Pergamon

Tetrahedron Letters, Vol. 36, No. 2, pp. 253-256, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02185-6

A Novel and Concise Synthesis of Aminocyclopentitols and 1-Deoxynojirimycin *via* Radical Cyclization of Oxime Ethers

Toshiko Kiguchi, Kazumi Tajiri, Ichiya Ninomiya, and Takeaki Naito*
Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658, Japan
Hajime Hiramatsu
Research Laboratory, Tanabe Seiyaku, Co., Ltd., Kawagishi, Toda, Saitama 335, Japan

Abstract: Tributyltin hydride-induced radical cyclization of the oxime ether **3** derived from *D*-glucose proceeded smoothly to give two amino alcohols **4** and **5** which were converted into two aminocyclopentitol pentaacetates **8** and **12** and 1-deoxynojirimycin known as glycosidase inhibitors.

Glycosidase inhibitors have been used to treat diabetes and other metabolic disorders and also have been implicated in the blocking of viral infections. Such inhibitors illustrated in Figure 1 are historically developed[1] in the following order; 1-deoxynojirimycin, its amidine derivatives, hydroxypyrrolidines, and very recently aminocyclopentitols.[2] The aminocyclopentitols are found to have powerful and specific inhibitory activity against glycosidases.[3]

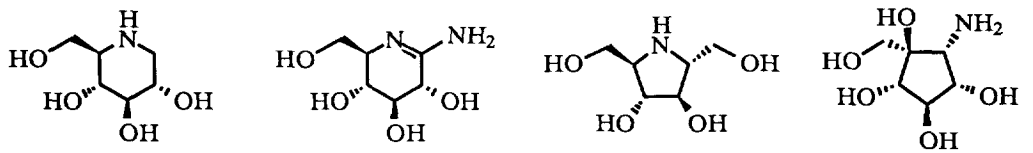


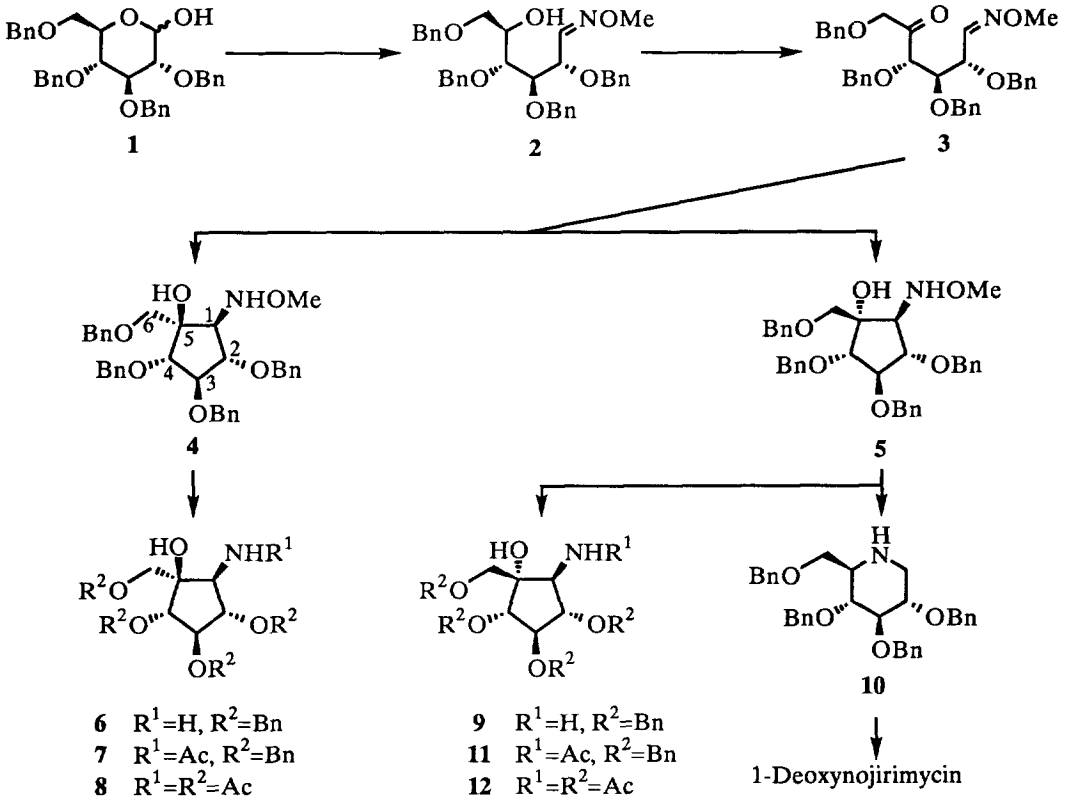
Figure 1. Glycosidase Inhibitors

In this report we wish to describe a novel and concise synthesis of two types of glycosidase inhibitors such as aminocyclopentitols and 1-deoxynojirimycin *via* the route involving the radical cyclization of the oxime ethers which was recently developed by our group.[4]

Treatment of commercially available tetra-*O*-benzyl-*D*-glucose **1** with methoxyamine hydrochloride in pyridine gave the oxime ether **2** in 92% yield which was oxidized with chromium trioxide-pyridine to afford the ketone **3** in 79% yield. Tributyltin hydride-induced radical cyclization[4] of the oxime ether **3** in the presence of AIBN proceeded very smoothly to give a 1.4:1 mixture of two amino

alcohols **4**[5] and **5**[5] in 68% combined yield. Relative configurations between C_1- and C_5-positions were firmly established by the formation of the corresponding acetonide in the 1,5-*cis*-isomer **4** while the 1,5-*trans*-isomer **5** recovered under the same reaction condition. Whole stereostructures of both cyclized products **4** and **5** were established from the NOESY spectra in ^{1}H-NMR of two penta-acetates **8** and **12** and X-ray analysis of the 1,5-*cis*-pentaacetate **8** described later.

Conversion of the 1,5-*cis*-methoxyamine **4** into the acetate **8** *via* the route involving the concomitant dehydrogenolysis (20% $Pd(OH)_2$-C/H_2) of both methoxyamino and *O*-benzyl groups and *N,O*-acetylation (Ac_2O-pyr.) resulted in the poor formation of the desired acetate **8**[5] in 27% total yield. Therefore, **4** was converted step by step into the acetate **8** in total 52% yield *via* reduction[6] of methoxyamino group by $LiAlH_4$, acetylation (Ac_2O-pyr.) of the resulting amine **6**, catalytic dehydrogenolysis of benzyl groups in the presence of 20% $Pd(OH)_2$-C, and finally reacetylation (Ac_2O-pyr.). Reduction of the 1,5-*trans*-methoxyamine **5** with $LiAlH_4$ gave a 5:2.3 mixture of two amines **9** and **10** in 73% yield which were found to be five-membered amine **9** and the ring expanded piperidine **10**[7] respectively. The amine **9** was converted into the pentaacetate **12**[5] in 87% yield *via* the *N*-acetate **11** as in the case of the *cis*-isomer **6**.



NOESY spectra of both acetates **8** and **12** exhibited cross peaks between C_1-H/C_6-H and C_1-H/C_3-H in the 1,5-*cis*-isomer **8** and C_4-H/C_6-H and C_1-H/C_3-H in the 1,5-*trans*-isomer **12** respectively. Furthermore, the structure of the *cis*-isomer **8** was firmly established by the X-ray analysis[8] as shown in Figure 2. Since the stereostructures of two cyclized products **4** and **5** were unambiguously established, we propose the reaction pathway of the radical cyclization of the oxime ether **3** as follows. The intermediary radicals would adopt two conformations **A** and **B** due to the minimum $A^{1,3}$-strain around oxime ether double bond as suggested by RajanBabu[9] (Figure 3). Owing to the almost same stabilities, both radicals **A** and **B** would cyclize to give the 1,5-*cis*- and 1,5-*trans*-methoxyamines **4** and **5** in the ratio of 1.4 to 1 respectively.

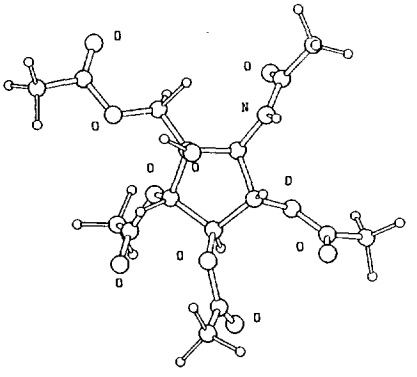
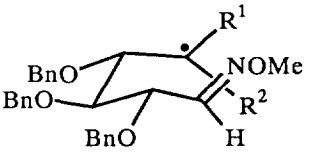


Figure 2. Crystal Structure of **8**



A R^1=$OSnBu_3$, R^2=CH_2OBn
B R^1=CH_2OBn, R^2=$OSnBu_3$

Figure 3. Conformation of Radicals **A** and **B**

Since the tetra-*O*-benzyl piperidine **10** was identical with the known key intermediate for the synthesis of 1-deoxynojirimycin[10] upon comparison of the spectral data with the known[7] spectral data, we have succeeded in the formal total synthesis of 1-deoxynojirimycin with five-step from tetra-*O*-benzyl-*D*-glucose.

In conclusion, the radical cyclization of the oxime ether **3** derived from *D*-glucose was successfully applied to the concise syntheses of new aminocyclopentitol pentaacetates **8** and **12** which are expected to be glycosidase inhibitors and 1-deoxynojirimycin.

ACKNOWLEDGEMENT We wish to thank the Ministry of Education, Science, and Culture (Japan) and to the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants. Thanks are also extended to Dr. N. Ikota (National Institute of Radiological Sciences, Japan) for providing the authentic sample.

REFERENCES AND NOTES

1. Look, G. C.; Fotsch, C. H.; Wong, C. -H. *Acc. Chem. Res.* **1993**, *26*, 182-190.
2. Ando, O.; Nakajima, M.; Hamano, K.; Itoi, K.; Takahashi, S.; Takamatsu, Y.; Sato, A.; Enokita, R.; Okazaki, T.; Haruyama, H.; Kinoshita, T. *J. Antibiotics* **1993**, *46*, 1116-1125; Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813-822 and references therein.
3. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444-458 and references therein.
4. Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205-2206.
5. **4**: oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.92-3.83 (3H, m, 2-, 3-, and 4-H), 3.77 and 3.66 (each 1H, ABq, *J*=10 Hz, CH_2O), 3.51 (1H, m, 1-H), 3.49 (3H, s, OMe); HRMS calcd for $C_{35}H_{39}NO_6$ (M^+) 569.2779, found 569.2770. **5**: mp 69-70°C (hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.16 (1H, br t, *J*=7 Hz, 3-H), 3.88 (1H, d, *J*=7 Hz, 4-H), 3.76 (1H, t, *J*=6 Hz, 2-H), 3.60 and 3.49 (each 1H, ABq, *J*=10 Hz, CH_2O), 3.47 (1H, m, 1-H), 3.44 (3H, s, OMe); HRMS calcd for $C_{35}H_{39}NO_6$ (M^+) 569.2779, found 569.2766. **8:** mp 91-93°C (AcOEt); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.14 (1H, d, *J*=9 Hz, N*H*Ac), 5.44 (1H, dd, *J*=10, 6 Hz, 2-H), 5.07 (1H, dd, *J*=6, 3 Hz, 3-H), 5.01 (1H, br d, *J*=3 Hz, 4-H), 4.53 (1H, dd, *J*=10, 9 Hz, 1-H), 4.21 and 4.09 (each 1H, ABq, *J*=12 Hz, CH_2O), 2.12, 2.09, 2.08, 2.07, and 2.01 (each 3H, s, Ac × 5); HRMS calcd for $C_{16}H_{24}NO_{10}$ (M^++1) 390.1401, found 390.1390. **12**: oil; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.60 (1H, d, *J*=4 Hz, N*H*Ac), 5.51 (1H, dd, *J*=8, 5.5 Hz, 3-H), 5.18 (1H, dd, *J*=10, 8 Hz, 2-H), 5.14 (1H, d, *J*=5.5 Hz, 4-H), 4.26 (1H, dd, *J*=10, 4 Hz, 1-H), 4.12 and 4.10 (each 1H, ABq, *J*=12 Hz, CH_2O), 2.16, 2.15, 2.14, 2.09, and 2.04 (each 3H, s, Ac × 5); HMRS calcd for $C_{16}H_{24}NO_{10}$ (M^++1) 390.1401, found 390.1397.
6. Shono, T.; Kise, N.; Fujimoto, T.; Yamanami, A.; Nomura, R. *J. Org. Chem.* **1994**, *59*, 1730-1740.
7. Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043-2053; Optimization of the newly found ring expansion reaction of the 1,5-*trans*-methoxyamine **5** to the piperidine **10** and the mechanistic investigation are now under progress.
8. Crystal data of **8:** $C_{16}H_{23}NO_{10}$, space group $P6_1$ with $a = b = 19.235$ (2), $c = 10.863$ (2) Å, $V = 3480.8$ (8) Å^3. Final R value was 0.075 for 2286 reflections.
9. RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139-145.
10. Ikota, N. *Heterocycles* **1989**, *29*, 1469-1472.

(*Received in Japan* 9 *September* 1994)