

SYNTHESIS OF 8-EPI-KIFUNENSINE

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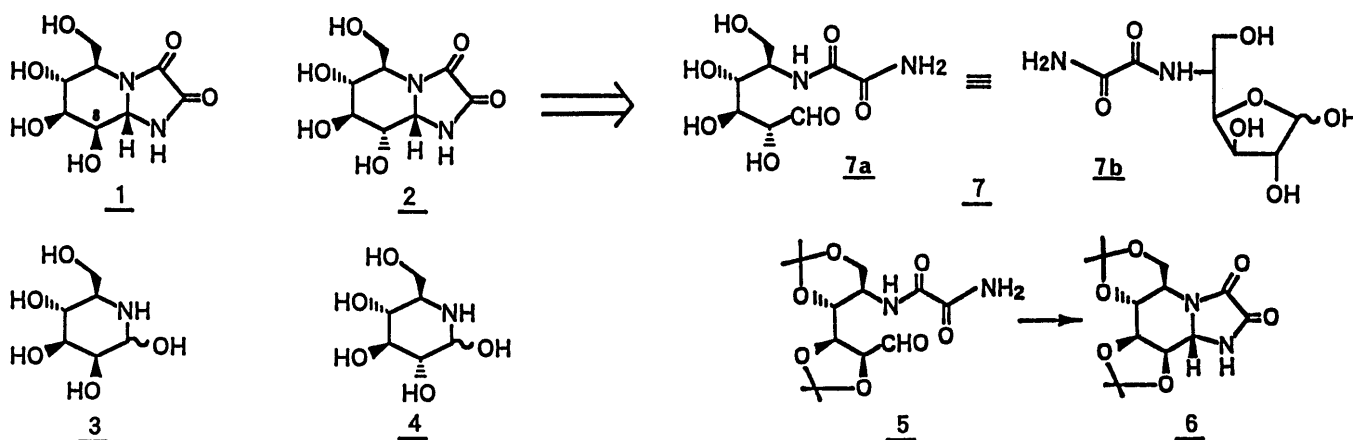
8-epi-Kifunensine(2) has been synthesized from D-glucose by a route involving a double cyclization of 7 as a key step.

KEYWORDS 8-epi-kifunensine ; polyhydroxylated piperidine ; 4,5-dioxoimidazolidine ; α -glucosidase inhibitor ; D-glucose

The pronounced glycosidase inhibitory activities of polyhydroxylated piperidines have stimulated considerable interest in studies of their biological and pharmacological properties. In the preceding papers,^{1,2)} we reported the structure and synthesis of kifunensine(1) isolated from an actinomycete as an immunomodulating substance with α -mannosidase inhibitory activity. Kifunensine(1) corresponds structurally to a cyclic oxamide derivative of 1-amino-substituted mannojirimycin(3).³⁾ This unique structure of 1 has further prompted us to exploit the synthesis of 8-epi-kifunensine(2) which is related similarly to nojirimycin(4), a representative of α -glucosidase inhibitors.⁴⁾ Herein we report its synthesis from D-glucose.

We demonstrated in a preceding paper²⁾ that the bicyclic piperidine-dioxoimidazolidine ring system of kifunensine(1) can be constructed via a double cyclization of oxamide-aldehyde 5 to 6. We anticipated that 8-epi-kifunensine(2) could be synthesized by a route involving a similar cyclization process as a key step. In executing this approach, we needed the oxamide derivative 7a of 5-amino-5-deoxy-D-glucose (nojirimycin(4)). The required derivative 7a would exist in equilibrium with its furanose form 7b, whose 1,2-O-isopropylidene derivative 14 (see Chart 1) could be prepared from 1,2-O-isopropylidene-5-amino-5-deoxy-D-glucofuranose (8), previously prepared by Tsuda et al. as an intermediate for their synthesis of nojirimycin (4).⁵⁾

After that procedure, we prepared 8 as a mixture with its 5-epimer 9. Acylation of the mixture with carbobenzyloxy chloride (NaOH/aqueous dioxane, 0°C, r.t.) gave, after chromatography on silica gel, the carbobenzyloxy(Cbz) derivative 10 in 19.7% yield (5-epimer 11, 7.4%).⁶⁾ Removal of the Cbz group in 10 by



hydrogenolysis (H_2 (3 atm)/10% Pd-C/MeOH), followed by silylation with bis(trimethylsilyl)acetamide (THF, r.t.) and subsequent acylation with EtOCOCOC_1 (THF, 0°C) gave, after acidic treatment (1N AcOH), compound 12 in 97.0% yield.⁷⁾ Alternatively, 12 was prepared directly from the mixture of 8 and 9 by the same acylation with EtOCOCOC_1 and chromatography on silica gel in 31.2% yield (5-epimer 13,⁶⁾ 12.5%). Ammonolysis of 12 (2.4N NH_3 -MeOH, r.t.) yielded the requisite intermediate 14 (100%).⁷⁾

Pursuing our initial approach, after removal of the acetonide protecting group in 14 (75% TFA- H_2O , 0°C), we investigated cyclization of the resulting furanose 7 (an anomeric mixture, ca 1:1; 76.9%)⁷⁾ with NH_3 according to the procedure used for the synthesis of kifunensine.²⁾ Despite all our efforts, however, the reaction never went to completion for reasons not well understood. On the other hand, when this cyclization was examined using MeNH_2 (40% MeNH_2 - H_2O , r.t., 6h), 15 was formed along with its diastereomer 16 (40.5% total yield).⁸⁾ These products were characterized after derivatization to the tetra acetates 17 and 18 and separation by silica gel chromatography (17, 59.4%; 18, 23.8%).⁸⁾ The configuration of 8a-H was assigned S for 17 and R for 18 on the basis of the $J_{8,8a}$ values of 2Hz (8,8a-cis) for 17 and 9Hz (8,8a-trans) for 18 in their ^1H NMR spectra.⁸⁾ Deacylation of each compound with 1N NaOH gave N^1 -methyl-8-epi-kifunensine (15) (85.1%) and its diastereomer 16 (63.2%), respectively.⁸⁾

For the synthesis of 2, we then exploited the reaction of 7 with an appropriate benzylamine and removal of the benzyl group. Thus 7 was allowed to react with 2,4-dimethoxybenzylamine (1.5 eq/MeOH, r.t., 3 d) to afford, as expected, the desired cyclization product 19 in 24.8% yield as the single diastereomer.⁷⁾ The configuration of 8a-H appeared to be S on the ^1H NMR evidence ($J_{8,8a}=1\text{Hz}$ (8,8a-cis)). The low yield is mainly due to the very slow reaction which may arise for a steric reason. The stereoselectivity may also be attributable to the bulkiness of the benzylamine. Oxidative removal of the benzyl group in 19 ($\text{K}_2\text{S}_2\text{O}_8/\text{Na}_2\text{HPO}_4/40\% \text{MeCN-H}_2\text{O}$, reflux) provided in 93.6% yield 8-epi-kifunensine (2),⁹⁾ whose structure was confirmed by X-ray crystal analysis (Fig.1).¹⁰⁾

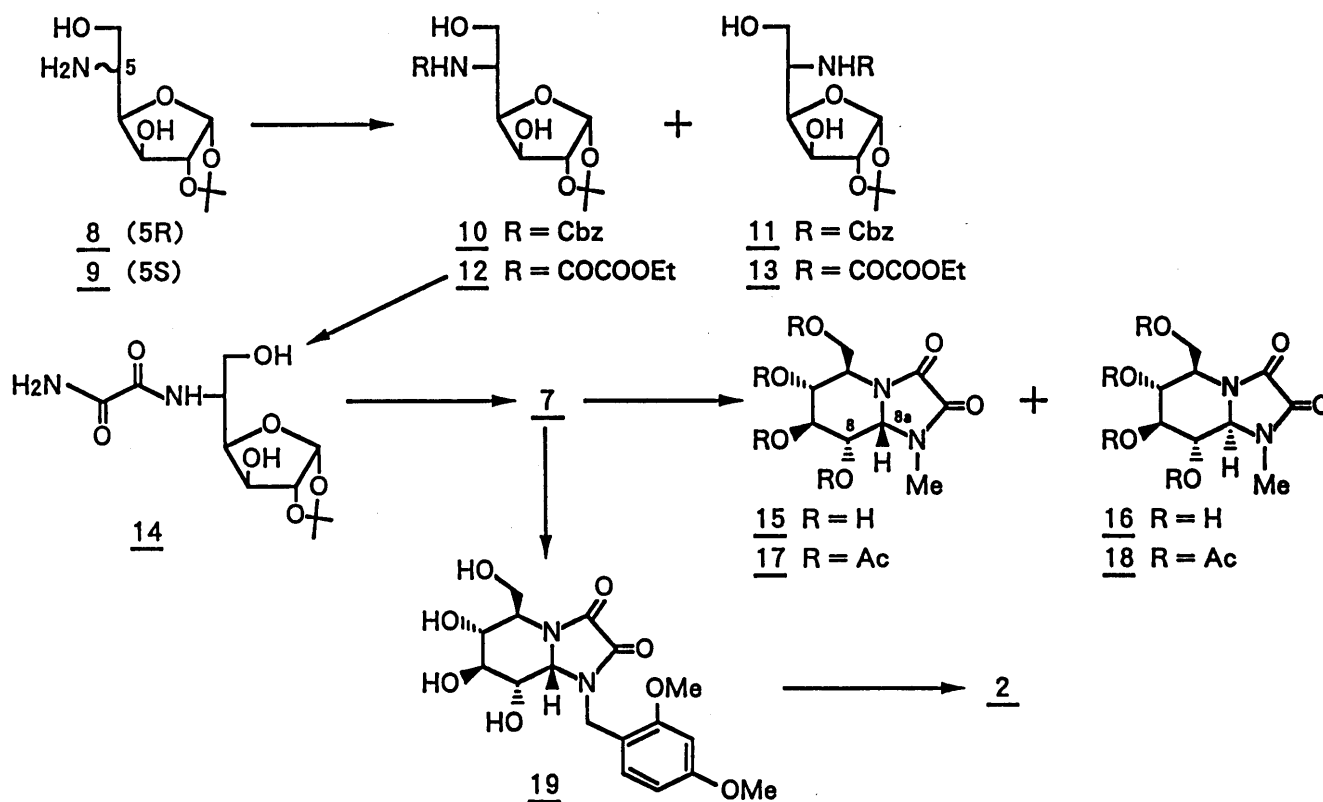


Chart 1

We have thus completed the synthesis of 8-epi-kifunensine(2) by adopting the double cyclization approach. 8-epi-Kifunensine(2) showed an inhibitory activity with an IC_{50} of $2.2 \times 10^{-4} M$ against α -glucosidase (yeast).

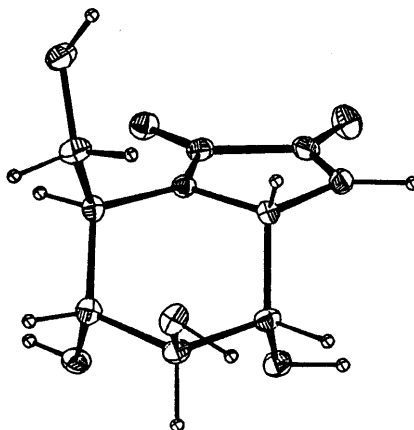


Fig.1. Molecular Structure of 2 by an ORTEP Drawing

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REFERENCES AND NOTES

- 1) H. Kayakiri, S. Takase, T. Shibata, M. Okamoto, H. Terano, M. Hashimoto, T. Tada, S. Koda, J. Org. Chem. **54**, 4015 (1989).
- 2) H. Kayakiri, C. Kasahara, T. Oku, M. Hashimoto, Tetrahedron Lett., submitted for publication.
- 3) T. Niwa, T. Tsuruoka, H. Goi, Y. Kodama, J. Itoh, S. Inouye, Y. Yamada, T. Niida, M. Nobe, Y. Ogawa, J. Antibiot. **37**, 1579 (1984).
- 4) S. Inouye, T. Tsuruoka, T. Ito, T. Niida, Tetrahedron **23**, 2125 (1968).
- 5) Y. Tsuda, Y. Okuno, K. Kanemitsu, Heterocycles, **27**, 63 (1988).
- 6) Selected physical data of 10, 11, and 13. 10: oil; $[\alpha]_D^{25} +32.2^\circ$ (c 1.0, $CHCl_3$) (lit: oil, $[\alpha]_D^{25} +25.5^\circ$ (c 1): A. Vasella, R. Voefray, Helv. Chim. Acta, **65**, 1134^D (1982)). 11: mp $140-141^\circ C$; $[\alpha]_D^{25} -24.5^\circ$ (c 0.5, $CHCl_3$); FABMS m/z 354 (M+H). 13: amorphous powder; FABMS m/z 320 (M+H); 1H NMR (CD_3OD) δ 5.87(d, J=4Hz, 1H), 4.51(d, J=4Hz, 1H), 4.40-4.26(m, 4H), 4.12(br s, 1H), 3.75-3.65(m, 2H).
- 7) Selected physical data of the intermediates for 2. 12: mp $164-165^\circ C$; FABMS m/z 320 (M+H); 1H NMR (CD_3OD) δ 5.89(d, J=4Hz, 1H), 4.50(d, J=4Hz, 1H), 4.40-4.22(m, 4H), 4.16(br s, 1H). 14: amorphous powder; FABMS m/z 291 (M+H); 1H NMR (CD_3OD) δ 5.89(d, J=4Hz, 1H), 4.50(d, J=4Hz, 1H), 4.29-4.08(m, 3H), 3.85-3.70(m, 2H). 7: amorphous powder; FABMS m/z 251 (M+H); 1H NMR (D_2O) δ 5.39(d, J=4Hz, 0.5H), 5.10(s, 0.5H), 4.30-3.95(m, 4H), 3.85-3.56(m, 2H). 19: amorphous powder; $[\alpha]_D^{25} +50.4^\circ$ (c 0.5, MeOH); FABMS m/z 383 (M+H); 1H NMR ($Me_2SO-d_6-D_2O$) δ 4.88(d, J=1Hz, 1H), 4.77(d, J=1.5Hz, 1H), 4.20(dd, J=6.6Hz, 1H), 4.12(d, J=1.5Hz, 1H), 4.03(dd, J=1.3Hz, 1H), 3.90(dd, J=3.3Hz, 1H).
- 8) Selected physical data of 15, 16, 17, and 18. 15: mp $259-260^\circ C$; $[\alpha]_D^{25} -67.6^\circ$ (c 0.5, H_2O); FABMS m/z 247 (M+H); 1H NMR (D_2O) δ 5.38(d, J=2Hz, 1H), 4.50(dd, J=5.9Hz, 1H), 4.37(dd, J=2.3Hz, 1H), 4.23(dd, J=3.3Hz, 1H), 4.08(d, J=3Hz, 1H), 3.98(dd, J=9.1Hz, 1H), 3.88(dd, J=5.1Hz, 1H). 16: mp $230-231^\circ C$; $[\alpha]_D^{25} -61.0^\circ$ (c 0.5, H_2O); FABMS m/z 247 (M+H); 1H NMR (D_2O) δ 4.78(d, J=9Hz, 1H), 4.40(dd, J=2.13Hz, 1H), 4.28(dd, J=5.13Hz, 1H), 3.73-3.44(m, 4H). 17: mp $228-229^\circ C$; $[\alpha]_D^{25} -24.5^\circ$ (c 0.4, $CHCl_3$); FABMS m/z 415 (M+H); 1H NMR ($CDCl_3$) δ 5.33-5.22(m, 2H), 5.19(d, J=2Hz, 1H), 4.92(m, 1H), 4.78(dd, J=5.10Hz, 1H), 4.49(dd, J=10.11Hz, 1H), 4.18(dd, J=5.11Hz, 1H). 18: mp $280^\circ C$; $[\alpha]_D^{25} -36.9^\circ$ (c 0.1, $CHCl_3$); FABMS m/z 415 (M+H); 1H NMR ($CDCl_3-CD_3OD$) δ 5.37-5.07(m, 3H), 4.88(d, J=9Hz, 1H), 4.82-4.69(m, 2H), 3.90(m, 1H).
- 9) Mp $272-274^\circ C$ dec; $[\alpha]_D^{25} -54.6^\circ$ (c 0.1, H_2O); FABMS m/z 233 (M+H); 1H NMR (D_2O) δ 5.45(d, J=2Hz, 1H), 4.47(m, 1H), 4.21-4.17(m, 2H), 4.04(m, 1H), 3.99(dd, J=9.12Hz, 1H), 3.88(dd, J=5.12Hz, 1H).
- 10) Crystal data for 2 ($C_{11}H_{12}N_2O$, MW=232.19): orthorhombic; space group $P2_12_12_1$; unit cell $a=14.407(1)\text{\AA}$, $b=9.070(1)\text{\AA}$, $c=6.938(1)\text{\AA}$; $V=906.6(2)\text{\AA}^3$; $Z=4$; $D_x=1.701\text{g cm}^{-3}$. Intensities were measured with $2\theta/\omega$ scan mode using graphite-monochromated $CuK\alpha$ radiation ($\lambda=1.54178\text{\AA}$). Parameters were refined by using anisotropic temperature factors to $R=0.061$ for 908 reflections used ($F_o \geq 3\sigma(F_o)$). Details will be reported in a forthcoming full paper.

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