Synthesis of 6-Azido and 6-Amino Analogues of 1-Deoxynojirimycin

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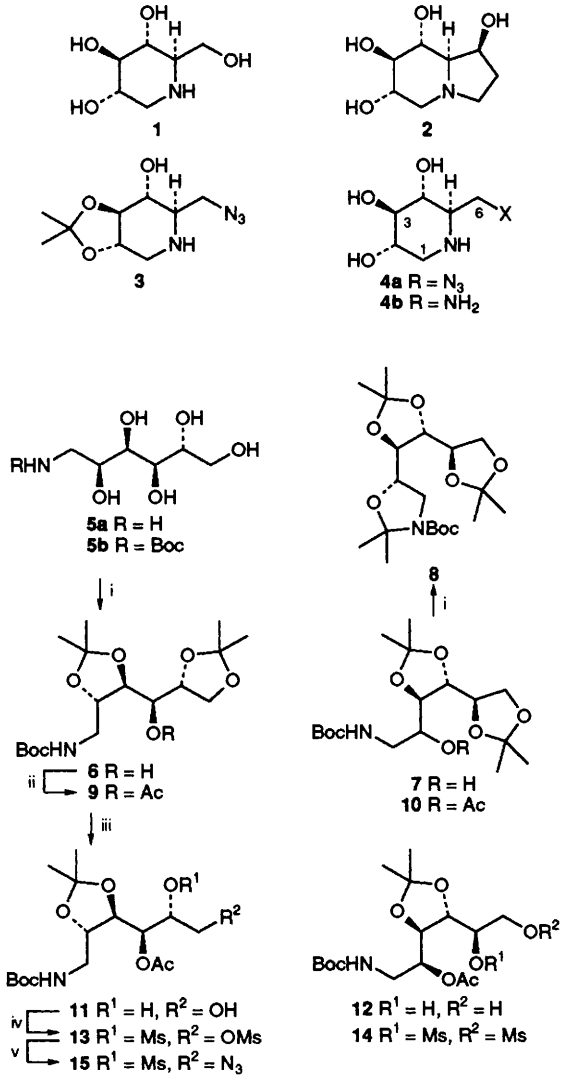
Selective isopropylidenation of the 2,3- and 5,6- hydroxy groups of 1-[(*tert*-butoxycarbonyl)amino]-1-deoxy-D-glucitol **5b** led to the diacetonide **6** which was converted in seven steps to the selectively protected 6-azido compound **3**, a valuable precursor of various derivatives of 6-amino-1,6-dideoxynojirimycin **4b**.

Recently, there has been considerable interest in the polyhydroxylated alkaloids 1-deoxynojirimycin[1] **1** and castanospermine[2] **2** (Fig. 1). As piperidine analogues of the glucopyranose ring, these compounds are inhibitors of several glucosidases and they further exhibit antidiabetic and antiviral, including anti-HIV, activities.[3] These properties warrant synthetic efforts towards structural modification of compound **1** such as the introduction of lipophilic (fluoro,[4] alkyl,[5] and acyl[6]), 2- or 3-amino,[7] and glucosyl[8] groups at specific positions of the piperidine ring system.

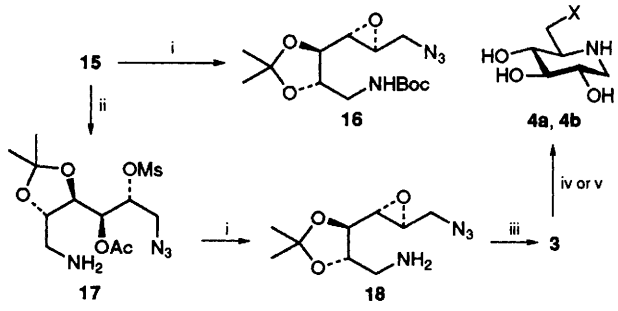


Scheme 1 *Reagents and conditions*: i, Me_2CO–$Me_2C(OMe)_2$ (4:1), *p*-$MeC_6H_4SO_3H$ (0.5 equiv.), room temperature, 10 min; silica, EtOAc–hexanes (3:7), 75%; ii, Ac_2O–pyridine, 4-dimethylaminopyridine, 0 °C, 5 min, room temperature, 1 h; iii, pyridinium toluene-*p*-sulfonate, MeOH–H_2O (9:1), 60 °C, 6 h; iv, CH_2Cl_2, $MeSO_2Cl$, 4-dimethylaminopyridine, Et_3N, room temperature, 10 min; silica, EtOAc–hexanes (3:2), 53%; v, NaN_3 (1.1 equiv.), DMF, 80 °C. 2 h; silica, EtOAc–hexanes (2:3), 73%

This report deals with the synthesis of the selectively protected azido compound **3**, a precursor of various derivatives of 6-amino-1,6-dideoxynojirimycin **4b**. The relative location of the amino nitrogen atoms in **4b** is similar to that in numerous alkaloids and piperazine or piperidine drugs. Therefore, structural features pertaining to both glucopyranose and the 1,2-diamino compounds can be accommodated *via* specific modification at either amino function. Moreover, the primary amine and iminophosphorane products derived from the suitably protected azide **3** can be transformed to the aldehyde[9] and 6-nitro[10] analogues, respectively, providing a handle for attachment of both carbon nucleophiles and electrophiles.

Our synthesis commenced with the known[11] *N*-Boc derivative **5b** of 1-amino-1-deoxy-D-glucitol, **5a** (Scheme 1). Various *N*-protected derivatives of **5a** have been employed as starting materials for specific microbiological oxidation at C-5 leading to patented syntheses of 1-deoxynojirimycin.[5,11] Treatment of **5b** with acetone, 2,2-dimethoxypropane and toluene-*p*-sulfonic acid for 10 min. afforded an inseparable mixture of diacetonides **6** and **7** (*ca* 9:1, yield 75%) and the triacetonide **8** (12%). The ratio of these compounds is time-dependent. Prolonged reaction times led to increased amounts of compounds **7** and **8**. Under acidic conditions, the kinetic product **6** equilibrates with regioisomer **7** which reacts further to form the triacetonide **8**.

A mixture of dimesylates **13** and **14** (*ca* 19:1, yield 53%) was derived from **6** and **7** by acetylation, deprotection of the 5,6-diol group, and sulfonylation. Selective cleavage of the terminal acetonide group was accomplished by heating the acetylated compounds **9** and **10** with pyridinium toluene-*p*-sulfonate in aqueous methanol. The resulting diols **11** and **12** were separated from unreacted **9** and **10** *via* sequential extraction of the acidic aqueous solution with hexanes and dichloromethane. In a non-acidic aqueous medium or in dichloromethane containing triethylamine, the 4-*O*-acetylated diol **11** transforms to the 6-*O*-acetyl compound. To avoid this acyl migration, sulfonylation of the diols **11** and **12** was directly carried out in the dichloromethane solvent used for extraction. On heating of dimesylates **13** and **14** with sodium azide in dimethylformamide, followed by chromatographic separation, the pure azido compound **15** was isolated in 73% yield.



Scheme 2 *Reagents and conditions*: i, MeONa (5 equiv.), MeOH (**16**, 83%); ii, Me_3SiI (1.5 equiv.), CH_2Cl_2, 10 min; Et_3N–MeOH; evaporation at 40 °C; iii, MeOH, reflux, 2 h; silica, EtOAc, 56% **3**; iv, HCl–MeOH, 30 min, silica column, NH_4OH–H_2O–MeOH–$CHCl_3$ (1:1:28:70), 92%; v, PPh_3, H_2O, THF, 7 h; HCl–MeOH, 30 min; 1 mol dm^{-3} NH_4OH, recrystallisation MeOH–Et_2O, 87%

Two ways were used to convert **15** to the cyclic azido compound **3**. The first proceeded *via* the base promoted deacetylation and further conversion to the *N*-protected epoxide **16** (Scheme 2). However, subsequent deprotection of the amino group and cyclisation of amino epoxide **18** gave compound **3** in low yield only. Considerable amounts of by-products were detected, probably due to reaction of the epoxide group with the reagent Me_3SiI used for deprotection of the amino function.[12] A better yield (56%) for **3** was obtained when the Boc group was removed in the first step. This was done by reaction of **15** with Me_3SiI for 10 min. and quenching with triethylamine and methanol. Treatment of the crude primary amine **17** with sodium methoxide in methanol gave the equally polar amino epoxide **18** which cyclised to the less polar secondary amine **3** in boiling methanol.

The structure and synthetic potential of azido compound **3** was confirmed by its conversion to the target compounds 6-azido- and 6-amino-1,6-dideoxynojirimycin. Acid deprotection of **3** provided the crystalline 6-azido compound **4a** in 92% yield after column chromatography on silica gel. Treatment of **3** with triphenylphosphine-water in tetrahydrofuran[13] and acid hydrolysis of the *trans*-fused 2,3-*O*-isopropylidene protecting group afforded the crystalline compound **4b** in 87% yield (14% overall yield from **5b**). The all-equatorial orientation of substituents in compounds **4a**,**b** and, hence, the D-configuration expected from a double inversion at C-5 was proved by the diaxial coupling constants observed in the 400 MHz ^1H NMR spectra for protons H-2 to H-5, *i.e.* $J_{4,5} = J_{4,3} = J_{3,2} = 9$ Hz. In the spectrum of compound **3**, severe overlap of signals was observed for protons H-1 to H-4.†

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Footnote

† The new compounds had compatible IR, MS, HRMS, ^1H and ^{13}C spectra.

References

1 S. Inouye, T. Tsunuoka, T. Ito and T. Niida, *Tetrahedron*, 1968, **24**, 2125; A. Vasella and R. Voeffray, *Helv. Chim. Acta*, 1982, **65**, 1134.
2 L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold and J. Clardy, *Phytochemistry* 1981, **20**, 811.
3 B. D. Walker, M. Kowalski, W. C. Goh, K. Kozarsky, M. Krieger, C. Rosen, L. Rohrschneider, W. A. Haseltine and J. Sodroski, *Proc. Natl. Acad. Sci. USA*, 1987, **84**, 8120; G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. G. Ramsdew, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob and T. W. Rademacher, *FEBS Lett.*, 1988, **237**, 128; D. A. Winkler and G. Holan, *J. Med. Chem.*, 1989, **32**, 2084.
4 C. G. A. De and D. P. Getman, *Eur. Pat. Appl.*, EP 481, 950, 1992; *Chem. Abstr.*, 1992, **117**, 27053r.
5 J. Stoltefuss, *Ger. Offen.*, DE 2,830,469, 1980; *Chem. Abstr.* 1980, **93**, 47104x; H. Kurihara, S. Yoshida, T. Tsuruoka, H. Yamamoto and H. Fukuyasu, *Jpn. Kokai Tokkyo Koho*, JP 02,306,962 [90,306,962], 1990; *Chem. Abstr.*, 1991, **114**, 185939b.
6 D. L. Delinck and A. L. Margolin, *Tetrahedron Lett.*, 1990, **31**, 3093.
7 M. Kiso, M. Kitagawa, H. Ishida and A. Hasegawa, *J. Carbohydr. Chem.*, 1991, **10**, 25; I. K. Khanna, R. A. Mueller, R. M. Weier and M. A. Stealey, *US Pat.* US 5,216,168, 1993; *Chem. Abstr.* 1993, 250376k.
8 Y. Ezure, *Agric. Biol. Chem.*, 1985, **49**, 2159.
9 T. F. Buckley and H. Rapoport, *J. Am. Chem. Soc.*, 1982, **104**, 4446.
10 E. J. Corey, B. Samuelsson and F. A. Luzzio, *J. Am. Chem. Soc.*, 1984, **106**, 3682.
11 G. Kinast, M. Schedel and W. Koebernick, *Eur. Pat. Appl.*, EP 49858, 1982; *Chem. Abstr.*, 1982, **97**, 182801v.
12 R. S. Lott, V. S. Chauhan and C. H. Stammer, *J. Chem. Soc., Chem. Commun.*, 1979, 495.
13 N. Knouzi, M. Vaultier and R. Carrié, *Bull. Soc. Chim. Fr.*, 1985, 815.