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Acetoxy Meldrum's Acid: A Versatile Acyl Anion Equivalent in the Pd-Catalyzed Asymmetric Allylic Alkylation

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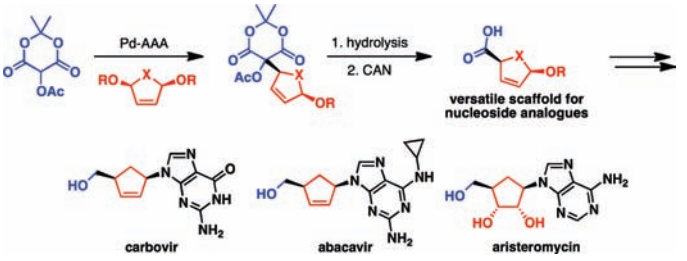
ABSTRACT



Acetoxy Meldrum's acid can serve as a versatile acyl anion equivalent in the Pd-catalyzed asymmetric allylic alkylation. The reaction of this nucleophile with various *meso* and racemic electrophiles afforded alkylated products in high yields and enantiopurities. These enantioenriched products are versatile intermediates that can be further functionalized using nitrogen- and oxygen-centered nucleophiles, affording versatile scaffolds for the synthesis of nucleoside analogues. These scaffolds were used to complete formal syntheses of the anti-HIV drugs carbovir, abacavir, and the antibiotic aristeromycin.

The high therapeutic value of nucleoside analogues in the treatment of viral infections including hepatitis, the herpes virus, and HIV is unquestionable.[1] Nucleoside analogues inhibit viral replication by acting as nonspecific chain terminators during DNA transcription. However, the high propensity for resistance caused by viral mutation necessitates the development of new nucleoside analogues.[2] Current methods for the synthesis of furanose nucleoside analogues rely on carbohydrate precursors, which are only available as the D-enantiomer from natural sources.[3] The use of highly oxygenated carbohydrate starting materials also requires the extensive use of protecting groups which reduces synthetic efficiency (Figure 1). Carbanucleosides, which contain a methylene group in place of the furanose oxygen, are synthesized using chiral pool strategies and enzymatic resolution, limiting access to both enantiomers.[4]

Recently, L-nucleosides have gained increased attention for their potent antiviral activity. These compounds frequently display lower toxicity, and higher activity due to their greater metabolic stability compared to D-nucleosides.[5] Hence, the development of methods that provide ready access to both enantiomers of nucleoside analogues is desirable.

Generally, nucleoside analogues contain a hydroxymethylene side chain on the "sugar" moiety. This functionality can be installed through the reaction of an aldehyde with a nucleophile.[3b,6] However, installation of a hydroxymethylene unit in an umpolung manner, using an acyl anion equivalent, remains a difficult transformation. Acyl

(1) (a) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745. (b) Simons, C. *Nucleoside Mimetics: Their Chemistry and Biological Properties*; Gordon and Breach Science Publishers: Amsterdam, 2001.

(2) Kiertiburanakul, S.; Sungkanuparph, S. *Curr. HIV Res.* **2009**, *7*, 273.

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(4) (a) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (b) Afonso, C. A. M.; Kurteva, V. B. *Chem. Rev.* **2000**, *109*, 6809. (c) Schneller, S. W. *Curr. Top. Med. Chem.* **2002**, *2*, 1087.

(5) (a) Jahnke, T. S.; Nair, V. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017. (b) Gosselin, G.; Mathé, C. *Antiviral Res.* **2006**, *71*, 276.

(6) (a) Lee, W.; Kim, K.-H.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 139. (b) Cesario, C.; Miller, M. J. *Org. Lett.* **2009**, *11*, 1293.

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anion equivalents provide a method to construct C–C bonds by reversing the inherent electrophilic reactivity of a carbonyl group.[7] While dithianes[8] as well as other acyl anions, have been studied extensively in this capacity, their asymmetric introduction, remains a challenge.[9]

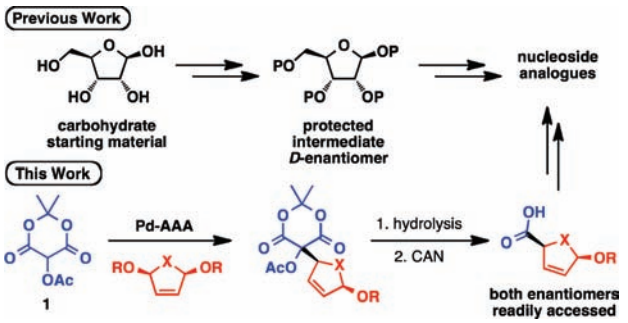
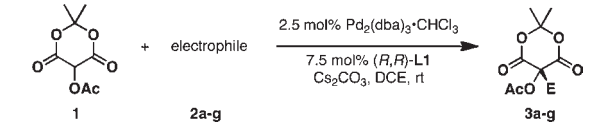


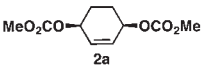
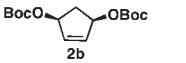
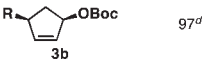
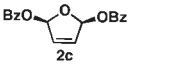
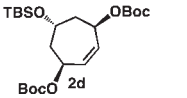
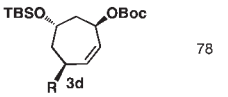
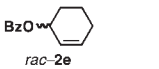
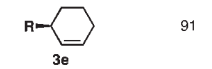
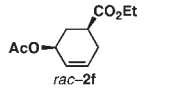
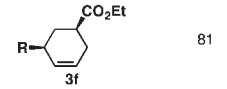
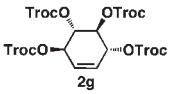
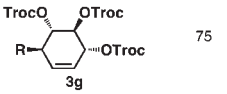
Figure 1. Strategies to access nucleoside analogues.

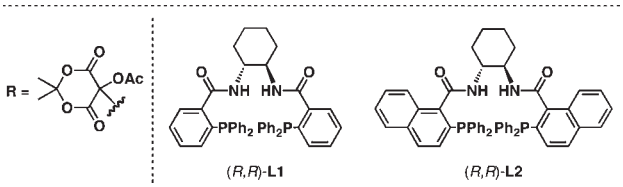
The Pd-catalyzed asymmetric allylic alkylation (Pd-AAA) is a powerful method for the stereoselective construction of C–C and C–X bonds.[10] In the past, the Pd-AAA has been used to construct nucleosides and their analogues by employing purine and pyrimidine nucleophiles.[11] However, use of an acyl anion equivalent in the Pd-AAA to access nucleoside analogues as well as other chiral scaffolds containing this functionality remains under studied. We imagined that acetoxy Meldrum's acid (**1**) could serve as a good nucleophile and a general acyl anion equivalent in such processes under mildly basic conditions.[12] Simple hydrolysis of the acetonide functionality followed by oxidative decarboxylation with ceric ammonium nitrate (CAN) should unmask the carboxylic acid functionality (Figure 1).[13] This carboxylic acid handle could be reduced to the corresponding aldehyde or hydroxymethylene as needed. Inspired by the significance of nucleoside analogues, we envisioned that the use of acetoxy Meldrum's acid as an acyl anion equivalent, and its application to the Pd-AAA would provide an enabling method for the rapid assembly of both enantiomers of carbocyclic and heterocyclic nucleoside analogues (Figure 1).

We began our studies by investigating the reaction of *meso* dicarbonate **2a** with acetoxy Meldrum's acid (**1**) (Table 1, entry 1). Treatment of this system with 2.5 mol % $Pd_2(dba)_3{\bullet}CHCl_3$ and (*R*,*R*)-**L1** in 1,2-dichloroethane (DCE) with Cs_2CO_3 as a base afforded the alkylated product **3a** in 99% yield and 99% ee. Reaction of the five-membered dicarbonate[14] **2b** under the same reaction conditions employing (*R*,*R*)-**L2** as ligand provided the alkylated product **3b** in 97% yield and 98% ee (entry 2). Likewise, the *meso* dihydrofuran[15] **2c** reacted smoothly to generate the alkylated dihydrofuran **3c** in 90% yield and 92% ee (entry 3). The success of the five-membered ring *meso* electrophiles is noteworthy due to their utility as building blocks in the synthesis of both carbocyclic and heterocyclic nucleoside analogues, respectively (*vide infra*). Additionally, **3b** and **3c** were easily prepared on gram scale without deterioration of yields or enantiopurities. Reaction of the tropone-derived *meso* dicarbonate **2d** provided the substituted product **3d** in 78% yield and 90% ee

Table 1. Scope of Electrophiles in the Pd-AAA with Acetoxy Meldrum's Acid (**1**)[a]



entry	electrophile	product	% yield[b]	% ee[c]
1	 2a	 3a	99	99
2	 2b	 3b	97[d]	98
3	 2c	 3c	90[d]	92
4	 2d	 3d	78	90
5	 *rac*–2e	 3e	91	99
6	 *rac*–2f	 3f	81	99
7	 2g	 3g	75	99



[a] All reactions were performed with 1.0 equiv of **1**, 1.0 equiv of of electrophile **2**, and 1.1 equiv of Cs_2CO_3, 0.25 M in DCE at ambient temperature. [b] Isolated yield. [c] %ee was determined by chiral HPLC. [d] (*R*,*R*)-**L2** was used.

(7) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
(8) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.
(9) (a) Aggarwal, V. K.; Esquivel-Zamora, B. N. *J. Org. Chem.* **2002**, *67*, 8618. (b) Seemann, M.; Schöller, M.; Kudis, S.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 2122. (c) Johnson, J. S. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 691. (d) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556. (e) Förster, S.; Tverskoy, O.; Helmchen, G. *Synlett* **2008**, 2803.
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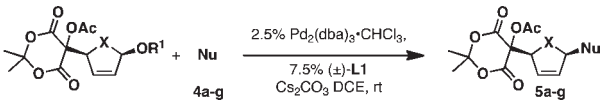
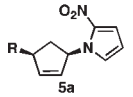
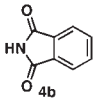
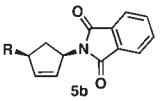
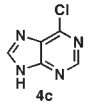
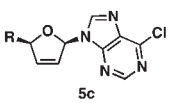
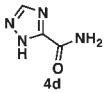
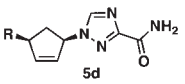
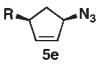
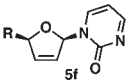
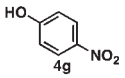
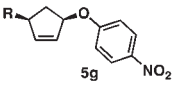
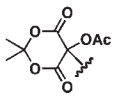
(11) (a) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745. (b) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3037. (c) Trost, B. M.; Kallander, L. S. *J. Org. Chem.* **1999**, *64*, 5427. (d) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947.
(12) Schank, K.; Blattner, R. *Chem. Ber.* **1981**, *114*, 1958.

(entry 4). Both carbonate and ester-leaving groups could be utilized in this transformation to afford the desired products in high yields and enantiopurities.

Table 2. Pd-Catalyzed Allylic Substitutions[a]



entry	electrophile	nucleophile	product	% yield[b]
1	**3b**	 **4a**	 **5a**	99
2	**3b**	 **4b**	 **5b**	97
3	**3c**	 **4c**	 **5c**	83[c]
4	**3b**	 **4d**	 **5d**	74
5	**3b**	$TMSN_3$ **4e**	 **5e**	99[d]
6	**3c**	 **4f**	 **5f**	81[e]
7	**3b**	 **4g**	 **5g**	81

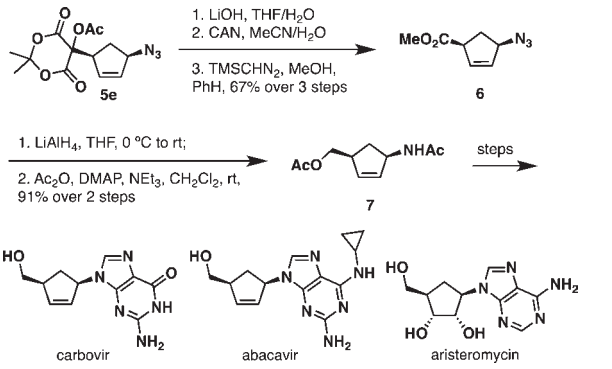
R = 

[a] All reactions were performed with 1.0 equiv of **3**, 1.0 equiv of **4**, and 1.1 equiv of Cs_2CO_3, 0.25 M in DCE at ambient temperature. [b] Isolated yield. [c] Performed using 5 mol % $Pd_2(dba)_3$•$CHCl_3$, 15 mol % (±)-**L1**, 10 mol % Bu_3SnOAc with 3.0 equiv of NEt_3 in THF. [d] Performed in THF in the absence of base. [e] Performed using 5 mol % $Pd_2(dba)_3$•$CHCl_3$, 15 mol % (±)-**L1**, with 3.0 equiv of NEt_3 in THF.

With conditions developed for *meso* electrophiles, we turned our attention to racemic substrates. Treatment of racemic cyclohexenyl benzoate *rac*-**2e** with acetoxy Meldrum's acid (**1**) under conditions used for *meso* electrophiles provided the alkylated product **3e** in 91% yield and 99% ee (entry 5). Incorporating substitution on the cyclohexene ring had little effect on the transformation, and *rac*-**2f** was alkylated to **3f** in 81% yield and 99% ee (entry 6). Likewise, C_2 symmetric tetracarbonate **2g** was examined in the transformation and provided the product **3g** in 75% yield and 99% ee (entry 7). In all cases examined, the alkylation product was obtained exclusively as a single regio- and diastereoisomer.

To provide a wide range of functionalized scaffolds for the synthesis of nucleoside analogues, the products **3b** and **3c** were alkylated a second time using a diastereoselective Pd-catalyzed allylic substitution. In this reaction, the use of enantiopure ligands was not necessary, since the chiral center established in the initial Pd-AAA would dictate the diastereoselectivity of the second alkylation. Both **3b** and **3c** were selected for their abilities to serve as scaffolds for a large number of nucleoside analogues. Both nitrogen- (Table 2, entries 1−6) and oxygen-centered (entry 7) nucleophiles were successfully utilized and afforded the substituted products (**5a**−**g**) in high yields as a single diastereomer. Both pyrrole **4a** and phthalimide **4b** underwent substitution with chiral cyclopentene **3b** in near-quantitative yields to afford cyclopentenes **5a** and **5b** (entries 1 and 2). Substitution of dihydrofuran **3c** with 6-chloropurine (**4c**) to afford **5c** (entry 3) is important, as it provides an appropriately functionalized intermediate for the synthesis of several purine-derived nucleoside analogues through manipulation of the dihydrofuran olefin and purine side chain. Reaction of cyclopentene **3b** with triazole **4d** provided **5d** (entry 4) in 74% yield, which contains the carbon skeleton of several biologically active analogues of the broad-spectrum antiviral agent ribavirin.[16] Coupling of dihydrofuran **3c** with 2-hydroxypyrimidine•HCl (**4f**) provided **5f** (entry 6), which contains the carbon skeleton for the DNA methylation inhibitor zebularine.[17]

Scheme 1. Formal Syntheses of Carbovir, Abacavir, and Aristeromycin



Pd-catalyzed substitution of cyclopentene **3b** with $TMSN_3$ (**4e**) generated allyl azide **5e** in 99% yield (entry 5). This compound was used to complete the formal syntheses of several biologically active nucleoside analogues (Scheme 1). Basic hydrolysis of allyl azide **5e** with LiOH followed by oxidative decarboxylation with CAN

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(14) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876.
(15) Elming, N.; Claason-Kaas, N. *Acta Chem. Scand.* **1952**, *6*, 535.
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and methylation of the liberated carboxylic acid with $TMSCHN_2$ provided ester **6** in 67% yield over three steps. Reduction of the ester and azide functionalities with $LiAlH_4$ yielded the corresponding amino alcohol that was acylated directly with acetic anhydride to afford acetylated amino alcohol **7** in 91% yield over two steps. Acetylated amino alcohol **7** is a known intermediate in the synthesis of the HIV drugs carbovir,[18] abacavir,[19] and the antibiotic aristeromycin.[20]

In conclusion, we have developed acetoxy Meldrum's acid (**1**) as a versatile nucleophile and acyl anion equivalent in the Pd-AAA. Both *meso* and racemic electrophiles reacted with acetoxy Meldrum's acid (**1**) to provide the desired alkylated products in high yields and enantiopurities in a chemo-, regio-, and diastereoselective fashion. The products from the Pd-AAA were then subjected to a second Pd-catalyzed allylic substitution using both nitrogen- and oxygen-centered nucleophiles. Formal syntheses of carbovir, abacavir, and aristeromycin were completed to demonstrate an application of this method in short syntheses of carbanucleoside analogues.

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Supporting Information Available. Experimental details and spectral data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.