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A Concise Synthesis of (-)-Neplanocin A

Naoyuki Yoshida, Takashi Kamikubo, and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan FAX +81-22-217-6845; E-mail konol@mail.cc.tohoku.ac.jp

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Abstract: A concise stereocontrolled route to (-)-neplanocin A, a naturally occurring carbocyclic nuleoside, has been developed by employing lipase-mediated kinetic resolution. © 1998 Elsevier Science Ltd. All rights reserved.

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(-)-Neplanocin A¹ 1, isolated from *Ampullariella regularis*, is a naturally occurring carbocyclic nucleoside exhibiting potent antitumor and antiviral activities. Although (-)-neplanocin A 1 itself is not practically used as a drug, it is a good lead for the development of more effective and less toxic therapeutic agents.² An expedient synthetic procedure capable of producing not only (-)-neplanocin 1 itself but also its various derivatives, therefore, has to be devised.^{3,4} We report here a concise synthesis of (-)-neplanocin A 1 starting from the readily accessible tricyclic ester⁵ (±)-2 employing a lipase-mediated kinetic resolution which may be applicable to the preparation of a variety of synthetic analogues of the natural product.

Reduction of the tricyclic keto ester (±)-2, obtained readily in 65% overall yield in two steps from the Diels-Alder adduct of benzoquinone and cyclopentadiene⁵, with diisobutylaluminum hydride (DIBAL) gave the racemic diol⁶ (±)-3. Treatment of (±)-3 with vinyl acetate in Bu'OMe in the presence of Lipase LIP (Toyobo) furnished the (-)-diacetate⁶ 4, $[\alpha]_{D}^{25}$ -81.03 (*c* 1.2, CHCl₃), and the (+)-monoacetate⁶ 5, $[\alpha]_{D}^{25}$ +133.89 (*c* 1.04, CHCl₃), in yields of 41 and 46%. Enantiomeric purities of the products were determined to be 92% ee for (-)-4 and >99% ee for (+)-5 by hplc using a chiral column (CHIRALCEL OD, Pr'OH-hexane 5:95). On alkaline methanolysis, each gave the enantiomeric diol 3, quantitatively. The optically pure diol (+)-3, $[\alpha]_{D}^{30}$ +138.4 (*c* 0.3, EtOH), mp 116-119 °C, obtained from (+)-5, was treated with *N*-bromosuccinimide (NBS) to discriminate one of the two double bonds to give the bromo-ether 6, $[\alpha]_{D}^{29}$ +153.1 (*c* 0.30, CHCl₃). After transformation of 6 into the silyl ether 7, $[\alpha]_{D}^{28}$ +114.1 (*c* 0.16, CHCl₃), the remaining double bond was dihydroxylated from the convex face to give stereoselectively the single glycol 8, $[\alpha]_{D}^{28}$ +57.1 (*c* 0.26, CHCl₃), which was transformed into the acetonide 9, $[\alpha]_{D}^{30}$ +73.2 (*c* 0.12, CHCl₃). The masked double bond was regenerated at this stage by treating 9 with zinc and acetic acid to give the olefin 10, $[\alpha]_{D}^{30}$ +147.0 (*c* 0.30, CHCl₃). On thermolysis in refluxing diphenyl ether, 10 afforded the cyclopentenol 11, $[\alpha]_{D}^{29}$ -12.8 (*c* 1.84, CHCl₃), whose secondary hydroxy center was inverted to give the epimer 13, $[\alpha]_{D}^{27}$ +22.5 (*c* 0.63, CHCl₃), by

oxidation followed by stereoselective reduction of the resulting enone 12, $[\alpha]_D^{29} -10.7$ (c 0.85, CHCl₃). Employing the Mitsunobu reaction⁷, 13 was coupled with adenine with inversion to give the penultimate 14, $[\alpha]_D^{29} -31.6$ (c 0.29, CHCl₃), which finally was treated with aqueous acid to give (-)-neplanocin A 1, mp 217 ~ 219 °C, $[\alpha]_D^{29} -155.7$ (c 0.06, H₂O) [lit.⁴; mp 214-5 °C, $[\alpha]_D^{20} -153.9$ (c 0.33, H₂O)]. Overall yield of (-)-neplanocin A 1 from the optically pure diol (+)-3 was 45% in 10 steps.



Scheme 1. Reagents and conditions: i) DIBAL, toluene, -78 °C (65% for (±)-3; 100% for 13). ii) Lipase LIP, vinyl acetate, Bu'OMe, rt, 8h. iii) K₂CO₃, MeOH (100%). iv) NBS, CH₂Cl₂ (100%). v) TBS-Cl, imidazole, DMF (97%). vi) OsO₄ (cat.), NMO, 70% aq. THF (80%). vii) 2,2-dimethoxypropane, PPTS, acetone (100%). viii) Zn, AcOH (cat.), MeOH (95%). xi) Ph₂O, reflux, 30 min (97%). x) PDC, CH₂Cl₂ (83%). xi) adenine, diisopropyl azodicarboxylate, PPh₃, THF (84%). xii) 1N HCI-MeOH rt, 3h (90%).

References and Notes

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