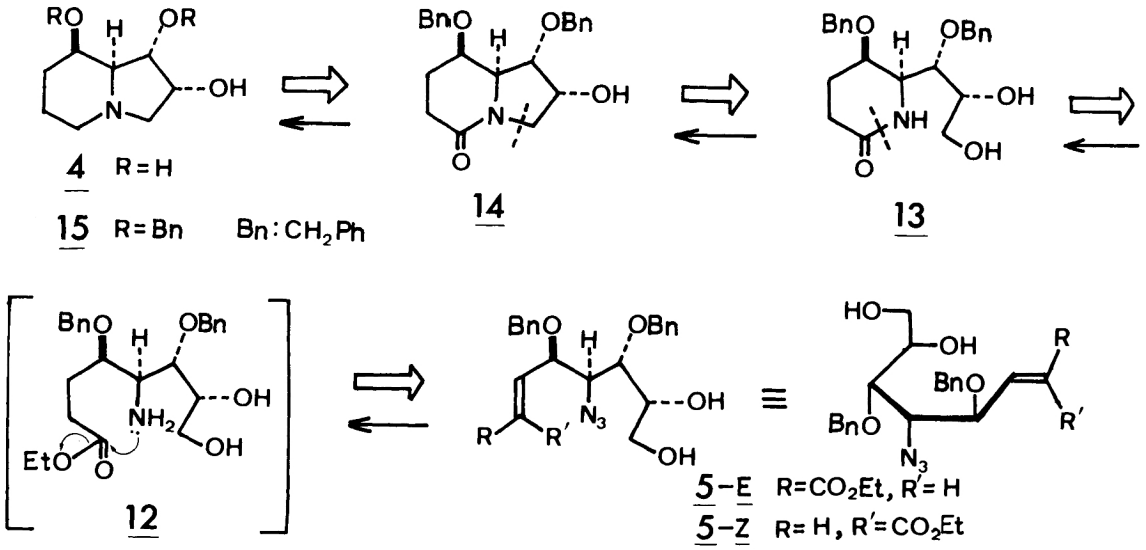


3

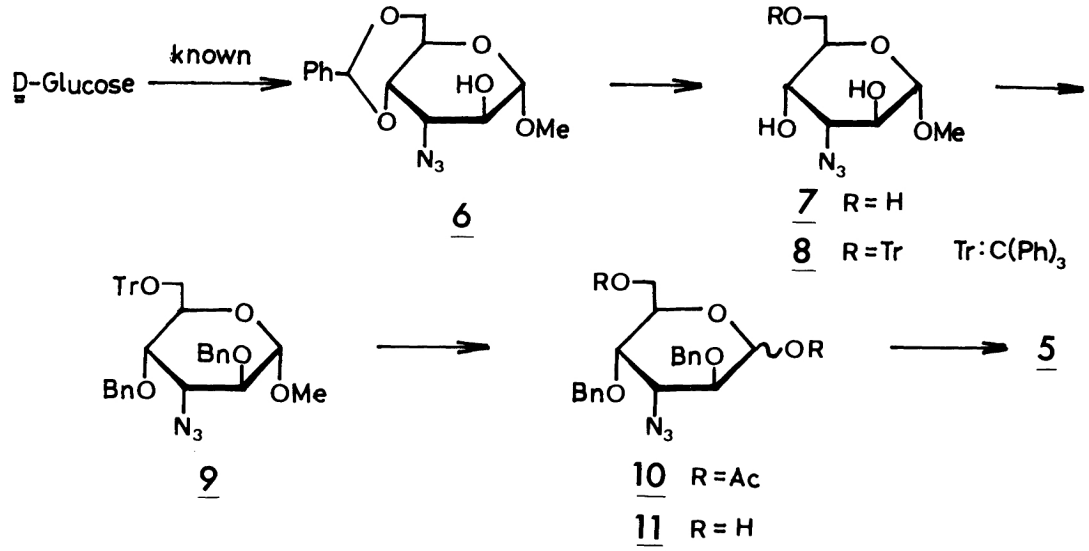


4

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-disubstituted 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.

We are grateful to Professor Anthony C. Richardson (Queen Elizabeth College, University of London) of his continuous interest and encouragement to this work. One of us (B. W.) also thanks to the International Children's Aid and Research Endowment for Mannosidosis for the support to this work.

References

1) S. M. Colegate, P. R. Dorling, and C. R. Huxtable, *Aust. J. Chem.*, 32, 2257 (1979); R. J. Molyneux and L. F. James, *Science*, 216, 190 (1982); M. J. Schneider, F. S. Ungemach, H. P. Broquist, and T. M. Harris, *Tetrahedron*, 39, 29 (1983); T. Kino, N. Inamura, K. Nakahara, S. Kiyoto, T. Goto, H. Terano, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, 38, 936 (1985).

2) T. Suami, K. Tadano, and Y. Iimura, *Chem. Lett.*, 1984, 513; *Carbohydr. Res.*, 136, 67 (1985); M. H. Ali, L. Hough, and A. C. Richardson, *J. Chem. Soc., Chem. Commun.*, 1984, 447; *Carbohydr. Res.*, 136, 225 (1985); G. W. J. Fleet, M. J. Gough, and P. W. Smith, *Tetrahedron Lett.*, 25, 1853 (1984); N. Yasuda, H. Tsutsumi, and T. Takaya, *Chem. Lett.*, 1984, 1201; C. E. Adams, F. J.

Walker, and K. B. Sharpless, *J. Org. Chem.*, 50, 420 (1985); H. Setoi, H. Takano, and M. Hashimoto, *ibid.*, 50, 3948 (1985).

3) The syntheses of 8-*epi*-swainsonine 2 and 2,8-di-*epi*-swainsonine have been published recently: N. Yasuda, H. Tsutsumi, and T. Takaya, *Chem. Lett.*, 1985, 31.

4) Y. Iimura, Y. Hotta, C. Fukabori, K. Tadano, and T. Suami, *J. Carbohydr. Chem.*, 5, 147 (1986); *Bull. Chem. Soc. Jpn.*, in press. The α-D-mannosidase inhibitory activities of the compounds 2 and 3 are approximately 15% and 20% of swainsonine 1, respectively.

5) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 1963, 5288.

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.

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

(Received September 29, 1986)