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Synthesis of 4′-Methyl and 4′-Cyano Carbocyclic 2′,3′-Didehydro Nucleoside Analogues via 1,4-Addition to Substituted Cyclopentenones

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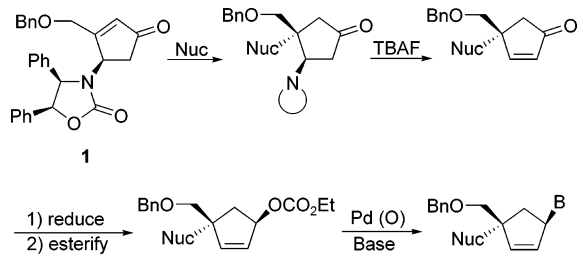
Abstract: Carbocyclic 4′-methyl and 4′-cyano nucleoside analogues were synthesized using the Michael reaction to introduce the 4′-substituent and Pd-catalyzed allylic substitution to introduce the nucleoside base. Use of both the desired β- and undesired α-1′-carbonate diastereomers in the Pd-catalyzed substitution was demonstrated in principle by epimerization of the α-diastereomer and kinetic diastereodifferentiation of a 1:1 α/β mixture of 1′-carbonates.

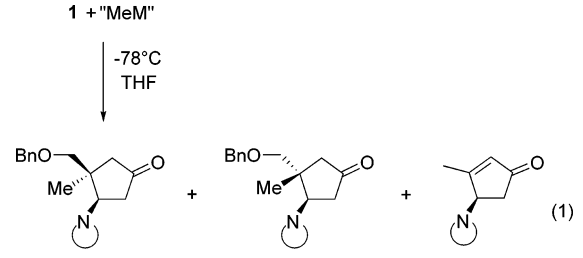
The broad antitumor and antiviral activity displayed by the naturally occurring carbocyclic nucleosides neplanocin A and aristeromycin[1] coupled with their greater metabolic stability relative to their glycosidic relatives[2] have made carbocyclic nucleoside analogues the focus of intensive synthetic studies.[3] The observation that 4′-substituted nucleosides also had wide-ranging biological activity[4] spurred similar interest in their synthesis.[5] Substantially less effort has been directed toward the synthesis of 4′-substituted *carbocyclic* nucleosides, although cyclopentanoid nucleosides having F,[6] OH,[6] alkyl,[7] and aryl[8] substituents at the 4′-position have been reported.

SCHEME 1



Approaches to 4′-substituted nucleoside analogues,[9] as well as the synthesis of cyclobut-A,[10] neplanocin A,[11] and aristeromycin and carbovir,[12] utilizing chromium carbene-derived optically active cyclobutanones[13] as precursors have recently been reported from these laboratories. Application of this approach to the synthesis of 4′-substituted carbocyclic nucleosides is presented below.

The approach taken to 4′-substituted carbocyclic nucleosides (Scheme 1) involved stereoselective conjugate addition to optically active cyclopentenone **1**, followed by oxazolidinone elimination,[14] ketone reduction and esterification, and introduction of the nucleoside base via well-established π-allylpalladium chemistry.[15] Cyclopentenone **1** was available in three steps in 70% overall yield utilizing previously developed methodology.[12] Conjugate methylation proved problematic (eq 1).



"MeM" =			
	Me_2CuLi	NR/decomp	
	$Me_2CuLi/BF_3 \cdot OEt_2$	52% (9:1)	8%
	$Me_2/Ni(acac)_2$	49% (1:2.5)	39%
	$MeCu/BF_3 \cdot OEt_2$	83% (3.3:1)	0

Typical conjugate alkylation conditions utilizing lithium dimethylcuprate resulted in no reaction when the mix-

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(5) For recent examples, see: (a) Haraguchi, K.; Takeda, S.; Tanaka, H.; *Org. Lett.* **2003**, *5*, 1399. (b) Jung, M. E.; Toyota, A. *J. Org. Chem.* **2001**, *66*, 2624. (c) Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016. (d) Crich, D.; Hao, X. *J. Org. Chem.* **1998**, *63*, 3796. (e) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440.

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(9) (a) Hegedus, L. S.; Geisler, L.; Riches, A. G.; Salman, S. S.; Umbricht, G. *J. Org. Chem.* **2002**, *67*, 7649. (b) Hegedus, L. S.; Hervert, K. L.; Matsui, S. *J. Org. Chem.* **2002**, *67*, 4076. (c) Reed, A. D.; Hegedus, L. S. *Organometallics* **1997**, *16*, 2313.

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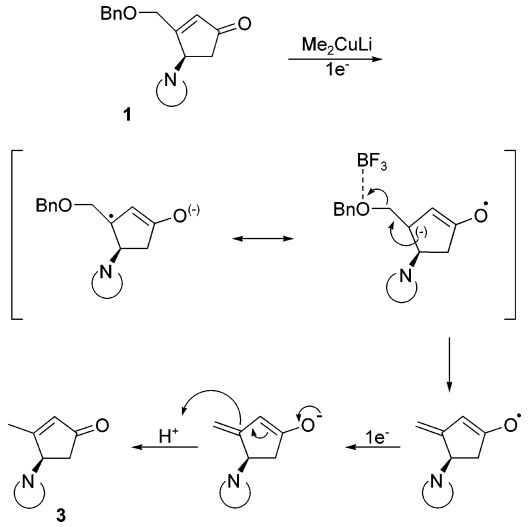
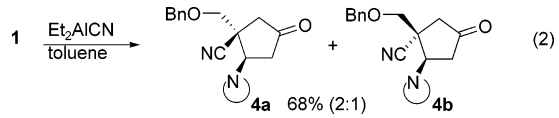
ture was quenched at −78 °C and decomposition (with free oxazolidinone as the sole identifiable product) when warmed to room temperature. The use of lithium dimethylcuprate/BF_3·OEt_2[16] gave modest yields of the desired conjugate addition, with good selectivity. However, varying amounts of enone **3**, resulting from loss of the benzyloxy group, were obtained. Dimethyl zinc/nickel(II) acetylacetonate[17] produced similar yields of conjugate addition product, but with low stereoselectivity, and favoring the other diastereomer. Upward of 40% of enone **3** was also observed depending on conditions. The most effective reagent for conjugate methylation was methyl copper/BF_3·OEt_2,[18] which produced good yields of **2** with modest selectivity and no byproduct **3**. The mixed cuprate MeCuCNLi/BF_3·OEt_2 gave similar results.

The formation of compound **3** warrants comment. Although electron-transfer pathways are not thought to be involved in most conjugate additions of copper complexes, they have been observed in special cases.[19] Lithium dimethylcuprate reductively cleaved γ-ester[20] and γ-carbamate[21] groups from α,β-unsaturated esters, while MeCuCNLi was unreactive.[20a] A likely path for this elimination is shown in Scheme 2 and involves single-electron transfer to give a radical anion intermediate, followed by ejection of the benzyloxy group, perhaps with assistance from the Lewis acid present. Reduction and protonation of the enolate completes the sequence.

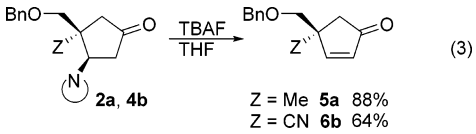
SCHEME 2



Nagata's reagent,[22] Et_2AlCN, introduced cyanide into the β-position of **1** in fair yield, but with lower stereoselectivity and favoring the opposite diastereoisomer (eq 2), while KCN/Et_3N·HCl and KCN/acetone cyanohydrin[23] were considerably less effective and trimethylsilyl cyanide failed to react. Enone **1** underwent conjugate addition with both azide ($TMSN_3$/HOAc/Et_3N)[24] and $PhCH_2$-SLi, but the adducts could not be purified or stored since they underwent spontaneous β-elimination,[25] returning starting material.

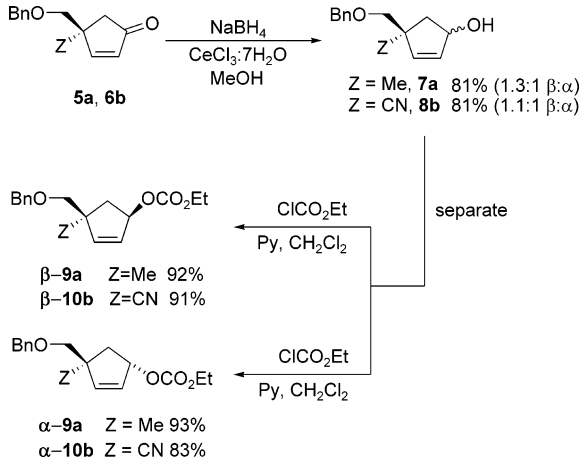


Treatment of the "natural" D-diastereoisomers **2a** and **4b** with TBAF in THF produced cyclopentenones **5a** and **6b** in moderate to good yield (eq 3). The absolute configurations of these compounds were assigned as follows. Monophenyl oxazolidinone analogues of cyclopentanones **2** and **4** were synthesized in optically pure form and their structures were determined by single-crystal X-ray diffraction. Subjecting these analogues to TBAF produced enones **5** and **6**, respectively, identical in all respects including the sign and magnitude of rotation to those produced from the same treatment of **2** and **4**.[26]



Reduction of the enones under Luche conditions[27] was virtually nonselective, slightly favoring the β-isomer.[28] The resulting alcohols were easily separated by chromatography and converted to their ethyl carbonates under standard conditions (Scheme 3). With these materials in hand, palladium-catalyzed coupling was addressed.

SCHEME 3



Experiments with **9a** using sodium dimethyl malonate and $Pd(PPh_3)_4$ gave excellent yields but revealed that the

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(20) (a) Logusch, E. W. *Tetrahedron Lett.* **1979**, 3365. (b) Ruden, R. A.; Litterer, W. E. *Tetrahedron Lett.* **1975** 2043.
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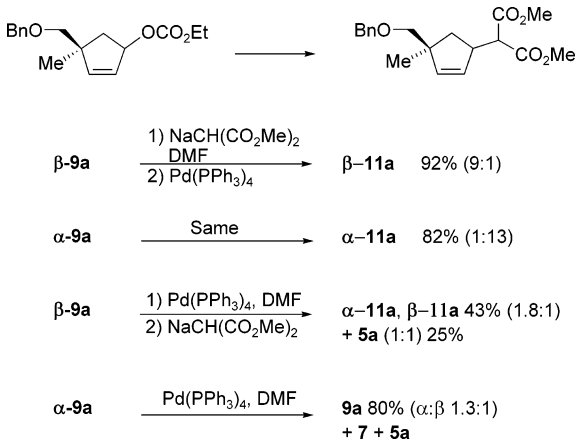
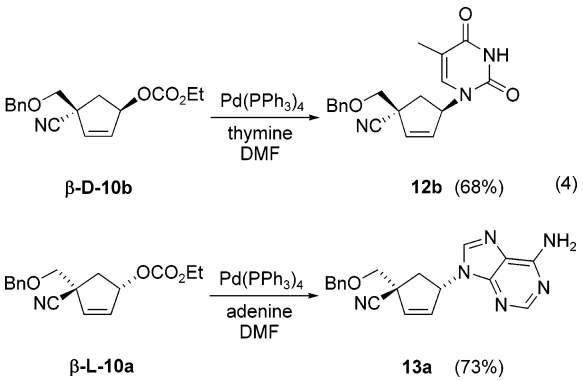
allylic carbonate substrate failed to retain stereochemistry during the reaction. Mixing β-**9a** first with sodium dimethyl malonate followed by addition of the $Pd(PPh_3)_4$ catalyst in DMF gave **11a** as a 9:1 β/α mixture of diastereomers; the same reaction with α-**9a** gave **11a** as a 1:13 β/α mixture. Adding the catalyst to **9a** *followed* 20 min later by addition of the malonate gave a lower yield of **11a** as a 1.8:1 α/β mixture of diastereoisomers along with substantial amounts of enone **5a** (see below). Stirring **9a** with catalyst in the absence of any nucleophile resulted in near-complete epimerization of the carbonate[29] (with small amounts of **5a** and epimerized **7a**),[30] accounting for the loss of stereochemistry observed above (Scheme 4).

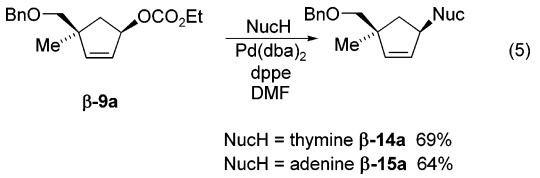
SCHEME 4



With the less reactive nucleophile adenine and $Pd(PPh_3)_4$ as catalyst, more extensive epimerization was observed, β-**9a** giving a 1.7:1 β/α ratio of products and α-**9a** giving a 1:1.7 ratio of the same two products. In contrast, cyanocarbonate β-**10b** underwent facile $Pd(PPh_3)_4$-catalyzed coupling with thymine without loss of stereochemistry. With adenine, only β-**10a** underwent reaction, with α-**10a** being recovered unchanged (eq 4).

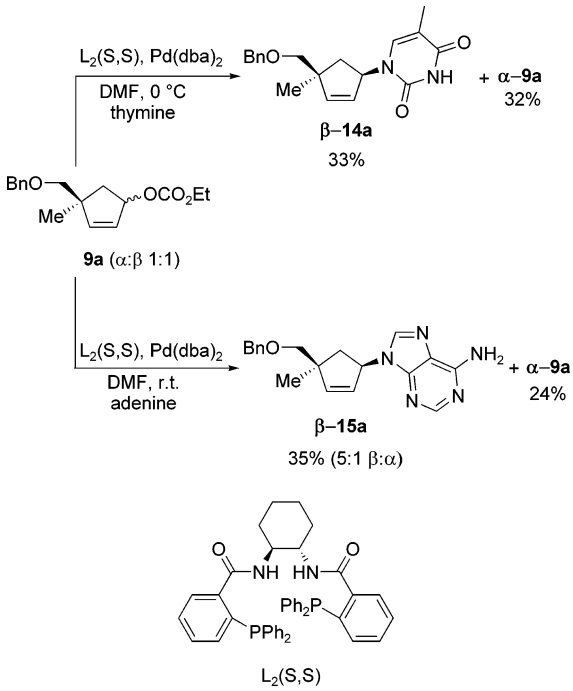


To prevent loss of stereochemistry in reactions of methyl adduct β-**9a**, a $Pd(dba)_2$/dppe catalyst system was used. Adenine and thymine both coupled with β-**9a** stereoretentively under these conditions. Adenine gave primarily the N-9 isomer with minor quantities of the N-7 isomer as a byproduct (eq 5).



Utilization of undesired carbonate α-**9a** was demonstrated in principle by epimerization of α-**9a** with $Pd(PPh_3)_4$ (see above) and Pd-catalyzed kinetic diastereodifferentiation of a 1:1 α/β mixture of carbonate **9a** with Trost ligand L_2*(*S*,*S*). Kinetic diastereodifferentiation proceeded without incident with thymine as nucleophile, giving the desired product β-**14a** in 95% de and returning carbonate α-**9a** in moderate yield. Adenine was more problematic, giving β-**15a** as a 5:1 α/β mixture and returning carbonate α-**9a**, in slightly lower overall yield. Attempts to run the epimerization and kinetic diastereodifferentiation in the same flask failed, giving substantial quantities of epimerized alcohol **7a** and enone **5a** due to extensive carbonate decomposition via hydrolysis and oxidation[30] (Scheme 5).

SCHEME 5



Deprotection of adenine and thymine adducts **12b** and **13a**–**15a** proceeded with BCl_3 without incident to give the products **16**–**19** in fair to excellent yield. The ster-

(27) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(28) The stereochemistry of compounds **7a** and **8b** was assigned by single-crystal X-ray crystallography of the derivative alcohols **17** and **19**.

(29) For studies on the mechanism of palladium-catalyzed epimerization of cyclic allylic substrates, see: (a) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858. (b) Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Moreno-Mañas, M.; Morral, L.; Pleixats, R. *Chem. Eur. J.* **2000**, *6*, 3372.

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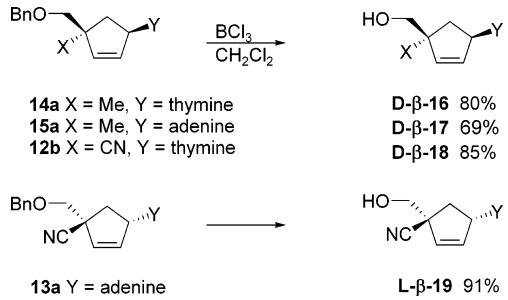
(31) Copper iodide was used within 48 h following purification according to Amareggo, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1998; p 381.

SCHEME 6



eochemistry of alcohols **17** and **19** was determined by single-crystal X-ray diffraction (Scheme 6).

A synthesis of four 4′ substituted carbocyclic nucleoside analogues was developed, allowing different 4′- and 1′-substituents. An unusual epimerization in conjunction with kinetic diastereodifferentiation allowed the undesired 4′ methyl carbonate α-**9a** in principle to be recycled in the synthesis of 4′-methyl-1′-thymine product **16**.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **2**—D-*β*-**18**; X-ray structural data for **2a**, **4b**, D-*β*-**17**, and L-*β*-**19** and synthetic procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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