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The Synthesis of 1,5-Dideoxy-1,5-(Alkyl)imino-2-C-Methyl-D-Glucitols

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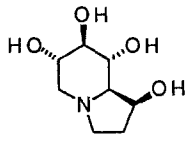
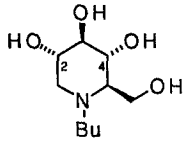
Abstract: The regio- and stereoselective synthesis of the title compounds **3** and **4** has been accomplished starting with deoxynojirimycin. The factors affecting the stereochemical outcome of Grignard addition to the key carbonyl intermediate are discussed.

Polyhydroxylated piperidines, pyrrolidines and octahydroindolizines such as castanospermine (**1**) and *N*-butyl-deoxynojirimycin (**2**) are α-glycosidase inhibitors and potentially useful antiviral agents.[1,2] The role of OH groups in deoxynojirimycin (DNJ) as H- acceptors or donors to the active site of enzyme has been studied by their substitution with groups such as OMe , F, H or NHR.[1-4] This paper describes the regio- and stereoselective synthesis of deoxynojirimycin analogs 1,5-dideoxy-1,5-(alkyl)imino-2-C-methyl-D-glucitol (**3** and **4**) starting from deoxynojirimycin (Scheme 1). The targeted compounds in this communication retain the H-binding ability of OH group at C-2 while imparting potential stability to oxidative metabolism



1



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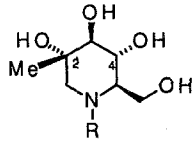
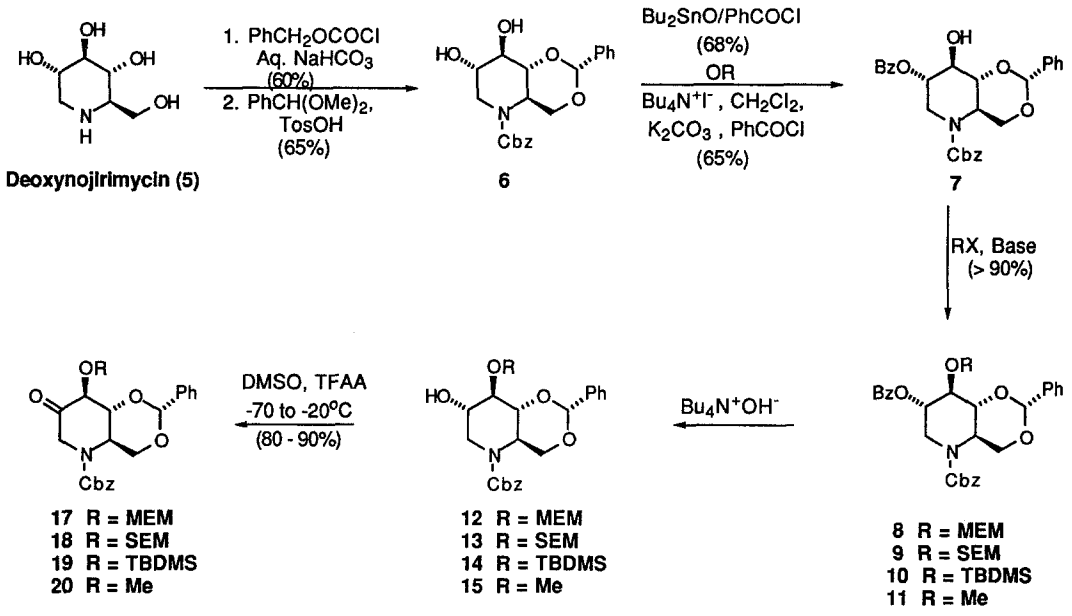


3 R = H
4 R = Bu

The synthesis of the protected diol **6** has been reported previously from these laboratories.[3,4] The selective protection of the C-3 hydroxyl in **6** was achieved by preferential *O*-acylation of the C-2 hydroxyl group followed by *O*-alkylation at C-3 (Scheme I). The selective benzoylation of the C-2 hydroxyl in **6** using stannylene chemistry (Bu_2SnO, NEt_3, PhCOCl, 25°C, 24 h, 68%)[10] or by treating a suspension of **6** and potassium carbonate in methylene chloride with tetrabutylammonium iodide and benzoyl chloride (25°C, 26 h, 65%) gave **7**. The ether formation (**8 - 11**) was achieved easily (isolated yield >90%) by treating **7** with excess alkylating agent (6 molar eqvt) and Hunig's base (6 molar eqvt). The compounds **8** and **9** were synthesized from **7** using MEM-Cl and SEM-Cl respectively, whereas compound **10** was synthesized using *tert*-butyldimethylsilyl trifluoromethanesulfonate. The ester hydrolysis of **8** and **9** ($Bu_4N^+OH^-$, aq. dioxane, 25°C) gave **12** and **13** in isolated yields of 93 and 91%, respectively. Depending upon the conditions used, the base hydrolysis of **10** also yielded varying amounts of the silicon scrambled product **16**. The oxidations of **12 - 15** to the key carbonyl derivatives **17 - 20** were achieved by using Swern conditions (DMSO - TFAA, -70° to -30°C in 3 h and at -30°C for 1 h, NEt_3 at -70°C for 1 h and 25°C for 1 h) in yields ranging from 76 - 97%.

Scheme I



Studies on the addition of organometallic reagents to the 2-keto derivatives (17 - 20). The reaction of **17** with the Grignard reagent (MeMgBr, 3 molar eqvt, -70 to -30°C in 2 h and -30°C for 5 h) gave **21A** and **21B** in a combined yield of 64% (**21A/21B** = 33/67).[5] The absolute stereochemistry of the addition products **21A** and **21B** at C-2 was established in an unambiguous manner using COSY, NOESY and H,H-decoupling NMR experiments.[7]

The studies on the reaction of methylmagnesium bromide with differently protected C-3 hydroxyl derivatives (Table 1) indicate that the stereochemical outcome of addition is greatly influenced by the substituent at C-3. The bulkier *tert*-butyldimethylsilyl group at C-3 in **19** sterically forces the incoming nucleophile to attack the carbonyl from the oppposite face, yielding the *manno*- derivative **22B** predominantly. It is hypothesized that with SEM-protected derivative **18** , the chelation of Grignard reagent to the oxygens at C-2 and C-3 predominates (Fig 1) and favors the addition of nucleophile, possibly by a second mole of Grignard reagent, from axial position[11]. In case of the MEM-protected derivative **17**, the presence of an additional heteroatom may disturb the chelation hypothesized in Fig 1 yielding the coordination-stabilized organometallic (Fig 2). The loss of chelation control in the vicinity of reaction site may explain the lower stereoselectivity observed in this reaction. The excellent stereoselectivity observed with the 3-methoxy compound **20** further supports the hypothesis advocated in Fig 1.

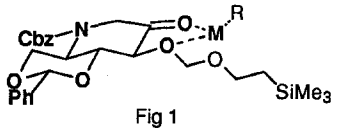


Fig 1

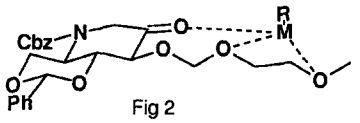
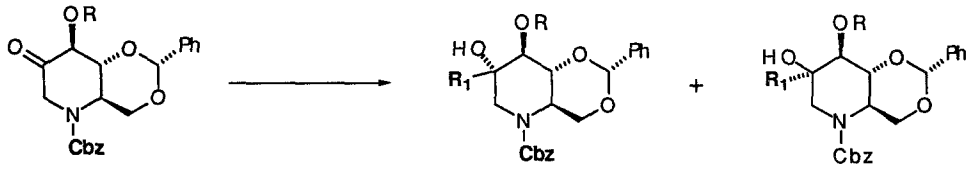


Fig 2

Table 1: Nucleophilic Addition to 2-Keto Derivatives

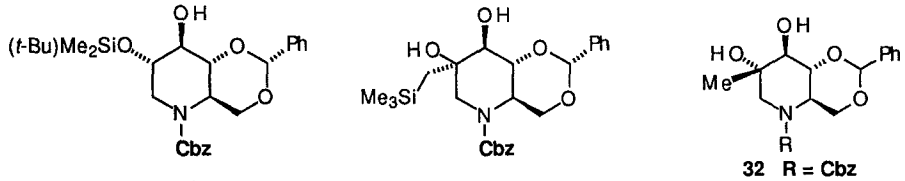


17 - 20 21A - 25A 21B - 25B

Compound (R) (17 - 20)	Reagent	R1	Diastereomeric Ratio of Products (A/B)[a]	Chem. Yield (%)
17 (MEM)	MeMgX	Me	**21A/21B** = 33/67	**21A** = 21, **21B** = 43
19 (TBDMS)	MeMgX	Me	**22A/22B** = <15/85	**22B** = 62
19 (TBDMS)	Me_3SiCH_2Li	CH_2SiMe_3	**23A/23B** = < 10/90	**23B** = 43
18 (SEM)	MeMgX	Me	**24A/24B** = 92/8	**24A** = 68, **24B** = 5
20 (Me)	MeMgX	Me	**25A/25B** = 93/7	**25A** = 54, **25B** = 4

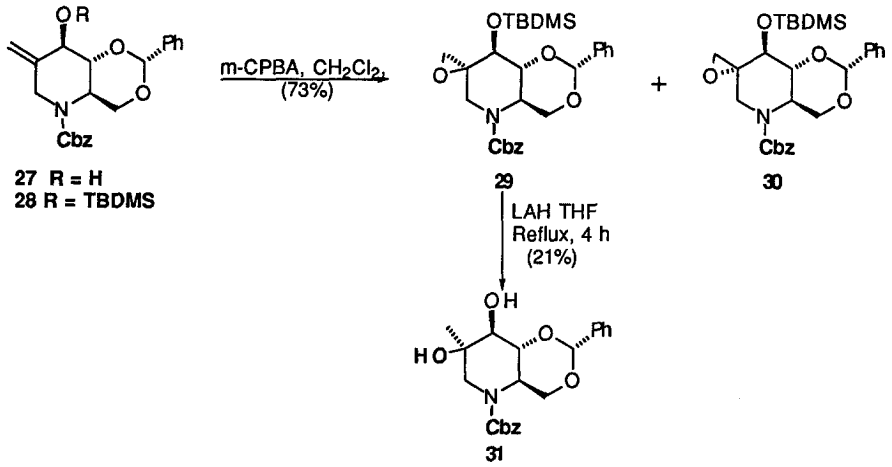
a. isolated yield

Synthesis of 2-methyl carbinol derivative by opening of epoxide from olefin 28. The predominant formation of *manno*- analogs (**22B and 23B**) during Grignard addition to **19** prompted us to investigate the epoxidation and reduction of olefin **28** (Scheme II). The reaction of **19** with Me_3SiCH_2Li using modified Peterson's reaction (Me_3SiCH_2Li, $CeCl_3$, -78° - 0°C) gave **23B** in 43% yield, mainly as a single isomer. Stirring of **23B** with tetrabutylammonium fluoride (3 molar eqvt., 25°C, 18 h) caused selective deprotection of the silyl ether to **26** (85%, isolated) and further reaction of **26** with tetrabutylammonium fluoride at reflux gave the olefin **27** (65%). Reprotection of the C-3 hydroxyl in **27** using *tert*-butyldimethylsilyl trifluoromethanesulfonate gave **28** in 95% yield. Epoxidation of **28** with 3-chloroperoxybenzoic acid gave a mixture of two isomers (**29** and **30**, 76: 24) in a combined yield of 75%. No attempts were made to assign the stereochemistry of epoxides **29** and **30** and the major isomer **29** was reduced with lithium aluminum hydride (4 molar eqvt, THF, reflux, 4 h) to give **31** in 21% yield.[9] These results, which indicate that epoxidation of olefin **28** takes place from the same face as the *tert*-butyldimethylsilyl group at C-3 are unexpected and may involve hydrogen bonding of the peracid to the C-3 silyl ether. The differences in the geometries of the nucleophilic addition to the carbonyl **19** *vs* the electrophilic addition to the olefin **28** may also explain the variabilty in the diastereofacial selectivity of the two reactions.



16 26 32 R = Cbz, 33 R = H

Scheme II



The *gluco*- analog **24A**, obtained in a highly regio- and stereoselective fashion, was deprotected to provide target compounds **3** and **4**. The SEM group in **24A** was removed under modified conditions developed by Lipschutz and co-workers.[8] The THF solution of **24A** was stirred with tetrabutylammonium fluoride for 30 min, the solvent removed and heated in DMPU at 80°C for 14 h to give **32** in 73% yield. The hydrogenolysis (10% Pd on C, 60 psi, 25°C, 1 h) of **32** gave the *N*-deprotected derivative **33** in 84% yield. Finally, removal of the benzylidine in **33** was accomplished using either transfer hydrogenation (20% Pd on C, cyclohexene, reflux, 73%) or sodium and ammonia reduction (45%). The *N*-butyl analog (**4**) was easily synthesized from **3** using a reductive amination procedure (PrCHO, 5% Pd on C, 5psi, 25°C, 70 h, 84%). The anti-viral activity of these and other n-butyl deoxynojirimycin analogs will be reported elsewhere.

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4. Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M. *Tetrahedron Lett.* **1991**, *32*, 5691.
5. The addition of Me_3Al or Me_3Al in combination with 2,6-di-*tert*-butyl-4-methyl-phenol or *N*-methyl aniline (Yamamoto's reagent[6]) to **17** gave poor yields of the products .
6. a) Maruoko, K.; Takayuki, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573 ; b) Maruoko, K.; Araki, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3101.
7. For example, irradiation of the axial methyl signal at C-2 ($CDCl_3$, δ 1.2) in **21A** shows reduction in the $w_{1/2}$ (d, J = 1Hz) of the H-1_{ax}. Irradiation of the axial OH signal at C-2 ($CDCl_3$, δ 2.5) in **21B** removed the 2.0 Hz coupling to H-1_{ax} (δ 2.8). The NOESY spectra of **21A** showed cross peaks between the axial methyl at C-2 and H-4 (δ 3.6) which were absent in the NOESY spectrum of **21B** in which H-4 had shifted downfield to δ 4.1. A detailed account of the NMR investigations will be reported separately.
8. Lipschutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1989**, *30*, 7149.
9. The absolute stereochemistry at C-2 in **31** was established by COSY, NOESY, H,H-decoupling NMR experiments and by comparison of its ^1H NMR spectrum with that of **21B**. Elemental analysis and mass spectrum (DCI, NH_3-PCI; 400 MH^+) further confirmed the structure.
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11. For mechanism of nuclephilic addition to cyclohexanone systems, see e. g., Ashby, E. C.; Laemmle, J. T. *J. Org. Chem* **1975**, *40*, 1469; b) Ashby, E. C.; Yu, S. H.; Roling, P.V. *J. Org. Chem* **1972**, *37*, 1469; c) Ashby, E. C.; Laemmle, J. T. *Chem Reviews* **1975**. *75*. 522: d) Cieplak. A. S. *J. Am. Chem. Soc.* **1981**. *103*. 4540.

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