

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

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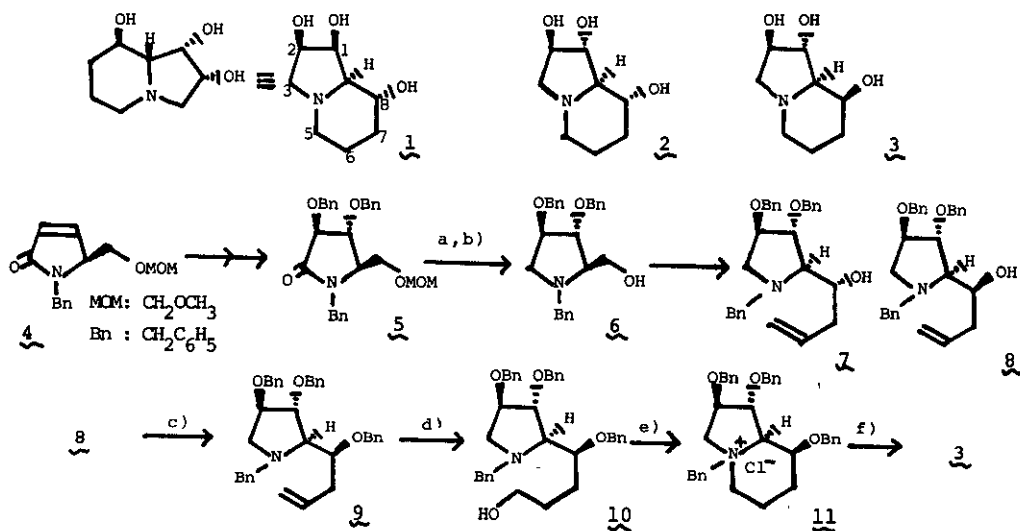
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Abstract — The syntheses of (-)-1-epi-swainsonine and (+)-1,8-di-epi-swainsonine have been achieved from (S)-glutamic acid.

In a previous communication,¹ we reported a total synthesis of (-)-swainsonine (1), which possesses an α -mannosidase inhibitory activity and an immunoregulating 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 OsO₄ followed by O-benzylation and subsequent epimerization, was converted to the pyrrolidine derivative 6² 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 7² and 8² 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 diastereoselectivity. The hydroxy group in 8 was protected as a benzyl ether to afford a compound 9,² which was converted into the alcohol 10² 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, $[\alpha]_D^{20} +24.2^\circ$ (c 0.3, MeOH) (lit.³ mp 138-140°C, $[\alpha]_D^{31} +18.2^\circ$ (c 0.57, MeOH)). It was identical with an authentic sample of 3 in the ¹H nmr and ¹³C 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); ¹³C nmr (CD₃OD, δ 48.97) δ 24.56, 34.53, 52.86, 61.96, 72.40, 76.29, 78.15, 84.55; calcd. for C₈H₅NO₃: m/z 173.1049, found; M, 173.1032.



Conditions a) $\text{BH}_3\text{Me}_2\text{S}$, 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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REFERENCES 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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