

# Synthesis of D- and L-Carbocyclic Nucleosides via Rhodium-Catalyzed Asymmetric Hydroacylation as the Key Step

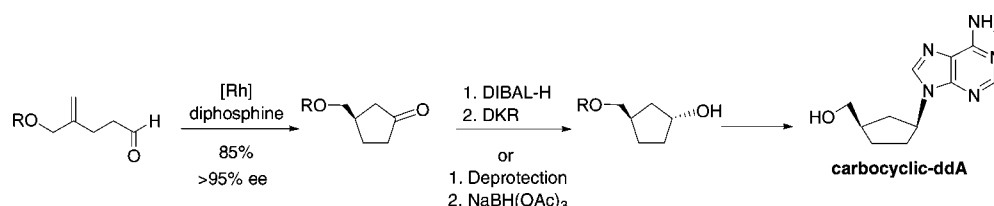
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## ABSTRACT



D- and L-carbocyclic nucleosides were obtained by a new procedure involving an enantioselective rhodium/duphos-catalyzed hydroacylation reaction as the key step. The 3-hydroxymethyl-cyclopentanol intermediate was obtained by stereoselective reduction of ketone and by dynamic kinetic resolution (DKR).

Carbocyclic nucleosides are structural analogues of natural and synthetic nucleosides, where the endocyclic oxygen atom is replaced by a methylene group. These analogues which lack the labile glycosidic bond are stable to cleavage by phosphorylases and hydrolases. Relevant members of this family of compounds are the naturally occurring carbocyclic nucleosides aristeromycin<sup>1</sup> and neplanocine A<sup>2</sup> (Figure 1) that exhibit powerful antitumor and antiviral activities.

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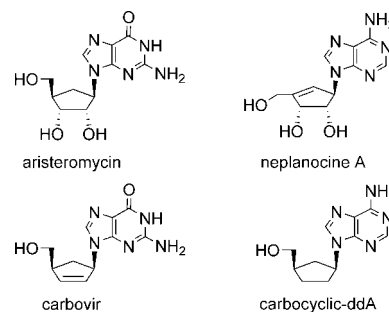
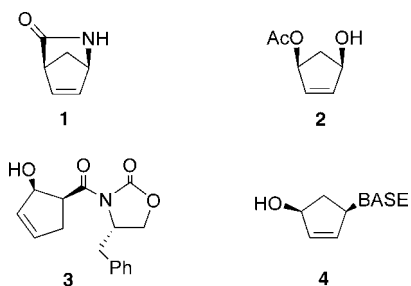


Figure 1. Relevant carbocyclic nucleosides.

Carbovir and carbocyclic-ddA are synthetic derivatives that showed high activity against HIV and hepatitis B virus, respectively.<sup>3</sup>

Carbocyclic nucleosides have been prepared starting from the chiral pool and by using asymmetric synthesis procedures.<sup>4</sup> Relevant examples of this last approach are the

synthesis of carbocyclic nucleosides precursors **1**<sup>5</sup> and **2**<sup>6</sup> which were obtained enantiomerically pure by enzymatic kinetic resolution, compound **3**<sup>7</sup> that was prepared by asymmetric aldol condensation followed by ring-closing metathesis, and compound **4**<sup>8</sup> prepared by palladium-catalyzed asymmetric allylic substitution from the cyclopentadiene monoepoxide (Figure 2). Carbocyclic-ddA has been

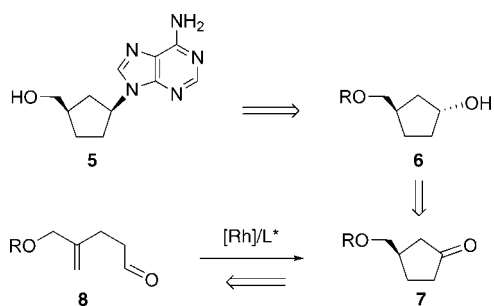


**Figure 2.** Carbocyclic intermediates in the synthesis of carbocyclic nucleosides.

prepared from D-ribose<sup>3a</sup> and from **1**.<sup>9</sup> In both cases, long reaction sequences are required for synthesizing the carbocycle or for introducing the purinic base. Herein, we report a short and efficient approach to L- and D-carbocyclic-ddA (**5**) that avoids those synthetic problems, via the use of an enantioselective hydroacylation reaction.

Intramolecular hydroacylation is a rhodium-catalyzed process that yields cyclopentanones from  $\gamma,\delta$ -pentenals.<sup>10</sup> This reaction has been scarcely used in organic and asymmetric synthesis.<sup>11</sup> Scheme 1 shows the retrosynthesis of **5**.

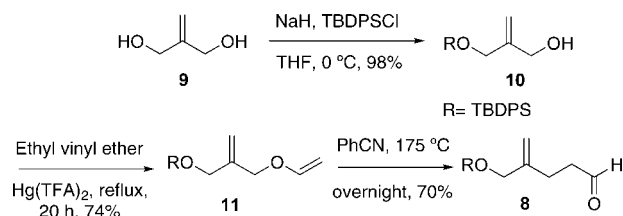
**Scheme 1.** Retrosynthesis of Carbocyclic-ddA (**5**)



We have considered that cyclopentanol **6**, a precursor of **5**, can be obtained from ketone **7** by a stereoselective reduction or by a nonstereoselective reduction followed by dynamic kinetic resolution (DKR). The key cyclopentanone **7** would be obtained by an enantioselective hydroacylation reaction from pentalenal **8**.

Thus, the required pentalenal **8** was prepared from diol **9** by selectively protecting one of the hydroxyl groups by reaction with NaH and TBDPSCI affording the alcohol **10**

**Scheme 2.** Synthesis of Intermediate **8**



in 98% yield<sup>12</sup> (Scheme 2). Compound **10** was then reacted with ethyl vinyl ether using Hg(TFA)<sub>2</sub> as catalyst<sup>13</sup> affording **11**, which was then heated in benzonitrile to give the pentalenal **8** in 70% yield through a [3 + 3] sigmatropic rearrangement.

The intramolecular hydroacylation of **8** was initially explored using Wilkinson's catalyst affording the expected cyclopentanone **7** in modest yield (entry 1, Table 1). The

**Table 1.** Intramolecular Hydroacylation of **8**<sup>a</sup>

entry	[Rh] (%)	mol % [Rh]	yield	ee % (config) <sup>d</sup>
1 <sup>b</sup>	RhCl(PPh <sub>3</sub> ) <sub>3</sub>	5	42%	--
2	[Rh(NBD)dpppe]BF <sub>4</sub>	5	--	--
3 <sup>c</sup>	[Rh(NBD)dppe]BF <sub>4</sub>	10	70%	--
4 <sup>c</sup>	[Rh(NBD)DPPF]BF <sub>4</sub>	30	--	--
5	[Rh(NBD)(R,R)-Me-Duphos]	5	85%	>95 (R) <sup>e</sup>
6	[Rh(NBD)(S,S)-Me-Duphos]	5	85%	>95 (S) <sup>e,f</sup>

<sup>a</sup> Acetone was used as the solvent at reflux, and the reaction was completed in 12 h. <sup>b</sup> CH<sub>2</sub>Cl<sub>2</sub> was used as a solvent. <sup>c</sup> The reaction was completed in 5 h. <sup>d</sup> ee determined by <sup>13</sup>C NMR. <sup>e</sup> The enantiomer was not observed. <sup>f</sup> *ent-7* was obtained.

use of a cationic catalyst bearing dppe as ligand gave no conversion at low catalyst loading even at high temperature (entry 2). Increasing the catalyst concentration to 10 mol % at room temperature did not afford the expected cyclopentanone either. When the reaction was performed at 65 °C, the cyclopentanone **7** was obtained in 70% yield (entry 3).

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The cationic Rh/DPPF<sup>14</sup> system was also tested, but the expected cyclopentanone was not obtained (entry 4). Since the highest activity was achieved with dppe as ligand, which forms a five-membered ring upon coordination at the metal, the reaction was next carried out using (*R,R*)-Me-Duphos.<sup>15</sup> Satisfactorily, the intramolecular hydroacylation using (*R,R*)-Me-Duphos, 5 mol % of catalyst, in acetone at reflux afforded cyclopentanone **7** in good yield and excellent enantioselectivity (entry 5). When (*S,S*)-Me-Duphos was employed, the reaction proceeded yielding the opposite enantiomer *ent*-**7** (entry 6). In both cases, the yield and the enantioselectivity were identical, and the results were reproducible.

At this point, the stereoselective reduction of **7** was essential to obtain the nucleoside **5** with the appropriate configuration. Initially, the reduction of the cyclopentanones **7** and *ent*-**7** was carried out with DIBAL-H in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C affording the epimeric mixture of cyclopentanol **6a** (*trans*) and **12** (*cis*), and *ent*-**6a** (*trans*) and *ent*-**12** (*cis*), respectively, in quantitative yield but low stereoselectivity (*cis/trans* = 2:1). We therefore considered two methodologies to obtain the alcohol derivative with the required configuration: (a) a dynamic kinetic resolution (DKR) of the diastereomeric mixture of alcohols<sup>16,17</sup> and (b) a directed reduction of the cyclopentanone using sodium triacetoxyborohydride.

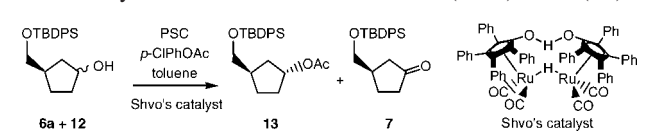
Initially, we optimized the conditions for the kinetic resolution process. *Candida antarctica* (Novozyme 435, N-435) and *Pseudomonas cepacia* (PSC) lipases were screened with different acyl donors. The best conditions found were employing PSC and *p*-chlorophenyl acetate<sup>18</sup> in toluene at 70 °C which provided high conversions and diastereoselectivities (dE = 100).

On the basis of our preliminary KR results, the KR of cyclopentanol **6a** + **12** was carried out in the presence of the Shvo's catalyst<sup>20</sup> to perform a DKR process. The results are summarized in Table 2. The first run was performed using **6a** + **12**, enzyme PSC, Shvo's catalysts, and *p*-ClPhOAc, but no acetylated product was obtained (entry 1). However, large amounts of the corresponding ketone **7** formed during the hydrogen transfer process were observed (entry 1). Hence, two hydrogen sources were tested to direct the reaction equilibrium back toward cyclopentanol **6a** + **12**. The addition of 0.015 mmol of 2,4-dimethyl-3-pentanol improved the reaction providing a 23% conversion of the acetylated product.

After 48 h, 77% of the reagents were converted into products, and the diastereomeric ratio was dE = 11 (entry 2); however, the ketone concentration was still high (54%).

To improve these results, H<sub>2</sub> gas (1 bar) was added. H<sub>2</sub> effectively inhibited ketone formation, and **13** was obtained

**Table 2.** Dynamic Kinetic Resolution of **6a** (*trans*) + **12** (*cis*)<sup>a</sup>

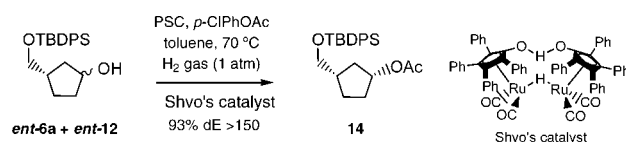


entry	time (h)	convn (%) <sup>b</sup>	<b>7</b> (%) <sup>b</sup>	<b>13</b> (%) <sup>b</sup>	<b>13</b> de (%) <sup>b,c</sup>	dE <sup>d</sup>
1 <sup>e</sup>	24	51	51	--	--	--
2 <sup>f</sup>	48	77	54	23	80	11
3 <sup>g</sup>	48	53	25	28	>95 <sup>i</sup>	>50
4 <sup>g</sup>	72	73	11	62	>95 <sup>i</sup>	>50
5 <sup>g,h</sup>	72	93	--	93	>95 <sup>i</sup>	>150

<sup>a</sup> Reactions were performed on a 0.03 mmol scale with 15 mg of enzyme, 0.09 mmol of *p*-ClPhOAc, and 4 mol % of [Ru] in 0.5 mL of toluene at 70 °C. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Diastereomeric excess. <sup>d</sup> Diastereomeric ratio. <sup>e</sup> 1.5 mg of enzyme was added. <sup>f</sup> 0.015 mmol of 2,4-dimethyl-3-pentanol was added. <sup>g</sup> H<sub>2</sub> gas (1 atm) was used. <sup>h</sup> 6 mol % of Ru was added. <sup>i</sup> The other diastereomer was not observed.

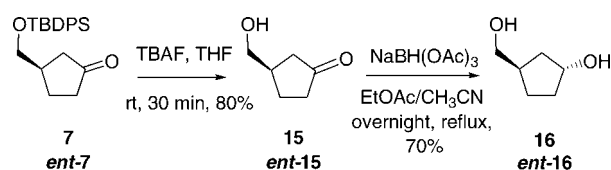
with excellent diastereoselectivities (>99%, entries 4 and 5). However, after 48 h, 25% of ketone **7** was still detected (entry 3), and after 72 h, the ketone concentration was only reduced to 11% (entry 4). To quench ketone formation, the catalyst loading was increased to 6 mol %. Under these conditions, the analysis of the reaction residue revealed the absence of ketone, and the obtained conversion rate and diastereomeric ratio were excellent (dE >150, entry 5). Similar results were obtained starting from *ent*-**6a**, but in this case the major isomer was acylated affording compound **14** (Scheme 3). These results are in agreement with Kaulauskas' rule.<sup>17</sup>

**Scheme 3.** Dynamic Kinetic Resolution of *ent*-**6a** + *ent*-**12**



The second approach involved the reduction of aldehydes and ketones using NaBH(OAc)<sub>3</sub>.<sup>21,22</sup> For this purpose, the *tert*-butyldiphenylsilyl group in **7** was deprotected by adding 1.5 equiv of TBAF in THF to afford **15** in 80% yield (Scheme 4). Compound **15** was diastereoselectively reduced using this reagent in different solvents such

**Scheme 4.** Diastereoselective Synthesis of **16**



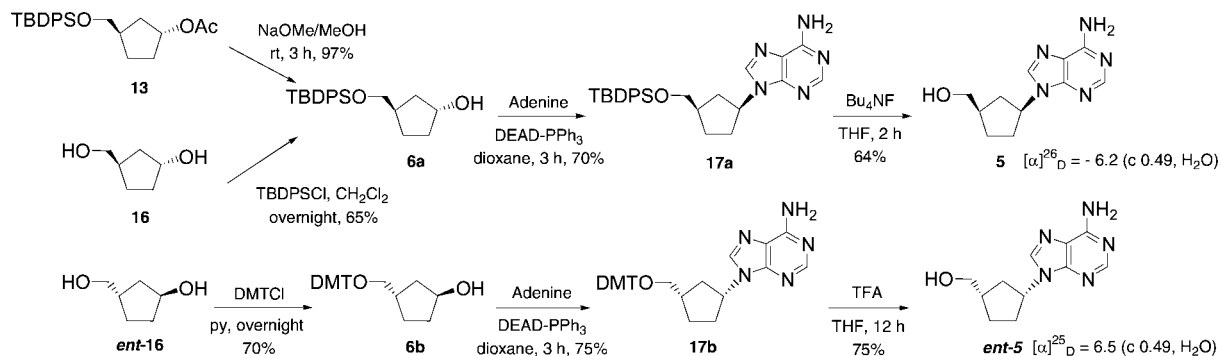
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**Scheme 5.** Synthesis of D- and L-Carbocyclic-ddA **5** and *ent*-**5** from **13** and Alcohols **16** and *ent*-**16**



as acetonitrile,<sup>23,19</sup> acetic acid,<sup>21b,22,24</sup> and ethyl acetate.<sup>21a,25</sup> The best results, however, were obtained when a mixture of ethyl acetate/acetonitrile 1:1 was used. In this case, compound **16** was obtained in 70% yield as the only diastereomer. Following a similar procedure, *ent*-**16** was obtained from *ent*-**7**.

Subsequently, **16** was reacted with TBDPSCI in CH<sub>2</sub>Cl<sub>2</sub> using Et<sub>3</sub>N and DMAP affording **6a**, in 65% yield. **6a** was also obtained in quantitative yield by hydrolysis of **13**. Additionally, the reaction of **6a** with adenine under Mitsunobu conditions furnished **17a** in good yields (70%, Scheme 5), and the further treatment with TBAF afforded the deprotected carbocyclic nucleoside **5**.

Since the removal of the tetrabutylammonium fluoride was tedious, compound *ent*-**16** was protected with the dimethox-

yltrityl group to give *ent*-**6b**. The reaction of *ent*-**6b** with adenine under Mitsunobu conditions afforded *ent*-**17b** in good yields. The deprotection of the DMT group using TFA in THF furnished *ent*-**5** in 75% yield.

In conclusion, we have demonstrated that both enantiomers of 3-hydroxymethyl-cyclopentanone **7** and *ent*-**7** can be obtained with high yields and enantioselectivities via a Rh/duphos-catalyzed asymmetric intramolecular hydroacylation. Ketones **7** and *ent*-**7** were stereoselectively reduced to cyclopentanol **6a** and *ent*-**6a**, which were efficiently transformed into D- and L-carbocyclic-ddA. This synthesis involves a new and enantioselective approach to carbocyclic nucleosides.

The key intermediate **6a** can also be obtained with excellent stereoselectivity from the diastereomeric mixture **6a** + **12** by DKR using PSC/ruthenium catalysts affording **13**, followed by methanolysis.

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**Supporting Information Available:** General experimental procedures, compounds characterization data, and NMR spectra for compounds **5–8**, **10**, **11**, and **13–17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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