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Sensible Improvements Induced by Ionic Liquids in the Reaction of Modified Carbasugars with Bases for the Building of Constrained Carbanucleosides

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Abstract: Starting from racemic 4-hydroxy-4-methyl-2-cyclopentenone, a family of enantiopure carbanucleosides locked in the northern conformation has been synthesized. The use of ionic liquids was determinant in the last step resulting in a tangible increase of the yields and dramatic reduction of reaction times and volumes of organic solvents. To our knowledge, this is the first example of the use of ionic liquids in the coupling of carbasugars with heterocyclic bases.

In the search for effective, selective, and nontoxic antiviral and antitumor agents, a variety of strategies have been devised to design nucleoside analogues. The discovery that natural carbocyclic nucleosides (carbanucleosides) aristeromycin and neplanocin A showed antibiotic and antitumor activities prompted a number of chemical modifications of the naturally occurring nucleosides, especially in their carbohydrate moiety,[1] leading to synthetic carbanucleosidic derivatives endowed with important therapeutic properties.[2]

These analogues display remarkable metabolic stability since they are unaffected by phosphorylases and hydrolases that cleave the glycosidic bond of natural nucleosides. However, many carbanucleosides are less biologically active than nucleosides containing the more conventional furanose ring. The diminished bioactivity may be attributed to a different conformation adopted by the cyclopentane ring with respect to the furanose moiety. The ribose unit exists in solution as a rapid dynamic equilibrium between the northern-type (N) conformation and the southern-type (S) conformation, according to the concept of pseudorotational cycle.[3] The cyclopentane ring in carbanucleosides adopts, instead, an unusual conformation that is relatively far from typical N or S conformations.[4]

The great rigidity conferred to the sugar moiety by the presence of a cyclopropane or epoxide fused to the five-membered ring prevents the equilibrium between N and S conformations from being observed in solution.[5] Carbanucleosides based on bicyclic systems of this type, and hence locked in the N conformation, have been isolated from natural sources, as in the case of neoplanocin C, but also obtained through synthetic methods.[6] Interestingly, simplified synthetic derivatives of neplanocin C (**1**) (Figure 1) retained the biological activity of the parent natural product, suggesting that **1** can be a useful lead compound for the synthesis of bioactive conformationally constrained carbanucleosides. Moreover, the corresponding isomers blocked in the *S* conformation were far less active or devoid of activity.[7] Compounds **2** and **3** are relatively good inhibitors of Herpes simplex virus type 1 and 2, and they also show weak activity against human cytomegalovirus.[8] Taken together, these facts give strong evidence to the importance of the N conformation in the recognition process of activating enzymes.

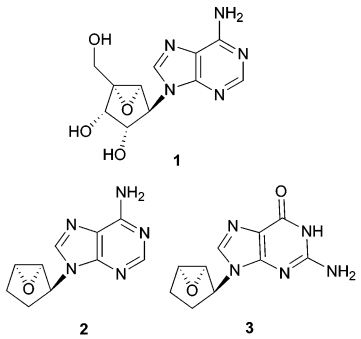

FIGURE 1. Natural (**1**) and synthetic (**2** and **3**) carbanucleosides locked in the northern conformation.

Following our interest in the synthesis of functionalized cyclopentanols,[9,10] we embarked on the synthesis of a new family of conformationally locked nucleoside analogues in view of their potential biological relevance, using as starting material the easily available 4-hydroxy-4-methyl-2-cyclopentenone, **4**.[9] The proposed strategy was to elaborate **4** toward a common intermediate suitably functionalized for the introduction of different nucleobases.

Thus, **4** was easily transformed into the epoxide **5** with H_2O_2, MeOH, and NaOH (80% yield) following a modified literature procedure.[11] The completely diastereoselective (97%) carbonyl reduction of **5** produced the epoxydiol **6**.

The relative stereochemistry of **5** and **6** was assigned by ^{1}H NMR and NOE experiments. Irradiation of the methyl protons gave NOE effects on H-3 (6.4%) in **5** and

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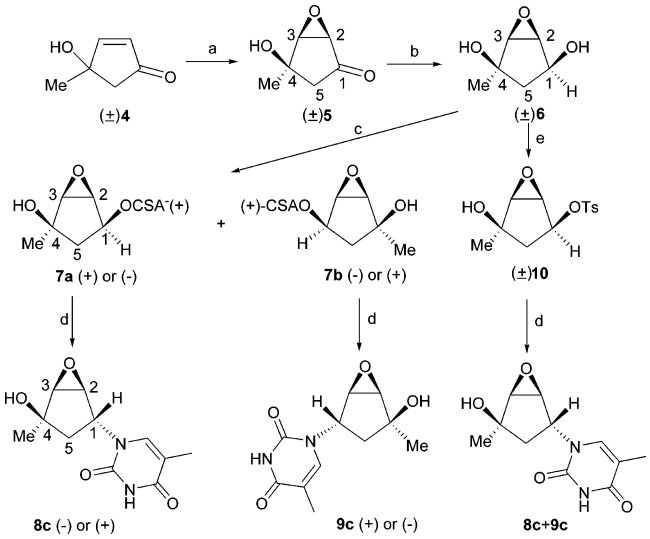
SCHEME 1[a]



[a] Key: (a) MeOH, H_2O_2 30%, NaOH 6 N (80% yield); (b) MeOH, $NaBH_4$, −10 °C (97%); (c) (+)-CSACl, Py, 13 h [(+), 35% and (−) 48%]; (d) thymine, DMF, NaH or Cs_2CO_3, 120 °C, 48 h [(+), 12% and (−), 15%; **8c** + **9c**, 17%]; (e) CH_2Cl_2, TsCl, TEA (80%).

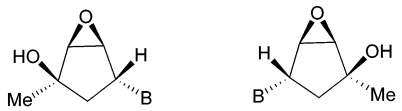
on H-1 (3.0%) and H-3 (4.2%) in **6** while on irradiation of H-1 in **6** a NOE effect was observed on H-2 (10.4%).

We envisaged that the conversion of the secondary hydroxyl group in **6** into a good leaving group (such as a sulfonate) could also be exploited for chiral resolution of this racemic mixture, thus allowing direct access to enantiopure carbanucleosides. Hence, **6** was treated with (+)-(1*S*)-10-camphorsulfonyl chloride (CSACl) to yield diastereoisomers **7a** and **7b** in 35% (+) and 48% (−) yields, respectively, after flash chromatography purification. Then treatment of **7a** (or **7b**) with the heterocyclic base in a nucleophilic substitution reaction, following one of the most used protocols for the direct attachment of the base to the sugar [12] (see Scheme 1), gave rise to **8c** (or **9c**). However, this last step, involving generation of the anion of the heterocyclic base with NaH or Cs_2CO_3 followed by its coupling with **7a** (or **7b**), went along with very poor yields in all cases (12−17%, see Table 1), spoiling the whole procedure. This poor result did not depend on the leaving group. Indeed, the tosylate derivative **10** subjected to the same reaction conditions used for **7a** (or **7b**) gave the corresponding racemic carbanucleosides (**8a** + **9a**, **8b** + **9b**, or **8c** + **9c**) in comparable yields (Table 1).

Therefore, it was evident that the nucleophilic substitution required a dramatic change in the reaction conditions. A first attempt was done running the reaction under microwave irradiation. Microwave-assisted organic reactions encompass nowadays a number of well-established procedures, and the appeal of such approach resides mainly on the microwaves' ability to increase reaction rates with consequent reduction of reaction time.[13] In our case, however, microwave irradiation was ineffective: only the reagents were recovered (Table 1).

Our attention then focused on ionic liquids, regarded in these days as very promising nonconventional reaction media.[14] Ionic liquids are attracting a rapidly growing interest that is manifested in the exponential increase

TABLE 1. Products Obtained by Reaction ofHeterocyclic Bases with 7a,b and 10



8a B=6-Cl-puryl **9a**
8b B=Adenyl **9b**
8c B=Thymyl **9c**

reagent	conditions	product	yield (%)
(±)-**10**	BH, NaH (or Cs_2CO_3), DMF, 120 °C, 48 h	**8a** + **9a**	15
		8b + **9b**	14
		8c + **9c**	17
7a	BH, NaH (or Cs_2CO_3), DMF, 120 °C, 48 h	**8a**	13
		8b	12
		8c	15
7b	BH, NaH (or Cs_2CO_3), DMF, 120 °C, 48 h	**9a**	15
		9b	17
		9c	12
7a	BH, NaH (or Cs_2CO_3), DMF, MW, 4 min, 205 °C		
7b	BH, NaH (or Cs_2CO_3), DMF, MW, 4 min, 205 °C		
7a	BH, Cs_2CO_3, [bmim][BF_4], 120 °C, 48 h		
7b	BH, Cs_2CO_3, [bmim][BF_4], 120 °C, 48 h		
7a	BH, Cs_2CO_3, [bmim][BF_4], MW, 4 min, 205 °C	**8a**	58
		8b	70
		8c	64
7b	BH, Cs_2CO_3, [bmim][BF_4], MW, 4 min, 205 °C	**9a**	64
		9b	65
		9c	60

of papers on their use.[15] Their advantages lie in their negligible vapor pressure, low environmental pollution, the ability to dissolve a wide array of substrates in small volumes and the possibility to be recycled; studies also report that, when used in place of molecular solvents, they can improve the yields and the selectivities in an array of different kinds of reactions. Concerning the present work, it should also be noted that ionic liquids are microwave active and that they have been used in nucleophilic substitutions[16] and, even though rarely, in nucleoside chemistry.[17] The ionic liquid chosen was 1-butyl-3-methyl-imidazolium tetrafluoroborate, [bmim][BF_4]. This is certainly the most used ionic liquid and was synthesized following a published procedure.[18]

However, the coupling reaction run in [bmim][BF_4] did not give the expected carbanucleosides. Once again, only the reagents were recovered from the reaction mixture (Table 1).

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Thus, we laid out a new reaction protocol based on dissolution of the heterocyclic base and Cs_2CO_3 in [bmim][BF_4] at room temperature, followed by addition of **7a** (or **7b**) dissolved in the least possible amount of DMF. Then, this homogeneous solution was subjected to microwave irradiation for 4 min at 100 W. The combination of ionic liquid and microwaves had a very strong synergic effect elevating the yields to 58−70% (5−6-fold increase with respect to conventional procedures; see Table 1). We did not find any evidence (^{1}H NMR spectra) of the occurrence of N3- (for thymine) or N7- (for purines) alkylated products (this holds true also for the corresponding conventional reaction).

The inversion of configuration at C-1 was evident in the change of coupling pattern for the H-1 signal. Indeed, H-1 appears as a broad triplet ($J_{1,5} = J_{1,5'} = 8.1$ Hz) in compounds **6** (in $CDCl_3$), **7a**,**b**, and **10** while it is a broad doublet in **8a**,**b** and **9a**,**b** and a multiplet in **8c** and **9c**. Moreover, on irradiation of H-2 or CH_3(4) protons no NOE effect was detected on proton H-1 for all nucleosides.

The absence of epimerization in the nucleophilic substitution was assessed by ^{1}H NMR spectra where only one series of signals for one diastereoisomer was always present.

The increase in the yields, however, is just one of the advantages of this protocol. Even more striking is the tangible reduction in the reaction time (from 48 h to 4 min) and solvent volume (from 15 mL to 1 mL of DMF). Nevertheless, the economic importance of ionic liquids regeneration is great; in this case, [bmim][BF_4] recycling was impossible and a chromatographic purification was needed in order to obtain pure compounds.

In conclusion, in the course of our ongoing studies on the synthesis of potentially active nucleosidic carbasugars, we have found a new convenient protocol for the direct coupling of heterocyclic bases to the five-membered ring in ionic liquid media. Our protocol improves the previously reported conventional procedures in many ways, allowing higher yields, full stereocontrol of the reaction, and reduced reaction times and volumes. Further studies are now underway in our laboratory aimed to explore the scopes and limits of the present procedure in the frame of the synthesis of biologically relevant modified nucleosides.

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Supporting Information Available: General procedures for obtaining compounds **5**, **6**, **7a**,**b**, and **10** and nucleosides **8a**−**c** and **9a**−**c**. ^{1}H NMR spectra of compounds **6**−**9**. ^{13}C NMR spectrum of compound **8b**. Selected NOE difference spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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