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Carbocyclic Analogs of Nucleosides via Modified Mitsunobu Reactions

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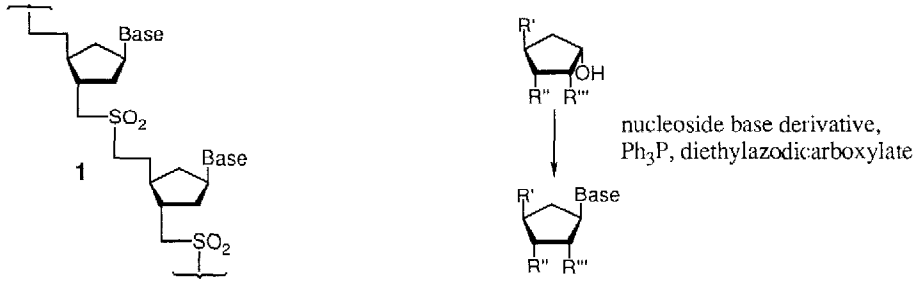
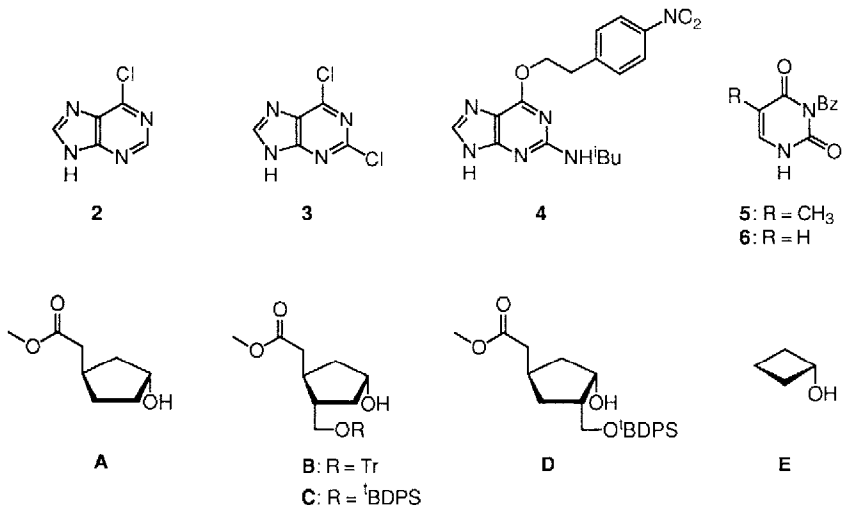
Key words: carbocyclic nucleosides, Mitsunobu reaction, anti-viral nucleosides, anti-sense nucleotide analogs

Abstract: A set of carbocyclic nucleoside analogs have been prepared using a novel modification of the Mitsunobu reaction. This approach helps solve an important synthetic problem in the preparation of carbocyclic analogs of nucleosides.

Analogs of oligonucleotides having dimethylene sulfide, sulfoxide, and sulfone units replacing the phosphate diester groups in the backbone, compounds that are potential antisense reagents, have been synthetic targets in these laboratories for some time[2,3,4]. As a part of this work, we wished to have a variant of these analogs with the ring oxygen replaced by a $-CH_2-$ group (e.g., **1**). Efforts to prepare building blocks for these analogs encountered several synthetic problems that are common in the synthesis of carbocyclic analogs of nucleosides generally.[5] Attachment of cyclopentane or other substituents to a purine via direct alkylation often yields both N^7 and N^9 substituted derivatives[6], while alkylation of pyrimidines (e.g., with tosylates and mesylates)[7] is generally low yielding. Alkylation of purines using epoxides has successfully yielded carbocyclic analogs of nucleosides [8,9,10,11,12]. However, this approach necessarily gives ring systems that are hydroxylated in an inconvenient position. Further, stepwise construction of purine and pyrimidine ring systems around a carbocyclic amine[13] proved in our hands to be tedious and low-yielding, and involved reaction conditions that were incompatible with groups used in our systems to protect functionality on the side chains of the cyclopentyl rings[14].

We therefore have extended Mitsunobu-type procedures[15] to append the heterocyclic rings 6-chloropurine (**2**), 2,6-dichloropurine (**3**), N^2-isobutyryl-O^6-[2-(*p*-nitrophenyl)ethyl]guanine (**4**)[16], N^3-benzoyl-thymine (**5**), and N^3-benzoyluracil (**6**)[17] to the cyclopentanol cores **A**, **B**, **C**, **D**[18] under modified Mitsunobu conditions. Other carbocyclic nucleoside analogs were prepared from these products by direct modification. Recently published work[19,20,21] reports the interest of many laboratories in analogous carbocyclic nucleosides, derived in part from the fact that carbocyclic oligonucleotide analogs may be useful both as anti-viral and as anti-sense drugs[22,23]. In view of this interest, and the fact that many laboratories encounter synthetic problems noted above, we believe that it is appropriate at this time to make these procedures available.





The experiments were carried out in two modifications. If the base is soluble in THF the Ph_3P-DEAD (diethylazodicarboxylate) complex is preformed in THF at 0°C, followed by the addition of a mixture of the alcohol and the nucleoside base derivative in THF at the desired temperature. If the base is insoluble in THF, a suspension of the nucleoside base derivative, the alcohol and Ph_3P in dioxane is treated with DEAD in THF at the desired temperature[24].

entry	carbocyclic ring	nucleoside base derivative	base [equiv]	Ph_3P [equiv]	DEAD [equiv]	time [h]	T [°C]	yield [%]
1	**A**	**2**	1.2	1.2	1.2	18	25	80[25]
2	**A**	**3**	2	3	3	96	-20	81
3	**A**	**4**	1	4	4	18	25	69[26]
4	**A**	**5**	2	2.5	2.5	18	-50	52[27]
5	**A**	**6**	2	2.5	2.5	18	-50	47[28]
6	**B**	**4**	1.5	2	2	18	25	71[29]
7	**C**	**2**	1.5	1.5	1.5	18	25	78[30]
8	**D**	**2**	1.5	1.5	1.5	18	25	44[31]
9	**E**	**4**	1.5	2	2	18	25	53[32]

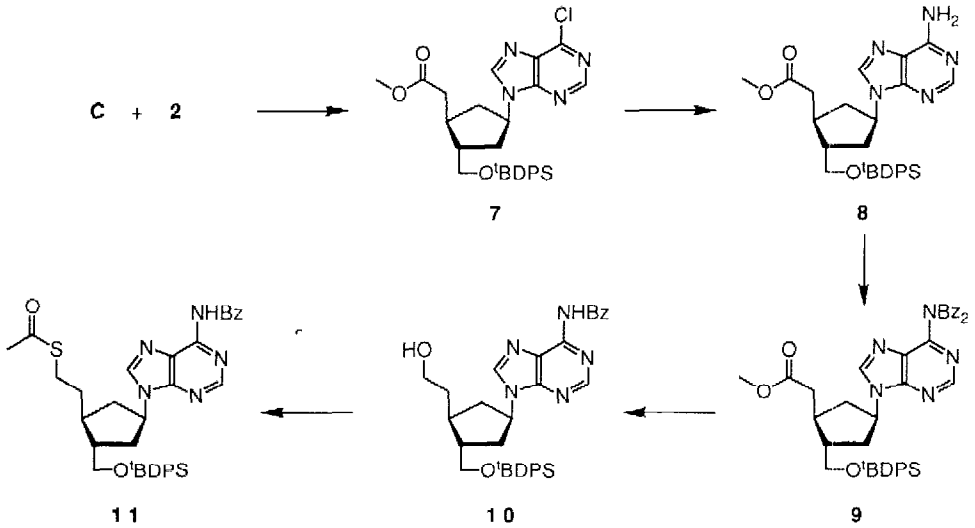
The success of the Mitsunobu procedures depends on the structure of the nucleoside base acting as a nucleophile in the reaction and the conditions under which the reaction was run, but not (apparently) on the structure of the alcohol. Even with strained cyclobutanol (**E**), the replacement of the hydroxy function with the guanine derivative **4** was possible in reasonable yield (entry 9). Side chains on the cyclopentanol seemed not to have a large influence on the yields (entry 6 and 7) unless they were adjacent to the hydroxyl group in the cyclopentane ring (entry 8).

One notable feature in the synthesis of derivatives bearing a purine ring is the absence of the formation of products bearing N^7 substituents. This fact is especially notable in the preparation of guanosine derivatives (entries 3, 6, and 9). Derivatives of guanine alkylated on N^9 are especially difficult to prepare by standard alkylation procedures, and this building block should be useful for the preparation of a range of these derivatives. While the origin of the high regioselectivity in this reaction is unknown, steric factors may play an important role.

In the preparation of thymine and uracil derivatives by this approach, the yields (entries 4 and 5) of the protected compounds are typically only between 47% and 52%. Some of this low yield is undoubtedly due to the

partial loss of the N-benzoyl group from the ring nitrogen during purification. If, as is normally the case, debenzoylation is the desired next step, the yields of deprotected compound are considerably higher. Nevertheless, the single step procedure presented here is considerably more efficient than alternative routes to these compounds involving the construction of the pyrimidine ring on a cyclic amine.

The building blocks for preparing carbocyclic oligonucleotide analogs with dimethylsulfide, -sulfoxide, and -sulfone linkers (e.g., **1**) are directly prepared from the carbocyclic nucleoside analogs containing the cyclopentanol cores **B** or **C**. In case of the adenosine building block, **7** was treated with ammonia (25% aqueous, in an equal vol. dioxane at 60°C) to yield **8**[25]. After protection of the free amino function with benzoyl chloride (6 equiv, in pyridine), the reduction of **9** with lithium triethylborohydride (in THF at -18°C) led to **10**, that was finally treated with thioacetic acid under Mitsunobu conditions[33] to give the desired, protected adenosine building block **11**.



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References and Notes

1 Present address: Department of Chemistry, M.I.T., Cambridge, MA 02139, USA.
2 Schneider, K. C., Benner, S. A. *Tetrahedron Lett.*, **1990**, 31, 335-338.
3 Uhlmann, E., Peyman, A. *Chemical Reviews*, **1990**, 90, 543-584.
4 Huang, Z., Schneider, K. C., Benner, S. A. *J. Org. Chem.*, **1991**, 56, 3869.
5 Marquez, V. A., Lim, M. I. *Medical Res. Rev.*, **1986**, 6, 1-40.
6 Jones, M. F., Roberts, S. M. *J. Chem. Soc. Perkin I* , 1990, 2927-2932.
7 Medich, J. R., Kunnen, K. B., Johnson, C. R. *Tetrahedron Lett.*, **1987**, 28, 4131-4134.
8 Kondo, K., Sato, T., Takemoto, K. *Chem. Lett.*, **1973**, 967-968.
9 DiMenna, W. S., Piantadosi, C., Lamb, R. G. *J. Med. Chem.*, **1978**, 21, 1073-1076.
10 Martin, J. C., Smee, D. F., Verheyden, J. P. H. J. *Org. Chem.*, **1985**, 50, 755-759.

11 Bindu Madhavan, G. V., Martin, J. C. *J. Org. Chem.*, **1986**, 51, 1287-1293.

12 Biggadike, K., Borthwick, A. D., Exall, A. M., Kirk, B. E., Roberts, S. M., Youds P. *J. Chem. Soc. Commun.*, **1987**, 1083-1084.

13 Borthwick, A. D., Evans, D. N., Kirk, B. E., Biggadike, K., Exall, A. M., Youds, P., Roberts, S. M., Knight, D. J., Coates, J. A. V. *J. Med. Chem.*, **1990**, 33, 179-186; Vince, R., Hua, M. *J. Med. Chem.*, **1990**, 33, 17-21.

14 Jenny, T. F. Dissertation E.T.H., No. 9262, **1990**.

15 Marquez, V. A., Tseng, C. K. H., Treanor, S. P., Driscoll, J. S.*Nucleosides Nucleotides*, **1987**, 6, 239-244; Bestmann, H. J., Roth, D. *Angew. Chemie*, **1990**, 102, 95-96.

16 Jenny, T. F., Schneider, K. C., Benner, S. A. submitted.

17 Cruickshank, K. A., Jiricny, J., Reese, C. B. *Tetrahedron Lett.*, 25 (**1984**), 681-684.

18 The synthesis of these cyclopentanol derivatives will be published elsewhere.

19 Ötvös, L., Beres, J., Sagi, Gy., Tomoskozi, I., Gruber, L. *Tetrahedron Lett.*, **1987**, 28, 6381.

20 Balzarini, J., Baumgartner, H., Bodenteich, M., de Clercq, E., Griengl, H. *J. Med. Chem.*, **1989**, 32, 1861-1865.

21 Sagi, J., de Clercq, E., Szemzö, A., Csarnyi, A., Kovacs, T., Ötvös, L. *Biochem. Biophys. Res. Commun.*, **1987**, 147, 1105-1112.

22 Szemzö, A., Szecsi, J., Sagi, J., Ötvös, L. *Tetrahedron Lett.*, **1990**, 31, 1463 1466.

23 Perbost, M., Lucas, M., Chavis, C., Pompon, A., Baumgartner, H., Rayner, B., Griengl, H., Imbach, J.-L. *Biochem. Biophys. Res. Commun.*, **1989**, 165, 742-747.

24 A typical protocol is as follows: To a solution of triphenylphosphine (790 mg, 3 mmol) in absolute THF (7 ml) was added diethylazodicarboxylate (DEAD, 95%, 0.48 ml, 3 mmol) at 0°C over a period of 20 min. The solution was stirred for 30 min to yield a precipitate of the triphenylphospine-DEAD complex. The mixture is cooled to -78°C, and then a solution of 2,6-dichloropurine (380 mg, 2 mmol) and **A** (160 mg, 1 mmol) in absolute THF (4 ml) is added. The mixture is allowed to stir at -20°C for 96 hours, and then warmed to room temperature. The crude product was adsorbed onto Kieselgel (4.5 g) and chromatographed (Kieselgel, CH_2Cl_2:MeOH 98:2 as eluant). Fractions containing product were collected and the solvents removed by rotary evaporation to yield 7 (270 mg, 81%) as a colorless foam. An analytical sample was obtained by recrystallization from ether:hexane: m.p. 120°C, ^{1}H-NMR ($CDCl_3$): 1.67-1.85 (m, 2H); 2.04-2.18 (m, 2H), 2.34-2.46 (m, 1H); 2.48-2.66 (m, 4H); 3.70 (s, 3H); 4.93-5.02 (m, 1H); 8.18 (s, 1H). All new compounds reported here gave satisfactory combustion analyses, and complete spectral characterization was obtained for these as well.

25 A mixture of product and Ph_3PO was obtained. Yield is calculated from NMR data. After reaction with NH_3 (as a mixture of aqueous ammonium hydroxide and dioxane) the corresponding adenosine analog was obtained in 45% overall yield.

26 After removal of the *p*-nitrophenylethyl group with DBU in pyridine.

27 Direct removal of the benzoyl group without isolation and purification of the protected thymine derivative led to the corresponding thymidine analog in higher yield.

28 Direct removal of the benzoyl group without isolation and purification of the protected uracil derivative led to the corresponding uridine analog in higher yield.

29 After removal of the *p*-nitrophenylethyl group with DBU in pyridine the corresponding N^2-protected guanosine analog was obtained in 68% overall yield.

30 After amination with NH_3 the corresponding adenosine analog was obtained in 55% overall yield.

31 In addition to the substitution product, the corresponding olefin arising from an elimination of water from **C** was a major side product (isolated in 40% yield).

32 After removal of the *p*-nitrophenylethyl group with DBU in pyridine.

33 Volante, R. P. *Tetrahedron Lett.*, **1981**, 3119-3122.

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