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STEREOSPECIFIC SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES FROM 2-AZABICYCLO-[2.2.1]HEPTAN-3-ONES VIA SODIUM BOROHYDRIDE MEDIATED CARBON-NITROGEN BOND CLEAVAGE[1]

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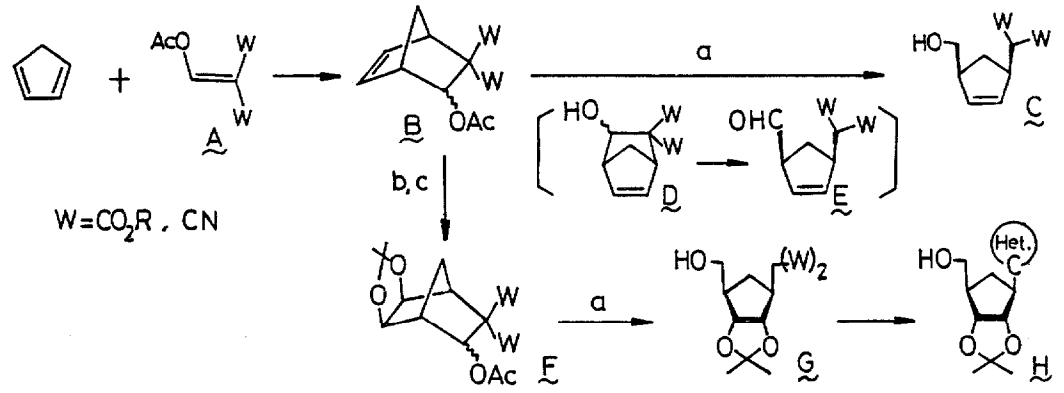
Abstract: New synthons for carbocyclic nucleosides have been synthesized from 2-azabicyclo[2.2.1]hept-5-en-3-one readily available from cyclopentadiene, through introduction of an electron-withdrawing substituent at the 2-position followed by reduction with sodium borohydride.

Previously, we have synthesized the adducts **B** by Diels-Alder reaction of 3-acetoxyacrylate **A** having an electron-withdrawing group at the 2-position with cyclopentadiene.[2] Since the carbon-carbon bond originated from the dienophiles of the bicyclic system thus formed can be cleaved stereospecifically by reductive retrograde aldol reaction [RRA reaction: (a) in Scheme I which permits sequential reactions: **B**⟶**D**⟶**E**⟶**C**], the adducts **B** serve as versatile precursors for carbocyclic C-nucleosides and their new derivatives. Thus, for example, the adducts were converted to a variety of carbocyclic C-nucleosides **H** via the more direct precursors **G** [2,3] derived from the acetonide **F** by RRA reaction.



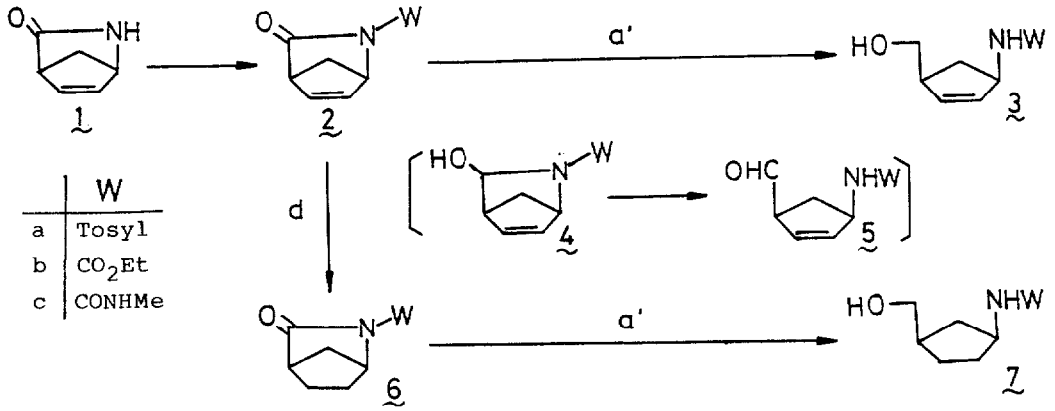
Scheme I (a) $NaBH_4$, K_2CO_3, MeOH, room temperature;
(b) OsO_4, 4-methylmorpholine N-oxide, acetone;
(c) $Me_2C(OMe)_2$, p-TsOH, acetone.

An extension of this method to the synthesis of carbocyclic nucleoside precursor (e.g. **4**) or its equivalent (e.g. **2**) would meet two problems: (1)

how one obtains these bicyclic systems (**2**, **4** etc.) and (2) how one cleaves the carbon-nitrogen bond under mild reductive conditions comparable to the aforementioned RRA reaction (a).

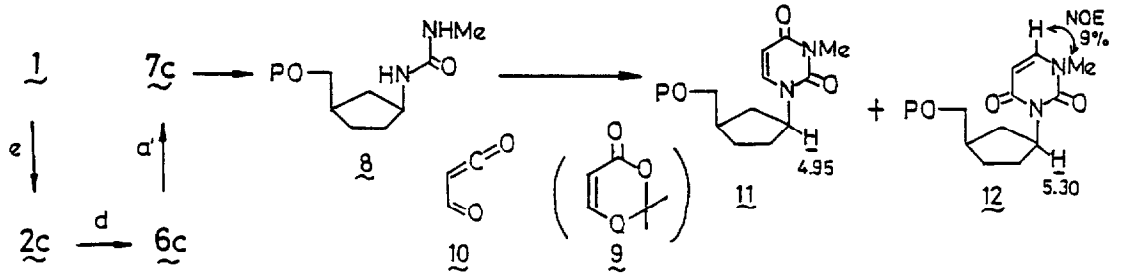
In this communication, we report a solution to these two problems and describe an efficient and stereoselective synthesis of new kinds of carbocyclic nucleoside precursors from cyclopentadiene.

Although the amide group of 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**), readily available from cyclopentadiene and tosyl cyanide[4] or chlorosulfonyl isocyanate,[5] does not suffer reduction by sodium borohydride, it has been found that the carbonyl function in these compounds having a suitable electron-withdrawing group at the 2-position (e.g. **2a** and **2b**: prepared from **1** and the corresponding chlorides in a usual manner using sodium hydride as the base) is reduced by the same reagent in methanol and the products thus formed readily afford in situ the corresponding aminoalcohols **3**. Thus, **2a**[6] (mp 110-112 °C) and its dihydro derivative **6a** (oil) afforded **3a** (mp 77-79 °C) and its dihydro derivative **7a** (oil) in nearly quantitative yields, respectively. Hence, as evident from successful conversion of **B** to a variety of carbocyclic C-nucleosides **H**,[2,3] the unsaturated lactams **2** offers unique possibilities as a starting material for the synthesis of a variety of carbocyclic nucleosides having the required cis configuration of the hydroxymethyl and amino (the latent heterocyclic functions) groups.



Scheme II (a') $NaBH_4$, MeOH, room temperature; (d) H_2, 10% Pd/C, $MeCO_2Et$.

In order to confirm this possibility, we have investigated the transformation of the bicyclic amide **1** to carbocyclic uridine derivatives. Thus, the amide **1** was treated with methyl isocyanate in the presence of sodium hydride to give the urea **2c** (mp 90-91 °C). Its dihydro derivative **6c** (oil) was treated with sodium borohydride in methanol to give **7c** (mp 90-91 °C) in almost quantitative overall yield. Silylation of the hydroxyl group of **7c** to **8** (mp 85-87 °C) followed by refluxing of the latter in benzene containing



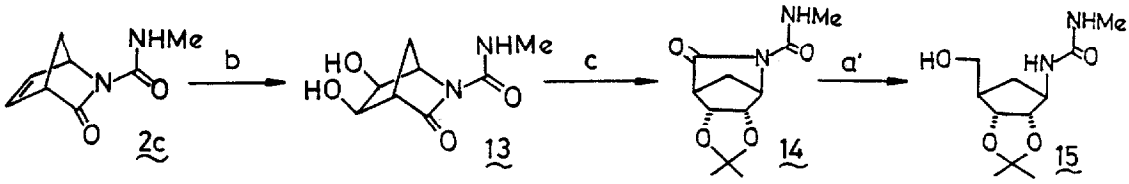
Scheme III (e) NaH, MeNCO, ether, room temperature; (f) $^{t}BuMe_2SiCl$, imidazole, DMF.

2,2-dimethyl-1,3-dioxin-4-one (**9**) resulted in the formation of a mixture of two uracils (**11** and **12**) in 67 and 17% yields, respectively.[7] The NMR spectra of both compounds fit well with the proposed structures and chemical shift of the proton at the 1'-position of the major product appears at 4.95 and at 5.30 ppm for the minor product. Since in the corresponding nucleoside series the same proton of **11**-type nucleoside appears at higher field than that of **12**-type one,[8] the above data suggest the correctness of the assigned structures. Significant NOE (9%) between methyl group and olefinic proton (C_6-H) observed only in the minor product **12** further confirmed that **11** is carbocyclic 3-methyl-2',3'-dideoxyuridine.

Since the carbonyl carbon of ketene function in **10** generated from **9** is the most reactive electrophilic center,[9] the predominant formation of **11** is explained by assuming that the less hindered amide nitrogen (CONHMe) reacts with **10** much faster than the other one (CONH-cyclopentyl).

The successful conversion of **8** to **11** demonstrates clearly that the choice of RNHCO group as the electron-withdrawing group at the 2-position of the bicyclic lactams **2** and **6**, which is the essential requisite for the reductive C-N bond fission, fits especially well to the synthesis of uridine-type nucleosides.

Finally, it seems worthy to note that another advantageous feature of **2** as the synthetic precursor of the nucleosides is that the attack of reagents to the double bond always occurs stereospecifically from the less hindered exo-face. Thus, for example, compound **2c** was treated with osmium tetraoxide



Scheme IV

and 4-methylmorpholine N-oxide in acetone to give the exo-diol **13**, selectively. The acetonide **14** (mp 111-112 °C) derived from crude **13** in a usual manner was then treated with sodium borohydride in methanol to give the desired precursor **15** (oil), quantitatively.

We are not only investigating to synthesize carbocyclic nucleosides having appropriate functionalities at 2'- and/or 3'-positions, in order to examine their biological activities, but also to determine the scope of the reductive N-C bond cleavage reaction.[10] The result of these studies will be reported in due course.

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