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SYNTHESIS OF KIFUNENSINE, AN IMMUNOMODULATING SUBSTANCE ISOLATED FROM MICROBIAL SOURCE

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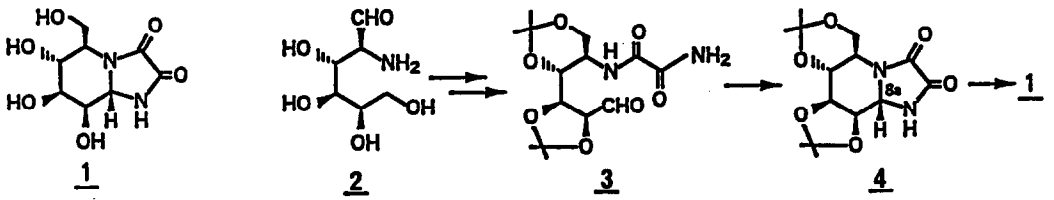
Summary : A synthesis of kifunensine(1) has been achieved by a route involving, as a key step, a double cyclization of aldehyde 3 with ammonia.

Polyhydroxylated piperidine and pyrrolidine alkaloids[1] have attracted considerable attention because of their potent glycosidase-inhibitory activity.

In the preceding paper,[2] we reported the structure of kifunensine(1) isolated from an actinomycete as an immunomodulating substance with α-mannosidase inhibitory activity.[3] Herein we report an enantiospecific synthesis of this novel natural product starting from D-mannosamine(2).

A key feature in the synthesis of kifunensine(1) is the construction of the dioxoimidazolidine ring of the molecule. We envisioned that this could be achieved by a double cyclization of the oxamide-aldehyde 3 derived from D-mannosamine(2). Ring closure of 3 would take place in favor of the desired, energetically stable (8aS)-diasteromer, kifunensine diacetonide 4.

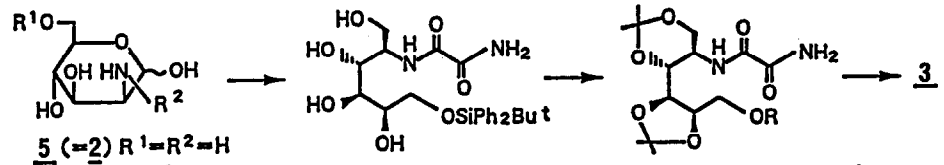


1 2 3 4

The requisite intermediate 3 was prepared from D-mannosamine(5(=2)) as follows:[4] 1) acylation(NH_2COCO_2H(1.5equiv)/DCC/HOBT/DMF,r.t.) to 6; 2) silylation(t-$BuPh_2SiCl$(2.0equiv)/imidazole/DMF, 0°C) to 7 (anomeric mixture (7:3), 66% from 5); 3) reduction($NaBH_4$/MeOH, r.t.) to 8 (92%); 4) acetonization(acetone/$BF_3 \cdot OEt_2$, -20°C) to 9 (86%); 5) desilylation(n-Bu_4NF/THF, -20°C) to 10 (100%); 6) oxidation($CrO_3 \cdot 2Py/CH_2Cl_2$, r.t.) to 3.

The aldehyde 3 was rather unstable and, without purification, was directly subjected to the key cyclization reaction. We found in this cyclization that ammonia effected the formation of the dioxoimidazolidine

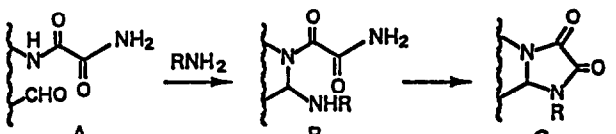
ring. Thus, on treatment of 3 with NH_3 (10%) in MeOH (r.t.), the objective compound 4[4] was obtained in 55% yield from 10. It is remarkable that no detectable amount of the undesirable epimer at C-8a was accompanied in this reaction. Removal of the acetonide protecting groups in 4 (75% TFA-H_2O, r.t.) afforded kifunensine(1) (mp >280°C, $[\alpha]_D$+58.7° (c 0.1, H_2O), 82%), identical with an authentic sample in all respects.[2]



5 (=2) R^1=R^2=H
6 R^1=H, R^2=COCONH$_2$
7 R^1=SiPh$_2$Bu^t, R^2=COCONH$_2$

8

9 R=SiPh$_2$Bu^t
10 R=H



A B C

R=H or Me

11 R^1,R^2=R^3,R^4=>CMe$_2$
12 R^1=R^2=R^3=R^4=H

Since this cyclization of 3 to 4 did not occurred with tertiary amines (e.g. Et_3N, i-Pr_2NEt, DBU etc), it was speculated that the reaction proceeded through the intermediacy of amine B. Evidence supporting this interpretation was provided by treating 3 with $MeNH_2$(30%)-MeOH in a similar manner to give the corresponding N-methyl derivative 11 (62% from 10).[5] Removal of the acetonide groups in 11 in the same way as described for 4 yielded N^1-methylkifunensine 12 (84%).[6]

We have thus established an efficient route for the synthesis of kifunensine(1) by adopting a double cyclization of oxamide-aldehyde 3 as the key step.

References and Notes

1) For a review on 1,5-iminopyranoses and 1,4-iminofuranoses, see Fleet, G. W.J. Spec. Publ. Royal. Chem. Soc. 1988, 65, 149.
2) Kayakiri,H.; Takase,S.; Shibata,T.; Okamoto,M.; Terano,H.; Hashimoto,M.; Tada,T.; Koda,S. J. Org. Chem. 1989, 54, 4015.
3) Iwami,M.; Nakayama,O.; Terano,H.; Kohsaka,M.; Aoki,H.; Imanaka,H. J.Antibiot. 1987, 40, 612.
4) Selected physical data of the intermediates. 7 : FABMS, m/z 511 (M+Na); ^{1}H NMR (Me_2SO-d_6) δ5.17(d, J=4Hz, 0.3H), 5.08(d, J=4Hz, 0.7H). 8 : mp 174-5°C; $[\alpha]_D$-16.9°(c 0.7, MeOH); FABMS, m/z 491 (M+H). 9 : FABMS, m/z 571(M+H); ^{1}H NMR (Me_2SO-d_6) δ4.42(dt, J=2, 6Hz, 1H). 10 : $[\alpha]_D$-77.5° (c 0.5, MeOH); FABMS, m/z 333(M+H). 3 : ^{1}H NMR($CDCl_3$) δ9.60(s, 1H), 4 : mp 275-8°C; $[\alpha]_D$-67.1°(c 0.5, MeOH); FABMS, m/z 313 (M+H);
5) mp 245-6°C; $[\alpha]_D$-64.8°(c 0.5, MeOH); FABMS, m/z 327(M+H).
6) mp 283-5°C dec; $[\alpha]_D$+66.0°(c 0.4, H_2O); FABMS, m/z 247(M+H); ^{1}H NMR(D_2O) δ5.08 (d, J=10Hz, 1H), 4.43(dd, J=10, 4Hz, 1H), 4.18(d, J=3Hz, 1H), 4.07 (dd, J=3, 3Hz, 1H), 3.98(d, J=10Hz, 1H), 3.92-3.78(m, 2H), 3.30(s, 3H).

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