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Solid-Phase Synthesis of Carbocyclic Nucleosides

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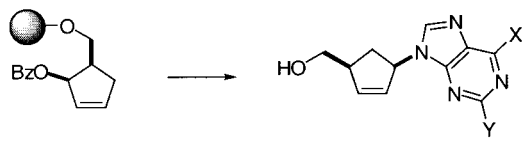
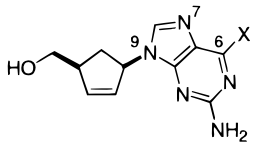
ABSTRACT

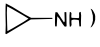


An efficient solid-phase synthesis of carbocyclic nucleosides has been developed. The key step is the palladium-catalyzed coupling of a purine derivative to a resin-bound allylic benzoate. The resulting products may be further functionalized on the solid phase. Acidic cleavage affords carbocyclic nucleosides, a class of compounds with demonstrated biological activity and substantial current interest.

The development of agents that function as nontoxic, selective inhibitors of kinases and polymerases for the control of viral diseases has been the focus of intense research.[1] However, despite significant progress, the need for new inhibitors of HIV, herpes simplex virus (HSV), Epstein−Barr virus (EBV), human cytomegalovirus (CMV), and hepatitis B virus (HBV) continues, and the ongoing problem of drug resistance adds to this need.[2] Carbocyclic nucleosides have demonstrated significant potential in this regard as new antiviral (as well as antitumor) agents.[3] For example, carbovir (**1**)[4] and abacavir (Ziagen) (**2**)[5] have both displayed inhibitory activity toward HIV.



1 (X = OH)

2 (X = )

We recently reported an efficient solution-phase enantioselective synthesis of carbocyclic nucleosides **1** and **2**.[6] Despite the success of this approach, there remained several areas in need of improvement. The yield of the coupling between the pseudosugar and the purine derivative was moderate (61−68%) and plagued by contamination with a minor amount of the N7 isomer (up to 26% of the product). Functionalization of the purine C6 also proceeded in moderate yield (60−70%) and was limited to volatile amines due to purification issues.

To expand the applicability of our synthesis of carbocyclic nucleosides **1** and **2**, we recognized that solid-phase organic synthesis provides certain potential advantages. A large excess of reagents may be used to drive reactions to completion, and product purification is facilitated by the attachment of the substrate to a polymer resin. Additionally, it was envisioned that by changing the environment around the pseudosugar, it might be possible to improve the N9:N7 product ratio in the coupling of the base to the sugar. Accordingly, we set out to develop a solid-phase synthesis

(1) (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571−623. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611−10670. (c) Huryn, D.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745−1768.

(2) Kavlick, M. F.; Shirasaka, T.; Kojima, E.; Pluda, J. M.; Hiu, F., Jr.; Yarchoan, R.; Mitsuya, H. *Antiviral Res.* **1995**, *28*, 133−146.

(3) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229−9272.

(4) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17−21.

(5) Abacavir (Ziagen) is the carbocyclic nucleoside formerly known as 1592U89: (a) Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; St. Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N.; Reardon, J. E.; Dornsfife, R. E.; Averett, D. R. Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082−1093. (b) Daluge, S. M. U.S. Patent 5,034,394, 1991.

(6) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192−4193.

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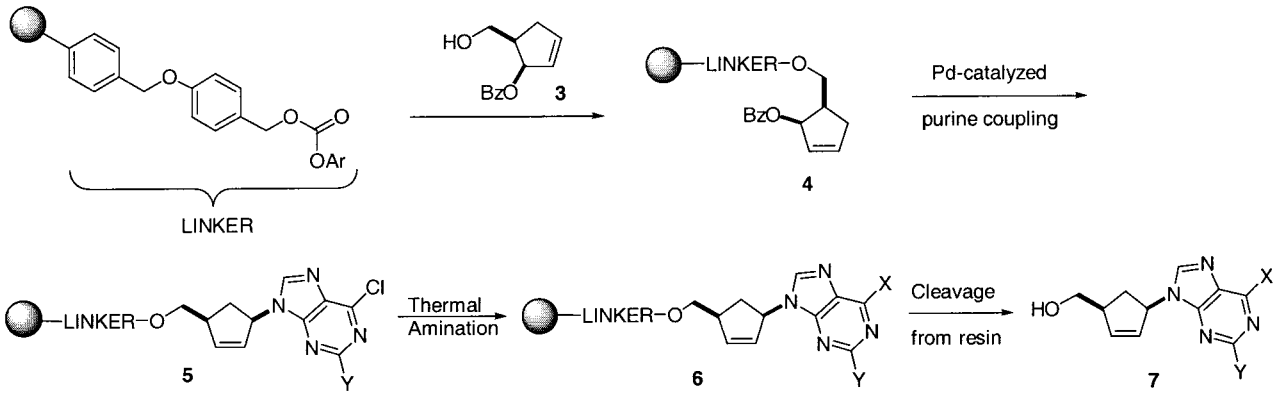
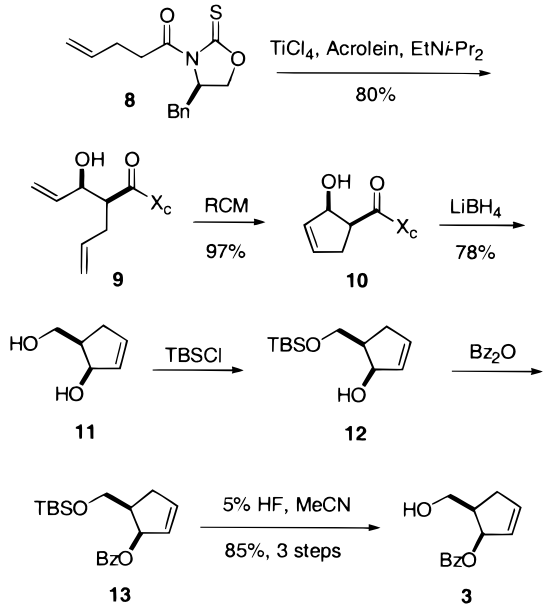
Scheme 1



of these biologically important structures based on our successful solution-phase strategy. The approach (Scheme 1) involves palladium-catalyzed coupling of the resin-bound carbocyclic pseudosugar **4** with a purine derivative to form nucleoside resin **5**; this is followed by further functionalization of the purine, affording resin **6** which, upon cleavage from the resin, yields purine-substituted carbocyclic nucleosides **7**.

Allylic benzoate **3**[7] served as the pseudosugar portion of the carbocyclic nucleoside (Scheme 2). Diol **11**, which is

Scheme 2



readily accessible in racemic[8] or enantiomerically pure[6] form, served as a key intermediate in the synthesis of **3**. Asymmetric aldol reaction of 4-pentenoyloxazolidinethione **8** and acrolein[9] formed adduct **9** which was elaborated to cyclopentene **10** by catalytic ring-closing metathesis (RCM). Reductive removal of the chiral auxiliary with $LiBH_4$ and MeOH formed diol **11**. Selective silylation of the primary alcohol in **11** with TBSCl and Et_3N was followed by acylation of the secondary alcohol in **12** with Bz_2O, Et_3N, and 4-DMAP to provide **13**. Desilylation of **13** with 5% HF in CH_3CN afforded **3** in 85% yield over the final three steps.Allylic benzoate **3** was loaded onto *p*-nitrophenyl Wang carbonate resin[10] in the presence of EtN-*i*-Pr_2 and 4-DMAP in CH_2Cl_2 at 40 °C overnight to produce resin **4**. Quantitation of the loading of **3** onto the resin was measured with attenuated total reflection (ATR) IR spectroscopy, and complete incorporation of the allylic benzoate was realized with 2 equiv of **3**. Excess **3** can be recycled by chromatographic purification of the reaction filtrate.

As in the solution-phase synthesis of carbocyclic nucleosides, palladium catalysis was utilized in the attachment of a chloropurine to the pseudosugar moiety.[11] Several reaction variables were investigated (Table 1), including palladium source, catalyst loading, ligand, and base. Conversion of the reaction was measured by ATR IR.[12] The solid-phase

Table 1. Palladium-Catalyzed Purine Coupling Reaction

entry	Y	Pd source	loading, mol %	base	convn, %
1	Cl	**15**	10%	EtN-*i*-Pr_2	<5
2	Cl	**15**	100%	EtN-*i*-Pr_2	30
3	Cl	**16**/P(O-*i*-Pr)$_3$	50	EtN-*i*-Pr_2	70
4	Cl	**16**/PPh_3	50	EtN-*i*-Pr_2	60
5	Cl	**14**/P(O-*i*-Pr)$_3$	50%	EtN-*i*-Pr_2	>95
6	Cl	**14**/P(O-*i*-Pr)$_3$	31	EtN-*i*-Pr_2	80
7	Cl	**14**/P(O-*i*-Pr)$_3$	16	EtN-*i*-Pr_2	60
8	Cl	**14**/P(O-*i*-Pr)$_3$	10	EtN-*i*-Pr_2	45
9	Cl	**14**/P(O-*i*-Pr)$_3$	31	Et_3N	55
10	Cl	**14**/P(O-*i*-Pr)$_3$	31	NMM	65
11	Cl	**14**/P(O-*i*-Pr)$_3$	31	Pempidine	85
12	Cl	**14**/PPh_3	31	EtN-*i*-Pr_2	85
13	Cl	**14**/PPh_3	10	Pempidine	>95
14	NH_2	**14**/PPh_3	12	Pempidine	>95

(7) All new compounds were fully characterized spectroscopically (^1H and ^{13}C NMR, IR, and HRMS).

(8) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Palmer, C. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 313−314.

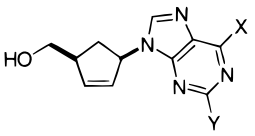
coupling reaction was found to require a much higher catalyst loading than the analogous solution-phase reaction (entry 1), and optimized conditions for the coupling utilized 10 mol % of $Pd_2(dba)_3$ (**14**), 0.4 equiv of PPh_3, 6.0 equiv of pempidine (1,2,2,6,6-pentamethylpiperdine), and 1.5 equiv of 2,6-dichloropurine in 1:1 THF:DMSO at 45 °C for 16 h (entry 13). Both $Pd(PPh_3)_4$ (**15**) and allylpalladium chloride dimer (**16**) were much less effective in this coupling, and both led to lower conversion at identical catalyst loading. The more electron rich PPh_3 effected a higher conversion than did P(O-*i*-Pr)$_3$. Bulkier tertiary amine bases led to the highest conversion (entries 6 and 9−11), a trend observed previously by Trost and co-workers.[13] Both 2,6-dichloropurine (entry 13) and 2-amino-6-chloropurine (entry 14) were effective nucleophiles in the coupling reaction to produce chloropurine resin **5a** (Y = Cl) and **5b** (Y = NH_2), respectively.

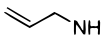
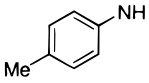
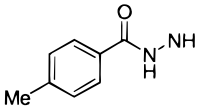
No product containing an isomeric N7 purine linkage was observed by ^{1}H NMR of the resin **5a** (Y = Cl) or **5b** (Y = NH_2) or in the products after cleavage with 5% TFA in CH_2Cl_2, and this constitutes an advantage over the solution-phase synthesis where N7 contamination can be significant. The isomeric N7 product results from a more hindered trajectory of the nucleophile, and it is presumed that the resin amplifies this effect; Trost has noted the steric protection of the metal center and a resulting steering of the incoming nucleophile in similar solid-phase reactions.[11]

Functionalization of the purine system at the 6-position with nitrogen-based nucleophiles was accomplished via a thermal S_NAr reaction to produce resins of type **6**.[14] Standard conditions were 5 equiv each of the amine and EtN-*i*-Pr$_2$ in BuOH at 80 °C for 4 h. A diverse range of functionality was incorporated, including primary and secondary amines, anilines, hydrazides, and alkoxyamines. ATR IR spectra indicated complete conversion from **5** to the derivatized resin **6**.

Cleavage of the product from the resin was accomplished by exposure to 5% TFA in CH_2Cl_2 for 1.5 h. The initially cleaved product was impure by TLC and by ^{1}H NMR, which showed signals for both the 5′-alcohol and its trifluoroacetate ester. Exposure of the mixture to a primary or secondary amine cleaved the TFA ester, and purification of the resulting alcohol by silica gel chromatography provided the pure purine-substituted carbocyclic nucleosides. Yields of the isolated, chromatographically purified products[15] were in the range 60−82% (Table 2).

Table 2. Results of Purine Functionalization with Nitrogen Nucleophiles



product	X	Y	isolated yield
7a	Cl	Cl	73%
7b		Cl	82%
7c		Cl	75%
7d		Cl	73%
7e		Cl	70%
7f	MeONH	Cl	68%
7g	Cl	NH_2	74%
2		NH_2	60%
7h		NH_2	66%

In conclusion, we have presented an efficient method for the solid-phase synthesis of carbocyclic nucleosides. This synthesis is amenable to combinatorial library synthesis, with the potential for diversity in the pseudosugar, the aromatic base, and the substitution of the base. Such investigations will be reported in due course.

Acknowledgment. The generous support of Glaxo-Wellcome is acknowledged. We thank Susan Daluge, Sam Gerritz, Doug Minick, Wendy White, and Andrea Sefler for helpful discussions and analytical support. W.J.Z. is grateful to the NIH for a Postdoctoral Fellowship.

Supporting Information Available: Complete spectral data (^{1}H and ^{13}C NMR, IR, and HRMS) for compounds **3** and **7a**−**7f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005614N

(9) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884.

(10) Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc., Chem. Commun.* **1977**, 798−799.

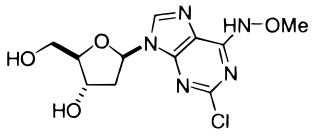
(11) Although Pd(0) is commonly employed in the deprotection of resin bound allylic esters (see: Guibe, F. *Tetrahedron* **1998**, *54*, 2967−3042 and selected references therein), reactions involving a resin-bound π-allylpalladium intermediate are rare. One example by Trost involves a supported Pd(0) catalyst: Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779−7781.

(12) Conversion was determined by measuring the amount of unreacted benzoate (1716 cm^{-1}) remaining. The dialkyl carbonate (1745 cm^{-1}) was used as an internal standard.

(13) Trost, B. M.; Madsen, R.; Guile, S. G.; Elia, A. E. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1569−1572.

(14) Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem.* **1997**, *62*, 201−203.

(15) Cleaved products **7a**−**7f** are carbocyclic analogues of 2-chloro-6-substituted adenosine analogues, structures which have demonstrated biological activity. For example, NNC 53-0017 is a potent inhibitor of TNFα production but does not interfere with the A_3 receptor. Bowler, A. N.; Raven, A.; Olsen, U. B.; Thomsen, C.; Knutsen, L. J. *Drug. Dev. Res.* **1998**, *43*, 26.



NNC 53-0017