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Total Synthesis of 1,3-Dideoxynojirimycin

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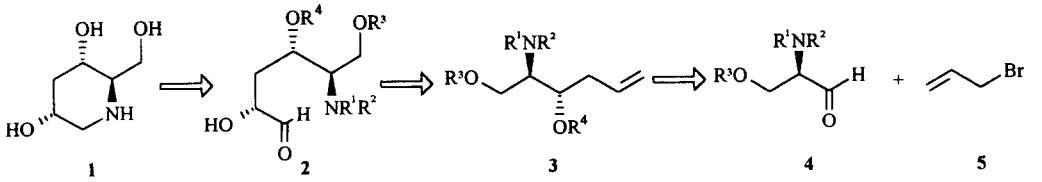
Abstract: Addition of allyl bromide (**5**) to *N*-benzyl-*N*-carbobenzoxy-*O*-*tert*-butyldimethyl-D-serinal (**4**) afforded with high diastereoselectivity *anti*-adduct **6** which subsequently transformed into (2*R*,4*S*,5*R*)-1,3-dideoxynojirimycin (**1**). © 1997 Elsevier Science Ltd.

Polyhydroxypiperidines constitute an interesting group of biologically active compounds of potential pharmacological importance, since they are effective inhibitors of glycosidases.[1,2] The known methods of their syntheses are minly based on transformation of naturally occurring D-pentoses or D-hexoses.[3-5] Polyhydroxypiperidines can also be synthesized from nonsugar precursors. For example, Johnson *et al.*[6] have recently published a new method of the synthesis of 1,3-dideoxynojirimycin (**1**) using an enzymatic dissymetrization of cyclopentadiene.

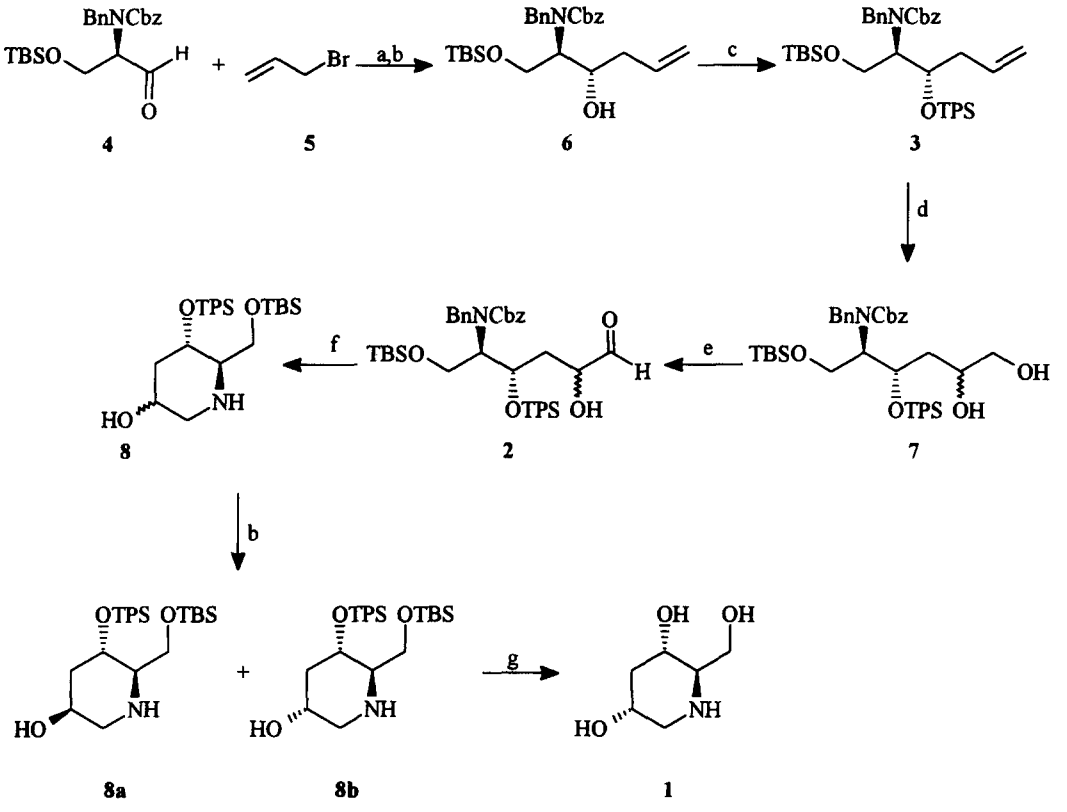
During our studies on applications of *N*-protected α-amino aldehydes in organic synthesis, we have found that they are very convenient, versatile and effective chirons.[7-9] Now we report a new application of our methodology to the synthesis of (2*R*,4*S*,5*R*)-1,3-dideoxynojirimycin (**1**). Retrosynthetic analysis, shown in Scheme 1, suggested that *N*-benzyl-*N*-carbobenzoxy-*O*-*tert*-butyldimethylsilyl-D-serinal (**4**)[10,11] and allyl bromide (**5**) could serve as starting materials.



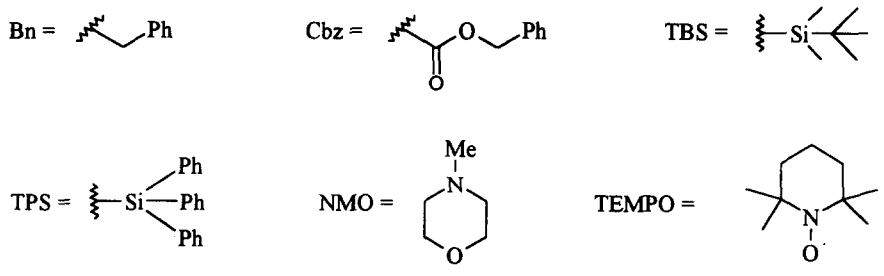
1 2 3 4 5

Scheme 1

Addition of allyl bromide (**5**) to aldehyde **4**, in the presence of $SnCl_2 2H_2O$ and sodium iodide in DMF at room temperature,[17,18] afforded with high diastereoselectivity (89:11) *anti*-adduct **6**[19] in 81% yield (Scheme 2).



Scheme 2. Reagents and reaction conditions: (a) $SnCl_2{\cdot}2H_2O$, NaI, DMF, RT; (b) chromatographic separation; (c) TPSCl, pyridine, CH_2Cl_2, RT; (d) NMO, OsO_4, *tert*-BuOH, H_2O, THF, RT; (e) NaOCl, TEMPO, NaBr, toluene, AcOEt, H_2O, 0°C; (f) H_2, Pd/C, MeOH, RT; (g) Ref. 26.



Chromatographcally pure *anti*-**6** was *O*-protected with TPS group[22] and the resulting compound *anti*-**3** (80% yield) was *syn*-dihydroxylated[23] to afford in 90% yield diol **7** as a 1:1 diastereoisomeric mixture. This mixture was regiospecifically oxidized using the TEMPO method,[15,16] and the resulting aldehyde **2** was subjected to hydrogenation in the presence of catalytic amounts of palladium-on-charcoal (Degussa), affording a 1:1 diastereoisomeric mixture of cyclization product **8** (75% overall yield, starting from **7**). The chromatographic separation of this mixture yielded both diastereoisomers **8a** and **8b** (less polar) in optically pure form.[24] The configuration (2*R*,4*S*,5*R*) was assigned to the less polar diastereoisomer **8b** on the basis of correlation ^{1}H-^{1}H and ^{1}H-^{13}C NMR spectra.[25] The final transformation of compound **8b** into 1,3-dideoxynojirimycin (**1**) could be easily achieved by simple removal of both silyl protecting groups.[26,27]

The presented total synthesis of 1,3-dideoxynojirimycin (**1**) proves to be a practical alternative to the known procedure.[3-6]

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11. The D-serinal derivative **4** was obtained as follows; *N*-benzyl-D-serine methyl ester was treated with benzyl chloroformate in the two-phase system,[12] affording *N*-Bn-*N*-Cbz-D-serine methyl ester (92% yield), which was then reacted with *tert*-butyldimethylsilyl chloride in the presence of imidazole in CH_2Cl_2/DMF,[13] giving *N*-Bn-*N*-Cbz-*O*-TBS-D-serine methyl ester (98% yield), which was reduced with $LiBH_4$ in THF/EtOH,[14] affording the corresponding alcohol (81% yield). Oxidation of the alcohol using the TEMPO procedure[15,16] gave aldehyde **4** (90% yield), which did not require further purification.

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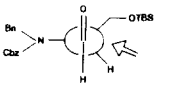
19. The stereochemical results of addition can be rationalized by the transition state model as proposed by Felkin *et al.*[20] and modified by Anh.[21]



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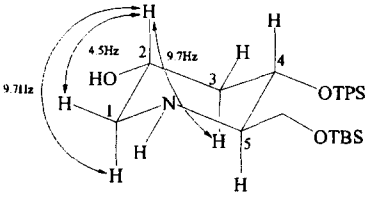
24. Satisfactory analyses and spectral data were obtained for all new compounds.
25. The signal originated from the proton H-2 is a doublet of doublets of triplets and exhibits three coupling constants J_1=J_2=9.7 and J_3=4.5 Hz, typical for axial-axial-equatorial interactions:



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27. Analytical data for **1**: mp 191-193°C (decomp.), [Lit.[6] mp 192-193°C (decomp.)], $[\alpha]_D^{20}$ +22.5 (*c* 0.3, H_2O), [Lit.[6] $[\alpha]_D^{20}$ +24.9 (*c* 0.5, H_2O); ^1H and ^{13}C NMR spectra were identical with those published in Ref.6.

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