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Solid Phase Synthesis of Carbocyclic L-2′-Deoxynucleosides

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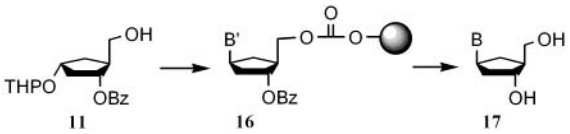
ABSTRACT



Carbocyclic L-2'deoxynucleosides 17 were synthesized on solid phase in four steps from the appropriately protected intermedate 11. The Mitsunobu reaction was used as a condensation method between the carbocyclic moiety and heterocyclic bases. The regioselectivity of the carbocyclic nucleosides was compared between the solid and solution phase syntheses.

Nucleosides have been playing a major role in combating tumor and virus, and a variety of modifications of natural nucleosides have been made to discover novel antitumor and/or antiviral agents.[1] Among nucleosides, carbocyclic analogues have been one of the interesting classes of compounds due to the nonglycosidic nature of the bond between the carbocyclic moiety and the heterocyclic base, which results in metabolic stability to phosphorylases. Several methods[2] of condensation between the carbocyclic moiety and heterocyclic bases have been reported: (1) a classical S_N2 type reaction with tosylate or mesylate, (2) an epoxide ring opening method, (3) a palladium-catalyzed coupling reaction, and (4) a Mitsunobu reaction.[3] The Mitsunobu reaction has been widely utilized for the synthesis of both purine and pyrimidine derivatives. However, solution phase synthesis needs to be improved. For example, the byproducts, reduced DEAD and triphenylphosphine oxide, are very difficult to separate from the products after reaction, and a regioisomeric mixture of N_1- and O^2-alkylated pyrimidines is usually produced. However, there has not been much effort to solve this regioselectivity problem. Recently, Crimmins et al. reported regioselective synthesis of purine nucleosides by using the palladium-catalyzed coupling method in solid phase synthesis.[4] Herein we report a comparison of solid phase synthesis with solution phase synthesis of carbocyclic nucleosides by Mitsunobu reaction, in which we focused on the regioselectivity of the condensation. Furthermore, this method can be proposed as a general strategy for a library of carbocyclic nucleosides.

Previously, we reported the syntheses of several carbocyclic L-nucleosides such as L-aristeromycin and L-carbovir[5] from alcohol **1**, which was synthesized by a known method[6] in five steps from D-ribose. By using the alcohol **1**, 2′-deoxy carbocyclic moiety **11** was synthesized as shown in Scheme 1. Appropriately protected carbocyclic moiety **11** was proposed as the key intermediate because the protecting groups could be kept stable under the reaction conditions on solid phase and removed at the time when the product is generated from the resin after the Mitsunobu reaction.

Alcohol **1** was protected by benzyl bromide to give the

(1) Mansour, T. S.; Storer, R. *Curr. Pharm. Design* **1997**, *3*, 227.
(2) (a) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.
(3) (a) Bonnal, C.; Chavis, C.; Lucas, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1401. (b) Cadet, G.; Chan, C.-S.; Daniel, R. Y.; Davis, C. P.; Guiadeen, D.; Rodriguez, G.; Thomas, T.; Walcott, S.; Sheiner, P. *J. Org. Chem.* **1998**, *63*, 4574. (c) Diaz, Y.; Bravo, F.; Castillon, S. *J. Org. Chem.* **1999**, *64*, 6508.
(4) Crimmins, M. T.; Zuercher, W. J. *Org. Lett.* **2000**, *2*, 1065.
(5) Wang, P. Y.; Gullen, B.; Newton, M. G.; Cheng, Y.-C.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 3390.
(6) (a) Ali, M.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, *31*, 1509. (b) Wang, P. Y.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1997**, *38*, 4207. (c) Wang, P. Y.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1999**, *64*, 4173.

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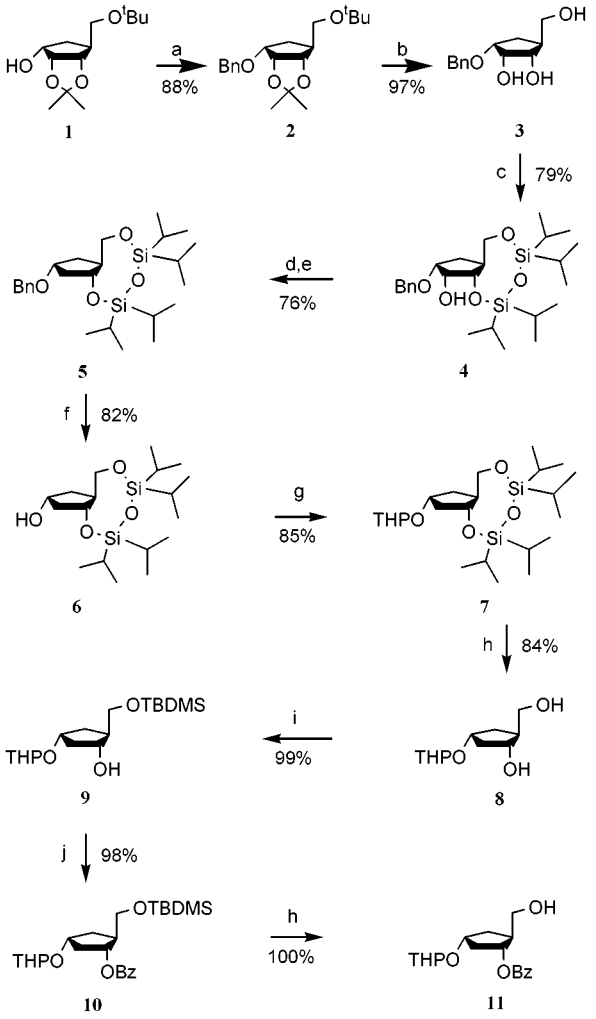
Scheme 1.[a] Synthesis of Carbocyclic Moiety **11**

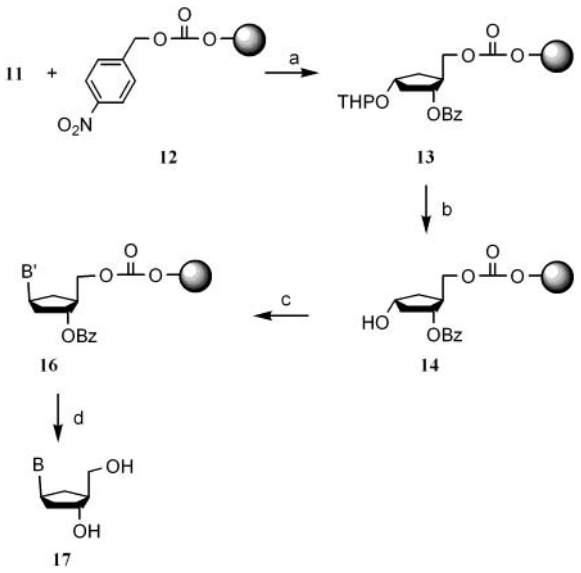


[a] Reagents and conditions: (a) NaH, BnBr, THF, 0 °C; (b) TFA/H_2O, 60 °C, then 1 N NaOH; (c) TIPDSCl, pyr, 0 °C; (d) NaH, CS_2, MeI, THF, 0 °C to rt; (e) Bu_3SnH, AIBN, toluene, reflux; (f) $Pd(OH)_2$, MeOH, H_2; (g) DHP, PPTS, CH_2Cl_2, rt; (h) TBAF, THF, rt; (i) TBDMSCl, imidazole, THF, 0 °C to rt; (j) BzCl, pyr, 0 °C.

fully protected intermediate **2** in 88% yield, which was deprotected by trifluoroacetic acid in water followed by treatment with 1 N NaOH to give compound **3** in 97% yield (Scheme 1). Compound **3** was treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSCl)[7] in pyridine to give compound **4** which was converted to a xanthate by successive treatment with sodium hydride, carbon disulfide, and methyl iodide. It was deoxygenated by tributyltin hydride and AIBN to give compound **5** in 76% yield in two steps. The benzyl group of compound **5** was removed by using palladium(II) hydroxide and hydrogen to give compound **6**. Compound **6** was protected by treatment with DHP and PPTS followed by deprotection of the TIPDS group to give compound **8** in 71% yield in two steps. To differentiate 5′-OH from 3′-OH, the TBDMS group was introduced to compound **8** to give compound **9** in 99% yield. Key intermediate **11** was obtained by benzoylation followed by deprotection of the TBDMS group in 98% yield in two steps.

The intermediate **11**, which was used in the amount of 3 equiv, was loaded onto *p*-nitrophenyl carbonate resin **12**[8] by treatment with 10 equiv of DIPEA and 1.0 equiv of 4-DMAP in CH_2Cl_2 under reflux for 24 h (Scheme 2). Unreacted **11**

Scheme 2.[a] Solid Phase Syntheis of Carbocyclic L-2′-Deoxynucleosides **17**



[a] Reagents and conditions: (a) DMAP, DIPEA, CH_2Cl_2, 40 °C; (b) PPTS, 1-butanol/1,2-dichloroethane, 60 °C; (c) B′H (**15a**−**e**), DEAD, Ph_3P, DMF/dioxane or DMF, rt; (d) K_2CO_3, THF/MeOH, rt.

was recycled after the reaction. Resin **13** was deprotected by PPTS in a 1:1 mixture of 1-butanol and 1,2-dichloroethane at 60 °C for 24 h.[9] The temperature was very critical in this step. If the temperature was below 55 °C, the reaction did

(7) Markiewicz, W. T. *J. Chem. Res.* **1979**, 24.

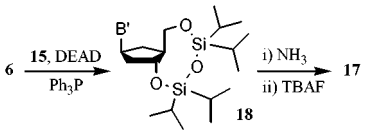
(8) Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc., Chem. Commun.* **1977**, 798.

(9) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333.

(10) **General procedure for Scheme 2:** DIPEA (10 equiv) and 4-DMAP (1 equiv) were added to a mixture of resin **12** and alcohol **11** (3 equiv) in CH_2Cl_2 at room temperature. The mixture was refluxed under N_2 for 24 h. After cooling, the resulting resin **13** was filtered, washed, and dried. Resin **13** and PPTS (10 equiv) were added to a 1:1 mixture of 1,2-dichloroethane and 1-butanol at room temperature. The resulting mixture was stirred overnight at 60 °C. After cooling, the resulting resin **14** was filtered, washed, and dried. PPh_3 (10 equiv) and **15** (10 equiv) were added to a mixture of resin **14** in the appropriate solvent. To this mixture was added DEAD (10 equiv) dropwise. After stirring for 24 h at room temperature, the resulting resin **16** was filtered, washed, and dried. A mixture of resin **16** in THF/MeOH (2:1) was treated with solid K_2CO_3 (10 equiv) at room temperature for 24 h. The reaction mixture was filtered through a short silica gel pad. The filtrate was concentrated and purified by column chromatography on silica gel.

(11) All carbocyclic nucleosides from solid phase synthesis were analyzed by HPLC and/or MS and compared with those from solution phase synthesis.

(12) The scheme for the solution phase synthesis is as shown below:



not go to completion even after 24 h. Completion of the reaction was confirmed by the cleavage of a small portion of resin **14**. Resin **14** was condensed with 10 equiv of heterocyclic bases **15a**−**e** (Figure 1) under Mitsunobu

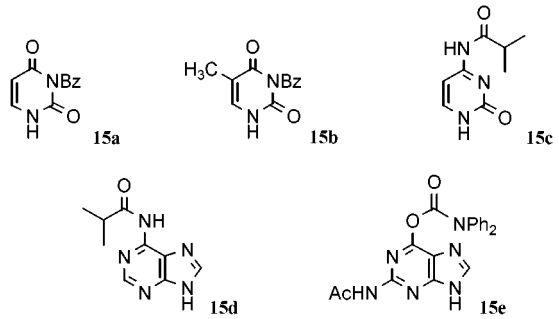


Figure 1. Structures of heterocyclic bases (B′H).

conditions. Carbocyclic nucleosides **17** were obtained from resin **16** by treatment with 10 equiv of K_2CO_3 in THF/MeOH (2:1) at room temperature for 24 h. The crude product was purified by silica gel chromatography to give the pure carbocyclic nucleosides **17** (Table 1).[10,11]

Table 1. Comparison between Solid and Solution Phase Syntheses

		solid phase		solution phase	
B′H (**15**)	**17**, B =	HPLC ratio[a]	% yield[b]	isolation ratio[a]	% yield[c]
a	uracil	97/3	51[d]	64/36	79[d]
b	thymine	85/15	100[d]	70/30	88[d]
c	cytosine	20/80	97[e]	17/83	39[e]
d	adenine	100/0	55[e]	100/0	43[e]
e	guanine	100/0	62[e]	100/0	47[e]

[a] Ratio between N_1- and O^2-alkylated pyrimidines or N_9- adn N_7-alkylated purines. [b] Yield in four steps from **12** to **17**. [c] Yield in three steps from **6** to **17**. [d] Solvent: DMF/1,4-dioxane (1:2). [e] Solvent: DMF only.

The results of solid phase synthesis of carbocyclic nucleosides **17** were compared with those of solution phase synthesis,[12] where the Mitsunobu reaction was used as a condensation method. Even though the solvent system of DMF/1,4-dioxane (1:2) was good in view of the yield,[13] it could not be generally used because the solubility of some protected bases (**15c**−**e**) was poor in this solvent. Therefore, in some cases (**15c**−**e**), the solvent was changed to DMF.

(13) Chong, Y.; Gumina, G.; Chu, C. K. *Tetrahedron: Asymmetry* **2000**, *11*, 4853.

Regioselectivity of N_1- and O^2-alkylated pyrimidines was increased in the case of uracil and thymine derivatives in the solid phase synthesis (Table 1). The regioselectivity can be explained by the relative stability of two resonance forms of the conjugate anion of pyrimidines. As noted by Crimmins et al.,[4] the different environment of the solid phase, where aromatic rings of the polystyrene resin solvate the reaction sites, is probably responsible for the improved regioselectivity. However, in the case of the cytosine derivative, the fully aromatized resonance form of the conjugate anion is more stable than the other one, and the preference for the aromatized resonance form results in the formation of O^2-alkylated cytosine as a major product. This preference does not seem to be effected by the unique environment of the solid phase and can explain the similar ratios of N_1- and O^2-alkylated cytosine in both solid and solution phase syntheses. In the case of purine derivatives, there was no regioisomeric problem in both syntheses.

This study on solid phase synthesis encouraged us to optimize and standardize the conditions in the solid phase synthesis in order to apply this method to automation. Therefore, DMF was chosen as a general solvent because of the favorable solubility of all the heterocyclic bases (**15a**−**e**). The results are shown in Table 2. Changing the solvent

Table 2. Optimized Solid Phase Synthesis

B′H (**15**)	**17**, B =	HPLC ratio[a]	% yield[b]
a	uracil	98/2	74
b	thymine	90/10	80
c	cytosine	30/70	82
d	adenine	100/0	69
e	guanine	100/0	58

[a] Ratio between N_1- and O^2-alkylated pyrimidines or N_9- and N_7-alkylated purines. [b] Yield in four steps from **12** to **17**.

from a 1:2 mixture of DMF and 1,4-dioxane to DMF did not affect the regioisomeric ratios significantly, which also supported the explanation of the increased regioselectivity in solid phase synthesis.

In summary, we have demonstrated that pyrimidine and purine derivatives of carbocyclic nucleosides were successfully synthesized on solid phase using the Mitsunobu reaction. This method could be applied to the synthesis of other nucleoside libraries.

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