Pergamon

Tetrahedron Letters 39 (1998) 7173–7176

TETRAHEDRON LETTERS

Asymmetric Synthesis of (+)-1-Deoxynojirimycin[1]

Ulf M. Lindström and Peter Somfai*

Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University
S-106 91 Stockholm, Sweden

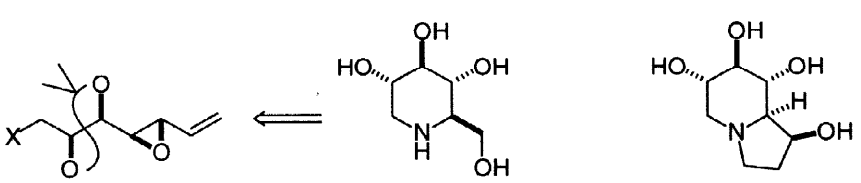
Received 17 June 1998; accepted 20 July 1998

Abstract

An asymmetric synthesis of (+)-1-deoxynojirimycin (**1**) in 14 steps starting from diene (**5**) is described. The key transformations in the sequence are a Sharpless dihydroxylation and epoxidation followed by a regio- and stereoselective aminolysis of vinyl epoxide **11** to give piperidine **12.**

Keywords: Alkaloids; Asymmetric synthesis; Cyclisation; Epoxides.

Several polyhydroxylated 1-aza sugars and indolizidines that show interesting glycosidase inhibitory activity have been isolated from natural sources. Typical examples are (+)-1-deoxynojirimycin (**1**)[1, 2] and castanospermine (**2**),[3] respectively, both of which show antiviral and antidiabetic activities. Consequently, a number of total syntheses of these compounds have been executed and, concerning **1**, most of them rely on the chiral pool but recently an asymmetric synthesis of this compound was also reported.[4] We recently described a protocol for the regio- and stereoselective aminolysis of vinyl epoxides resulting in a novel entry to *vic*-amino alcohols.[5, 6] As a continuation of that investigation we became interested in applying this transformation to the synthesis of aza sugar **1**, being a representative member of this class of compounds, through a sequence that should have the flexibility to also allow for the preparation of **2**, and herein detail our preliminary results.

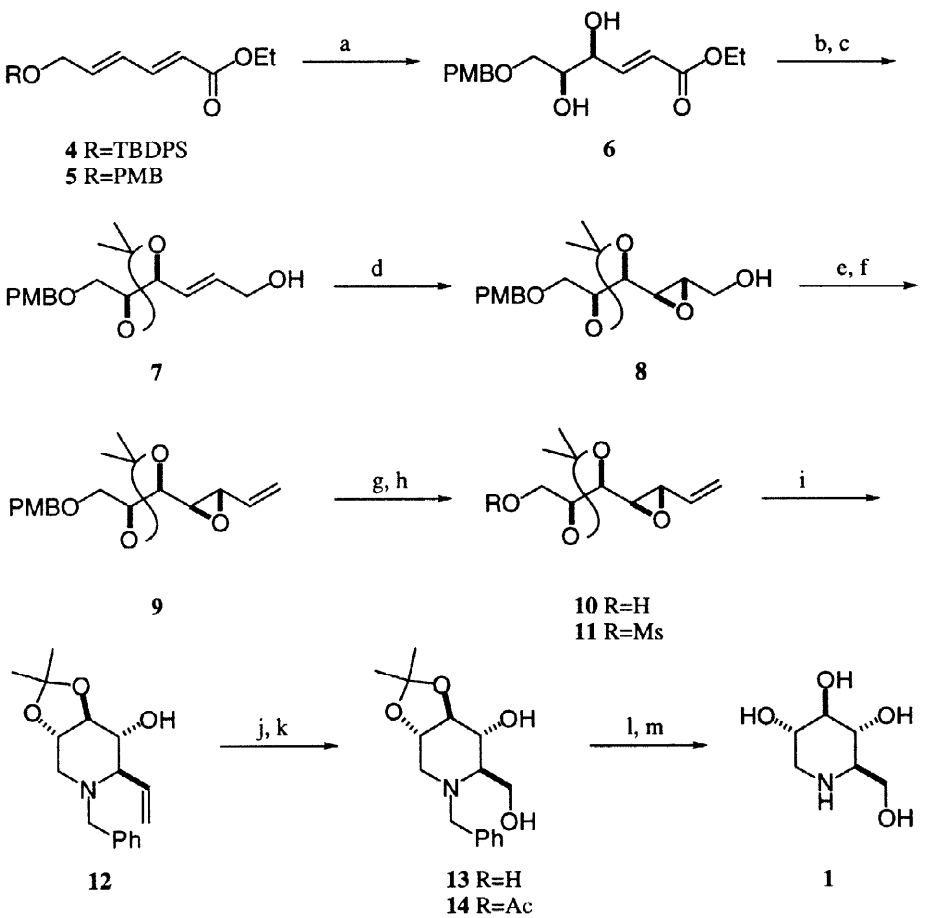


3 (+)-1-Deoxynojirimycin (**1**) Castanospermine (**2**)

[1] Dedicated to Professor S. Masamune on the occasion of his 70th birthday.

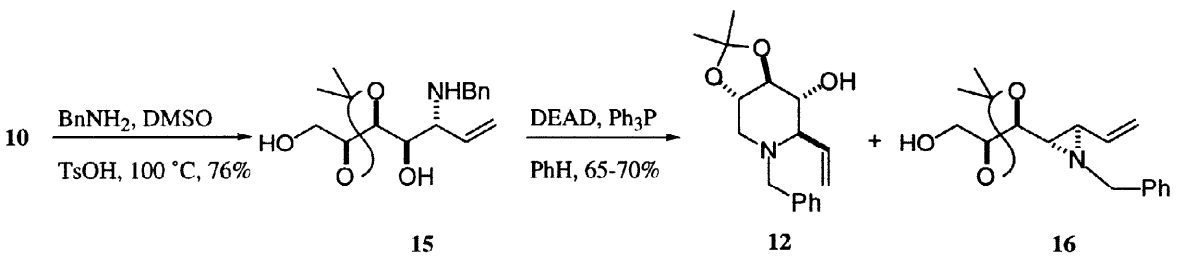
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01536-6

Our strategy for the synthesis of **1** was focused on the known propensity of vinyl epoxides to be attacked by amines, and other nucleophiles, regio- and stereoselectively at the allylic position,[5, 7] resulting in **3** (X=leaving group) as the projected key intermediate. Opening of the epoxide moiety in **3** by a primary amine and subsequent ring closure was expected to give a piperidine derivative from which **1** should be easily obtained, while **3** was to be derived from a properly functionalized 6-hydroxy sorbate ester. Towards this end, attempted dihydroxylation of silyl ether **4** gave only recovered starting material and none of the expected diol (Scheme 1). It has previously been shown that the enantioselectivity in the asymmetric dihydroxylation of allylic alcohols is sensitive to the nature of the hydroxyl protecting group and,[8] during the course of this investigation, it was shown by Guzman-Perez and Corey, that this type of diene can be readily dihydroxylated when protected as a *p*-methoxyphenyl ether.[9] For strategic reasons, however, the *p*-methoxybenzyl ether **5**[10, 11] was chosen as a suitable starting material and it was gratifying to find that, when subjected to the AD-mix-α reagent, diol **6** was obtained in reasonable yield and 97% *es*.[12]



Scheme 1. (a) AD-mix-α, t-BuOH, H_2O, 62%, 97% *es* (b) 2-methoxypropene, DMF, 97% (c) DIBAL, CH_2Cl_2, -78 °C, 93% (d) (+)-DIPT, $Ti(Oi\text{-}Pr)_4$, TBHP, CH_2Cl_2, -20 °C, 80%, >95% *ds* (e) $(COCl_2)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C (f) Ph_3PCH_3Br, KHMDS, THF, PhMe, 73% (g) DDQ, CH_2Cl_2, H_2O, 88% (h) MsCl, i-Pr_2NEt, CH_2Cl_2, 0 °C, 88% (i) $BnNH_2$, TsOH, DMSO, 120 °C, 76% (j) OsO_4, NMO, t-BuOH, THF, H_2O; $NaIO_4$, THF, H_2O (k) $LiAlH_4$, THF, 0 °C, 84% (from **12**) (l) TFA, MeOH, 87% (m) H_2, Pd/C, EtOH, 89%.

Protection of the diol moiety in **6** followed by reduction of the ester group then gave allylic alcohol **7**. Epoxidation of this material using the catalytic Sharpless procedure proved unsuccessful,[13] resulting only in a low yield of the corresponding epoxide, but was eventually accomplished by using the stoichiometric protocol to afford **8** in high yield and *es*, as has been described previously for similar substrates.[14] Swern oxidation of **8** followed by Wittig olefination of the resultant aldehyde then gave vinyl epoxide **9**,[5] standard deprotection of which gave alcohol **10**.



15 12 16

Scheme 2.

Initial efforts to convert compound **10** into piperidine **12** started with opening of **10** with $BnNH_2$ to give, as a single detectable isomer, amino alcohol **15** in good yield (Scheme 2). However, attempts to cyclize **15** using the Mitsunobu protocol resulted in a mixture of **12** and vinyl aziridine **16** in a 65-70% yield, with the former one being slightly favoured (**12**:**16** 1.2:1).[15, 16] Although three-membered rings are normally formed faster than six-membered ones in intramolecular cyclizations,[17] we have previously noted that formation of aziridines from *vic*-amino alcohols having a *sec*- or *tert*-carbon atom adjacent to the alcohol moiety is a disfavoured process, making the present observation somewhat surprising. Similar results were also obtained using other cyclization procedures based on Ph_3P.[18] To overcome this problem **10** was converted into mesylate **11** (Scheme 1). Subjecting this material to benzyl amine in the presence of a catalytic amount of *p*-toluenesulfonic acid in DMSO at 120 °C resulted in opening of the epoxide moiety and concomitant intramolecular displacement of the mesylate, furnishing **12** in 76% yield. When the reaction was terminated before completion small amounts of the corresponding vicinal *sec*-amino alcohol along with **12** could be detected, which seems to indicate that the opening of the allylic epoxide moiety precedes the displacement of the mesylate. Next, cleavage of the vinyl group in **12** was best affected by treatment with OsO_4 followed by cleavage of the so obtained diol with $NaIO_4$ to give the corresponding aldehyde,[19] the reduction of with $LiAlH_4$ which furnished the protected deoxynojirimycin derivative **13**. To verify that correct relative stereochemistry had indeed been established diol **13** was converted into diacetate **14** (Ac_2O, C_5H_5N, DMAP), which showed the expected coupling constants in its ^1H NMR spectrum.[2] Sequential removal of the isopropylidene and benzyl protecting groups in **13** by standard procedures then gave (+)-1-deoxynojirimycin (**1**), its physical data being in accordance with literature values.[4]

In summary, we have described a novel asymmetric synthesis of the α-glycosidase inhibitor (+)-1-deoxynojirimycin (**1**) in 14 steps and 12.5% overall yield starting from diene **5**. The key steps in the sequence are a Sharpless dihydroxylation, epoxidation and a regio- and stereoselective aminolysis of vinyl epoxide **11**.

---

[2] Diacetate **14**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 5.24 (dd, 1H, J=9.7, 8.7 Hz), 4.48 (dd, 1H, J=12.9, 2.3 Hz), 4.16 (dd, 1H, J=12.9, 3.4 Hz), 4.10 (d, 1H, J=13.4 Hz), 3.59 (m, 1H), 3.53 (d, 1H, J=13.4 Hz) 3.44 (t, 1H, J=9.7 Hz), 3.20 (dd, 1H, J=10.3, 3.3 Hz), 2.65 (br dt, 1H, J=8.7, 3.1 Hz), 2.34 (t, 1H, J=10.3 Hz), 2.14 (s, 3H), 2.10 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H).

We are currently investigating the possibility of using a similar approach for the synthesis of castanospermine (**2**), the results of which will be described elsewhere.

Acknowledgments. This work was supported financially by the *Swedish Natural Science Research Council.*

References

[1] Daigo K, Inamori Y, Takemoto T. Chem. Pharm. Bull. 1986;34:2243.

[2] Evans SV, Fellows SE, Shing TKM. Phytochemistry 1985;24:1953.

[3] Hohenschutz LD, Bell EA, Jewess PJ, Leworthy DP, Pryce PJ, Arnold EA, Clardy J. Phytochemistry 1981;20:811.

[4] Rudge AJ, Collins I, Holmes AB, Baker R. Angew. Chem. Int. Ed. Engl. 1994;33:2320, and references cited therein.

[5] Lindström UM, Somfai P. Synthesis 1998:109.

[6] Lindström UM, Franckowiak R, Pinault N, Somfai P. Tetrahedron Lett. 1997;38:2027.

[7] Jaime C, Ortuño RM, Font J. J. Org. Chem. 1988;53:139.

[8] Corey EJ, Guzman-Perez A, Noe MC. J. Am. Chem. Soc. 1995;117:10805.

[9] Guzman-Perez A, Corey EJ. Tetrahedron Lett. 1997;38:5941.

[10] Bérubé G, Deslongshamps P. Can. J. Chem. 1990;68:404.

[11] Nakajima N, Horita K, Abe R, Yonemitsu O. Tetrahedron Lett. 1988;29:4139.

[12] Sharpless KB, Amberg W, Bennani YL, Crispino GA, Hartung J, Jeong K-S, Kwong H-L, Morikawa K, Wang Z-M, Xu D, Zhang X-L. J. Org. Chem. 1992;57:2768.

[13] Gao Y, Hanson RM, Klunder JM, Ko SY, Masamune H, Sharpless KB. J. Am. Chem. Soc. 1987;109:5765.

[14] Ko SY, Lee AWM, Masamune S, Reed I, L. A., Sharpless KB, Walker FJ. Tetrahedron 1990;46:245.

[15] Hughes DL. Org. React. 1992;42:335.

[16] Mitsunobu O. Synthesis 1981:1.

[17] Eliel EL, Wilen SH. Stereochemistry of Organic Compounds. New York: Wiley, 1994: 678.

[18] Shishido Y, Kibayashi C. J. Org. Chem. 1992;57:2876.

[19] Evans DA, Ng HP, Rieger DL. J. Am. Chem. Soc. 1993;115:11446-11459.