Synthesis of Carbocyclic Pyrimidine Nucleosides Using the Mitsunobu Reaction – Part I: Influence of the Alcohol on N1- versus O^2-Alkylation

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Abstract: The Mitsunobu reaction is an important tool in carbocyclic nucleoside chemistry for the direct coupling of alcohols with heterocyclic bases under mild conditions. Here, we report on the influence of the alcohol on the N1- vs. O^2-alkylation of *N*3-benzoylthymine under Mitsunobu conditions. Moreover, a method for predicting the product ratio of the alkylation reaction will be introduced.

Key words: Mitsunobu reaction, carbocyclic nucleosides, regioselectivity, antiviral agents, medicinal chemistry

Carbocyclic nucleosides in that the furanose oxygen is replaced by a methylene unit have attracted considerable interest due to their wide range of biological activity.[1] Recently, carbocyclic nucleoside analogues like carbovir **1**[2] and the structurally related abacavir **2** (Ziagen™)[3] were found to be potent inhibitors of HIV reverse transcriptase. Moreover, the guanine derivative entecavir **3** (Baraclude™)[4] was approved by the FDA in early 2005 for the treatment of chronic HBV infections, a common co-infection in people with HIV.

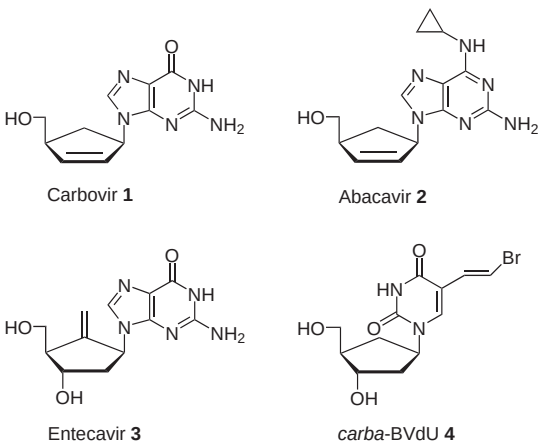


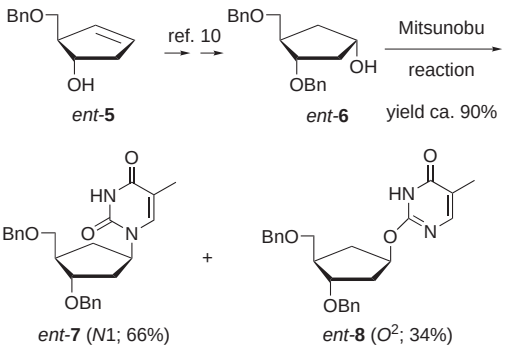
Figure 1 Examples of antiviral active carbocyclic nucleoside analogues.

Beside carbocyclic purine analogues, an example of a bioactive pyrimidine analogue is *carba*-BVdU **4** which shows significant anti-HSV-1 activity.[5]

As they lack a glycosidic bond, these nucleosides are stable towards hydrolysis by phosphorylases and therefore display enhanced biostability.[6] Moreover, in contrast to natural nucleosides particularly, carbocyclic 2′,3′-dideoxy- or 2′,3′-dideoxy-2′,3′-didehydro-purine nucleosides are acid-stable due to the missing hemiaminal structure. However, the removal of the hemiaminal oxygen abolishes the anomeric and gauche effects responsible for forcing the furan system into two distinct conformations.[7] Since the conformation of the five-membered ring is believed to play a critical role in modulating biological activity, the behavior of nucleosides with a cyclopentane moiety sometimes differs significantly from that of their natural counterparts.[8]

A number of strategies have been designed for the preparation of carbocyclic nucleosides.[9] The strategies can be subdivided into two categories: i) the linear approach involves initial synthesis of a functionalized cyclopentylamine and a step-wise synthesis of the heterocyclic base and ii) the convergent approach, here, the appropriate heterocycle is coupled directly to a functionalized carbocyclic moiety, leading to a variety of carbocyclic nucleosides starting from one common cyclopentane precursor.

Recently, we published a new convergent route to carbocyclic nucleoside analogues starting from enantiomerically pure (1*S*,2*R*)-2-benzyloxymethylcyclopent-3-enol (**5**).[10] In the key step cyclopentanol **6** is condensed with a N3-protected pyrimidine nucleobase using a modified Mitsunobu protocol (Scheme 1).[11]



Scheme 1 Mitsunobu reaction conditions: (a) PPh_3, DIAD, *N*3-benzoylthymine **8**, THF, –40 °C to r.t., 16 h (b) 1% NaOH in MeOH, r.t., 12 h.

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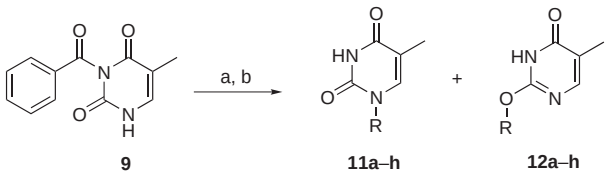
This strategy can also be used for the synthesis of carbocyclic α-, *iso*- and 3′-*epi*-nucleosides.[12] Unfortunately, the nucleobases react as ambident nucleophiles (Figure 2), leading to mixtures of isomers [*N*1-(**7**)/O^2-(**8**) isomers for pyrimidines, *N*7/*N*9-isomers for purines].

Figure 2 Alkylation of ambident pyrimidine nucleobases.

In order to maximize reaction yields and to minimize purification, reaction conditions leading predominantly to one isomer are needed. In our attempts to develop a convenient synthesis for carbocyclic nucleoside analogues, we investigated in detail the influence of the alcohol on the Mitsunobu coupling reaction with pyrimidine bases.

The regioselectivity of the alkylation of an ambident nucleophile in a given aprotic solvent clearly depends on the substrate and can be correlated to the HSAB-principle (hard soft acid base) by Pearson.[13] In the ambident nucleophile *N*3-benzoylthymine the O^2-atom represents a 'hard' alkylation site, while the N1-atom is a 'soft' nucleophilic center. The hardness of the carbon connected to the hydroxyl group in an alcohol depends upon their respective chemical environment, i.e. from the substituents or the structure (e.g. strain) in the molecule. According to the HSAB-principle it can be predicted, that the harder the carbon atom, the more O^2-alkylation should occur. To measure the hardness of this carbon atom, its ^{13}C NMR chemical shift can be taken as an estimate. A 'hard' carbon atom is hardly polarizable, i.e. the electron density at the nucleus is low, therefore the ^{13}C absorption appears at low magnetic fields and vice versa.

To investigate the electronic influence of the alcohol on the alkylation under the conditions of the Mitsunobu reaction, *N*3-benzoylthymine **9** was condensed with alcohols **10a**–**h** in THF (Scheme 2) leading to the *N*1-products **11a**–**h** and the O^2-compounds **12a**–**h** (Table 1). THF was used because it is the commonly used solvent for Mitsunobu reactions. To avoid possible steric effects caused by bulky substituents, only simple alcohols were chosen as model compounds.



Scheme 2 (a) PPh_3, DIAD, alcohol **10a–h** (see Table 1, THF, –40 °C to r.t., 16 h (b) 1% NaOH in MeOH, r.t., 12 h.

Table 1 Alkylation of *N*3-Benzoylthymine **9** with Alcohols **10a**–**h** in THF

Alcohol **10**	^{13}C NMR shift (ppm)[a]	Yield (%)[b]	N1/O^2 alkylation (%)[c]
1-Pentanol (**10a**)	61.1	89	100:0
Benzylalcohol (**10b**)	63.3	92	100:0
Cyclohex-2-enol (**10c**)	64.3	90	95:5
2-Pentanol (**10d**)	65.8	94	80:20
1-Phenylethanol (**10e**)	68.4	87	79:21
Cyclohexanol (**10f**)	68.6	90	73:27
Cyclopentanol (**10g**)	72.1	92	66:34
2,2,2-Trichloroethanol (**10h**)	75.1	90	60:40

[a] Chemical shift is given for the *ipso*-carbon atom of the alcohol.
[b] Yield of both isolated products.
[c] Determined by ^1H NMR spectroscopy

After isolation of the isomeric mixtures, the product ratio was correlated with the ^{13}C chemical shifts of the respective carbon in DMSO-d_6. Interestingly, the primary alcohols with a 'soft' carbon atom, e.g. 1-pentanol (**10a**) and benzyl alcohol (**10b**), exclusively led to the *N*1-product. As expected, with increasing 'hardness' of the carbon atom, more of the O^2-isomer was formed.

The results obtained can be used to predict the product ratio of a Mitsunobu condensation with *N*3-benzoylthymine **9** with any given alcohol by measuring the ^{13}C chemical shift of the carbon atom. This method has been applied to (1*S*,3*S*,4*R*)-3-benzyloxy-4-benzyloxymethylcyclopentanol (**6**),[10] a precursor for carbocyclic 2′-deoxynucleoside analogues. The chemical shift of C-1 is 69.5 ppm in DMSO-d_6. Therefore, a product distribution of approximately 70% of *N*1-product to 30% of O^2-isomer was expected (Scheme 1).

To prove this prediction, the alkylation reaction was performed analogously to the above procedure in THF. After chromatography of the crude product, a mixture of 66% *N*1-**7** and 34% O^2-isomer **8** was isolated. This is surprisingly close to the predicted distribution because one should keep in mind that cyclopentanol **6** has two substituents on the ring while none of the model compounds were substituted. Consequently, the method seems to give reasonable predictions for the isomeric ratio for carbocyclic nucleosides.

Further work is currently in progress in our laboratories to fine-tune the parameters of the Mitsunobu condensation in the synthesis of carbocyclic nucleosides. Our aim is to find optimized general reaction conditions for the synthesis of either carbocylic pyrimidine or purine nucleosides.

General Procedure

DIAD (545 μL, 2.80 mmol) was added slowly to a suspension of PPh_3 (787 mg, 3.00 mmol) in anhydrous THF (11 mL). The mixture was stirred for 0.5 h at 0 °C. This preformed complex was slowly added to a suspension of the *N*3-Bz-thymine **9** (506 mg, 2.2 mmol) and alcohol **10** (1.00 mmol) in anhydrous THF (6.0 mL) at –40 °C under nitrogen. The reaction was slowly warmed to r.t. and stirred overnight. The solvent was removed from the reaction mixture and a NaOH solution in MeOH (1%; 15 mL) was added and stirred overnight at r.t. to cleave the *N*3-benzoyl protecting group. The solution was neutralized by the addition of 1 M HCl and then concentrated. The crude product was purified by silica gel chromatography (hexanes–EtOAc, 1:2) to yield *N*1-products **11a**–**h** and the O^2-isomers **12a**–**h** as colorless solids. The product ratio was determined by ^{1}H NMR spectroscopy by integration of the H-1′ protons.

References

(1) Marquez, V. E. In *Advances in antiviral drug design*, Vol. 2; De Clercq, E., Ed.; JAI Press: Greenwich, **1996**, 89–146.

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

(3) Daluge, S. M.; Martin, M. T.; Sickles, B. R.; Livingston, D. A. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 297.

(4) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.

(5) (a) Balzarini, J.; Baumgartner, H.; Bodenteich, M.; De Clercq, E.; Griengl, H. *Nucleosides Nucleotides* **1989**, *8*, 855. (b) Wyatt, P. G.; Anslow, A. S.; Coomber, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sollis, S. L.; Tapolczay, D. J.; Weingarten, G. G. *Nucleosides Nucleotides* **1995**, *14*, 2039.

(6) Agrofoglio, L. A.; Challand, S. R. *Acyclic, Carbocyclic and L-Nucleosides*; Kluwer Academic Publishers: Dordrecht / Boston / London, **1998**.

(7) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H.; Feldman, R. J.; Mitsuja, H.; George, C.; Barchi, J. J. *J. Am. Chem. Soc.* **1998**, *120*, 2780.

(8) Béres, J.; Sági, G.; Tömösközi, I.; Gruber, L.; Baitz-Gács, E.; Ötvos, L.; De Clercq, E. *J. Med. Chem.* **1990**, *33*, 1353.

(9) (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.

(10) (a) Ludek, O. R.; Meier, C. *Synthesis* **2003**, *13*, 2101. (b) Ludek, O. R.; Balzarini, J.; Meier, C. *Eur. J. Org. Chem.* **2005**, submitted

(11) (a) Jenny, T. F.; Previsani, N.; Benner, S. A. *Tetrahedron Lett.* **1991**, *32*, 7029. (b) Jenny, T. F.; Horlacher, J.; Previsani, N.; Benner, S. A. *Helv. Chim. Acta* **1992**, *75*, 1944. (c) Bonnal, C.; Chavis, C.; Lucas, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1401. (d) Pérez-Pérez, M. J.; Rozenski, J.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1995**, *60*, 1531. (e) Borthwick, A. D.; Crame, A. J.; Exall, A. M.; Weingarten, G. G.; Mahmoudian, M. *Tetrahedron Lett.* **1995**, *36*, 6929. (f) Schmitt, L.; Caperelli, C. A. *Nucleosides Nucleotides* **1997**, *16*, 2165. (g) Choo, H.; Chong, Y.; Chu, C. K. *Org. Lett.* **2001**, *3*, 1471.

(12) Ludek, O. R.; Balzarini, J.; Krämer, T.; Meier, C. *Synthesis* **2005**, submitted

(13) (a) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827. (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.