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AN IMPROVED METHOD OF SYNTHESIS OF NEPLANOCIN AND RELATED CYCLOPENTENYL-CONTAINING NUCLEOSIDES

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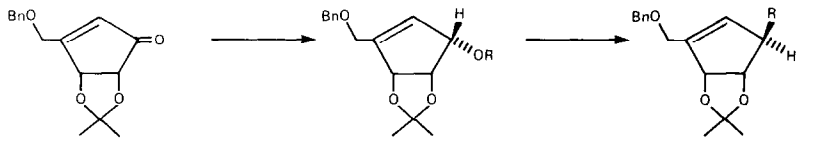
Abstract: A facile one-step condensation of the cyclopentenyl α-tosylate 2c with the alkali metal salts of 6-chloropurine and uracil, afforded the protected carbocyclic nucleosides 5a and 8, respectively, which were converted to neplanocin A (6) and cyclopentenyl uracil (9) by established methods.

In a previous communication from this Laboratory, we reported a fifteen-step total synthesis of the nucleoside antibiotic neplanocin A, starting with the readily available D(+)-ribonic acid γ-lactone.[1] An important feature of this synthesis was the stereoselective reduction of 2-cyclopentene-1-one (1)[2] to the corresponding allylic alcohol 2a possessing the α-configuration.



This compound, in turn, allowed access to the versatile 2-cyclopentenylamine 3b (with the β-configuration) after a three-step sequence which included mesylation, SN_2 displacement with sodium azide, and reduction.[1] The carbocyclic amine obtained then required four additional steps to complete the 6-aminopurine ring of neplanocin (6), and five extra steps to complete the uracil ring of the carbocyclic uridine analogue (9).[1,3] We believed that

improvements in the number of synthetic steps required, reaction versatility, and yield in securing these compounds was possible, if the mesylate 2b could be used directly with purine and pyrimidine bases as nucleophiles. This appeared possible since direct alkylation of purines and pyrimidines with alkyl halides has been well documented.[4] Such an approach also bears some similarity to the recently reported stereospecific glycosylation procedure of Robins et al., where the sodium salts of purine bases were reacted with an α-halogenosugar to give exclusively the β-anomers.[5]

Preliminary investigations utilizing the sodium salt of 6-chloropurine revealed that the mesylate 2b was very unstable under the experimental conditions and the reaction proceeded with very low product formation. Subsequently, the tosylate 2c, prepared from alcohol 2b in 82% yield (2 equiv. of TsCl and 4 equiv. of Et_3N, CH_2Cl_2, 25°C, 20 h) proved to be more useful and a 31% yield of 5a was produced after properly adjusting the reaction conditions (Table I). Despite the fact that unreacted tosylate 2c still remained in the reaction mixture, no further improvement in yield was realized by the addition of excess amounts of the sodium salt of 6-chloropurine (4). In those cases where the reaction was conducted at

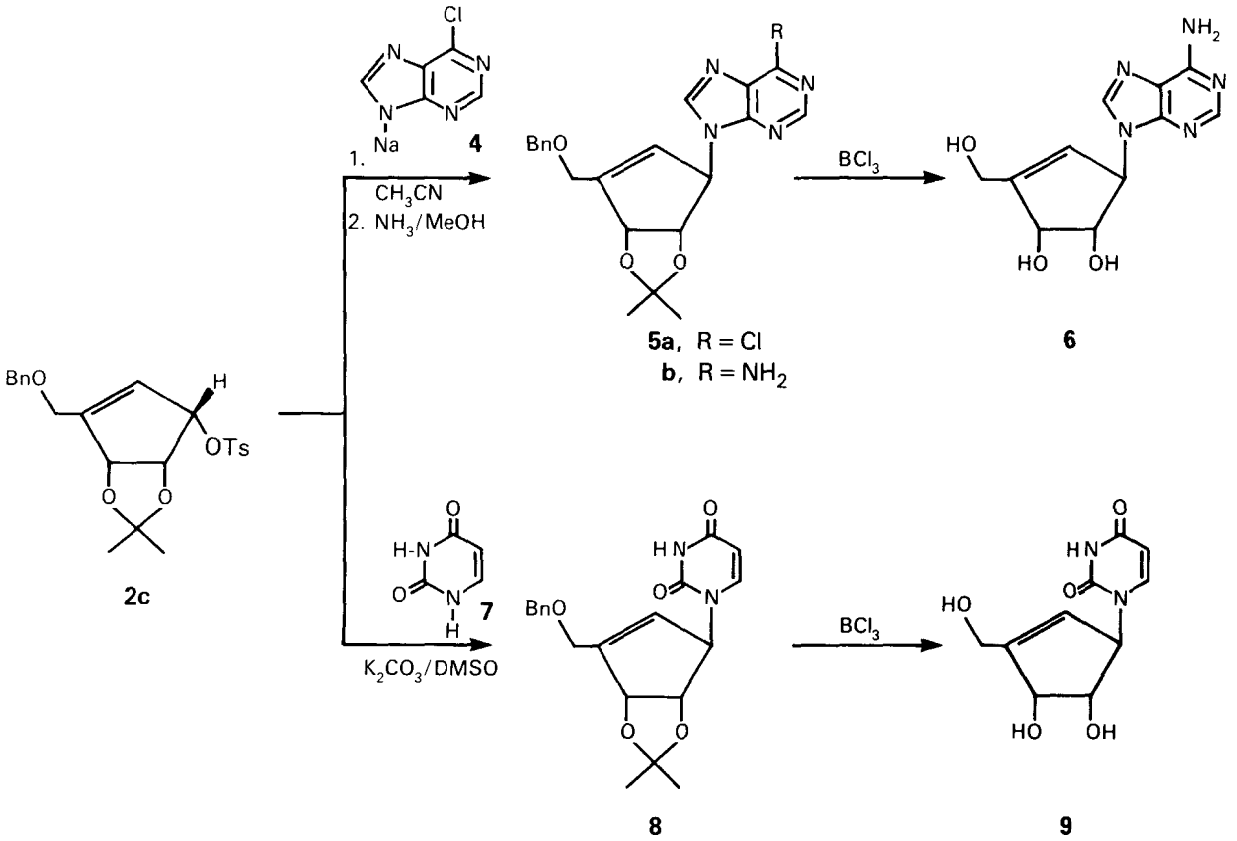
Table I. Reaction Conditions for the Synthesis of Cyclopentenyl 6-Chloropurine

Entry	4 (equiv.)	2c (equiv.)	temp (°C)	time (h)	yield (%)
1	1.25	1	50	50	24
2	3.50	1	50	42	31
3	1.50	1	90	3	22
4	3.50	1	90	3	31

50°C, isolation of the unreacted tosylate was possible by conventional silical gel chromatography, whereas under the high temperature conditions, the starting tosylate was degraded. The isolated cyclopentenyl 6-chloropurine (5a), obtained as the major isomer, was identical in all respects to the material prepared previously in five steps from the mesylate 2b.[1] Furthermore, under these conditions very little of the N-7 isomer was detected by thin layer chromatography.[6] Treatment of 5a with methanolic ammonia to afford 5b, and deprotection with BCl_3 as reported previously,[1] produced neplanocin A (6) identical to the naturally occurring antibiotic.[7]

Conversion of the alcohol 2a to neplanocin A by our previous route was carried out in 13% yield in seven steps. The present method accomplishes the same task with essentially the same yield (12%) utilizing only three steps, and with additional economy in time and reagents.

The method was also found general enough to generate other purine and pyrimidine carbocyclics.[8] For example, the previously reported cyclopentenyl uracil (8) was prepared by the direct condensation of the tosylate 2c with uracil in the presence of K_2CO_3 in DMSO (26% yield, 24 h, rt). Even though the conditions have not been optimized, the simplicity of


Cl
N
N
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N
Na
4
1.
CH3CN
2. NH3/MeOH
BnO
H
OTs
O
O
2c
R
5a, R = Cl
b, R = NH2
BCl3
NH2
HO
HO
OH
6
H-N
O
N
H
7
K2CO3/DMSO
8
9

this methodology contrasts with the laborious stepwise ring formation of former syntheses. The cyclopentenyl uracil 8 obtained by the new procedure proved identical in all respects to the material synthesized previously.[3]

In summary, this new synthetic approach greatly simplifies access to the cyclopentenyl nucleoside isosteres already reported. It also opens the possibility of generating, in an expedient manner, other members of the cyclopentenyl family of carbocyclic nucleosides, which promise to have very interesting pharmacological and potentially useful therapeutic properties.[3,9]

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