SYNTHESES OF (-)-1-EPI-SWAINSONINE AND (+)-1,8-DI-EPI-SWAINSONINE

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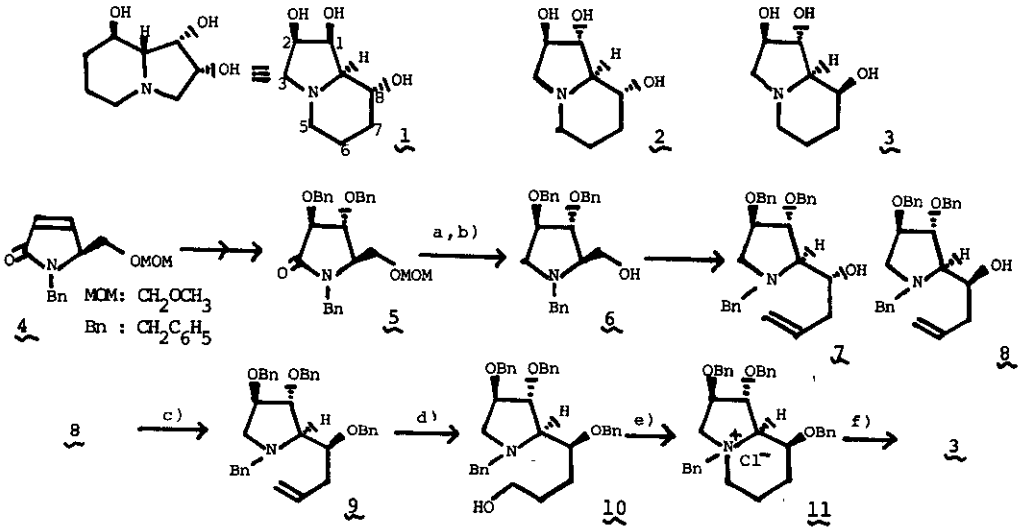
Abstract ——— The syntheses of (-)-1-epi-swainsonine and (+)-1,8-di-epi-swainsonine have been achieved from (S)-glutamic acid.

In a previous communication,[1] we reported a total synthesis of (-)-swainsonine (1), which possesses an α-mannosidase inhibitory activity and an immunoregurating activity, from (R)-glutamic acid. Interested in this biological activity, the synthesis of stereoisomers of 1 is a current interest. We now describe the syntheses of 1-epi-swainsonine (2) and 1,8-di-epi-swainsonine (3) from (S)-pyroglutamic acid derivative with the use of similar strategy to prepare (-)-swainsonine.[1] A compound 5,[1] which was prepared by cis-dihydroxylation of the unsaturated lactam 4 with OsO_4 followed by O-benzylation and subsequent epimerization, was converted to the pyrrolidine derivative 6[2] in 78% yield by removal of the methoxymethyl group followed by reduction with borane-dimethylsulfide complex. Swern oxidation of 6 furnished the aldehyde, which was condensed with allylmagnesium chloride in THF at -78°C to afford a 1.6: 1 ratio of 7[2] and 8[2] in 81% yield. On the other hand, reaction of the same aldehyde with diallylcopper lithium in ether at -78°C afforded a 1:2.2 ratio of 7 and 8 in 68% yield. The reactions of Grignard and *organocopper reagents with the aldehyde derived from 6 showed opposite diastereo*-selectivity. The hydroxy group in 8 was protected as a benzyl ether to afford a compound 9,[2] which was converted into the alcohol 10[2] by hydroboration-oxidation. Mesylation of 10 leads to a bicyclic compound (11), which without purification was debenzylated by catalytic hydrogenation to furnish (+)-1,8-di-epi-swainsonine (3) in 43% yield after purification with Dowex 50W-X8 (H^+ form), mp 142-143°C, mmp 140-142°C, $[\alpha]_D^{20}$ +24.2°(c 0.3, MeOH) (lit.[3] mp 138-140°C, $[\alpha]_D^{31}$ +18.2°(c 0.57, MeOH)). It was identical with an authentic sample of 3 in the ^1H nmr and ^{13}C nmr spectra. By a parallel series of reactions, 7 was transformed to (-)-1-epi-

swainsonine (2)[2] in 39% yield, mp 109-110°C; $[\alpha]_D^{20}$ -33.2°(c 0.85,MeOH); ^{13}C nmr (CD_3OD,δ 48.97)δ 24.56, 34.53, 52.86, 61.96, 72.40, 76.29, 78.15, 84.55; calcd. for $C_8H_5NO_3$: m/z 173.1049, found; M,173.1032.



Conditions a) BH_3:Me_2S, THF,reflux. b) aq. HCl/MeOH, 70°C. c) NaH, BnBr/DMF-THF. d) BH_3, THF; then 30% H_2O_2, 12% aq. NaOH. e) MsCl(1.2 eq.), triethylamine, CH_2Cl_2. f) H_2-10%Pd/C,HCl-EtOH.

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REFERRENCES AND NOTES

1) N. Ikota and A. Hanaki, Chem. Pharm. Bull., 1987, 35, 2140. References for the other synthesis of 1 and its stereoisomers were cited therein.

2) Satisfactory spectral and analytical data were obtained for this compound.

3) The $[\alpha]_D$ value of 3 was first reported to be -35.6°(MeOH). Y. Iimura, Y. Hotta, C. Fukabori, K. Tadano, and T. Suami, J. Carbohydr. Chem., 1986, 5, 147; idem, Bull. Chem. Soc. Japan, 1986, 59, 3885. Prior to submitting this paper, we had communications regarding the $[\alpha]_D$ of 3 with Prof. K. Tadano. Prof. Tadano re-examined the $[\alpha]_D$ of 3 previously prepared and found that 3 had $[\alpha]_D$ +18.2°(MeOH).

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