



## An Expeditious Route to Carbocyclic Nucleosides: (-)-Aristeromycin and (-)-Carbodine

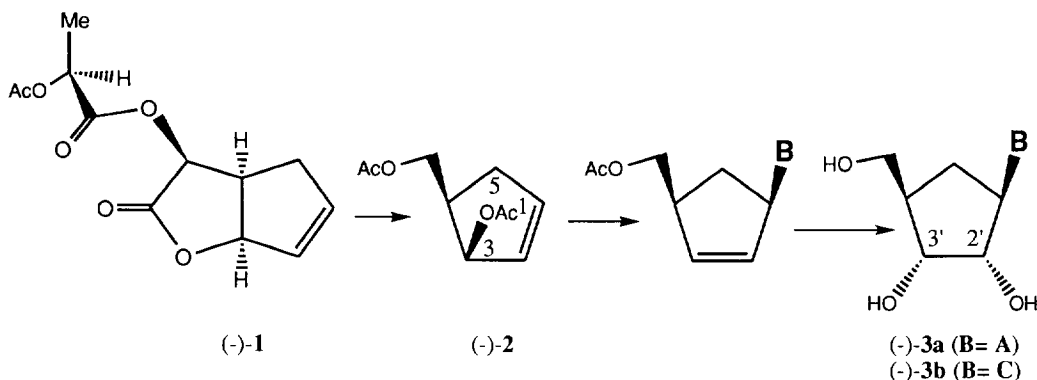
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**Abstract:** The readily available bicyclic lactone (-)-**1** was transformed into diacetate (-)-**2** which served in an expeditious route to (-)-aristeromycin (**3a**) and (-)-carbodine (**3b**) in acceptable yields. © 1997, Elsevier Science Ltd. All rights reserved.

The development of asymmetric synthetic routes to carbocyclic nucleosides is attracting considerable attention.<sup>1</sup> This is due to the fact that these compounds, which are close structural analogues of natural nucleosides, are endowed with potent biological activities.<sup>2</sup> Thus, (-)-aristeromycin (**3a**), a secondary metabolite of *Streptomyces citricolor*, which is the carbocyclic analogue of adenosine<sup>3</sup>, manifests cytostatic and antiviral properties. It is also well recognized as an inhibitor of *S*-adenosylhomocysteine hydrolase.<sup>4</sup>

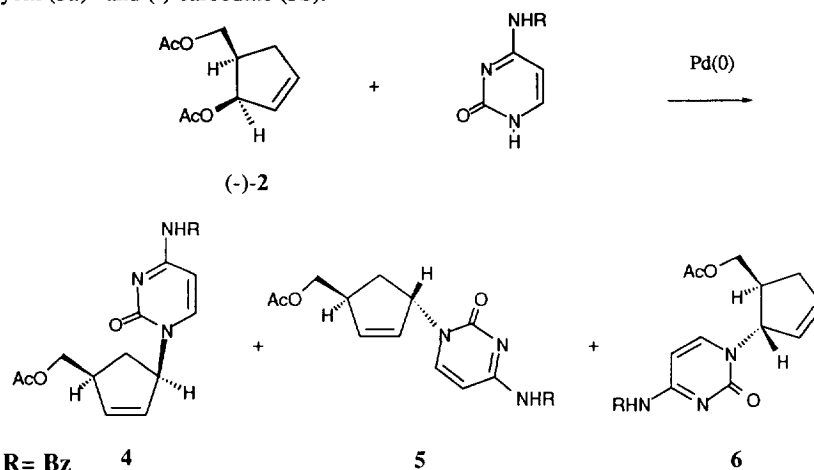


Presently, another important area in which carbocyclic nucleosides should have promise, is as building blocks for antisense oligonucleotides.<sup>5</sup> Indeed, it is a reasonable expectation that DNA and/or RNA sequences containing this type of residue should exhibit an increased resistance to nucleases. Unfortunately in this series, only the naturally occurring (-)-aristeromycin (**3a**) is commercially available at relatively considerable cost. Accordingly, chemical synthesis is the only means to obtain these ribonucleoside analogues in useful amounts. A survey of the methods which have been proposed in the literature indicated that most strategies involved the lengthy elaboration of a suitably functionalized cyclopentane unit to permit, in the ultimate stages, the introduction of a pyrimidine or a purine base.<sup>1</sup> It seemed to us that the proposed methods were of no avail to obtain in a

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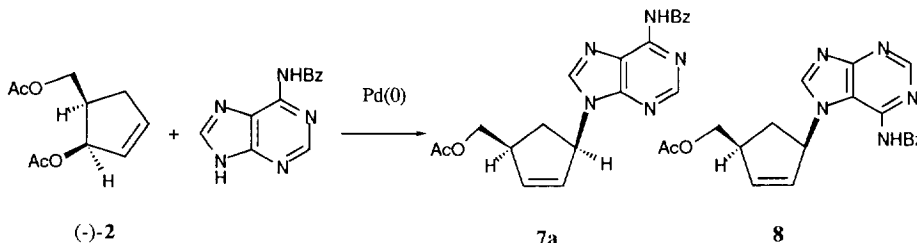
reasonable period of time the desired carbocyclic nucleosides which had to be further elaborated to their corresponding phosphoramidites in view of standard oligonucleotide synthesis.<sup>6</sup>

Recently, in this laboratory, we have devised an easy access to lactone (-)-**1** (30 g scale).<sup>7</sup> Herein we have accomplished uneventfully the conversion of lactone (-)-**1** to diacetate (-)-**2** (in moderate overall yield) by application of standard reactions.<sup>8</sup> Accordingly, this readily prepared derivative was finally used as a new key synthon in a straightforward synthetic scheme to yield carbocyclic nucleosides as illustrated by the preparation of (-)-aristeromycin (**3a**)<sup>3</sup> and (-)-carbodine (**3b**).<sup>11</sup>



Scheme 1

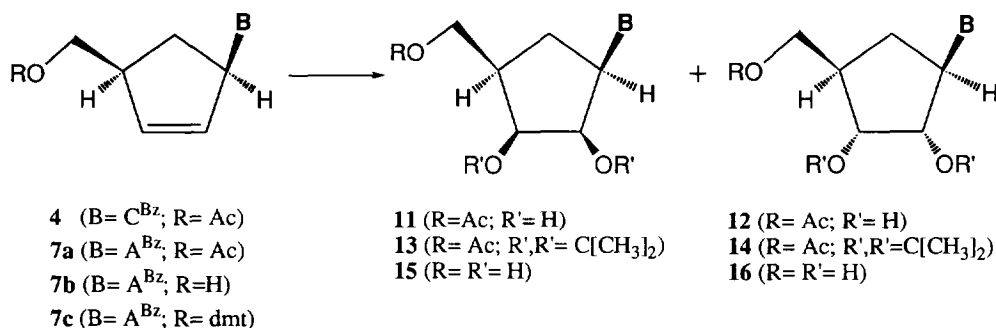
The next important stage in the proposed synthetic scheme was the introduction of the nucleobase (pyrimidine, purine) by application of a Pd(0) mediated reaction, as pioneered by Trost.<sup>12</sup> Such a well studied reaction is reputed for its high stereospecificity.<sup>13</sup> However in our hands, treatment of diacetate **2** with the lithium salt of *N*<sup>4</sup>-benzoylcytosine<sup>14</sup> in the presence of tetrakis(triphenylphosphine)palladium (0) in DMF at 55°C gave three compounds which were assigned structures **4**, **5** and **6**, in agreement with their analytical and spectral data (Scheme 1). The desired compound **4** was obtained as the major reaction product in 48% yield, together with minor amounts of **5** and **6** which were isolated in 10 and 7% yields, respectively. The 2D NOE spectrum of **4** showed a significant interaction between H-1' and H-4'. Similarly in the case of **5**, interactions were noticed between H-3' and H-5' and between H-4' and H-6 in support of the proposed structure. Finally, structure **6** was established on the basis of NOESY interactions, namely between the protons of the cytosine moiety and H-3', H-4' and H-6'α. Confirmation of the structural assignment for compound **4** was ascertained after its transformation into the protected carbodine derivative **14** (R = C<sup>Bz</sup>) (see below).



Scheme 2

By using the cesium salt of *N*<sup>4</sup>-benzoylcytosine, in the palladium triggered reaction, we were pleased to observe that the yield of **4** could be greatly improved (85%). When the same reaction conditions were applied in the case of *N*<sup>6</sup>-benzoyladenine, derivative **7a** was obtained in 43% yield, together with another minor compound which was assigned structures **8** (13%) (Scheme 2). These structures **7a** and **8** could be confidently proposed on the basis of spectral and analytical data.<sup>15</sup> In particular, as in the case of **4**, the  $\beta$ -orientation of the adenine unit of **7a** was established by NOE correlations showing an interaction between H-1' and H-4'. Definitive structural assignment for compound **7a** was fully ascertained after its transformation into (-)-aristeromycin (**3a**).

The introduction of the two hydroxyl groups on the cyclopentene system was accomplished by subjecting derivatives **4** and **7a** to the osmium tetroxide/ trimethylamine *N*-oxide reagent (Scheme 3). In agreement with other examples in the literature<sup>9</sup> for related compounds, and in contrast with our own observations in the nor-aristeromycin series<sup>16</sup>, this step proved to be poorly stereoselective. In both cases the outcome of this reaction was disappointing, leading to a roughly 1/1 mixture of stereoisomers **11** and **12** ( $B = C^{Bz}$  or  $A^{Bz}$ ) (overall yield 70-77%). In the case of the adenine derivative we tried, unsuccessfully, to improve this ratio, in favour of the  $\alpha$ -oriented dihydroxylation product, by using **7b** (obtained by *O*-deacetylation of **7a** using NaOH in THF/H<sub>2</sub>O) or **7c** having a bulky dimethoxytrityl (dmt) protecting group at the hydroxymethyl position.<sup>17</sup>



**Scheme 3**

Finally, we were pleased to succeed in the separation of the two diols in both series by simple silica gel column chromatography.<sup>18</sup> In the case of derivatives **11** and **12** ( $B = C^{Bz}$ ), each compound was transformed into its 2',3'-*O*-isopropylidene derivative **13** and **14** ( $B = C^{Bz}$ ), respectively (2,2-dimethoxypropane, acetone, TsOH). A complete 2D NMR study (COSY, NOESY) allowed an unambiguous determination of their respective stereochemistry. On the other hand, the adenine derivatives **15** and **16** ( $B = A^{Bz}$ ), obtained after dihydroxylation of **7b**, were separately *N*-debenzoylated after being treated with ammonia. The resulting carbocyclic nucleosides were compared with an authentic sample of (-)-aristeromycin under HPLC conditions. This analytical experiment showed the nucleoside analogue derived from **16** ( $B = A^{Bz}$ ) to be identical with (-)-aristeromycin **3a** allowing the determination of the stereochemistry of each diol as proposed in scheme 3. Similarly, ammonia deprotection of **12** ( $B = C^{Bz}$ ) led to (-)-carbodine.

In conclusion, we have developed a remarkably simple preparative procedure for carbocyclic nucleosides starting from the readily obtained lactone (-)-**1**. In continuation of this work, efforts will be directed at illustrating its versatility to obtain a large variety of such compounds. Moreover, in the oligoribonucleotide series, the nucleoside analogues synthesized here, have been introduced in RNA sequences corresponding to an hammerhead ribozyme domain. The catalytic activity together with the increased nuclease resistance of this system has just been reported.<sup>19</sup>

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- 8)  $\text{LiAlH}_4$ , THF;  $\text{NaIO}_4$  then  $\text{NaBH}_4$ ,  $\text{MeOH}/\text{H}_2\text{O}$ ;  $\text{Ac}_2\text{O}$ , DMAP, pyridine (30%, 4 steps). (-)-2:  $[\alpha]_D^{25}$  -143° (c 1.3 in  $\text{CHCl}_3$ ).  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.10 (m, 1H, H-1); 5.85 (m, 1H, H-2); 5.74 (m, 1H, H-3); 4.16 (m, 2H, CH<sub>2</sub>); 2.70 (m, 1H, H-4); 2.46 (m, 2H, H-5); 2.00 (s, 6H, Me).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 170.7; 169.5; 136.7 (C-1); 129.5 (C-2); 78.1 (C-3); 63.4 (CH<sub>2</sub>); 39.6 (C-4); 34.6 (C-5); 21.0; 20.8. (+/-)-2 (no spectral data) has already been obtained as a constituent of a mixture of acetates resulting from the acetylation of the product of the reaction between cyclopentadiene and paraformaldehyde.<sup>9a, 10a</sup> An efficient method for the preparation of the racemic allylic regioisomer of **2** has been reported.<sup>10b</sup>
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