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A New Approach to 1-Deoxy-Azasugars: Asymmetric Synthesis of Deoxymannojirimycin

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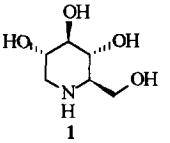
Abstract: A concise and flexible method based upon the kinetic resolution of the α-furfurylamine derivative (3) for asymmetric synthesis of 1-deoxy-azasugars has been provided and deoxymannojirimycin (2) has been synthesized.

Naturally occurring polyhydroxylated piperidine alkaloids such as deoxynojirimycin (1) and deoxymannojirimycin (2) which can be regarded as 1-deoxy-azasugars have received much attention in recent years. Due to their biological activity as inhibitors of glycosidase enzyme from a variety of sources[1] and their potential value as therapeutic agents,[2] much effort has been directed toward the stereoselective synthesis of these alkaloids.[3] The majority of these syntheses lack flexibility and general applicability. Recently two flexible synthetic methods have been published using the dihydro-pyridone system as the building block but proceeding through a relative long route.[2b,4] Consequently development of a concise and flexible method for construction of these 1-deoxy-azasugars continues to be important in order to probe structure-activity correlations.



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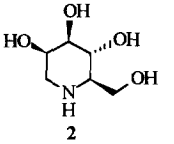

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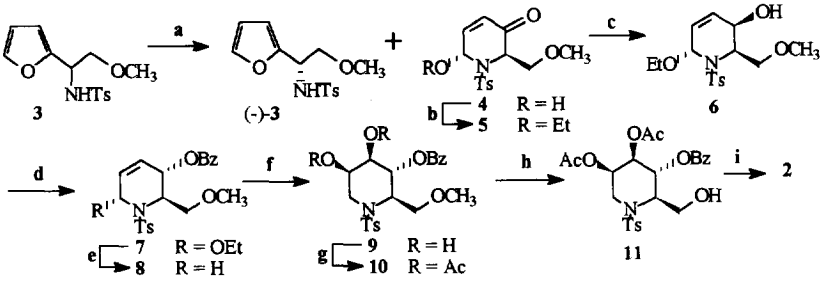
Our group has previously developed an efficient method for kinetic resolution of racemic α-furfuryl amine derivatives.[5] This reaction has been employed for syntheses of several types of alkaloids.[6] In this paper we wish to report the application of this kinetic resolution to synthesis of 1-deoxy-azasugars.

Starting from 2-furaldehyde, the α-furfurylamine derivative (3) could be prepared in 40% overall yield in three steps.[5b] Kinetic resolution of (3) in the reported procedure[5] yielded (2R, 6R)-(4) and (-)-(3) which could be converted to enantiomer of (4) by treatment with m-CPBA. Both (4) and its enantiomer can be applied for the synthesis of 1-deoxy-azasugars. Evidently our strategy has a potential to generate all isomers of 1-deoxy-azasugars. Here we describe the synthesis of deoxymannojirimycin (2) as an example of this strategy.

As depicted in **Scheme 1**, treatment of (4) with triethyl orthoformate generated (5). Reduction of (5) with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ afforded solely the alcohol (6) in which the configuration of hydroxyl group was assigned by 2D-NOESY spectroscopic analysis and this configuration was found to be opposite to that desired for the target molecule. Inversion of this configuration was successfully achieved by employing Mitsunobu reaction. Removal of ethoxy group of (7) by $NaBH_4$, then Sharpless asymmetric dihydroxylation[7] led exclusively to the diol (9) which was protected to give diacetate (10). Attempts to selectively remove

methyl group in (10) with $(CH_3)_3SiI$ failed, whereas demethylation proceeded smoothly by using BBr_3 . Finally deprotection of (11) by sodium naphthalide and chromatography on column of Dowex-50 (H^+) gave deoxymannojirimycin (2). m.p. 185°C; $[\alpha]^{20}_D$ -27° (c 0.1 in MeOH); [lit.[8] m.p.185-187°C, $[\alpha]^{20}_D$ -26.7° (0.12 inMeOH)]. The proton NMR spectrum and the mass spectrum of (2) were identical with those of authentic sample.[9]



Scheme 1. Reagents and conditions: a) $Ti(OiPr)_4$, L-(+)-DIPT, TBHP, silica gel, CaH_2 ,CH_2Cl_2 , 25°C, 3days; b) $HC(OEt)_3$, $BF_3 \bullet OEt_2$,THF, 0°C (76.5%); c) $NaBH_4$, $CeCl_3 \bullet 7H_2O$, -30°C (72.3%); d) DEAD-TPP, PhCOOH, THF, r.t. (91.7%); e) $NaBH_4$, HCOOH, 0°C(86.7%); f) $(DHQ)_2$-PHAL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH, r.t., 2days (84.8%); g) Ac_2O, Pyridine, DMAP, r.t.(100%); h) BBr_3, CH_2Cl_2,-78°C (71.6%); i) Na/Naphthalene, DME, -60°C (50.7%)

In summary, a new strategy for enantioselective synthesis of 1-deoxy-azasugars based upon kinetic resolution of the α-furfurylamime derivative (3) has been proposed.[10] By this strategy, work on deoxynojirimycin (1) and other analogues is in progress.

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