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A Concise Synthesis of (–)-Neplanocin A

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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.

Keywords: Catalysts; Nickel and compounds; Protecting groups; Resolution

(–)-Neplanocin A[1] **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 ester[5] (±)-**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 cyclopentadiene[5], with diisobutylaluminum hydride (DIBAL) gave the racemic diol[6] (±)-**3**. Treatment of (±)-**3** with vinyl acetate in Bu^{t}OMe in the presence of Lipase LIP (Toyobo) furnished the (–)-diacetate[6] **4**, $[\alpha]_D^{25}$ –81.03 (*c* 1.2, $CHCl_3$), and the (+)-monoacetate[6] **5**, $[\alpha]_D^{25}$ +133.89 (*c* 1.04, $CHCl_3$), 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^{i}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, $CHCl_3$). After transformation of **6** into the silyl ether **7**, $[\alpha]_D^{28}$ +114.1 (*c* 0.16, $CHCl_3$), 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, $CHCl_3$), which was transformed into the acetonide **9**, $[\alpha]_D^{30}$ +73.2 (*c* 0.12, $CHCl_3$). 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, $CHCl_3$). On thermolysis in refluxing diphenyl ether, **10** afforded the cyclopentenol **11**, $[\alpha]_D^{29}$ –12.8 (*c* 1.84, $CHCl_3$), whose secondary hydroxy center was inverted to give the epimer **13**, $[\alpha]_D^{27}$ +22.5 (*c* 0.63, $CHCl_3$), by

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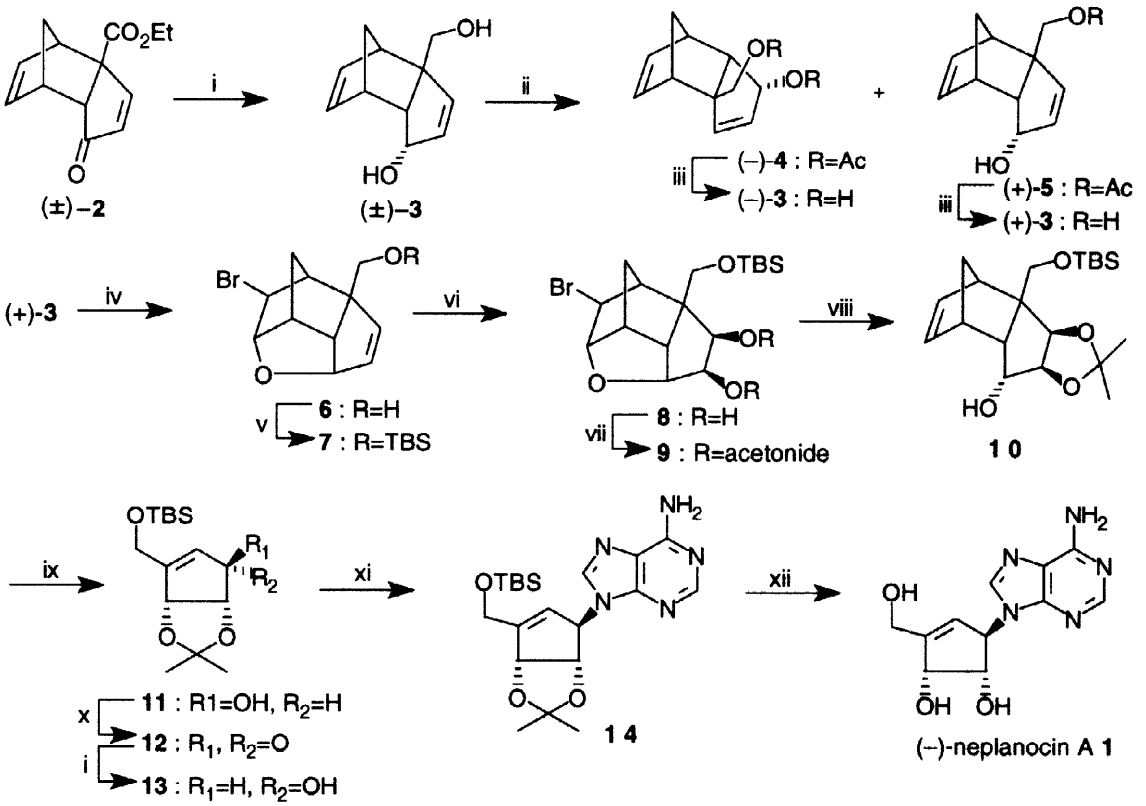
oxidation followed by stereoselective reduction of the resulting enone **12**, $[\alpha]_D^{29}$ -10.7 (*c* 0.85, $CHCl_3$). Employing the Mitsunobu reaction[7], **13** was coupled with adenine with inversion to give the penultimate **14**, $[\alpha]_D^{29}$ -31.6 (*c* 0.29, $CHCl_3$), which finally was treated with aqueous acid to give (–)-neplanocin A **1**, mp 217 ~ 219 °C, $[\alpha]_D^{29}$ -155.7 (*c* 0.06, H_2O) [lit.[4]; mp 214-5 °C, $[\alpha]_D^{20}$ -153.9 (*c* 0.33, H_2O)]. 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) K_2CO_3, MeOH (100%). iv) NBS, CH_2Cl_2 (100%). v) TBS-Cl, imidazole, DMF (97%). vi) OsO_4 (cat.), NMO, 70% aq. THF (80%). vii) 2,2-dimethoxypropane, PPTS, acetone (100%). viii) Zn, AcOH (cat.), MeOH (95%). xi) Ph_2O, reflux, 30 min (97%). x) PDC, CH_2Cl_2 (83%). xi) adenine, diisopropyl azodicarboxylate, PPh_3, THF (84%). xii) 1N HCl-MeOH rt, 3h (90%).

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