Communications to the Editor

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SYNTHESIS OF 1-DEOXYNOJIRIMYCIN AND 1-DEOXYMANNOJIRIMYCIN

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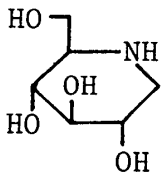
Here the synthesis of 1-deoxynojirimycin (1) and 1-deoxymannojirimycin (2) from D-mannose is reported and their immunostimulating activity is evaluated.

KEYWORDS——piperidine alkaloid; azapyranose; D-mannose; immunostimulating activity

Polyhydroxylated alkaloids having piperidine or indolizidine skeletons have been the focus of intensive investigation because of their interesting biological activities. 1-Deoxynojirimycin (1)[1] and castanospermine (3)[2] inhibit glucosidases while 1-deoxymannojirimycin (2)[3] and swainsonine (4)[4] inhibit mannosidases. Also we have found recently[5] that in mice 4 restores mitogenic responses depressed by immunosuppressive factors. This is probably accomplished through its inhibition of glycosidases.



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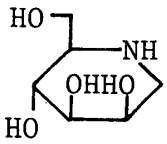

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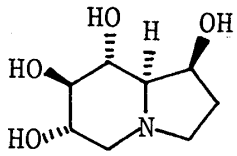

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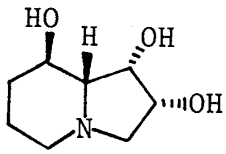

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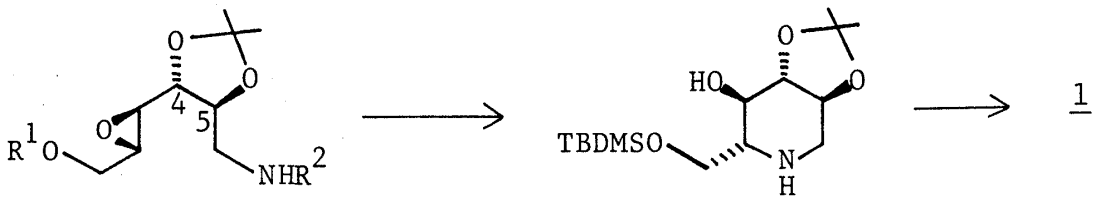
In the preceding papers, we reported enantiospecific total synthesis of the indolizidine alkaloids, swainsonine[6] and castanospermine,[7] starting from D-mannose. As a part of our investigation in this field, we aimed at synthesizing polyhydroxylated piperidine alkaloids, 1-deoxynojirimycin (1) and 1-deoxymannojirimycin (2).[8] Here we report the synthesis of these two alkaloids, starting from the intermediates used for our synthesis of swainsonine and castanospermine, and an analysis of their immunostimulating activity.

1-Deoxynojirimycin (1)

The starting epoxy-alcohol 5, prepared from D-mannose as described in the preceding paper,[7] was converted to *t*-butyldimethylsilyl(TBDMS) ether 6 (77%) by silylation with TBDMSCl (imidazole/DMF, r.t., 2 days). The Cbz group in 6 was removed by catalytic reduction (H_2 (3 atm)/ Pd-black/ EtOH) to give amine 7, which, without purification, was refluxed in methoxyethanol to afford piperidine 8 (74% from 6). Fixation of the 4,5-*trans*-diol in 7 by acetonide protection thus induced the selective formation of the 6-membered piperidine ring in 8. Removal of the protecting groups in 8 by treatment with 75% aqueous TFA (r.t., overnight) provided 1 (mp 192-195°C, $[\alpha]_D^{20}$+46.7° (c 0.2, H_2O), 90%).



5 : R^1=H, R^2=Cbz

6 : R^1=TBDMS, R^2=Cbz

7 : R^1=TBDMS, R^2=H

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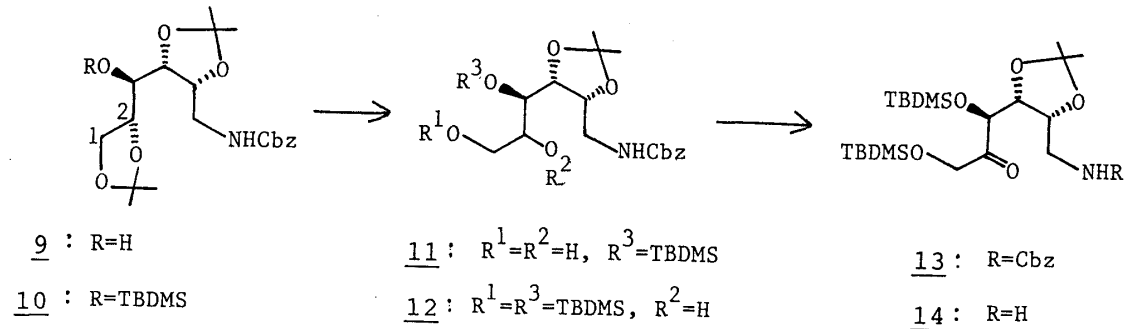
1-Deoxymannojirimycin (2)

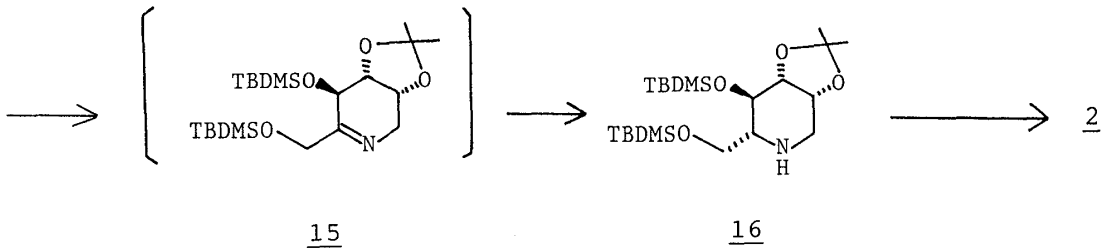
The hydroxy group in the starting material 9, prepared from D-mannose as described in the preceding paper,[6] was protected as TBDMS ether in a manner similar to that described above to give 10 (77%). Selective removal of the 1,2-acetonide protecting group in 10 by treatment with *p*-TsOH (0.1 eq) in 90% aqueous acetone (r.t., 30 h) produced diol 11 (15%) along with a 43% recovery of the starting 10. The 1-hydroxy group in 11 was selectively silylated by treating it with 1 eq of TBDMSCl (imidazole/DMF, r.t., 6 h) to provide 12 (94%). Oxidation of 12 with Collins reagent (CH_2Cl_2, r.t.) afforded ketone 13 (unstable)[9] in 80% yield. Removal of the Cbz group in 13 by catalytic reduction (H_2 (3 atm)/ Pd-black/ EtOH) directly provided piperidine 16 (74%), which was produced via stereoselective, intramolecular reductive alkylation of the intermediate amino-ketone 14. The reduction seemed to occur selectively from the less hindered β-side of the cyclic imine intermediate 15. Removal of the protecting groups in 16 by treatment with 75% aqueous TFA (r.t., overnight) afforded 2 (mp 183-185°C, $[\alpha]_D^{19}$-33.7° (c 0.2, MeOH), 86%).



9 : R=H
10 : R=TBDMS

11 : R^1=R^2=H, R^3=TBDMS
12 : R^1=R^3=TBDMS, R^2=H

13 : R=Cbz
14 : R=H



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The immunostimulating activity of 1 and 2 was evaluated by measuring their competitive effect against immunosuppressive factors which suppress Con A-stimulated lymphocyte proliferation.[5] The minimum effective concentrations (MEC) of 1 and 2 were 50 and 32 μg/ml, respectively, while the MEC for swainsonine, a standard compound, is 0.01 μg/ml. It is interesting that 1 and 2 have the activity, though considerably less than swainsonine.

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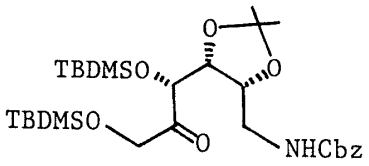
7) H.Setoi, H.Takeno, and M.Hashimoto, Tetrahedron Lett., 26, 4617 (1985).
8) For the previously reported syntheses of 1 and 2, see R.C.Bernotas and B.Ganem, Tetrahedron Lett., 26, 1123 (1985) and references cited therein.
9) Ketone 13 tends to be epimerized probably to the diastereoisomer 17 via an enolate intermediate.



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10) The selected physical data. 8: mp 109-110°C; $[\alpha]_D^{20}$+20.1° (c 0.2, $CHCl_3$); ^{1}H-NMR($CDCl_3$)δ:2.16(br s, 2H), 2.50(dd, J=3.5, 9Hz, 1H), 2.6-2.9(m, 1H), 3.3-3.5 (m, 3H), 3.60(m, 1H), 3.7-4.0(m, 2H). 1: ^{1}H-NMR (D_2O)δ:2.41(dd, J=8, 10.5Hz, 1H), 2.55(m, 1H), 3.10(dd, J=4.5, 10.5Hz, 1H), 3.2-3.6(m, 3H), 3.59(dd, J=5, 10Hz, 1H) 3.83(dd, J=5, 10Hz, 1H). 13: $[\alpha]_D^{20}$+8.12° (c 0.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$)δ:3.2-3.5(m, 2H), 4.0-4.5(m, 3H), 4.62(ABq, J=12Hz, 2H), 5.13(s, 2H), 5.13(br s, 1H). 16: mp 43-45°C; $[\alpha]_D^{20}$-36.5°(c 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ:2.33(dt, J=9, 4Hz, 1H), 2.94(dd, J=3, 15Hz, 1H), 3.41(d, J=15Hz, 1H), 3.53 (dd, J=3, 9Hz, 1H), 3.4-4.0(m, 3H), 4.11(m, 1H). 2: ^{1}H-NMR (D_2O) δ:2.71(dt, J=5, 10Hz, 1H), 2.93(d, J=14Hz, 1H), 3.15(dd, J=3, 14Hz, 1H), 3.61(dd, J=3, 10Hz, 1H), 3.71(t, J=10Hz, 1H), 3.80(dd, J=5, 11Hz, 1H), 3.86(dd, J=4, 13Hz, 1H), 4.09(m, 1H).

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