SYNTHESIS OF 8-EPI-KIFUNENSINE

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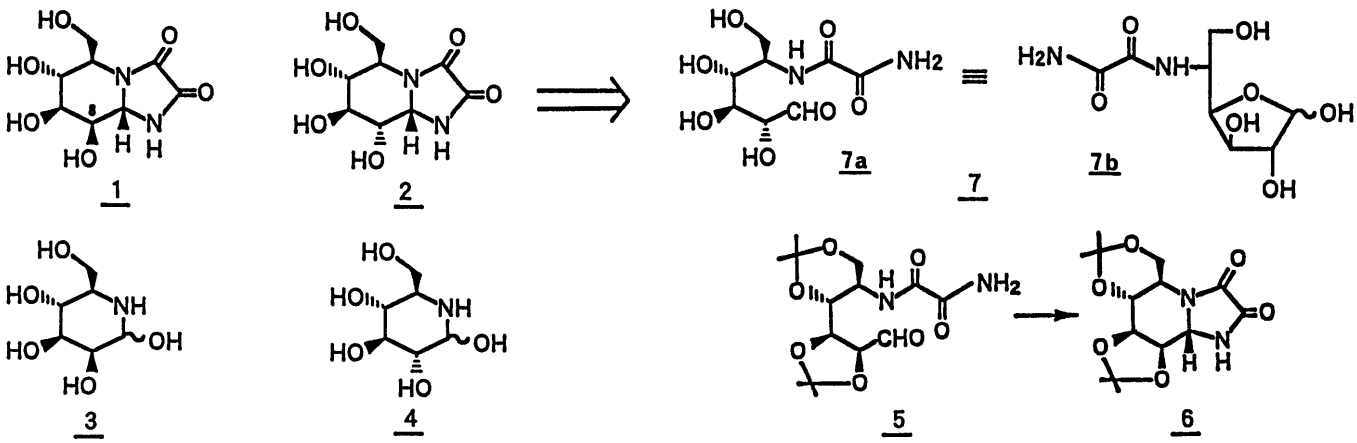
8-epi-Kifunensine(2) has been synthesized from D-glucose by a route involving a double cyclization of 7 as a key step.

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 paper [2] 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 EtOCOCOCl (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 EtOCOCOCl 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 ^{1}H 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 ^{1}H NMR evidence ($J_{8,8a}$=1Hz (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 ($K_2S_2O_8$/Na_2HPO_4/40% MeCN-H_2O, reflux) provided in 93.6% yield 8-epi-kifunensine (2),[9] whose structure was confirmed by X-ray crystal analysis (Fig.1).[10]

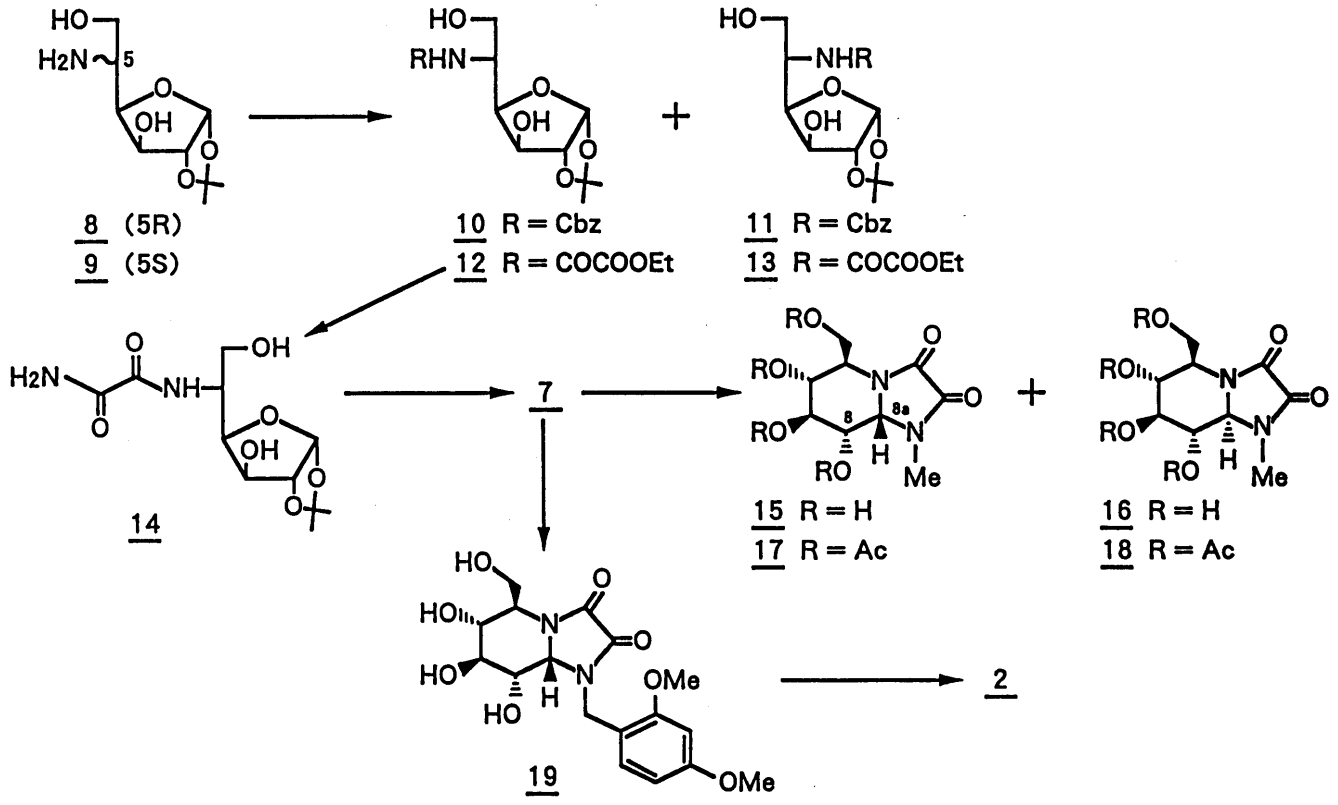


Chart 1

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 2.2×10^{-4}M against α-glucosidase (yeast).

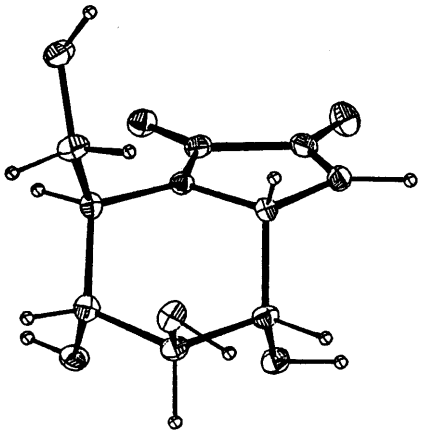


Fig.1. Molecular Structure of 2 by an ORTEP Drawing

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6) Selected physical data of 10, 11, and 13. 10 : oil; $[\alpha]_D$ +32.2°(c 1.0, $CHCl_3$) (lit :oil, $[\alpha]_D$ +25.5°(c 1): A. Vasella, R. Voeffray, Helv. Chim. Acta, 65, 1134 (1982)). 11 : mp 140-141°C; $[\alpha]_D$ -24.5°(c 0.5, $CHCl_3$); FABMS m/z 354 (M+H). 13 : amorpous powder ; FABMS m/z 320 (M+H) ; ^{1}H NMR (CD_3OD) δ5.87(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°C ; FABMS m/z 320 (M+H) ; ^{1}H NMR (CD_3OD) δ5.89(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) ; ^{1}H NMR (CD_3OD) δ5.89(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) ; ^{1}H NMR (D_2O) δ5.39(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 ; $[\alpha]_D$ +50.4°(c 0.5, MeOH) ; FABMS m/z 383 (M+H) ; ^{1}H NMR (Me_2SO-d_6-D_2O) δ4.88(d, J=1Hz, 1H), 4.77(d, J=15Hz, 1H), 4.20(dd, J=6,6Hz, 1H), 4.12(d, J=15Hz, 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°C ; $[\alpha]_D$ -67.6°(c 0.5, H_2O) ; FABMS m/z 247 (M+H) ; ^{1}H NMR (D_2O) δ5.38(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=9,12Hz, 1H), 3.88(dd, J=5,12Hz, 1H). 16 : mp 230-231°C ; $[\alpha]_D$ -61.0°(c 0.5, H_2O) ; FABMS m/z 247 (M+H) ; ^{1}H NMR (D_2O) δ4.78(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°C; $[\alpha]_D$ -24.5°(c 0.4, $CHCl_3$) ; FABMS m/z 415 (M+H) ; ^{1}H NMR ($CDCl_3$) δ5.33-5.22(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°C ; $[\alpha]_D$ -36.9°(c 0.1, $CHCl_3$) ; FABMS m/z 415 (M+H) ; ^{1}H NMR ($CDCl_3$-CD_3OD) δ5.37-5.07(m, 3H), 4.88 (d, J=9Hz, 1H), 4.82-4.69(m, 2H), 3.90(m, 1H).
9) Mp 272-274°C dec ; $[\alpha]_D$ -54.6°(c 0.1, H_2O) ; FABMS m/z 233 (M+H) ; ^{1}H NMR (D_2O) δ5.45(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 ($C_8H_{17}N_2O_6$, MW=232.19) : orthorhombic ; space group $P2_12_12_1$; unit cell a=14,407(1)Å, b = 9,070(1)Å, c = 6,938(1)Å; V = 906.6(2)Å^3 ; Z = 4 ; Dx = 1.701g cm^{-3}. Intensities were measured with 2θ/ω scan mode using graphite-monochromated CuKα radiation (λ=1.54178Å). Parameters were refined by using anisotropic temperature factors to R=0.061 for 908 reflections used ($Fo \geq 3\sigma(Fo)$). Details will be reported in a forthcoming full paper.

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