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Palladium(II)-Catalyzed Cyclization of Urethanes and Total Synthesis of 1-Deoxymannojirimycin

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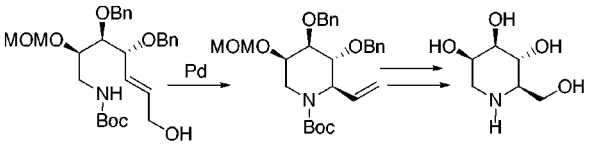
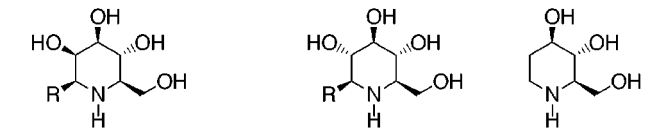
ABSTRACT



8 **9**

The palladium(II)-catalyzed cyclization of the urethane 8, which was derived from D-mannitol, gave the cyclic compound 9 with excellent diastereoselectivity. During these transformations, the Pd(II) species are not reduced and thus the catalyst can recycle without its reoxidation. The cycloadduct 9 was converted to 1-deoxymannojirimycin.

Stereoselective amino cyclization of alkenylamines is one of the most important methodologies for the stereoselective construction of nitrogen hetero alicycles.[1] Recently we developed an intramolecular substitution of an allylic alcohol by a heteroatom using a palladium catalyst without activation of an allylic alcohol.[2] As a continuation of this work, we decided to investigate the synthesis of azasugars using this reaction. Carbohydrates play an important role in many in vivo biological phenomena. Recently many azasugars were found to be efficient inhibitors of the carbohydrate hydrogenase and transferase.[3] In these azasugars, 1-deoxymannojirimycin (**1**), isolated from *Lonshocarpus sericeus* by L. E. Fellows in 1979,[4] showed significant biological activity as an inhibitor of α-L-fucosidase, α-D-mannnosidase and α-D-glucosidase.[5] As a result, much synthetic effort[6] has been directed toward the stereoselective synthesis of 1-deoxymannojirimycin (**1**). Herein we report the preparation of the optically active piperidine **9** using Pd(II)-catalyzed cyclization and the conversion of this piperidine **9** to 1-deoxymannojirimycin (**1**).



Our starting material, 3,4-di-*O*-benzyl-5,6-*O*-isopropylidene-D-mannitol (**2**), was prepared from D-mannitol by a

(1) (a) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q, *Bull. Chem. Soc, Jpn.* **1981**, *54*, 488. (b) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797. (c) Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803. (d) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731 and references therein.

(2) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776. Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21. Hirai, Y.; Terada, T.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893.

(3) (a) Fleet, G. W. J.; et al. *FEBS Lett.* **1998**, 237. (b) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3174. (c) Sinnott, L. M. *Chem. Rev.* **1990**, *90*, 1171. (d) Tsukamoro, K.; et al. *Clin. Res.* **1989**, *37A*, 722. (d) Gruters, R. A.; Niefies, J. J.; Tersmette, M. I.; DeGroede, R. E.; Tulp, A.; Heisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (e) Bermaki, R. J.; Korytnyk, W. *Cancer Metastasis Rev.* **1985**, *4*, 81.

(4) Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, *22*, 977.

(5) (a) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*. 1953.

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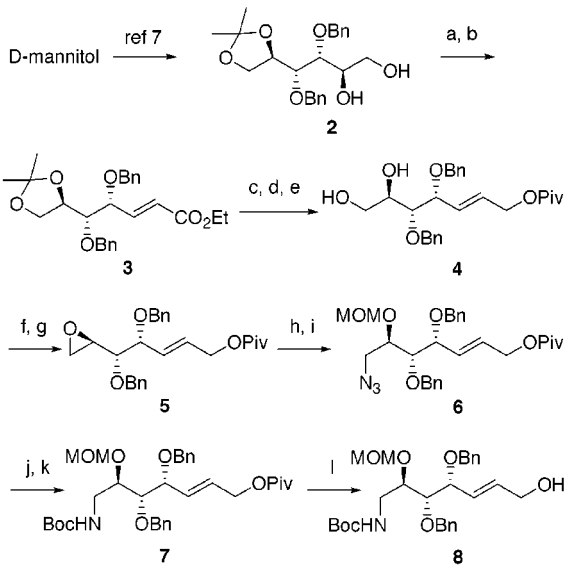
known procedure.[7] Oxidative cleavage of the diol **2** followed by Horner−Wadsworth−Emmons reaction afforded the α,β-unsaturated ester **3** in 70% overall yield (Scheme 1).

Scheme 1



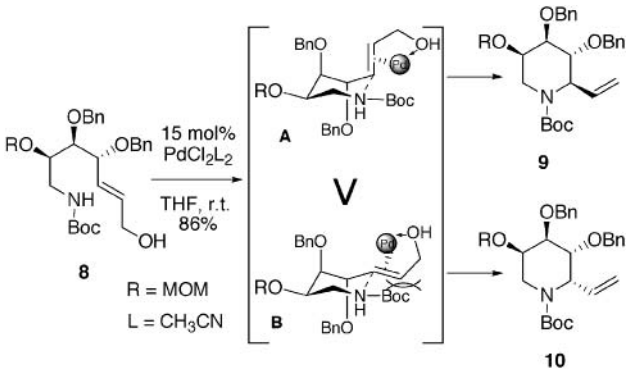
(a) $NaIO_4$, H_2O-Et_2O, 0 °C (79%); (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C (89%); (c) DIBAL, THF , -78°C (94%); (d) PivCl, Pyridine, THF, 0°C (93%); (e) 10% HCl aq., THF, 40 °C (95%); (f) TsCl, Pyridine, CH_2Cl_2, 0°C (85%); (g) K_2CO_3, MeOH, 0 °C (89%); (h) NaN_3, NH_4Cl, 15-crown-5, DMF, r.t. (47%); (i) MOMCl, $^iPr_2NEt$, 0 °C (83%); (j) PPh_3, THF, r.t. (46%) ; (k) $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t. (95%); (l) K_2CO_3, MeOH, r.t. (quant.)

Reduction of the ester group of **3** and protection of the resulting alcohol by the pivaloyl (Piv) group gave, in 88% yield, the pivaloyl ester, which was treated with hydrochloric acid to give the diol **4** in 95% yield. Tosylation of the diol **4** followed by treatment with potassium carbonate gave the epoxide **5** in 76% yield.

Regioselective ring-opening of **5** with sodium azide and subsequent protection of the resulting alcohol with the methoxy methyl group gave the azide **6** in 39% yield. Reduction by PPh_3 and protection of the resulting amine gave, in 44% yield, the pivaloyl ester **7**, the pivaloyl group of which was deprotected to afford the allyl alcohol **8** in a quantitative yield.[8]

The allyl alcohol **8** was treated with 15 mol % $PdCl_2(CH_3CN)_2$ in THF at room temperature to give the cyclized mixtures **9**[9a] and **10**[9b] in 86% yield, the ratio of which was >26:1 (Scheme 2). The structure of the major product **9** was

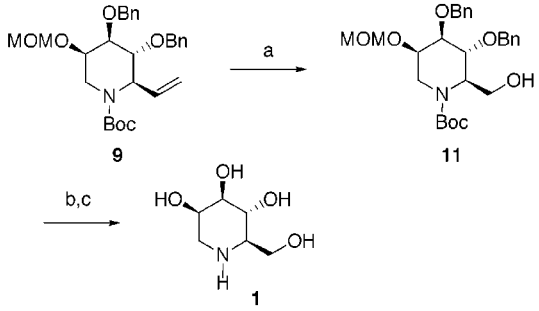
Scheme 2



confirmed by its spectral data. The stereoselective formation of **9** could be explained by assuming the cyclization proceed via transition state A. Transition state B, which leads to **10**, would be disadvantageous because of nonbonding gauche repulsion between the Boc group and the π-allyl-oxy palladium complex.

Conversion of **9** to 1-deoxymannojirimycin (**1**) was effected by the three-step sequence shown in Scheme 3.

Scheme 3



(a) O_3, CH_2Cl_2-MeOH, -78 °C ; $NaBH_4$, -78 °C (92%); (b) TFA, CH_2Cl_2 , 0°C→ r.t.; (c) H_2, Pd/C, conc.HCl, EtOH, r.t. (2steps 33%)

Ozonolysis of **9** and reductive workup ($NaBH_4$) gave the alcohol **11** in 92% yield. Removal of the benzyl group and the *N*-*tert*-butoxy carbonyl group (Boc) in **11** [TFA, CH_2Cl_2; H_2, Pd/C, EtOH] afforded 1-deoxymannojirimycin (**1**),

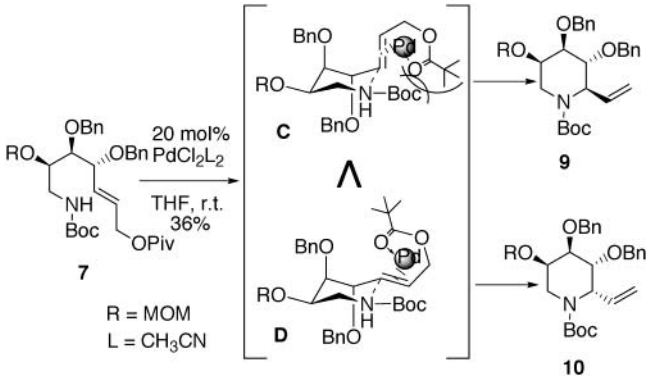
(6) (a) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931. (b) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575.

(7) This procedure was three steps (overall 25% yield). cf. Takano, S.; Ogasawara, K. *J. Synth. Org. Chem., Jpn.* **1987**, *45*, 1157 and references therein.

(8) Data of **8**: $[\alpha]^{28}_D$ 35.1° (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 10H), 5.99 (ddd, *J* = 4.6, 5.9, 15.6 Hz, 1H), 5.66 (dd, *J* = 8.1, 15.6 Hz, 1H), 5.14−5.06 (m, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.20 (dd, *J* = 4.6, 13.4 Hz, 1H), 4.14 (dd, *J* = 5.9, 13.4 Hz, 1H), 3.97 (brt, 1H), 3.81−3.74 (m, 2H), 3.53 (ddd, *J* = 2.4, 8.1, 14.4 Hz, 1H), 3.36 (s, 3H), 3.13 (ddd, *J* = 4.4, 8.1, 14.4 Hz, 1H), 1.41 (s, 9H); IR (neat) 3434 (NH, OH), 1695 (C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{39}NO_7$: C, 67.04; H, 7.84; N, 2.79; O, 22.33. Found: C, 67.22; H, 8.08; N, 2.54; O, 22.16

(9) (a) Data of **9**: $[\alpha]^{26}_D$ −1.21° (*c* 1.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39−7.22 (m, 10H), 6.00 (ddd, *J* = 6.2, 10.0, 17.6 Hz, 1H), 5.08 (dd, *J* = 2.5, 11, 7 Hz, 1H), 5.00−4.75 (br, 1H), 4.73−4.62 (m, 4H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.06 (brd, 1H), 3.94 (ddd, *J* = 3.0, 4.9, 11.2, Hz, 1H), 3.82 (t, *J* = 3.1 Hz, 1H), 3.72−3.61 (m, 1H), 3.35 and 3.34 (two s, 3H), 3.23 (t, *J* = 12.0 Hz, 1H), 1.45 (s, 9H); IR (neat) 1694(C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90. Found: C, 69.54; H, 7.70; N, 2.66. (b) Data of **10**: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41−7.21 (m, 10H), 6.08 (ddd, *J* = 3.7, 10.7, 17.6 Hz, 1H), 5.27 (brd, 1H), 5.13 (brd, 1H), 4.86−4.66 (m, 7H), 4.20−4.03 (m, 2H), 3.99−3.92 (m, 1H), 3.45 (dd, *J* = 3.2, 10.2 Hz, 1H), 3.41 (s, 3H), 2.96−2.73 (m, 1H), 1.45 (s, 9H).

Scheme 4



whose structure was established by comparison of its NMR data with that of the natural compound.[6b]

We also examined the Pd(II)-catalyzed cyclization of the pivaloyl ester **7**. Compound **7** was treated with 20 mol % $PdCl_2(CH_3CN)_2$ in THF at room temperature to give the piperidines **9** and **10** in 36% yield (76% conversion yield), the ratio of which was 2:9. The transition state model for this reaction is shown in Scheme 4. Transition state C would be disadvantageous because of nonbonding gauche repulsion between the Boc group and the pivaloyl group.

In conclusion, we have described a novel asymmetric synthesis of 1-deoxymannnojirimycin (**1**), the α-glycosidase inhibitor, started from D-mannitol (16 steps, overall 2% yield from **2**). The key step in the sequence is the palladium(II)-catalyzed cyclization of the urethane **8**.

Acknowledgment. We are grateful to Dr. John R.Stille, Eli Lilly and Company, for kindly providing us with NMR data of the natural 1-deoxymannojirimycin. This work was supported by a grant-in-aid for Scientific Research (C) from the Ministry of Education, Science, Sports, and Culture of Japan.

Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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