

Communications to the Editor

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SYNTHESIS OF 1-DEOXYNOJIRIMYCIN AND 1-DEOXYMANNOJIRIMYCIN

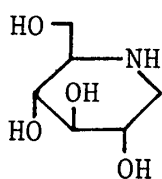
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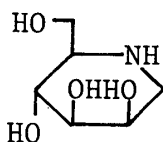
Here the synthesis of 1-deoxynojirimycin (1) and 1-deoxymannojirimycin (2) from D-mannose is reported and their immunostimulating activity is evaluated.

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

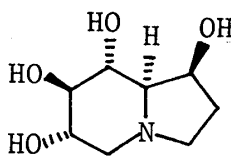
Polyhydroxylated alkaloids having piperidine or indolizidine skeletons have been the focus of intensive investigation because of their interesting biological activities. 1-Deoxynojirimycin (1)¹⁾ and castanospermine (3)²⁾ inhibit glucosidases while 1-deoxymannojirimycin (2)³⁾ and swainsonine (4)⁴⁾ inhibit mannosidases. Also we have found recently⁵⁾ that in mice 4 restores mitogenic responses depressed by immunosuppressive factors. This is probably accomplished through its inhibition of glycosidases.



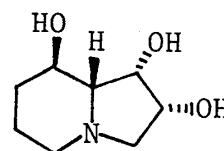
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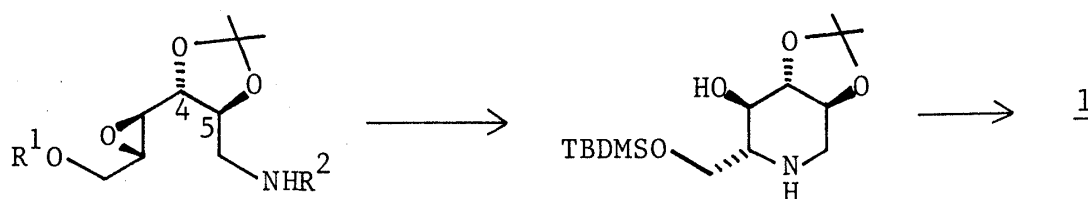


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In the preceding papers, we reported enantiospecific total synthesis of the indolizidine alkaloids, swainsonine⁶⁾ and castanospermine,⁷⁾ starting from D-mannose. As a part of our investigation in this field, we aimed at synthesizing polyhydroxylated 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, $[\alpha]_D^{20} +46.7^\circ$ (c 0.2, H_2O), 90%).



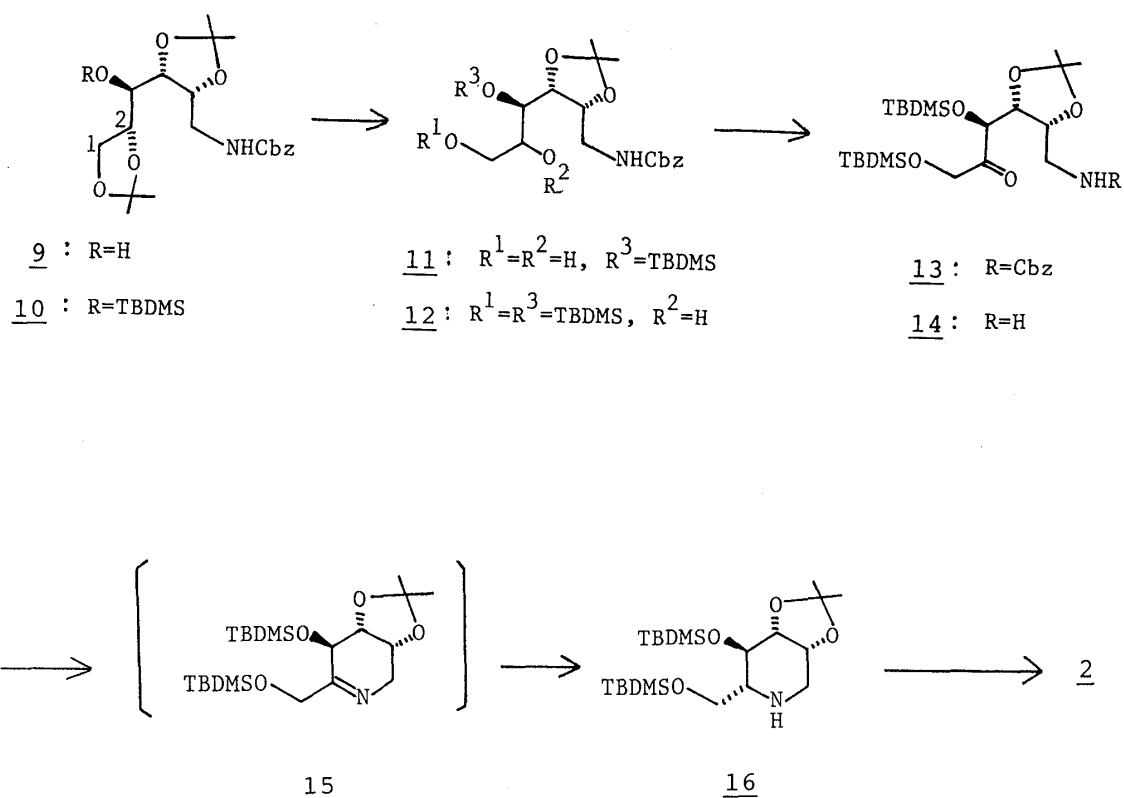
5 : $R^1=H$, $R^2=Cbz$

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

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

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, $[\alpha]_D^{19} -33.7^\circ$ (c 0.2, MeOH), 86%).



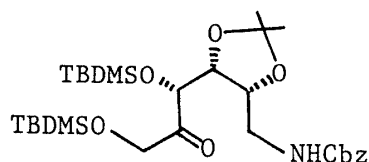
The immunostimulating activity of 1 and 2 was evaluated by measuring their competitive effect against immunosuppressive factors which suppress Con A-stimulated lymphocyte proliferation.⁵⁾ The minimum effective concentrations (MEC) of 1 and 2 were 50 and 32 $\mu\text{g/ml}$, respectively, while the MEC for swainsonine, a standard compound, is 0.01 $\mu\text{g/ml}$. 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; $[\alpha]_D^{20} +20.1^\circ$ (c 0.2, CHCl₃); ¹H-NMR (CDCl₃) 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: ¹H-NMR (D₂O) 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: $[\alpha]_D^{20} +8.12^\circ$ (c 0.6, CHCl₃); ¹H-NMR (CDCl₃) 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; $[\alpha]_D^{20} -36.5^\circ$ (c 0.5, CHCl₃); ¹H-NMR (CDCl₃) 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: ¹H-NMR (D₂O) 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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