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# Synthesis of D- and L-Deoxymannojirimycin via an Asymmetric Aminohydroxylation of Vinylfuran

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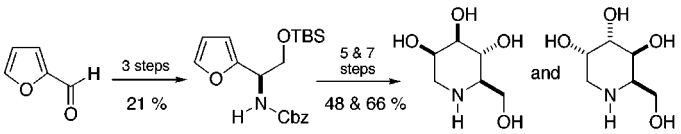
## ABSTRACT




**The Sharpless catalytic asymmetric aminohydroxylation has been applied to 2-vinylfuran, producing β-hydroxyfurfurylamine 5a with enantioexcess of >86% and 21% yield from furfural. The Cbz and TBS protected amino alcohol 5a was converted into both the D- and L-isomers of deoxymannojirimycin (DMJ) and deoxygulonojirimycin in five to seven steps and 48% and 66% overall yields. The key steps include the use of an aza-Achmatowicz reaction, a diastereoselective Luche reduction, diastereoselective dihydroxylation, and a tandem Cbz deprotection/reductive amination.**

In an effort to find new glycosidation inhibitor-based antifungal agents, we are interested in a short and flexible route to the 1-deoxy iminosugar natural product deoxymannojirimycin (DMJ).[1,2] Deoxymannojirimycin has been shown to be a potent inhibitor of the mammalian Golgi α-mannosidase-1 activity, blocking the conversion of high-mannose oligosaccharides to complex oligosaccharides[3] without inhibiting the biosynthesis of lipid-linked oligosaccharides.[4]

Iminosugars (azasugars) are compounds that result from the replacement of a sugar ring O-atom with an NH-group and typically are excellent glycosidase inhibitors.[5] Some examples of these iminosugars are deoxymannojirimycin (**1**, DMJ, mannosidase inhibitor),[1,2] deoxynojirimycin (**2**, DNJ, glucosidase inhibitor),[6,7] and deoxygulonojirimycin (**3**, DGJ, fucosidase inhibitor)[8] (Figure 1). The enzymatic recognition


**Figure 1.**

of differences in charge and shape of these inhibitors determines the inhibition selectivity.[9]

(1) Isolation from *Lonchocarpus sericeus*. Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977.

(2) For the first synthesis of DMJ, see: Kinast, G.; Schedel, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 805.

(3) (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer Res.* **1988**, *48*, 1410. (b) Dennis, J. W.; Koch, K.; Beckner, D. J. *Natl. Cancer Inst.* **1989**, *81*, 1028.

(4) (a) Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer Res.* **1997**, *3*, 1077−1086. (b) Kornfeld, R.; Kornfeld, S. *Annu. Rev. Biochem.* **1985**, *54*, 631. For a review, see: (c) Schachter, H.; Roseman, S. In *The Biochemistry of Glycoproteins and Proteoglycans*; Lennarz, W. J., Ed.; Plenum Press: New York, 1980; Chapter 3.

(5) (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301−2324. (b) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340−347.

(6) Isolated from mulberries. Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *Nippon Nogeikaku Kaishi* **1976**, *50*, 571.

(7) For the first synthesis of DNJ, see: (a) Paulsen, H.; Sangster, I.; Heyns, K. *Chem. Ber.* **1967**, *100*, 802. For a recent synthesis, see: (b) Polt, R.; Sames, D.; Chruma, J. *J. Org. Chem.* **1999**, *64*, 6147. For a recent review, see: (c) Fechter, M. H.; Stutz, A. E.; Tauss, A. *Curr. Org. Chem.* **1999**, *3*, 269−285.

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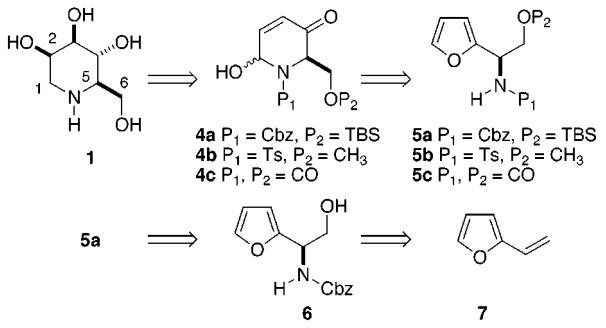
There have been several successful approaches to DMJ (**1**), most of which obtain their asymmetry from carbohydrates, chiral auxiliaries, or resolution methods.[2,10] Because of the flexibility it offered in terms of diastereo- and enantiocontrol through ligand selection, we were interested in the synthesis of iminosugars via an asymmetric aminohydroxylation/aza-Achmatowicz approach (Scheme 1).[11]

**Scheme 1**

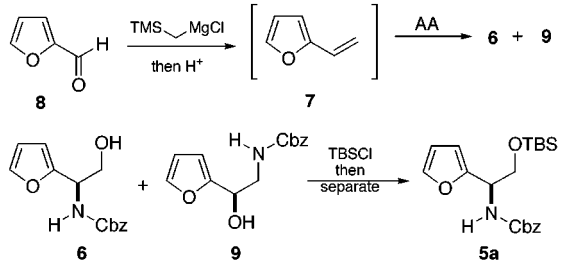



By employing the aza-Achmatowicz reaction, $\beta$-hydroxyfurfurylamine **5**[12] can be converted into various piperidines, including iminosugar **1** (DMJ).[10o,p,13] In his studies of the aza-Achmatowicz reaction, Ciufolini observed that carbamates similar to **5a** and **5c** were unstable and hydrolyzed to 3-hydroxypyridines under aza-Achmatowicz conditions (Scheme 1).[11] In contrast, Zhou[13b] and Altenbach[14] found that a sulfonamide protecting group was compatible with the aza-Achmatowicz reaction (*m*CPBA). Nevertheless, we choose to carry forward a *N*-Cbz protecting group because of the potential for step reduction and ease of purification. In addition, we found that the preparation of furyl sulfonamide **5b** via the Sharpless asymmetric aminohydroxylation (AA)[15] reaction of vinylfuran proved problematic.[16]

Drawing from our successful experience with the Sharpless asymmetric dihydroxylation of vinylfuran and subsequent diastereoselective conversion to D- and L-sugars,[17] we envisioned the synthesis of the manno-iminosugar **1** being synthesized via an analogous route (Scheme 1). Herein we report our application of the asymmetric aminohydroxylation to vinylfuran and the subsequent highly diastereoselective conversion into two iminosugars, deoxymannojirmycin (DMJ) **1** and deoxygulonojirimycin (DGJ) **3**.

Enantiomerically enriched *N*-Cbz-protected amino alcohols **6** and **9** were obtained by application of the Sharpless asymmetric aminohydroxylation (AA) chemistry to vinylfuran **7** (Scheme 2).[18] Key to this approach is a simple in

**Scheme 2**




situ preparation of vinylfuran. Treatment of an ether solution of vinylfuran with the sodium salt of *N*-chlorobenzylcarbamate and a 4% $OsO_4$/5% $(DHQ)_2PHAL$ admixture leads to a good yield of regioisomers (84%). The regioisomers **6** and **9** (1:2 ratio) were easily purified by selective TBS protection of the primary alcohol followed by silica gel chromatography. The highest enantiomeric excess of **6** was obtained with the $(DHQ)_2PHAL$ ligand system, which gives **5a** in a ~21% yield from furfural **8** (>86% ee). The enantiomer of **5a** was also prepared by this sequence (24%, >86% ee) with the use of $(DHQD)_2PHAL$ ligand.[19] This

(8) For the first synthesis of DGJ, see: (a) Leontein, K.; Lindberg, B.; Lonngren, J. *Acta Chem. Scand. B* **1982**, *36*, 515−518. (b) For more recent syntheses, see: Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S. Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519−533. (c) Liao, L.-X.; Wang, Z.-M.; Zhou, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3649−57.

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(10) For syntheses of DNJ/DMJ before 1994 and a concise approach to DNJ/DMJ from dicarbonyl sugars, see: (a) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175. For syntheses of DMJ after 1994, see: (b) Asano, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commun.***1999**, 41−42. (c) Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602−4616. (d) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575−3584. (e) Dondoni A.; Perrone, D. *J. Org. Chem.* **1995**, *60*, 47−49. (f) Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.* **1994**, *116*, 5099−5107. (g) Johnson, C. R.; Golebiowski, A.; Schoffers, E.; Sundram, H.; Braun, M. P. *Synlett* **1995**, 313−314. (h) Lee, S. G.; Yoon, Y. J.; Shin, S. C.; Lee, B. Y.; Cho, S. D.; Kim, S. K.; Lee, J. H. *Heterocycles* **1997**, *45*, 701−706. (i) Lemerrer, Y.; Poitout, L.; Depezay, J. C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M. J. *Bioorg. Med. Chem.* **1997**, *5*, 519−533. (j) Liao, L.-X.; Wang, Z.-M.; Zhang, H.-X.; Zhou, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3649−3657. (k) Meyers, A. I.; Price, D. A.; Andres, C. J. *Synlett* **1997**, 533. (l) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931−8952. (m) Park, K. H.; Yoon, Y. J.; Lee, S. G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2621−2623. (n) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841−859. (o) Xu, Y.-M.; Zhou, W.-S. *Tetrahedron Lett.* **1996**, *37*, 1461−1462. (p) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 741−746. (q) Asano, K.; Hakogi, T.; Iwama, S. Katsumura, S. *Chem Commun*. **1999**, 41−42.

(11) For an excellent review of the subject, see: Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105.

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(13) (a) Xi, N.; Ciufolini, M. A. *Tetrahedron Lett*. **1995**, *36*, 6595. (b) Yang, C.-F.; Xu, Y.-M.; Liao, L.-X.; Zhou, W.-S. *Tetrahedron Lett.* **1998**, *39*, 9227.

(14) Altenbach, H.-J.; Wischnat, R. *Tetrahedron Lett*. **1995**, *36*, 4983.

(15) Li, G. G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813−2817.

(16) Bushey, M. L.; Haukaas, M. H.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2984.

(17) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A., *J. Org. Chem.* **1999**, *64*, 2982.

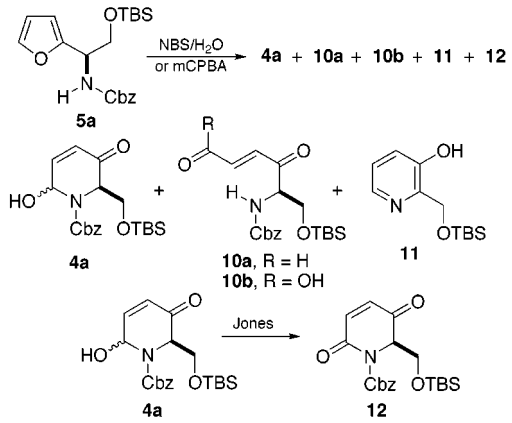
(18) This constitutes an improved procedure as to our previously published procedure (ref 16).

(19) At a smaller scale, the level of enantioinduction has been as high as 94%, as determined by Mosher ester analysis. (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

route compares well with the resolution procedures of Zhou and Wong/Ciufolini.[12]

With access to either enantiomer of furan **5a**, we decided to investigate the aza-Achmatowicz rearrangement of **5a** (Scheme 3). Treatment of a buffered aqueous THF solution

**Scheme 3**



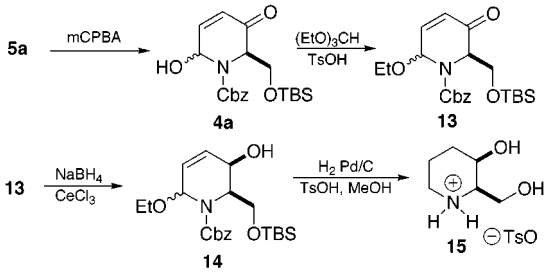

of furan **5a** with 1 equiv of NBS afforded moderate yields of **4a** as a mixture of hemiaminal diastereomers (55%) along with **12** and more polar products (such as **10a**, **10b**, and **11**). Consistent with Ciufolini's observation, we found small amounts of 3-hydroxypyridine **11** under these NBS bromonium ion conditions. Initially we were concerned about the instability of the hemiaminal **4a**; however, **4a** was stable to chromatographic purification ($SiO_2$) and benchtop storage (white solid, mp 72−74 °C). In addition, **4a** was compatible with the strongly acidic conditions of the Jones oxidation, forming ketolactam **12** in good yields (80%).

We speculated that the aqueous NBS conditions lead to a greater amount of the ring-opened form of **4a**, which in turn leads to double bond isomerization to form aldehyde **10a** and overoxidation to form carboxylic acid **10b**. This was evident in that use of anhydrous peracid conditions (*m*CPBA in $CH_2Cl_2$, 0 °C) reproducibly provided improved yields of **4a** (81%, along with 7% recovered starting material), whereas exposure of **4a** to excess *m*CPBA and 1.5 equiv of $H_2O$ at room temperature led to variable yields of **10b** (31−53%). Additionally, this reaction was sensitive to the amount of peracid; for instance, use of 2.2 equiv of *m*CPBA led to a 30% yield of **4a** and 50% yield of **12**.

Hemiaminal **4a** was also stable to the acid-catalyzed conditions required for conversion to the ethylaminal **13** ($HC(OEt)_3$, 5% TsOH, 93%). The ethylaminal **13** can be reduced under Luche[20] conditions to provide **14** in an 86% yield ($CH_3OH/CH_2Cl_2$, −78 °C). The allylic alcohol functionality was introduced in **14** with complete stereocontrol with respect to the C-6 substituent. This stereoselection was proven by conversion of both diastereomers of **14** into a single diastereomer **15**. The stereoselectivity of this reduction was consistent with the results of Zhou[13b] and others.[10m,n] Subject-

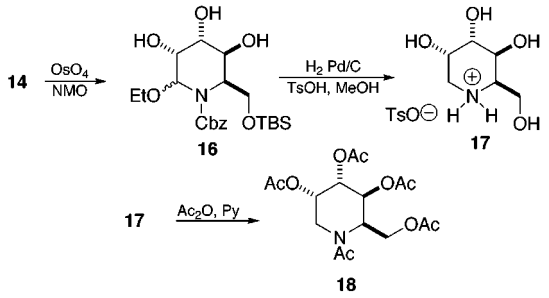
(20) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *110*, 2226.

**Scheme 4**




ing **14** to hydrogenolysis conditions yields the tri-1,2,3-deoxy iminosugar **15** in a near quantitative yield (96%), which was isolated as a TsOH salt without chromatography.The gulo-stereochemistry of deoxygulonojirimycin was diastereoselectively introduced in **3** via $OsO_4$-catalyzed dihydroxylation ($CH_2Cl_2/H_2O$, 0 °C) of **14** to form **16** in a 96% yield (Scheme 5). Neither epimer at C-1 adversely effected the

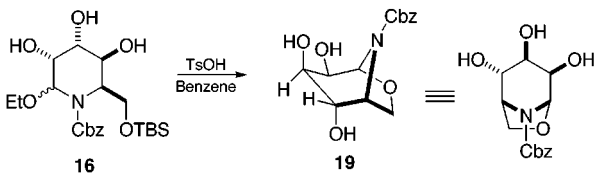
**Scheme 5**




diastereoinduction during the dihydroxylation of **14**. A single diastereomer of the iminosugar deoxygulonojirimycin was produced by hydrogenolysis of **16** in 99% yield. The azasugar was easily purified by isolation as the TsOH salt and washing with chloroform. In an attempt to find any diastereomeric impurities, the crude reaction mixture of **17** was peracylated, affording **18** as a mixture of amide rotamers with no indication of diastereomeric impurities (74%). The spectral data for **17** and **18** were consistent with those from previously prepared deoxygulonojirimycin.[8]

An attempt to isomerize the mixture of epimers at C-1 into a single diastereomer resulted in cyclization of **16** into a bicycle **19** (5% $TsOH/C_6H_6$, 73%) as a single diastereomer (Scheme 6). Proton NMR analysis ($C_6D_6$) showed the

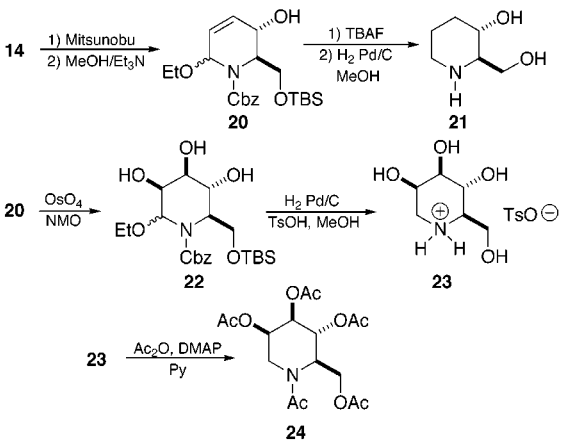
**Scheme 6**



disappearance of one of the two amomeric protons (5.99 and 5.67 ppm) to a single signal at 5.43 ppm (3.0 Hz). Detailed analysis of the vicinal H−H coupling constants of this rigid bicyclic structure was also consistent with the gulose stereochemistry.

Finally, the manno-stereochemistry of DMJ was introduced by conversion of **14** into its C-4 epimer **20** by Mitsunobu inversion (Scheme 7). Treatment of a $CH_2Cl_2$ solution of

**Scheme 7**




the allylic alcohol **14** with *p*-nitrobenzoic acid, $PPh_3$, and DEAD afforded a 84% yield of an ester, which was easily hydrolyzed with $Et_3N$ in MeOH to give **20** (94%). As with allylic alcohol **14**, its C-4 epimer **20** was easily converted into the 1,2,3-trideoxy iminosugar **21**[21] by treatment of **20** with a TBAF solution (for TBS removal, 86%), and then exposure to hydrogenolysis conditions ($H_2$, 5% Pd/C, 61%) afforded the aminodiol **21** in 52% overall yield. Similarly, exposure of the allylic alcohol **20** to $OsO_4$-catalyzed dihydroxylation conditions ($CH_2Cl_2/H_2O$, 0 °C) stereoselectively converts **20** into the mannose stereoisomer **22** in a 92% yield. As with **14**, both epimers of **20** react under the dihydroxylation conditions from the less hindered face to install the mannose stereochemistry.[22] After TBS deprotection of **22** (TBAF, 74%), a single diastereomer of the iminosugar **1** (DMJ) was produced by hydrogenolysis (95%). The azasugar was easily isolated as the TsOH salt **23** (99%). In fact, improved overall yields of **23** were achieved by skipping the TBS deprotection step. The TsOH salt **23** was produced in a near quantitative yield upon exposure of **22** to the same hydrogenation/TsOH conditions (95%). In these improved routes, the *N*-Cbz group along with the C-1 ethoxy substitution provided improved selectivity in the dihydroxylation of **14** and **20** over both Zhou's analogue (*N*-Ts)[10o,p] and Mariano's C-1 deoxy analogue (*N*-Bz).[10n] Because of inconsistencies due to concentration effects on the $^1$H NMR shifts the mannose isomer **23** was converted into the penta-acetate **24** (73%), which had spectral data identical to the literature values.[23]

In conclusion, we have demonstrated the completely diastereoselective conversion of amino alcohol **5a** into the iminosugar deoxymannojirmycin (**1**) in seven steps and 48% overall yield and deoxygulonojirimycin (**3**) in five steps and 66% overall yield. These synthetic studies have allowed us to further define the scope of the aza-Achmatowicz reaction and to optimize the diastereoselective introduction of the C-2/C-3 hydroxyl groups of DMJ. We feel these improvements have led to a significantly improved enantioselective synthesis of deoxymannojirmycin (DMJ) **1** and deoxygulonojirimycin (DGJ) **3**.

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

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(21) Mocerino, M.; Stick, R. V. *Aust. J. Chem.* **1990**, *43*, 1183−1193.

(22) The mannose stereochemistry of **22** was assigned from the observation that the anomeric proton in both epimers appear in the $^1$H NMR as doublets with coupling constant of <2 Hz.

(23) Hardick, D. J.; Hutchinson, D. W.; Trew, S. J.; Wellington, E. M. H. *Tetrahedron* **1992**, *48*, 6285.