JOC*Note*

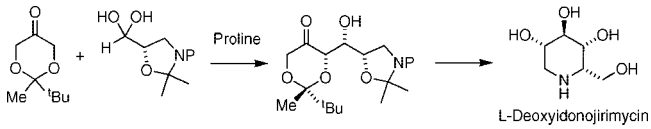
# Organocatalytic *syn*-Aldol Reactions of Dioxanones with (*S*)-Isoserinal Hydrate: Synthesis of L-Deoxymannojirimycin and L-Deoxyidonojirimycin

Nagarjuna Palyam and Marek Majewski*

*Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK S7N 5C9, Canada*

*majewski@usask.ca*

*Received February 12, 2009*




We report a new protocol for synthesis of L-1-deoxymannojirimycin, L-1-deoxyidonojirimycin, and the *N*-isopropyl derivative of the latter compound from the readily available precursors (*S*)-isoserinal hydrate and 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one. The key steps include diastereoselective proline-catalyzed *syn* aldol transformation and a reductive amination/cyclization.



Naturally occurring piperidine iminosugars (azasugars) comprise a group of polyhydroxylated derivatives having a monocyclic (e.g., nojirimycins) or bicyclic (e.g., swainsonine or calystegines) skeleton with the nitrogen atom in place of the ring oxygen of the corresponding carbohydrate (Figure 1).[1] For some time, these compounds and their synthetic derivatives attracted attention as this class includes some potent glycosidase inhibitors as well as natural products with other wide-ranging types of biological activity.[2] For example, 1-deoxynojirimycin (DNJ, **1**) is a glucosidase inhibitor, and its *N*-butyl derivative, known as Zavesca (**2**), is a prescription drug for Gaucher disease and a promising HIV inhibitor.[3] Therapeutic applications of compounds from this group include use in treatment of diabetes, cancer, AIDS, viral infections, and metabolic disorders.[4] Not surprisingly, a large number of strategies have been developed for their synthesis.[5]

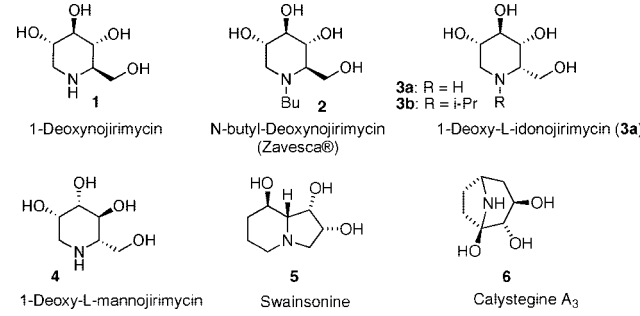



**FIGURE 1.** Selected iminosugars (synthesis of **3a**, **3b**, and **4** is described below).

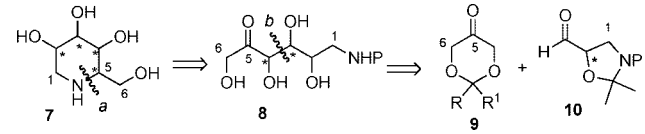


**FIGURE 2.** Retrosynthetic analysis of the deoxynojirimycin skeleton.

For some time, we have been interested in developing the chemistry of 2,2-dialkyl-1,3-dioxan-5-ones (dioxanones) in the context of natural product synthesis.[6] These compounds have proven to be rather attractive scaffolds and were used by several groups in synthesis of carbohydrate derivatives including iminosugars and aminosugars.[7]

Below, we report a new protocol for synthesis of L-1-deoxyidonojirimycin (L-DIJ, **3a**), *N*-isopropyl-DIJ (**3b**), and L-1-deoxymannojirimycin (L-DMJ, **4**) via proline-catalyzed *syn* aldol reactions of (*S*)-isoserinal hydrate with 2-*tert*-butyl-2-methyl-dioxanone.

Our retrosynthetic analysis of the monocyclic 1-deoxyiminosugar skeleton (Figure 2, stereogenic centers indicated with asterisks) illustrates that the structure could be reduced to simple starting materials such as dioxanone (**9**) and protected isoserinal (**10**) using aldol and intramolecular reductive amination transforms.[8] Thinking in the forward direction, it was envisaged that the stereochemistry control might be achieved by combination of the aldol reaction involving catalysis with (*S*)- or (*R*)-proline in the first step with the use of the isoserinal derivative (**10**) as the chiral aldehyde buiding block.

We have previously described a number of aldol reactions involving dioxanones and a variety of aldehydes either under organocatalytic conditions or mediated by lithium or boron enolates (Scheme 1, top).[6] In all cases the relative stereochemistry of the major aldol product was *anti*, and the diastereose-

* To whom correspondence should be addressed. Tel: +1 306- 966 4671. Fax: +1 306- 966 4730.

(1) (a) Compain, P.; Martin, O. R. *Iminosugars: From Synthesis to Therapeutic Applications*; John Wiley & Sons Ltd.: Chichester, UK, 2007. (b) Stütz, A. E., Ed. *Iminosugars as glycosidase inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999.

(2) (a) Wrodnigg, T. M.; Sprenger, F. K. *Mini-Rev. Med. Chem.* **2004**, *4*, 437–459. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680. (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199–210.

(3) (a) Jacob, G. S.; Bryant, M. L. *Persp. Drug Discovery Design* **1993**, *1*, 211–224. (b) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Nat. Acad. Sci. U.S.A.* **1988**, *85*, 9229–9233.

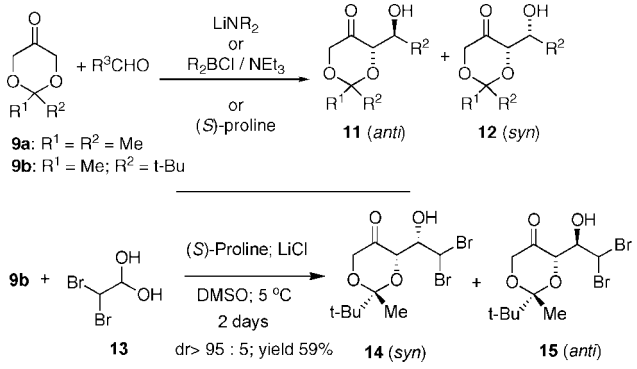
(4) (a) Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 77–85. (b) Greimel, P.; Spreitz, J.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513–523.

(5) (a) de Melo, E. B.; Gomes, A. da S.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277–10302. (b) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, *13*, 5–162, and references cited therein. (c) Ayad, T.; Genisson, Y.; Baltas, M. *Curr. Org. Chem.* **2004**, *8*, 1211–1233. (d) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678–6680. (e) 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. (f) Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238–1242.



10.1021/jo900263s CCC: $40.75 
Published on Web 04/30/2009

**SCHEME 1. Aldol Reactions of Dioxanones**

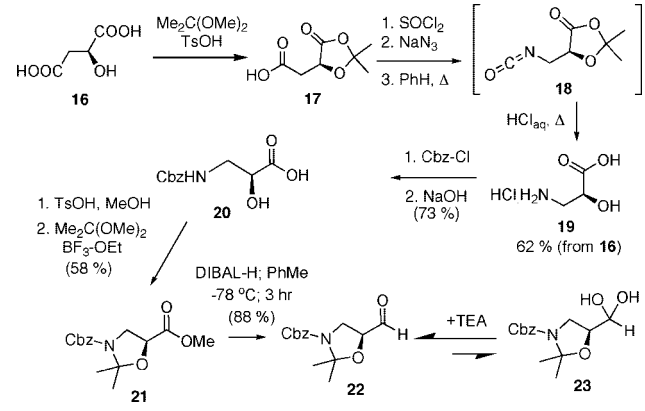



lectivity (*anti*/*syn*) was good or excellent. We were also able to assign the absolute stereochemistry to the aldol products by correlation with naturally occurring carbohydrates.[6a] Other workers in the field reported analogous trends.[7]

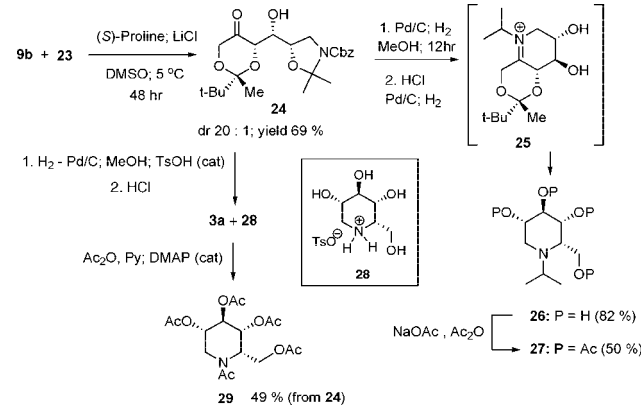
We were therefore intrigued when an organocatalytic reaction of dioxanone **9b** with a hydrate (**13**) resulted in the formation of a product that, in contrast to all previously performed experiments involving aldehydes (not hydrates), appeared to be of *syn* relative configuration (Scheme 1, bottom, see the Supporting Information for relevant spectral data of **14** and **15**; dr >95:5). Chloral hydrate gave a similar result.[9] This welcome development allowed us to plan synthesis of some less common deoxynojirimycin isomers (vide infra).

The necessary chiral building block, the protected (*S*)-isoserinal hydrate (**23**), is readily available from the commercially available (*S*)-malic acid (**16**), and we synthesized this compound following published procedures with some modifications. The synthesis is summarized in Scheme 2 (for full experimental details, see the Supporting Information). Briefly, isoserine hydrochloride (**19**) was synthesized in 62% yield from malic acid (**16**) via a short sequence of reactions involving the Curtius rearrangement without isolating the intermediates.[10] Following the Schmidt protocol,[11] amino acid **19** was transformed into the Cbz-protected (*S*)-isoserinal acetonide **22**, which readily formed the stable hydrate (**23**).[12] With the hydrate **23** in hand the stage was set for an organocatalytic aldol reaction.

**SCHEME 2. Synthesis of (*S*)-Isoserinal Hydrate**




**SCHEME 3. Synthesis of L-1-Deoxyidonojirimycin and Its *N*-Isopropyl Derivative**




(*S*)-Proline-catalyzed aldol reaction of 2-*tert*-butyl-2-methyldioxanone (**9b**) with (*S*)-isoserinal hydrate derivative (**23**) gave the aldol adduct (**24**) in 69% yield and high diastereoselectivity (the *syn* isomer was the major product). The absolute stereochemistry of the aldol adduct is believed to be as shown in Scheme 3.[13]

In our initial experiments aimed at transformation of the aldol adduct (**24**) to the corresponding iminocyclitol (**3a**), hydrogenolysis of the Cbz group proceeded along with reductive ring opening of the oxazolidine moiety to give the *N*-isopropyl derivative (**25**).[14] Compound **25** was then subjected to a reductive amination/cyclization via hydrogenolysis under acidic conditions that resulted in formation of *N*-isopropyl-L-ido-DNJ (**26**) in 82% yield, which was characterized as the tetraacetate derivative **27**.

(6) (a) Majewski, M.; Nowak, P. *J. Org. Chem.* **2000**, *65*, 5152. (b) Majewski, M.; Nowak, P. *Tetrahedron: Asymmetry* **1998**, *9*, 2611–2617. (c) Majewski, M.; Niewczas, I.; Palyam., N. *Synlett* **2006**, *15*, 2387–2390. (d) Palyam, N.; Niewczas, I.; Majewski, M. *Tetrahedron Lett.* **2007**, *48*, 9195–9198. (e) Niewczas, I.; Majewski, M. *Eur. J. Org. Chem.* **2009**, *3*, 3–37.

(7) (a) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857–7870. (b) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304–1325. (c) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329–337. (d) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *J. Org. Chem.* **2006**, *71*, 3822–3828. (e) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343–1345. (f) Calderón, F.; Doyagüez, E. G.; Cheong, P. H.; Fernández-Mayoralas, A.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 7916–7920. (g) Calderón, F.; Doyagüez, E. G.; Fernández-Mayoralas, A. *J. Org. Chem.* **2006**, *71*, 6258–6261. (h) Calderón, F.; Fernández, R.; Sánchez, F.; Fernández-Mayoralas, A. *Adv. Synth. Catal.* **2005**, *347*, 1395–1403. (i) Calderón, F.; Doyagüez, E. G.; Fernández-Mayoralas, A. *J. Org. Chem.* **2007**, *72*, 9353–9356. (j) Markert, M.; Mahrwald, R. *Chem.—Eur. J.* **2008**, *14*, 40–48, and references therein.

(8) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1995.

(9) *Syn*-selective aldol: (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986. (b) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2007**, *46*, 5572–5575. (c) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F., III. *Org. Lett.* **2007**, *9* (17), 3445–3448.

(10) Milewska, M.; Polonski, T. *Synthesis* **1988**, *6*, 475.

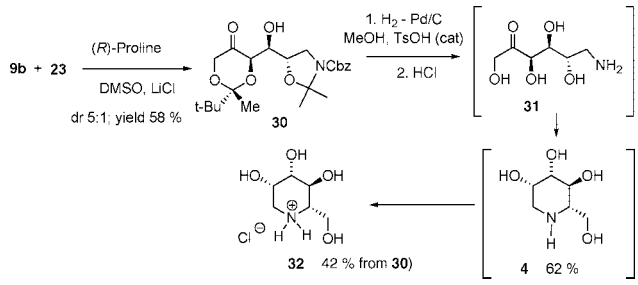
(11) (a) Schmidt, U.; Meyer, R.; Leitenberger, V.; Stabler, F.; Lieberknecht, A. *Synthesis* **1991**, *5*, 409–413. (b) Schmidt, U.; Meyer, R.; Leitenberger, V.; Lieberknecht, A.; Griesser, H. *Chem. Commun.* **1991**, 275–277.

(12) Protected (*S*)-isoserinal (**22**) readily forms the corresponding hydrate (**23**). The IR spectrum of this compound showed the absence of the carbonyl and the presence of a broad peak corresponding to the hydroxyl functional groups (3540−3090 $cm^{-1}$). The H NMR spectrum showed a small signal for the aldehyde (CHO) at $\delta$ of 9.7 (integration for 0.23 proton); addition of $Et_3N$ enhanced the CHO peak (integration of 0.62 protons), due the equilibrium shifting to the aldehyde form **22**.

(13) It should be noted that the total number of stereoisomers possible in this reaction is eight. The R configuration at the acetal stereogenic centre and also the *cis* arrangement of the largest groups on the dioxanone ring were established by previous studies in our group.[6a,d] The *syn* relative stereochemistry assignments of the aldol adducts **24** and **30** were based on NMR studies. The coupling constants from proton decoupling experiments were: peak at 4.47 ppm (d, $J = 3.0$ Hz, α-CH) for compound **24** and at 4.20 ppm (d, $J = 2.3$ Hz, α-CH) for **30** (for the full spectra and also 2D NMR data see the Supporting Information). Note the agreement of the spectral data of the final products with these of the known natural products L-DIJ and L-DMJ.

(14) Falb, E.; Bechor, Y.; Nudelman, A.; Hassner, A.; Albeck, A.; Gottlieb, H. E. *J. Org. Chem.* **1999**, *64*, 498–506.

**SCHEME 4. Synthesis of L-Deoxymannojirimycin Hydrochloride**




To avoid ending up with the isopropyl group connected to the nitrogen, the aldol adduct **24** was transformed into the iminocyclitol (**3a**) via selective oxazolidine ring hydrolysis in the presence of a catalytic amount of *p*-TsOH in methanol (note the difference in conditions comparing with the previous route). The Pd/C catalyzed hydrogenation of the Cbz group followed by acetal deprotection and in situ cyclization/reductive amination gave a mixture of **3a** and the corresponding tosyl salt of 1-deoxy-L-idonojirimycin (**28**);[15] this mixture was converted into the acetate derivative for characterization.

1-Deoxymannojirimycin is a natural product isolated from *Lonchocarpus sericeus* and is an inhibitor of α-D-mannosidase, α-D-glucosidase, and α-L-fucosidase.[16] The L-enantiomer of DMJ (**4**) was synthesized by an analogous route using (*R*)-proline as the catalyst (Scheme 4) and was characterized as the corresponding hydrochloride salt **32**. It should be noted that the synthesis of the natural products **3a** (vide supra) and **4**, spectra of which were in agreement with the literature, served as an additional proof of stereochemical assignments for all new compounds synthesized in this study.

The optical rotation, melting point values, and NMR data for compounds (**28**) and (**32**) were in good agreement with the previously reported data.[16b,c,17]

In summary, *N*-isopropyl-L-deoxynojirimycin (**26**), L-deoxyidonojirimycin (**3a**), and L-deoxymannojirimycin (**4**) were synthesized from readily available dioxanone (**9b**) and (*S*)-isoserinal hydrate (**23**) in short sequences of reactions. The key step involved the proline-catalyzed *syn s*elective direct aldol reaction. The intriguing question is: How general is the tendency of hydrates, or perhaps of aldehydes that readily form stable hydrates, to yield *syn* aldols predominantly? This question is being pursued in our laboratory.

## Experimental Section

**Compound 24.** Dioxanone **9b** (216 mg, 1.25 mmol), the hydrate **23** (300 mg, 1.15 mmol), (*S*)-proline (40 mg, 0.34 mmol), and LiCl (48 mg, 1.15 mmol) were dissolved in DMSO (5 mL), and the mixture was stirred at rt for 15 min. The mixture was then refrigerated at 5 °C for 48 h. Quenching with satd $NH_4Cl_{aq}$ and extractive workup afforded the crude product (dr 96:04) that was fractionated by FCC (15−20% AcOEt in hexane) to yield **24** as a gummy solid (342 mg, 69%). Data: $[\alpha]^{24}_D$ −51 (*c* 1.05, $C_6H_6$); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$7.36−7.28 (br, 5H), 5.10 (br, 2H), 4.47 (d, 1H, $J$ = 3.0 Hz), 4.35 (d, 1H, $J$ = 18.1 Hz), 4.30 (ddd, 1H, $J_1$ = 7.0, $J_2$ = 7.6, $J_2$ = 8.1 Hz), 4.19 (d, 1H, $J$ = 18.1 Hz), 4.10 (ddd, 1H, $J_1$ = 3.0, $J_2$ = 6.1, $J_3$ = 7.0 Hz), 3.79 (dd, 1H, $J_1$ = 8.1, $J_2$ = 10.6 Hz), 3.48 (dd, 1H, $J_1$ = 7.6, $J_2$ = 10.6 Hz), 2.40 (d, 1H, $J$ = 6.1 Hz), 1.54 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1.01 (s, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 206.3, 152.4, 136.6, 128.5, 128.0, 127.8, 103.5, 94.5, 78.34, 73.9, 73.1, 72.6, 69.5, 66.6, 48.5, 40.2, 25.9, 25.4, 25.2, 24.3, 15.9; HRMS exact mass calcd for $[M + H]^+$ $(C_{23}H_{33}NO_7 + H)^+$ requires 436.2335, found *m*/*z* 436.2335; IR $\nu_{max}$ 3622−3202, 1732 cm$^{-1}$.

**Acknowledgment.** We thank NSERC Canada and the University of Saskatchewan for financial support and Saskatchewan Structural Sciences Centre for help with the analytical measurements.

**Supporting Information Available:** Detailed procedures for synthesis of new compounds and spectral data for all "title compounds". This material is available free of charge via the Internet at http://pubs.acs.org.

JO900263S

(15) 1-Deoxyidonojirimycin: (a) Fowler, P. A.; Haines, A. H.; Taylor, R. J. K.; Chrystal, E. J. T.; Gravestock, M. B. *Carbohydr. Res.* **1993**, *246*, 377–381. (b) Ruiz, M.; Ruanova, T. M.; Blanco, O.; Núñez, F.; Pato, C.; Ojea, V. *J. Org. Chem.* **2008**, *73*, 2240–2255, and references therein. (c) Schaller, C.; Vogel, P.; Jaeger, V. *Carbohydr. Res.* **1998**, *314*, 25–35. (d) Lee, B. W.; Jeong, I.-Y.; Yang, M. S.; Choi, S. U.; Park, K. H. *Synthesis* **2000**, *9*, 1305–1309.

(16) 1-Deoxymannojirimycin: (a) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387–2391. (b) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45* (1), 319–326; *Proc. Nat. Acad. Sci. U.S.A.* **1988**, *85*, 9229−9233. (c) Meyers, A. I.; Anders, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931–8952. (d) Hardick, D. J.; Hutchinson, D. W.; Trew, S. J.; Wellington, E. M. H. *Tetrahedron* **1992**, *48* (30), 6285–6296. (e) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401–404. (f) Boglio, C.; Stahlke, S.; Thorimbert, S.; Malacria, M. *Org. Lett.* **2005**, *7* (22), 4851–4854. (g) Takahata, H.; Banba, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, 8199–8205. (h) Ferreira, F.; Botucha, C.; Chemal, F.; Pérez-Luna, A. *J. Org. Chem.* **2009**, *79*, 2238–2241.

(17) For spectral data of compounds **29** and **32**, cf. the Supporting Information.