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TETRAHEDRON: *ASYMMETRY*

A concise synthesis of unnatural (+)-5-*epi*-nojirimycin-δ-lactam via asymmetric reduction of a *meso*-imide

Jahyo Kang,[a,*] Choon Woo Lee,[a] Geun Jho Lim [b] and Byung Tae Cho [c]

[a]*Department of Chemistry, Sogang University, Seoul 121-742, South Korea*
[b]*Dong-A Pharmaceutical Research Laboratories, 47-5 Sanggal-ri, Yongin-gun, Kyunggi-do 449-900, South Korea*
[c]*Department of Chemistry, Hallym University, Chunchon 200-702, South Korea*

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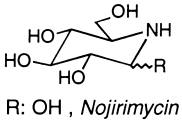
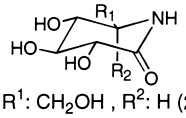
Abstract

Nojirimycin-δ-lactam skeleton was synthesized by asymmetric reduction of a cyclic triacetyloxy *meso* imide with a chiral β-amino thiol ligand. The resulting product was converted to unnatural (+)-5-*epi*-nojirimycin-δ-lactam.

The synthetic challenge of naturally occurring monosaccharide-like alkaloids containing a piperidine moiety, **1a** and **1b**, and their analogues such as nojirimycin-δ-lactams **2a**,**b** are significant since they are potent and selective glycosidase inhibitors,[1,2] and thus are expected to have potential chemotherapeutic utilities such as antidiabetic agents,[3] novel anticancer[4,5] and anti-HIV agents.[6,7] The syntheses of nojirimycin-δ-lactams **2a**,**b** have so far been accomplished by oxidation of nojirimycin,[8] amination of idofuranose[9] and from glucose as a mixture.[8] Many synthetic methods have been reported to present the flexibility of approaches to the synthesis of the nojirimycin skeleton by the preparation of analogues. However, they have little advantage in the synthesis of the enantiomer as well as their C-1 and C-5 derivatives.



R: OH , *Nojirimycin* (**1a**)
R: H , 1- *Deoxynojirimycin* (**1b**)



R^1: CH_2OH , R^2: H (**2a**)
R^1: H , R^2: CH_2OH (**2b**)

We appreciate that another possible synthetic strategy would be the use of enantioselective reduction in the presence of a catalytic amount of β-amino thiol ligand **7**[10] of a six-membered cyclic *meso* imide **3** bearing three equatorial hydroxy groups at C-2, 3 and 4 positions. Subsequent substitution of the C-5 hydroxyl group with a hydroxymethyl group through a chiral acyliminium ion **5** would furnish the desired product. This strategy has the advantage that the syntheses of C-5 analogues and their enantiomers could

* Corresponding author. E-mail: kangj@ccs.sogang.ac.kr

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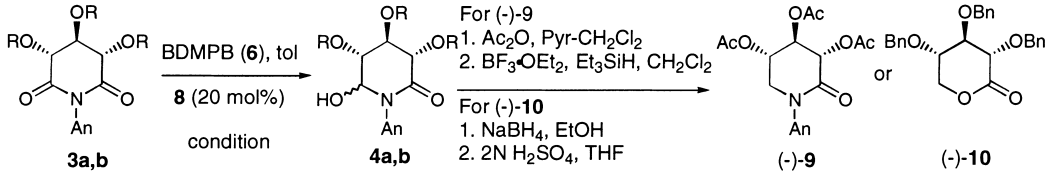
Table 1
Asymmetric reduction of cyclic imides with β-amino thiol ligand **7**[a]



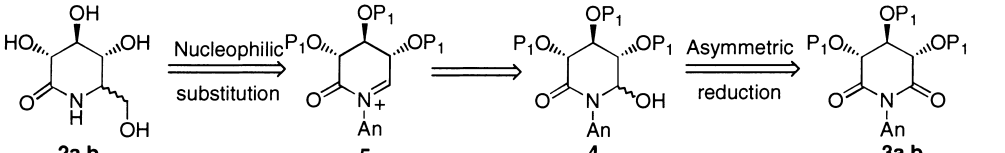
3a,b **4a,b** (-)-**9** (-)-**10**

Entry	Imide	Temp (°C)	Time (hr)	Ee[b] (%)	Yield[c] (%)	Conf[d]	Optical Rotation
1	**3a** (R=Ac)	0	12	78	50	(-)-**9**	
2	**3a**	-10	16	85	62	(-)-**9**	$[\alpha]_D^{25}$ –4.8 (c 0.66, $CHCl_3$)[e]
3	**3a**	-20	48	70	12[f]	(-)-**9**	
4	**3b**(R=Bn)	-10	48	24	92	(-)-**10**	$[\alpha]_D^{31}$ –1.1 (c 0.56, $CHCl_3$)[g]

[a]Reactions with the ligand **7** (20 mol%), Et_2Zn (20 mol%) and BDMPB (3 eq.) in toluene (0.3 M). [b]Determined by HPLC (Chiralcel OD column) of the lactam **9** or lactone **10**. [c]Isolated yields of **4a** and **4b**. [d]Confirmed by comparison of optical rotation and chiral HPLC elution order with authentic (+)-**9** and (+)-**10**. [e]Specific rotation of (+)-**9**[14]: $[\alpha]_D^{25}$ 5.6 (c 0.95, $CHCl_3$). [f]Most of the starting material remained unchanged even after 48 h. [g]Specific rotation of (+)-**10**[15]: $[\alpha]_D^{21}$ 4.4 (c 0.85, $CHCl_3$), $[\alpha]_D^{25}$ 5.2[h] (c 0.53, $CDCl_3$).

be accomplished by properly controlling chiral ligands and nucleophiles. In this communication, we wish to disclose the use of the asymmetric reduction of a *meso*-imide for the enantioselective synthesis of an unnatural nojirimycin-δ-lactam enantiomer.

In fact, chiral catalytic reduction of the *meso* imides by optically active ligands occupies an important position in the field of modern organic synthesis, and nucleophilic additions to resulting chiral acyliminium ion are important methods for the preparation of nitrogen containing natural products.[11]



2a,b **5** **4** **3a,b**

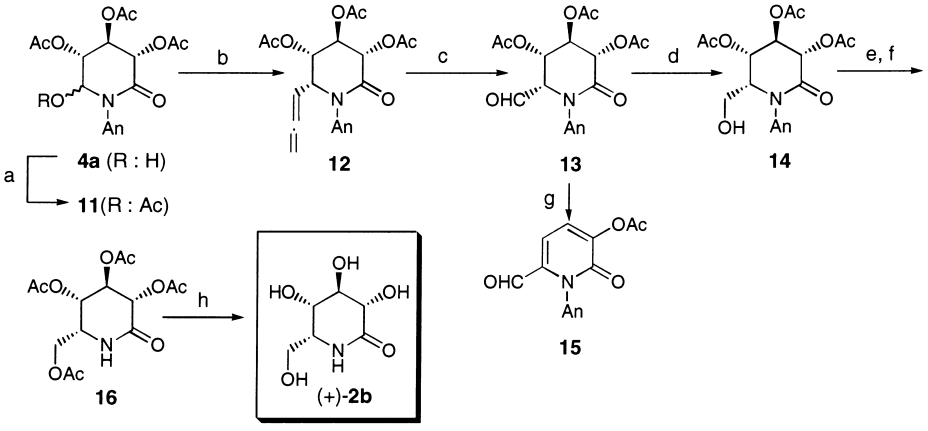
Our asymmetric reduction of *meso* triacetyloxy imide **3a**[12] and tribenzyloxy imide **3b**[13] was carried out with BDMPB (bis(2,6-dimethylphenoxy)borane: **6**)[10] as a reducing agent in toluene in the presence of a catalytic amount (20%) of the thiazazincolidine complex **8**, generated in situ from enantiomerically pure amino thiol ligand **7** and Et_2Zn.[10]

7 **8**

The corresponding hydroxy δ-lactams **4a** and **4b** were individually converted to a δ-lactam, (−)-**9** (1: Ac_2O, Pyr, CH_2Cl_2; 2: Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2), and a δ-lactone, (−)-**10** (1: $NaBH_4$, EtOH; 2: 2 N H_2SO_4, THF), respectively. The products were analyzed by chiral HPLC for enantioselectivity for the reduction of *meso* imide, the results of which are summarized in Table 1. Although the enantioselectivity in the reduction of *meso* tribenzyloxy imide **3b** was relatively low, it was gratifying to find that the same reduction of triacetyloxy *meso* imide **3a**, using identical conditions, gave higher enantioselectivity.

The reduction product, **4a** [resulting from the reaction of imide **3a** with BDMPB (3 equiv.) in the

presence of **8** (20 mol%), −10°C, 16 h; 62% yield, 85% ee] was ultimately converted to the unnatural nojirimycin skeleton as shown in Scheme 1, which was initiated by acetylation to the corresponding acetate **11** in 87% yield. Subsequently, substitution of lactam acetate **11** with propargyltrimethylsilane[16] produced allenic compound **12** in 88% yield with a form under a mixed Lewis acid combination of $BF_3 \cdot OEt_2$ and *t*-butyldimethylsilyl triflate[17] to give 5-*epi*-compound **12**. It was noteworthy that the nucleophilic addition of propargylsilane on the resulting acyliminium ion center took place exclusively from the axial direction.[18,19] Compound **12** was transformed to hydroxymethyl product **14** by ozonolysis followed by reduction of crude aldehyde **13** with $NaBH_4$ in 86% yield for two steps. Attempted base-induced epimerization of the α-carbon of crude aldehyde **13** to the corresponding C-5 equatorial compound under various conditions[20] invariably produced an elimination product **15**. After acetylation of monoalcohol **14** followed by oxidative cleavage of the *p*-methoxyphenyl group with CAN (58% yield for the steps to **16**), the final compound (+)-**2b**[21] was obtained by removal of all acetyl moieties with NaOH (81% yield) (Scheme 1).



Scheme 1. Reagent: (a) Ac_2O, Py–CH_2Cl_2, rt, 87%. (b) Propargyltrimethylsilane, $BF_3 \cdot OEt_2$, TBSOTf (0.2 equiv.), CH_3CN, 88%. (c) O_3, CH_2Cl_2, −78°C. (d) $NaBH_4$, EtOH, 0°C, 86% (2 steps). (e) Ac_2O, Py–CH_2Cl_2, rt. (f) CAN, CH_3CN–H_2O, rt, 58% (2 steps). (g) Et_3N, *i*-PrOH–CH_2Cl_2, 28%. (h) 2 N NaOH, MeOH, 0°C, 81%

In conclusion, we have shown that enantioselective reductive differentiation of the carbonyl groups in a *meso*-imide, axial addition of an organometallic to iminium ion center derived therefrom and subsequent removal of the nitrogen protecting group can be applied to a concise and efficient synthesis of potentially biologically active nitrogen heterocycles.

Acknowledgements

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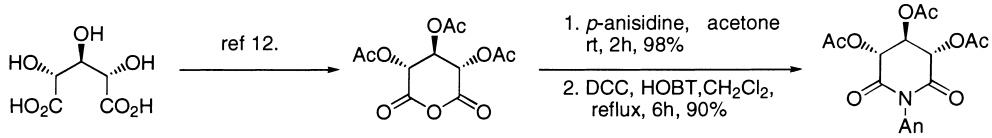
References

1. For a review, see: Nishimura, Y. *J. Synth. Org. Chem. Jpn*. **1991**, *49*, 846–857.
2. Hughes, A. B.; Rudge, A. J. *Natural Product Reports* **1994**, *11*, 135–162.
3. Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem*. **1989**, *54*, 2539–2542.
4. Wong, C.-H.; Dumas, D. P.; Ichikawa, Y.; Koseki, K.; Danishefsky, S. J.; Westone, B. W.; Lowe, J. B. *J. Am. Chem. Soc*. **1992**, *114*, 7321–7322.

5. Tsuruoka, T.; Fukuyasu, H.; Ishii, M.; Usui, T.; Shibahara, S.; Inouye, S. *J. Antibiot*. **1996**, *49*, 155–161.
6. Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74–77.
7. Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 9229–9233.
8. Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *23*, 2125–2144.
9. Fleet, G. W. J.; Carpenter, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett*. **1990**, *31*, 409–412.
10. Kang, J.; Lee, J. W.; Kim, J. I.; Pyun, C. *Tetrahedron Lett*. **1995**, *36*, 4265–4268.
11. Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1998**, *63*, 220–221.
12. The imide **3a** was prepared by the following scheme. See Cantrell, C. E.; Kiely, D. E.; Abruscato, G. J.; Riordan, J. M. *J. Org. Chem*. **1977**, *42*, 3562–3567.



3a

13. Compound **3b** was obtained from oxidation of a related hydroxy lactam which was synthesized by the known method. Miller, S. A.; Chamberin, A. R. *J. Am. Chem. Soc*. **1990**, *112*, 8100–8112.
14. Authentic compound (+)-**9** (100% ee) was synthesized by application of the method used in Ref. 13.
15. Authentic compound (+)-**10** (100% ee) was obtained by a known method. Lopez, R.; Fernandez-Mayoralas, A. *J. Org. Chem*. **1994**, *59*, 737–745.
16. Nativi, C.; Taddei, M.; Mann, A. *Tetrahedron* **1989**, *45*, 1131–1144.
17. Nicolaou, K. C.; Hwang, C. K.; Duggan, M. E. *J. Am. Chem. Soc*. **1989**, *111*, 6682–6690.
18. Equatorial product was not detected on TLC and NMR.
19. Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett*. **1992**, *33*, 737–740 and 3109–3112.
20. Bernotas, R. C.; Ganem, B. *Tetrahedron Lett*. **1985**, *26*, 1123–1126, and also see Ref. 19.
21. Compound (+)-**2b**: ^{1}H NMR (D_2O, 300 MHz) δ 3.87 (dd, *J*=8 Hz, 4.2 Hz, 1H), 3.85 (d, *J*=8 Hz, 1H), 3.78 (t, *J*=8 Hz, 1H), 3.60 (d, *J*=1.6 Hz, 1H), 3.57 (s, 1H), 3.48 (m, 1H); ^{13}C NMR (D_2O, 75.5 MHz) δ 173.44, 72.66, 71.39, 68.70, 59.70, 54.01; IR (KBr) 1666.6 cm^{-1} (C=O). The enantiomeric excess of (+)-**2b** was identified by HPLC analysis of the corresponding tetraacetate **16** prepared from the synthetic (+)-**2b** (Ac_2O, Pyr, CH_2Cl_2) on Daicel Chiralcel OD-H (40% *i*-PrOH in hexane, flow rate: 0.7 mL/min, 230 nm UV detector). In the case of **4a** with 81% ee has shown it to be 82% ee in this analysis (t_R: 25.71 min; minor, t_R: 36.37 min; major).