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AN ENANTIO- AND DIASTEREO-CONTROLLED SYNTHESIS OF (-) NEPLANOCIN A AND ITS 2,3-DI-EPI ISOMER

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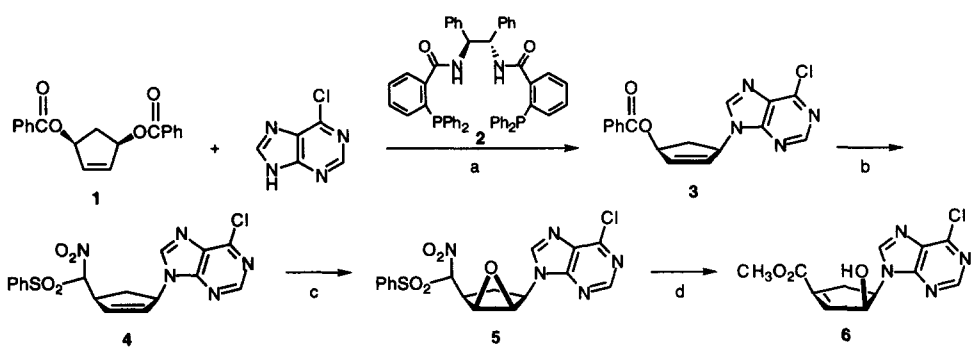
Summary: An enantioselective Pd catalyzed desymmetrization of cis-3,5-dibenzoyloxycyclopent-2-ene combined with a diastereoselective epoxidation provided a common intermediate that can bifurcate to form either (-)-neplanocin A or its 2,3-di-epi isomer. © 1997 Elsevier Science Ltd. All rights reserved.

Carbanucleosides are emerging as possible clinically useful anti-tumor and anti-viral agents.[1] Early stimulus for these studies came from the discovery of such analogues as natural products. (-)-Neplanocin A (**16b**), isolated from the culture filtrate of the soil fungus *Ampullariella regularis*,[2] inhibits cellular S-adenosylmethionine dependent methyltransferases.[3] This behavior may account for its anti-tumor and anti-viral activity but not necessarily its lower general toxicity.[4] The high promise of interesting biological activity stimulates synthetic endeavors.

Our recent studies outlined a short synthesis of dideoxycarbanucleosides.[5] The diastereoselectivity of the functionalization of the double bond has proven to be a most interesting dilemma since osmium catalyzed dihydroxylation favors approach *cis* to the two allylic substituents.[6] With a total synthesis of (-)-neplanocin A[7,8] as our target, we have developed a diastereocontrolled approach for introduction of the diol functionality that culminated in a synthesis of (-)-neplanocin and its 2,3-di-epi analogue.

The Pd(0) catalyzed desymmetrization of bis-benzoate **1** with 6-chloropurine as the nucleophile best employed the stilbenediamine based ligand **2**[9] in the presence of triethylamine in THF at room temperature (see Scheme 1).[5,10] The monoalkylated product **3**[11] was determined to possess the absolute configuration

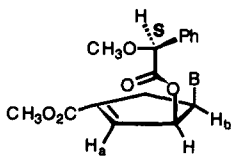
Scheme 1. Asymmetric Synthesis of Pivotal Intermediate



a) 1% $(dba)_3Pd_2{\bullet}CHCl_3$, 3% **2**, $(C_2H_5)_3N$, THF, r.t., 76%. b) 0.5% $(dba)_3Pd_2{\bullet}CHCl_3$, 4% Ph_3P, $PhSO_2CH_2NO_2$, $(C_2H_5)_3N$, THF, r.t., 95%. c) MCPBA, CH_2Cl_2, r.t., 73%. d) DBU, THF, CH_3OH, O_3, -78° to r.t., 67%.

depicted and to have a 94% ee (93-97% ee range over several runs) by conversion of the benzoate to its S-O-methylmandelate.[12] The one carbon unit was introduced regio- and diastereoselectively by a second Pd(0) catalyzed allylic alkylation to give **4**[11] in nearly quantitative yield. Since dihydroxylation of similar systems was known to occur selectively from the face syn to the two allylic substituents, which may involve coordination with osmium, we examined a non-metal base oxidation, epoxidation with a peracid. Interestingly, epoxidation to **5**[11] occurred rather well. The fact that the phenylsulfonyl-nitromethane unit of **5** was a mixture of epimers at the carbon bearing these two substituents made it difficult to assess the diastereoselectivity of the epoxidation. Removal of this stereogenic center occurred upon oxidative cleavage to the methyl ester[13] which was accompanied by elimination to open the epoxide. Characterization of the resultant alcohol **6**[11], devoid of extraneous stereogenic centers, established its homogeneity and, by extension, the high diastereoselectivity of the epoxidation. At this point, the relative stereochemistry could not ascertained by available spectral data.

In order to assess the relative stereochemistry, we can consider the set of four O-methylmandelates **7-10**. If the hydroxyl group is β, then changing from the S-mandelate (**7**) to the R-mandelate (**8**) should reveal an



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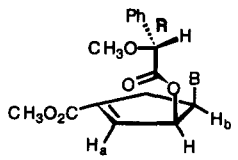

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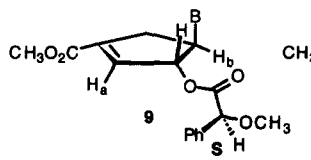

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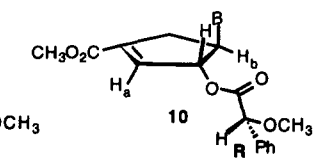

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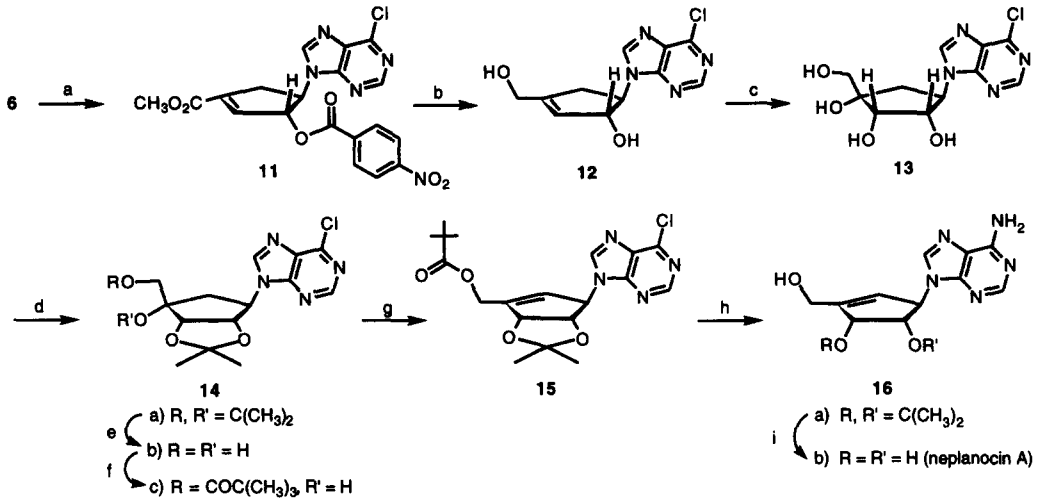
upfield shift for the vinyl proton H_a and a downfield shift for H_b in the ^1H nmr spectra as a result of the differential shielding by the phenyl ring.[12] On the other hand, the reverse trends should occur if the hydroxyl group is α—i.e., the vinyl proton H_a in **9** should be upfield of this proton in **10** and the reverse for the shifts for H_b. In the event, H_a and H_b, which appear at δ 6.89 and 5.51 in the S-mandelate, shift to δ 6.79 and 5.65 respectively for the R-mandelate. These results are consistent with the assignments of the mandelates as **7** and **8** and, consequently, **6** as the β-hydroxyl epimer. Thus, epoxidation occurred selectively syn to the substituents, just like dihydroxylation.

The high level of the diastereoselectivity in the epoxidation offered a simple solution to the synthesis of the normal stereochemistry of the natural carbanucleosides—esterification with inversion of configuration to give **11** by a Mitsunobu reaction (see Scheme 2). Reduction then provided the diol **12**.[11] Interestingly, dihydroxylation led to a single tetraol whose stereochemistry was suggested as depicted by the ease with which a bis-acetonide **14a** formed. If the dihydroxylation occurred from the opposite face, creating a *trans* fused bicyclo[3.3.0] system upon reaction with acetone should have hampered formation of such a derivative. The completion of the synthesis verifies this assignment. The source of the complete complementary of the stereochemistry of dihydroxylation of **4** and **12** likely lies in the conformation of the cyclopentene ring although a directing effect of the allylic hydroxyl group cannot be ruled out. Selective hydrolysis of the bis-acetonide **14a** to the mono acetonide **14b**[11] required a sterically bulky Lewis acid—thus the choice of ferric chloride on silica gel.[14] To direct the regioselectivity of the elimination, a sterically hindered ester, the pivalate, was chosen for the primary hydroxyl group. Dehydration of **14c**[11] with thionyl chloride in pyridine containing 1 equiv of DMF gave the best regioselectivity to cyclopentene **15**.[11] Aminolysis removes the pivalate and simultaneously

Scheme 2. Synthesis of (-)-Neplanocin A.

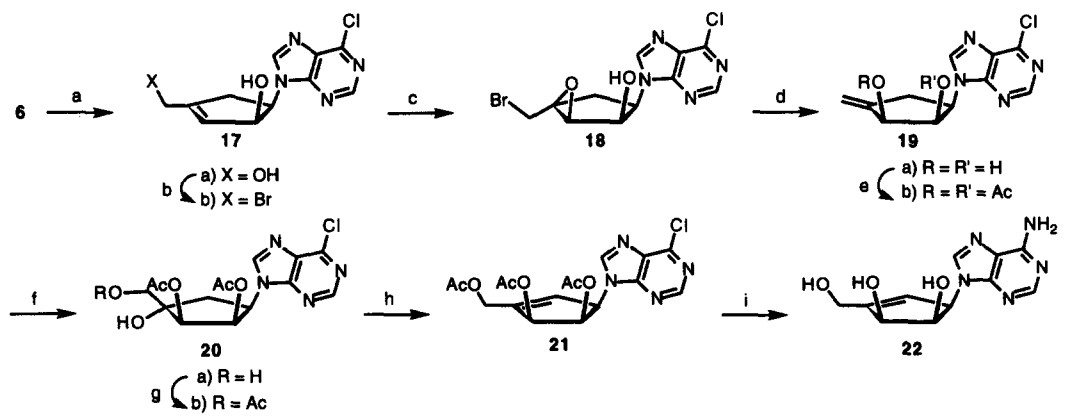


a) $HO_2CC_6H_4NO_2$-p, Ph_3P, DEAD, THF, 62%. b) DIBAL-H, THF-CH_2Cl_2, -78°, 79%. c) NMO, 2% OsO_4, CH_3COCH_3, H_2O, r.t., 89%. d) $(CH_3O)_2C(CH_3)_2$, TsOH, r.t., 71%. e) $FeCl_3$•$6H_2O$ on silica gel, CH_2Cl_2, r.t., 94%. f) $(CH_3)_3CCOCl$, C_5H_5N, r.t., 95%. g) $SOCl_2$, C_5H_5N, DMF (1 equiv), r.t., 60%. h) NH_3, CH_3OH, r.t., 73%. i) HCl, H_2O, 91%.

converts the chloropurine to adenine **16a**. Acid hydrolysis completes the synthesis of (-)-neplanocin, mp 214-5°C, $[\alpha]_D^{20}$ -153.9 (c 0.33, H_2O), in excellent accord with the literature.[6]

The availability of allylic alcohol **6** allowed ready access to the 2,3-di-epi neplanocin A as shown in Scheme 3. The stereochemistry was set by the hydroxyl directed epoxidation[15] of **17b**[11] to give **18**[11] as a single

Scheme 3. A Synthesis of (+)-2,3-di-epi-Neplanocin A



a) DIBAL-H, THF, CH_2Cl_2, -78°, 92%. b) Ph_3P, CBr_4, THF, r.t., 95%. c) *t*-C_4H_9OOH, $VO(acac)_2$, CH_2Cl_2, 95%. d) Zn(Cu), C_2H_5OH, ultrasound, 50°, 93%. e) Ac_2O, $(C_2H_5)_3N$, DMAP, r.t., 98%. f) NMO, OsO_4, CH_2Cl_2, r.t. g) see: e), 65% overall. h) $POCl_3$, DMAP, CH_2Cl_2, 0°, 98%. i) NH_3, CH_3OH, r.t., 70%.

diastereomer nearly quantitatively. The ease of formation of an acetonide from **19a**[11] confirmed the stereochemical assignment. Dehydration of **20b**[11] proceeded with no complications to give the desired endocyclic cyclopentene **21**[11] in contrast to the dehydration of **14**. The acetate becomes the preferred hydroxyl protecting group since aminolysis of triacetate **21**[11] not only converts the chloropurine to adenine but simultaneously removes all of the acetates to form 2,3-di-epi-neplanocin A (**22**),[11] mp 228-230°C, $[\alpha]_D^{20}$ +16.0 (c 0.33, H_2O).

The Pd catalyzed asymmetric desymmetrization combined with a diastereoselective epoxidation provides an enantio- and diastereoselective approach for the synthesis of diverse nucleosides. By avoiding carbohydrate precursors, facile entry to either enantiomeric series is available. Through diols **12** and **17**, many different ring substituted analogues should be accessible. Thus, these methods improve our flexibility in exploring structural variation of carbanucleosides as potential chemotherapeutic agents.

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