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Rapid Access to 2'-Branched-Carbocyclic Nucleosides and their 4'-Epimers from 2-Alkyl-Cyclopentene-1-Ones

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RAPID ACCESS TO 2'-BRANCHED-CARBOCYCLIC NUCLEOSIDES AND THEIR 4'-EPIMERS FROM 2-ALKYL-CYCLOPENTENE-1-ONES

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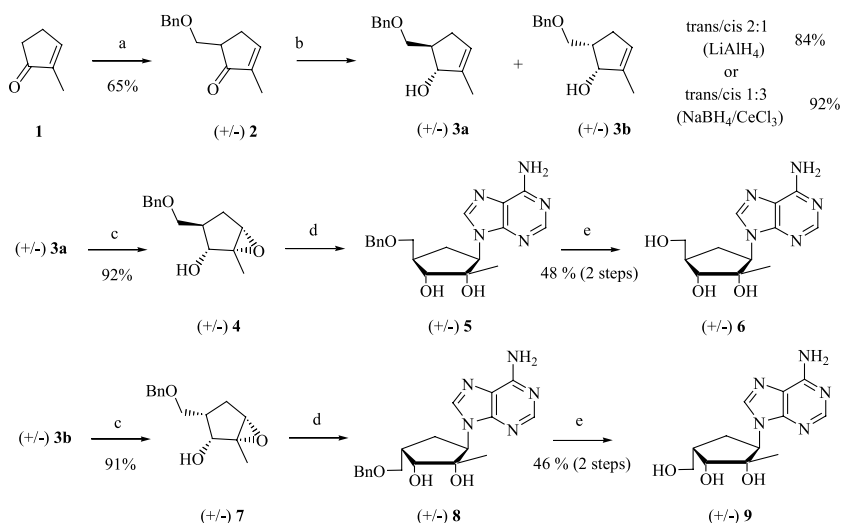
□ *2-Methyl-2-cyclopentene-1-one was used as starting material in a novel route toward 2'-branched-carbocyclic nucleosides. This methodology was efficiently adapted to the preparation of 4'-epi-carbocycles. A series of this new class of molecules was synthesized as potential antiviral compounds.*

Keywords 2'-C-Methyl Branched Nucleosides, Carbocyclic Nucleosides, Cyclopentenones

INTRODUCTION

Modified nucleosides are currently the object of a huge effort in medicinal chemistry as they remain amongst the most promising molecules for potential antiviral activity. For instance telbivudine (L-dT), the L enantiomer of natural 2'-deoxythymidine, is a powerful new drug candidate selective against hepatitis B virus.^[1,2] Furthermore, 2'-C-methyl ribonucleosides were recently shown to possess very interesting potential for hepatitis C chemotherapy.^[3,4] These observations prompted us to consider the preparation of carbocyclic analogs of 2'-C-branched ribonucleosides. In general, carbocycles show increased stability in vivo when compared to nucleosides,^[5,6] coupled with biological activity in some examples

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SCHEME 1 Reagents: (a) Lithium diisopropylamide (LDA), benzylbromomethyl ether, THF, -78 to -50°C ; (b) LiAlH₄, ether, -78 to -60°C or CeCl₃·7 H₂O, NaBH₄, MeOH, 0°C ; (c) 3-chloroperoxybenzoic acid (*m*-CPBA), methylene chloride, 0°C ; (d) NaH, adenine, DMF, 100°C ; (e) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.

(*e.g.*, carbovir).^[7] Since 2'-branched carbocycles* had not been reported when this work was initiated, a need for the design of a new synthetic route giving rapid access to this class of molecules became obvious.

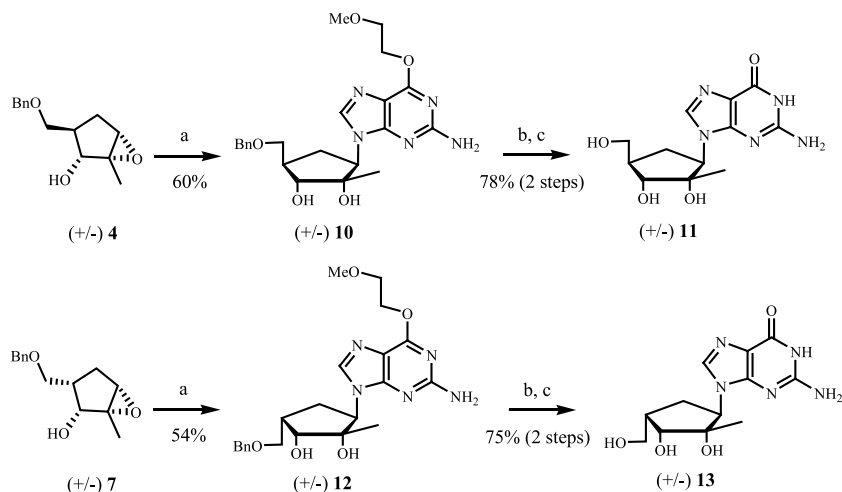
In this article, we wish to present the shortest synthesis of racemic carbocyclic nucleosides reported to date using 2-alkyl-cyclopentenones as versatile starting materials.

CHEMISTRY

Since both enantiomers of 2'-methyl-branched nucleosides were our initial targets, the choice of the starting material was oriented toward achiral 5-membered-rings already bearing a methyl group. The commercially available 2-methyl-2-cyclopenten-1-one **1** possesses the desired features and was our preferred starting material.

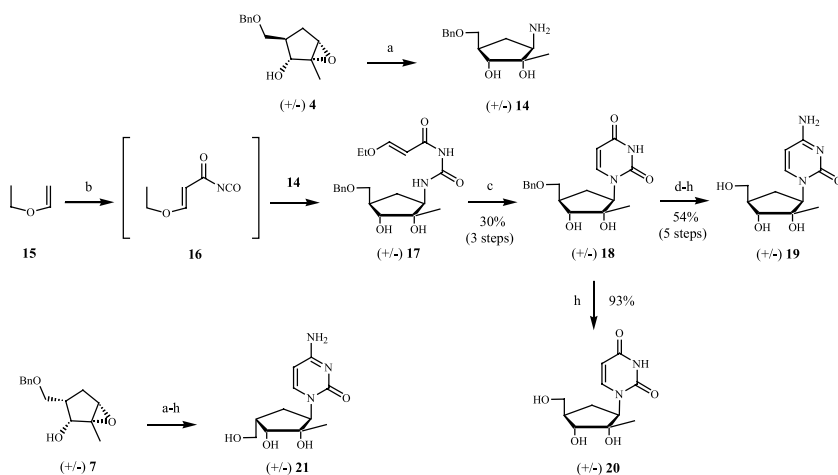
As they are prone to self-condensation, cyclopentenones are reported as challenging substrates for α -alkylation reactions.^[8,9] Indeed, we encountered some difficulties in introduction of a hydroxymethyl group on the ketone **1**. For instance, an attempt with gaseous formaldehyde following the procedure of Jernow et al.^[10] gave disappointing results, but, fortunately, **1** could be cleanly alkylated in acceptable yield using freshly prepared benzylbromomethyl ether^[11] (Scheme 1). Ketone **2** was reduced with LiAlH₄ to get an easily separable 2:1 mixture of diols

*In this poster, numbers are given by analogy with the parent ribonucleosides.



SCHEME 2 Reagents: (a) NaH, 2-amino-6-(methoxyethoxy)-purine, DMF, 120°C; (b) 3N HCl, dioxane, 80°C; (c) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.

3a and **3b** favoring the *trans* isomer. The ratio of diols could be dramatically modified by a simple change of the reducing agent, NaBH₄ in presence of CeCl₃ giving **3b** as the major product in a 3:1 ratio. Both **3a** and **3b** were epoxidized to get **4** and **7**, which were submitted to the same chemistry: the epoxides were opened with the sodium salt of adenine, and the carbocycles **5** and **8** were then deprotected to obtain 2'-methyl-aristeromycin **6** and its 4'-epimer **9** in 5 steps.



SCHEME 3 Reagents: (a) NH₃, MeOH, 130°C; (b) *N*-(chlorocarbonyl)-isocyanate, THF, 0°C; then Et₃N, 0°C; then **14**, -40°C; (c) 1N H₂SO₄, dioxane, 100°C; (d) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (e) trifluoroacetic anhydride, *N*-methylpyrrolidine; then *p*-nitrophenol, MeCN, 0°C; (f) NH₃, MeOH, 60°C; (g) trifluoroacetic acid 90%, 0°C; (h) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.

In a similar fashion, guanosine analogues **11** and **13** were prepared from **4** and **7** respectively using protected guanine.^[12] We then focused our attention on pyrimidine nucleosides. Even though uracil salts were shown to react slowly with epoxides^[13] we found it more advantageous to build the pyrimidine ring starting from the amine **14**. Epoxide **4** was opened with ammonia with perfect regio- and stereoselective control. Resulting cyclopentylamine **14** was used without purification in a uracil ring-construction process adapted from previously described procedures,^[14,15] isocyanate **16** being condensed in situ with **14**. Compound **17** was then cyclized under acidic conditions to afford carbocycle **18**. The latter was used for the preparation of both cytidine and uridine derivatives **19** and **20**. Compound **19** was synthesized by adaptation of the method of Miah et al.^[16] Again, it was possible to use epoxide **7** in the same route to get the 4'-epimers of **19** and **20** (Schemes 2 and 3).

CONCLUSION

A new synthetic method for the preparation of carbocyclic nucleosides has been developed from 2-alkyl-cyclopentenones, giving a rapid access to racemic 2'-branched carbocycles. The versatility of this method allows the preparation of seldom reported 4'-epi-carbocyclic nucleosides.^[17] This method is adaptable to the synthesis of a large number of potential antiviral targets through the key intermediates **4** and **7**. Furthermore, introduction of various 2'-branching-groups can be achieved by using the appropriate ketone as a starting material.

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