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SYNTHESIS OF THE CARBOCYCLIC NUCLEOSIDE (-)-NEPLANOCIN A

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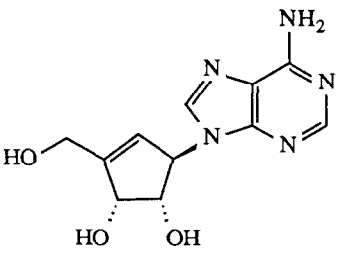
Summary: (-) - Neplanocin A has been prepared in 14 steps from cyclopentadiene (11% overall yield).

The recent attention directed at the synthesis of compounds for the treatment of viral infections has resulted in a large number of nucleoside analogues displaying antiviral activity. Neplanocin A (NPC-A) **1**, a naturally-occuring but scarce analogue of the nucleoside adenosine **2**, is a compound with significant antitumor as well as antiviral activity[1] and has high current interest as a clinical candidate.



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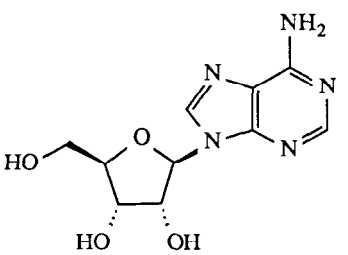

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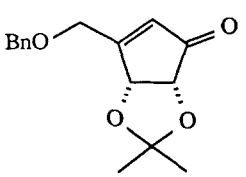
Three total syntheses of NPC-A have been reported, two of which were enantioselective.[2-4] The synthesis by Marquez and Lim was based on the preparation of the 2-cyclopenten-1-one **3** from D-(+)-ribonic acid γ-lactone.[4] The stereoselective reduction of **3** provided the allylic alcohol **4** possessing the α-configuration. This compound then allowed for the introduction of the amine functionality with the proper β-configuration **5**. This route provided for the possibility of preparing a variety of purine and pyrimidine analogues of NPC-A. It appeared to us that (+)-cyclopentenone **6** would be an attractive precursor to alcohol **4**.



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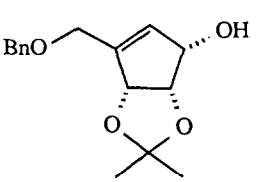

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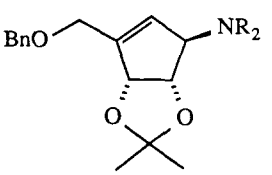

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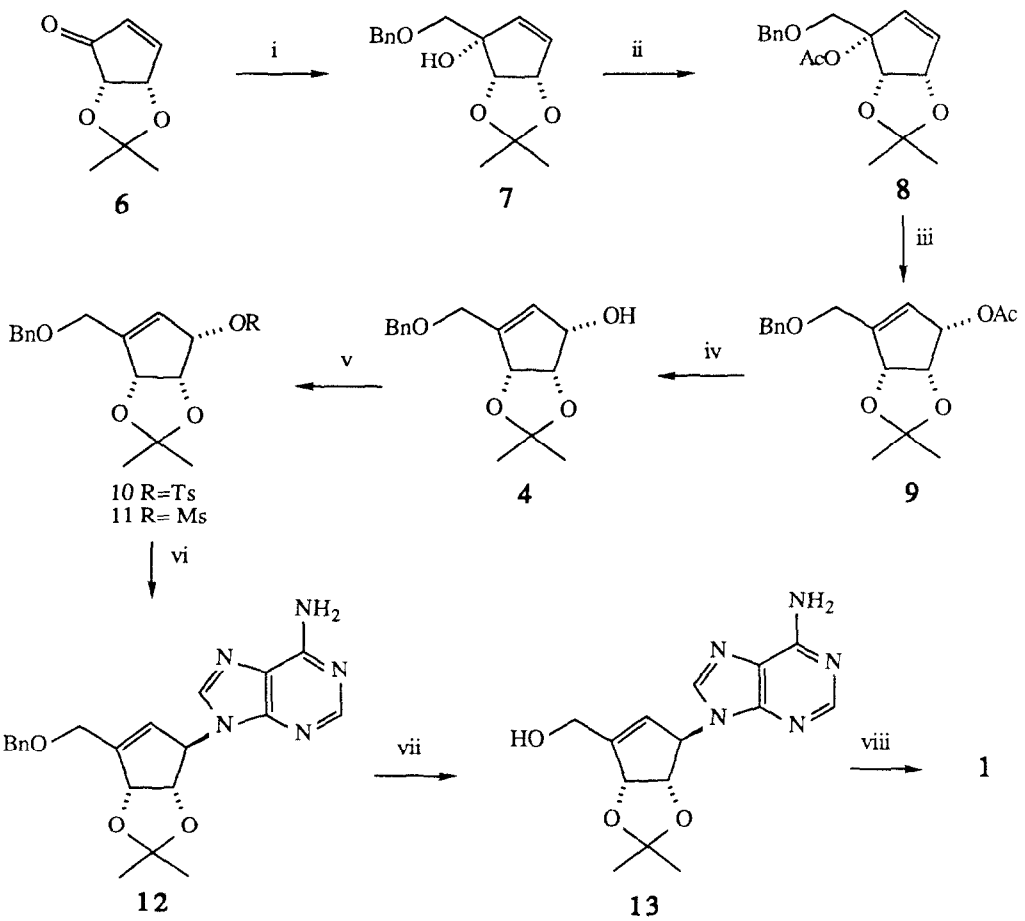
Scheme 1



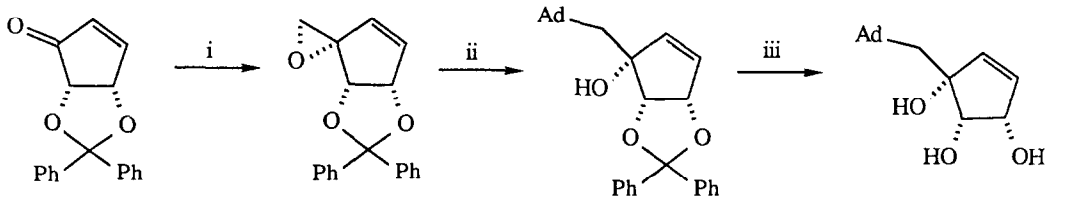
i) n-Bu_3SnCH_2OBn, n-BuLi, THF, -78°C, (86%); ii) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, R. T., (99%); iii) 3 mol % $PdCl_2(CH_3CN)_2$, 0.4 eq. benzoquinone, THF, reflux, 14h, (92%); iv) K_2CO_3, MeOH, 4h, (99%); v) MsCl, Et_3N, 0°C, 10 min., (99%); vi) 2 eq. adenine, 2 eq. K_2CO_3, 1 eq. 18-crown-6, DMF, 75°C, 18h, (46%); vii) $Pd(OH)_2$, cyclohexene, EtOH, 80°C, 6h, (92%); viii) 2N HCL / MeOH, 1/2 v/v, 18h, (95%).

(+)-Cyclopentenone **6** prepared previously in our lab in 36% yield from cyclopentadiene[5] has also recently been shown to be available from toluene in four steps.[6] With enone **6** readily available, the most direct route to ketone **3** appeared only to require introduction of the benzyloxymethyl moiety and subsequent oxidative rearrangment of the tertiary allylic alcohol.[7] Treatment of **6** with

(benzyloxymethyl)lithium, prepared from (benzyloxymethyl)tributylstannane[8], afforded the tertiary allylic alcohol **7** in 86% yield (Scheme 1). Treatment of **7** with a variety of oxidizing agents, however, did not produce ketone **3**. Alcohol **7**, however, could be acetylated to produce the allylic acetate **8** in quantitative yield. Allylic acetates are known to rearrange upon treatment with catalytic $PdCl_2(CH_3CN)_2$ in THF at room temperature[9]; acetate **8** when subjected to these conditions was recovered unchanged. Heating the reaction mixture resulted only in formation of palladium metal,[10] and recovered starting acetate. It was found, however, that addition of benzoquinone, to maintain the palladium in the oxidized state, to a reaction mixture consisting of acetate **8**, $PdCL_2(CH_3CN)_2$ (3 mol %) in THF at reflux, resulted in the formation of a 92% yield of the rearranged acetate **9**. Acetate **9** was easily separated by flash chromatograghy from the starting acetate (5%). Such rearrangments are known to occur with complete retention of optical purity.[9] Hydrolysis of the acetate yielded **4** in quantitative yield. With alcohol **4** in hand we wished to study the possibility of introducing adenine intact to the cyclopentene ring. Marquez and Lim introduced the purine ring system by displacement of the cyclopentenyl tosylate **10** with the sodium salt of 6-chloropurine (31% yield).[4b] Completion of the adenine ring was accomplished by treatment with methanolic ammonia. They reported that the mesylate **11** was very unstable under the reaction conditions and gave very low product formation. In our hands the difficulty in using the sodium salt of adenine for this displacement seemed to be a result of poor solubility of the salt in organic solvents. To overcome the solubility problem 18-crown-6 was used in conjunction with K_2CO_3. Thus, reaction of the tosylate **10** with adenine, K_2CO_3 and 18-crown-6 in DMF at 75°C led to the production of protected NPC-A **12** in 40% yield. A similar reaction could be carried out with the mesylate (which could be prepared in shorter time and higher yield than the tosylate) to give **12** in 46% yield. Debenzylation of **12** was achieved by refluxing in ethanol in the presence of $Pd(OH)_2$ and cyclohexene to give 92% yield of **13**. Removal of the isopropylidine group from **13** by stirring with 2N HCl in MeOH provided (-) - NPC-A in 95% yield: mp 220°d; $[\alpha]_D^{25}$ = -152.8°(c 0.50, H_2O) [lit[11] mp 220-222°; $[\alpha]_D^{23}$ = -157.0°(c 0.50, H_2O)]. The synthetic sample was identical with authentic neplanocin A by thin-layer chromatography, ^{13}C NMR and ^1H NMR (300 MHz). In summary, this synthesis produced (-) - NPC-A in 11% yield from cyclopentadiene (32% from cyclopentenone **6**).

In an earlier attempt to prepare NPC-A by a short, convergent route, *dl*-enone **14** was transformed to epoxide **15**. The plan to convert epoxide **15** to NPC-A and related compounds by ring opening of the vinyl epoxide in an S_N2' manner was thwarted as all nitrogen nucleophiles examined opened the epoxide in an S_N2 manner at the primary site. The preparation of a NPC-A isomer **16** is illustrated in Scheme 2.

Scheme 2



i) $(CH_3)_2S{=}CH_2$, DMSO,THF, (76%); ii) adenine,K_2CO_3, DMAC, 130°C, (80%); iii) HCL / MeOH (92%)

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References and Notes

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10) In an attempt to keep the palladium in the oxidized state while heating the reaction mixture Oehlschlager added $CuCl_2$; this resulted in the formation of many chlorinated products.[9]

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