ORGANIC LETTERS

2010
Vol. 12, No. 6
1145−1147

Short and Straightforward Synthesis of (−)-1-Deoxygalactonojirimycin

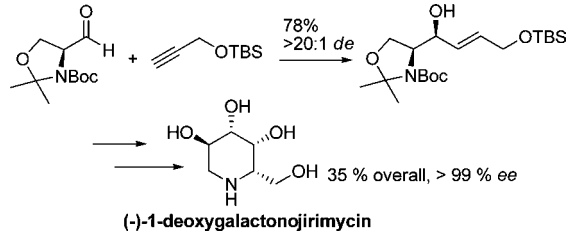
Oskari K. Karjalainen, Mikko Passiniemi, and Ari M. P. Koskinen*

Aalto University School of Science and Technology, Faculty of Chemistry and Materials Sciences, Department of Chemistry, P.O. Box 16100, FI-00076 Aalto, Finland

ari.koskinen@tkk.fi

Received January 6, 2010

ABSTRACT



The mildness and low basicity of vinylzinc species functioning as a nucleophile in addition to α-chiral aldehydes is characterized by lack of epimerization of the vulnerable stereogenic center. This is demonstrated by a highly diastereoselective synthesis of 1-deoxygalactonojirimycin in eight steps from commercial starting materials with overall yield of 35%.

Nojirimycins are a family of polyhydroxylated piperidine alkaloids. The first congener of these sugar mimics, nojirimycin (**1**, Figure 1), was isolated in 1966 from the fermentation broths of several *Streptomyces* strains.[1] Originally, nojirimycin was found to possess antibiotic activity; it was later reported to be a potent α-glycosidase inhibitor.[2] Today, more than 20 natural piperidine aza-sugars are known, as well as a plethora of synthetic derivatives. Already, their glycosidase inhibitory potential has been realized in the treatment of type II diabetes mellitus[3] and lysosomal storage disorders.[4] 1-Deoxygalactonojirimycin (DGJ, **2**) is not a naturally occurring iminosugar but is nevertheless a potent galactosidase inhibitor.[5] A simple and concise route to enantiopure **2** and derivatives thereof should prove invaluable.

The deoxynojirimycin family of iminosugars comprises a six-carbon skeleton with different configurations at carbon atoms C-2, C-3, C-4, and C-5. For DGJ, the configuration is (2*R*,3*S*,4*R*,5*S*). The first synthesis of deoxynojirimycin was reported in 1967 by Paulsen et al.,[6] and since then all of the possible eight diastereomers have been synthesized by different groups.[7]

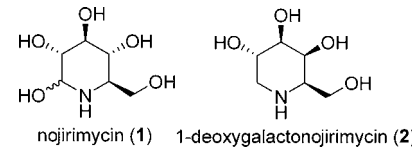


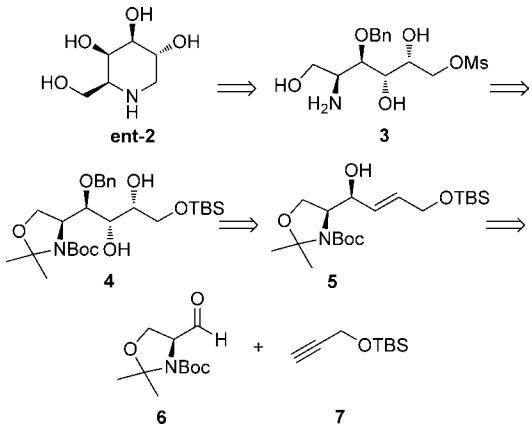
Figure 1. Structures of nojirimycin (**1**) and DGJ (**2**).

We reasoned (Scheme 1) that **ent-2** can be obtained by direct S_N2-type displacement of a leaving group by the amino group in **3**. The required mesylate **3** can in turn be synthesized from the partly protected tetraol **4**, the product

(1) Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot.* **1966**, *19*, 288–292.
(2) Niwa, T.; Inouye, S.; Tsuruoka, T.; Niida, T.; Koaze, Y. *Agric. Biol. Chem.* **1970**, *34*, 966–967.
(3) Fattorusso, E.; Scafati, O. T. *Modern Alkaloids*; Wiley-VCH: New York, 2008; pp 111−133.
(4) Cox, T.; Lachmann, R.; Hollak, C.; Aerts, J.; van Weely, S.; Hribicek, M.; Platt, F.; Butters, T.; Dwek, R.; Moyses, C.; Gow, I.; Elstein, D.; Zimran, A. *Lancet* **2000**, *355*, 1481–1485.
(5) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036–2044.
(6) Paulsen, H.; Sangster, I.; Heyens, K. *Chem. Ber.* **1967**, *100*, 802–815.

10.1021/ol100037c
Published on Web 02/19/2010

Scheme 1. Retrosynthetic Analysis of **ent-2**

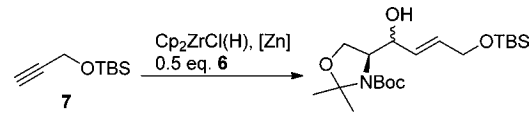


of a diastereoselective dihydroxylation of **5**. We envisioned that the highly functionalized key intermediate **5** could be obtained by reductive coupling of Garner's aldehyde **6** and protected propargyl alcohol **7**, both of which are commercially available. Compounds **6** and **7** can also be synthesized from readily available starting materials L-serine and propargyl alcohol, respectively.

Several methodologies for synthesis of allylic amino alcohols such as **5** have been previously investigated in our group. Horner−Wadsworth−Emmons-type olefination[8] followed by Lüche reduction of the resulting α,β-unsaturated ketone delivers amino alcohols in up to 3:1 syn/anti ratio.[9] Unfortunately, the enantiomeric purity is eroded in the process, which is unacceptable. Direct addition of lithium nucleophiles to Garner's aldehyde (**6**) produces the anti diastereomers in high dr (17:1) as exemplified in our synthesis of pachastrissamine.[10] In the search for a complementary method for producing the *syn* diastereomers we turned to vinylzinc nucleophiles. Vinylzinc species have been reported to add to α-chiral aldehydes with high *syn* selectivity.[11b] The nucleophile is generated conveniently from an alkyne such as **7** by a hydrozirconation−transmetalation sequence pioneered by Peter Wipf.[11] Herein we further show the utility of this reaction and prove for the first time that these conditions are nonepimerizing.

We first tackled the reductive coupling of **6** and **7**. Several solvents and zinc sources were screened for optimal conditions as summarized in Table 1. The best results were obtained using methylene chloride as solvent and either Me_2Zn or Et_2Zn as the zinc source (entries 1 and 2). The alkyne failed to react with zirconocene hydrochloride in toluene. Instead, the vinylzirconium species had to be pregenerated in CH_2Cl_2, followed by solvent evaporation and redissolution in toluene (entry 4). THF (entry 5) impressively reversed the stereochemical outcome, although yields were low and numerous side products were evident. The vinylzirconium species was not soluble in Et_2O (entry 7), which accounted for the poor (less than 10%) conversion. Interestingly, changing the zinc source to $ZnBr_2$ produced a 1:1 mixture of diastereomers in dichloromethane (entry 3), while in THF no reaction took place (entry 6).

Table 1. Screening of Conditions for the Reductive Coupling of **6** and **7**[a]



entry	solvent	zinc source	yield[b] (%)	dr (syn/anti)[c]
1	CH_2Cl_2	Et_2Zn	78	>20:1
2	CH_2Cl_2	Me_2Zn	78	>20:1
3	CH_2Cl_2	$ZnBr_2$	55	1:1
4	toluene[d]	Et_2Zn	62	>20:1
5	THF	Et_2Zn	20	>1:20
6	THF	$ZnBr_2$	n.r.	
7	Et_2O[c]	Et_2Zn	n.d	>1:20

[a] To a suspension of $Cp_2Zr(H)Cl$ (2 mmol) in the appropriate solvent at 0 °C under Ar was added **7** (2 mmol). After the suspension had dissolved, the reaction was cooled to −40 °C and R_2Zn (2 mmol) or $ZnBr_2$ (1 mmol) was added followed by **6** (1 mmol). The reaction was allowed to warm to 0 °C and stirred until completion. [b] Isolated yields after chromatography. [c] Determined by ^1H NMR analysis. [d] The zirconium species was pregenerated in CH_2Cl_2; the solvent was evaporated and replaced by the listed one.

With the optimal conditions in hand, the synthesis was set into motion as outlined in Scheme 2. Treating **7** with zirconocene hydrochloride in methylene chloride furnished the vinylzirconium intermediate which was then transmetalated to the corresponding zinc species by treating it with diethylzinc. Addition of Garner's aldehyde **6** to the solution delivered the desired allylic alcohol **5** in good yield (73−78%) with virtually complete diastereocontrol.[11a] We were not able to isolate or detect the *anti*-congener. The stereochemistry was assigned by mechanistic considerations and later confirmed through analysis of **ent-2.** Similar results regarding the diastereoselectivity have been published by Murakami et al.[11b] Higher yields (78%) were obtained when the Schwartz reagent was generated in situ using the Negishi's protocol.[12] Benzyl protection (with in situ generation of BnI)[13] of the free alcohol followed by dihydroxylation under Upjohn conditions[14] delivered diol **4** in an acceptable 61% yield over two steps. Diastereoselectivity was excellent

(7) For reviews of synthetic methods, see: (a) Pearson, M. S. M.; Mathe-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191. (b) Afarinkia, K.; Bahar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1239–1287. (c) Stütz, A. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: New York, 1999. For more recent syntheses of members of the deoxynojirimycin family, see: (d) Palyam, N.; Majewski, M. *J. Org. Chem.* **2009**, *74*, 4390–4392. (e) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2009**, *12*, 136–139. (f) Remgasamy, R.; Curtis-Long, M. J.; Ryu, H. W.; Oh, K. Y.; Park, K. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 1531–1534.

(8) Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501–502.

(9) Koskinen, A. M. P.; Koskinen, P. M. *Tetrahedron Lett.* **1993**, *34*, 6765–6768.

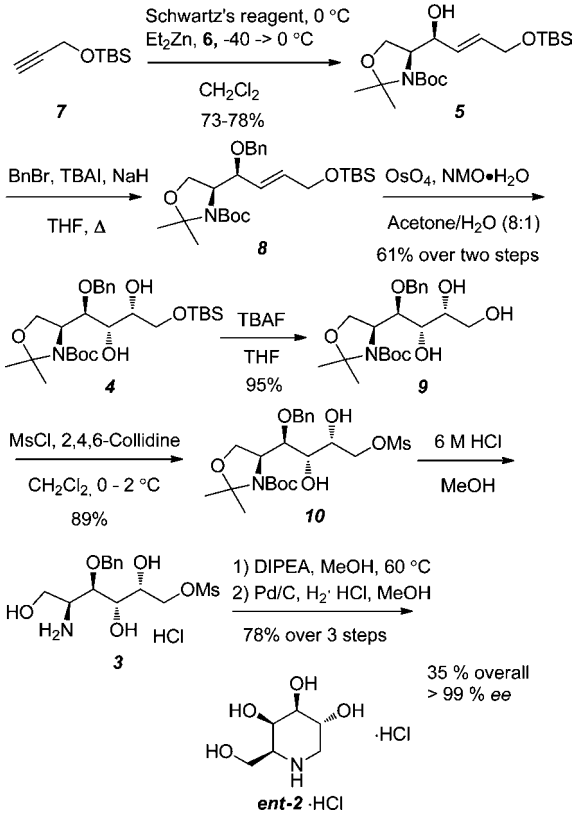
(10) Passiniemi, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **2008**, *49*, 980–983.

(11) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197–5200. (b) For an application in total synthesis, see: Murakami, T.; Furusawa, K. *Tetrahedron* **2002**, *58*, 9257–9263.

(12) Huang, Z.; Negishi, E. *Org. Lett.* **2006**, *8*, 3675–3678.

(13) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535–3536.

Scheme 2. Synthesis of (−)-DGJ (**ent-2**)



(>12:1),[15] and the unwanted all-syn diastereomer could be separated by column chromatography at this point. Again, the stereochemistry was proven by analyzing **ent-2**. Removal of the TBS protection prior to dihydroxylation only made the isolation of the desired triol more problematic and caused the diastereomers to be inseparable. With all the stereocenters in place, we set out to prepare for the cyclization. Removal of the silyl protection from the primary alcohol delivered triol **9**. Selective mesylation of the primary alcohol with mesyl chloride and 2,4,6-collidine as the base proved straightforward giving **10** with an 89% yield.[16] Removal of the *N*,*O*-acetonide and Boc proceeded smoothly in moist HCl(g)/MeOH delivering **3** in essentially quantitative yield. Moist HCl/MeOH was found to be most suitable reagent combination for this deprotection step. TFA worked almost as efficiently, but gave a colored crude product. The cyclization in the presence of Hünig's base in methanol provided the cyclized product contaminated with DIPEA salts. Deprotection with palladium on charcoal under hydrogen atmosphere in acidic methanol delivered **ent-2** as its hydrochloride salt. Simple washing with chloroform, followed by recrystallization from H_2O/EtOH gave pure **ent-2** HCl in 78% yield over three steps. The physical and spectral properties matched fully those reported in the literature.[17] The enantiopurity was confirmed by NMR analysis of both C-2 Mosher's esters of tetraacetylated **ent-2** and was determined to be >99% by NMR.[18]

In summary, we have synthesized enantiopure (−)-**2** in a highly diastereoselective manner from readily available starting materials in 8eight steps. We are currently exploring the use of **5** and *anti*-**5** as building blocks for other stereoisomers of the 1-deoxynojirimycin family.

Acknowledgment. Helsinki University of Technology is gratefully acknowledged for the funding of this project.

Supporting Information Available: Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100037C

(14) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

(15) Generally, dihydroxylations of acyclic allylic alcohols are expected to proceed with 4−7:1 anti/syn diastereoselectivity. Cha, J. K.; Christ, W. G.; Kishi, Y. *Tetrahedron Lett.* **1983**, *37*, 3943–3946.

(16) Burke, S. D.; O'Donnell, C. J. *J. Org. Chem.* **1998**, *63*, 8614–8616.

(17) (a) Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701–3706. (b) Paulsen, H.; Matzke, M.; Orthen, B.; Nuck, R.; Reutter, W. *Liebigs Ann. Chem.* **1990**, 953–963.

(18) See the Supporting Information for details.