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# Practical synthetic routes to carbon-substituted nucleosides

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ABSTRACT

Robust practical routes to three different carbon-substituted nucleosides are described. Short synthetic procedures for preparing 1′-homonucleosides, 2′-*C*-methyl-carbanucleosides and 2′-*C*-methyl-cyclopropyl/cyclopentyl fused bicyclic ribose analogues are described starting from readily available building blocks.



Nucleosides represent a useful class of both anti-viral and anti-cancer agents.[1] The nucleoside first requires activation by cellular kinases to the corresponding triphosphate, which can then act as either a competitive inhibitor of viral and/or cellular nucleic acids or a pseudo-substrate which is incorporated into a growing nucleic acid strand. Due to many nucleosides and/or their triphosphates showing poor selectivity and unacceptable toxicity, much research has gone into finding more specific and less toxic analogues.[2] This has been attempted through modifications to either the base or the sugar component of the nucleosides. The latter strategy has enjoyed some considerable success, with many examples now of clinically useful nucleoside analogues such as acyclovir[3] **1**, emtricitabine[4] **2** and NM283[5] **3** (Fig. 1).

In this Letter, we wish to describe novel syntheses of several carbon-substituted nucleoside analogues (Fig. 2).

In particular, we describe routes to 1′-homonucleosides **4** in which an extra methylene has been inserted between the base and the 1′-position, 2′-*C*-Me-carbanucleosides **5** and 2′-*C*-Me substituted versions of cyclopropyl/cyclopentyl fused ribose analogues **6**.

The routes described herein represent some diverse and practically useful chemistry to access a range of substituted nucleoside structures.

1′-Homonucleosides of general structure **10** are well known in the literature.[6] Their synthesis generally can be achieved in one of the two ways shown in Figure 3. Firstly, base attachment to the sugar through activation of a substituted methylene group at the 1′-position (viz. **8**), or de novo construction of the base from a 1′-aminomethyl intermediate (viz. amine **9**). Amine **9** can clearly be accessed directly from **7**.[7]

Typically, the requisite methylene-substituted grouping in **8** and/or **9** is derived from a ribose analogue, for example, a glycosyl halide **7**, and a C–N synthon such as a nitrile group. These methods introduce a mixture of diastereoisomers at the anomeric centre, and typically use benzyl protecting groups for the ribose hydroxyl groups. Ideally, we wished to access the building blocks **8** and **9** in diastereoisomerically pure form and be able to use simple acid-labile protecting groups.

We initially looked into known methods of synthesising ribose analogues in which the 1′-position featured a hydroxymethyl group. Several syntheses of such substrates have been reported, for example the epoxide opening route shown in Scheme 1.[6b] By

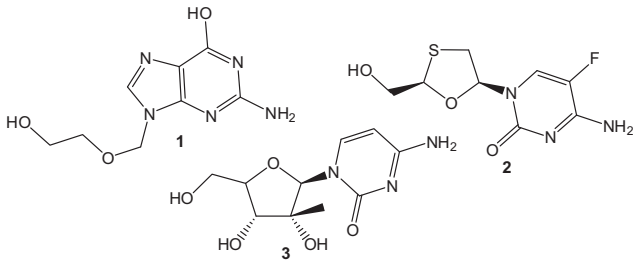


**Figure 1.** Clinically precedented nucleoside analogues.

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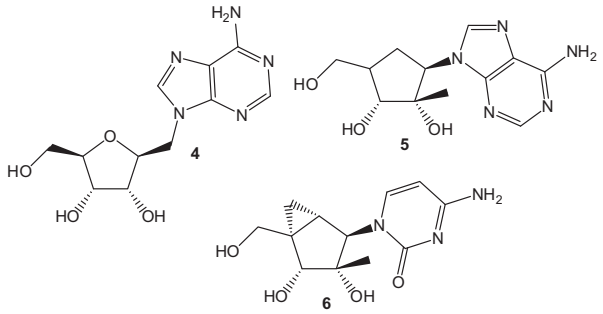


**Figure 2.** Target carbon-substituted nucleosides.

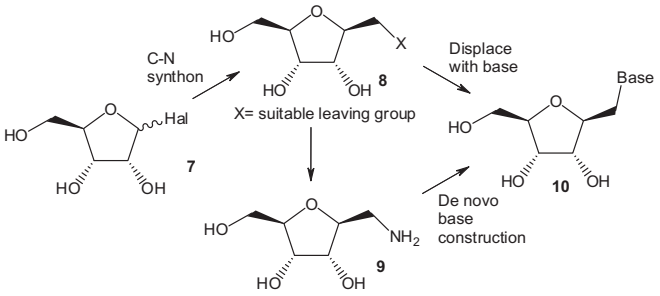
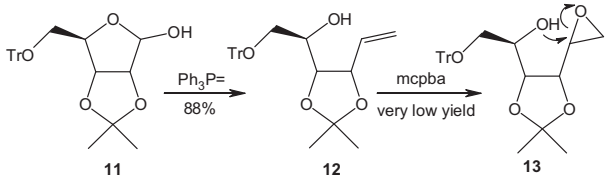



**Figure 3.** Literature strategies towards 1′-homonucleosides.

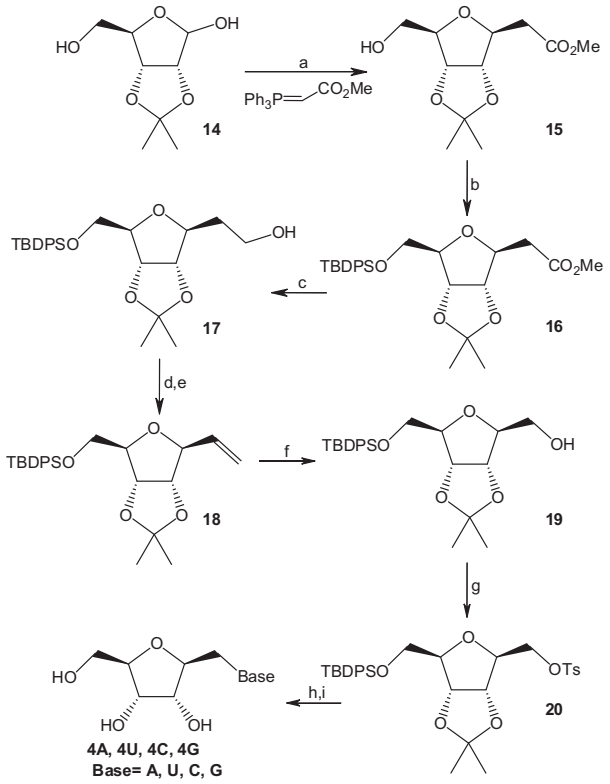



**Scheme 1.** Attempted synthesis of 1′-homologated nucleoside core. Reagents and conditions: (a) methyltriphenylphosphonium bromide, $^{n}$BuLi, THF, −78 °C→rt, 16 h; (b) *m*-CPBA, DCE, reflux.

incorporating an acetonide function at the 2′/3′-position it was hoped to bias the diastereoselectivity of the epoxide-opening reaction, but in our hands we were not able to secure acceptable yields of any desired products, possibly as a consequence of this choice of protecting groups. Derivatisation of the known ribose analogue **11** and then addition of *m*-chloroperbenzoic acid (*m*-CPBA) to the acetonide-protected ribose analogue **12** gave a very low yield of the desired homonucleoside in what was a very messy reaction.

We then investigated ways of increasing the effectiveness of this type of ring-closure through olefin activation (Scheme 2). Treatment of the known protected ribose **14** with methoxycarbonylmethylene triphenylphosphorane gave the ester **15** as a single diastereoisomer according to the method of Moffat.[8] While this strategy introduced an extra carbon atom at the anomeric centre, by fixing the stereochemistry at the anomeric position at this early stage, we felt this to be acceptable. Alcohol protection to give **16** and functional group interconversion through alcohol **17** and olefin **18** led to the 1′-homoribose analogue **19**. Activation of the hydroxymethyl group as its tosylate **20** and displacement with all four of the nucleobases proceeded well.

In the majority of cases the desired base was used directly in the displacement reaction, that is, adenine, cytosine and uracil, but in the case of the target guanine base, displacement was carried out with 2-amino-6-chloropurine followed by the conversion of chlorine into oxygen with 2-mercaptoethanol prior to deprotection.[9]




**Scheme 2.** A robust synthetic route to all four 1′-homonucleosides. Reagents and conditions: (a) $Ph_3PCHCO_2Me$, MeCN, reflux, 3 h; (b) TBDPSCl, imidazole, dichloromethane, rt, 73% over two steps; (c) DIBAL-H, dichloromethane, −78 °C→rt, 24 h, 87%; (d) MsCl, dichloromethane, 1 h, 0 °C→rt, 99%; (e) KO$^{t}$Bu, THF, 2 h, rt, 63%; (f) $OsO_4$, NMO, acetone, rt, 4 h then $NaIO_4$, $NaBH_4$, EtOAc, 3 h, rt, 41%; (g) TsCl, $Et_3N$, dichloromethane, reflux, 4 h, 94%; (h) nucleobase, LiH, DMSO, 90 °C, 5–16 h, 36–60%, then (i) deprotection, 40–80% (see Supplementary data for more detail).

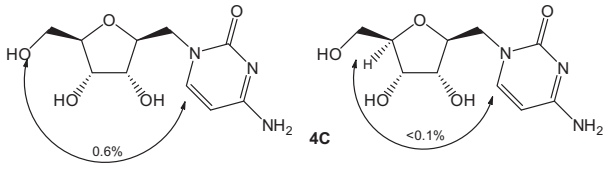


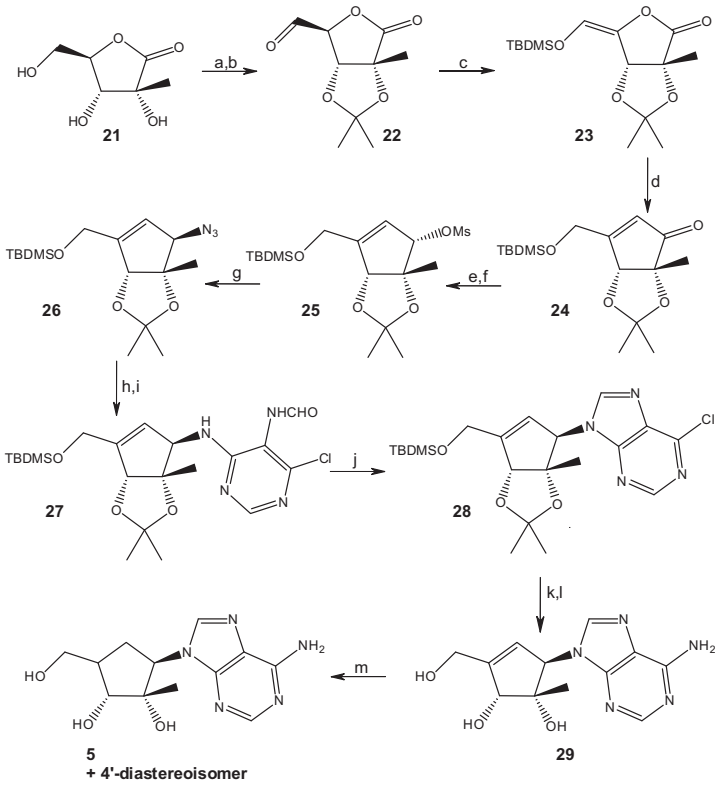

**Figure 4.** NOE data for compound **4C**.

Confirmation of the *cis*-stereochemistry was confirmed by the NOE analysis on **4C** (Fig. 4).

Full experimental detail is provided in the Supplementary data. This completed a practically useful synthesis of all four ribose homonucleosides as single diastereoisomers.

Carbocyclic ribose analogues have been synthesised in a variety of ways, including methods to build up the cyclopentane ring using ring closing metathesis and constructing a cylopentane ring starting from a ribose analogue precursor. As mentioned above, ribose systems that contain substitution, for example methyl group substitution at the 2′-position, have been the subject of considerable research efforts as potential treatments for HCV infection.[5,10] The insertion of a 2′-*C*-methyl group favours the 3′-*endo* northern conformation. Methods for the stereospecific introduction of a 2′-*C*-Me group into a carbanucleoside are much less well precedented.[11] Liao et al.[12] recently described a novel route to 2′-β-*C*-methyl-neplanocin derivatives, however we developed alternative route to this class of nucleosides (Scheme 3).

We chose to start from the chiral pool, in which the stereochemistry of the 2′/3′ centres was already fixed, and the required




**Scheme 3.** Synthetic route to an adenine substituted 2′-*C*-Me-carbanucleoside. Reagents and conditions: (a) acetone, $H_2SO_4$, rt, 100%; (b) Dess–Martin periodinane, dichloromethane, rt, 84%; (c) TBDMSCl, MeCN, $Et_3N$, rt, 44%; (d) $^tBuOK$, $^tBuLi$, $BrCH_2PPh_3$, THF, −78 °C, 64%; (e) $NaBH_4$, $CeCl_3$, EtOH, rt, 50%; (f) MsCl, dichloromethane, $Et_3N$, rt; (g) $NaN_3$, DMF, rt, 46% over two steps; (h) $PPh_3$, $H_2O$, THF, rt, 91%; (i) 4,6-dichloro-5-(*N*-formyl)-aminopyrimidine, dioxane, $Et_3N$, reflux, 99%; (j) diethoxymethyl acetate, 120 °C, 51%; (k) ammonia, MeOH, 100 °C, 84%; (l) 90% aqueous TFA, rt, 82%; (m) 1 atm $H_2$, 5% Pd(C), MeOH, rt, 25%.

2′-*C*-Me group was already installed. In particular, 2′-*C*-Me-ribonolactone[13] **21** was used as a versatile and readily available starting material.

The ribonolactone **21** was protected as its acetonide, oxidised to the aldehyde **22** and then converted to the silyl enol ether **23** in good overall yield according to the method of Shiozaki et al.[14] Treatment of **23** with bromomethyl triphenylphosphine gave the cyclopentenone **24** which was selectively reduced[12] using a mixture of $NaBH_4$ and $CeCl_3$ and then mesylated to give **25**. Azide displacement proceeded smoothly to yield **26**, from which the adenine ring of **28** was built up via the pyrimidine analogue **27**. Chloride displacement and a global deprotection gave the cyclopentene nucleoside **29**. The final step that remained was the hydrogenation of the olefin. A simple hydrogen pressure heterogeneous reduction using palladised charcoal gave an approximately 1:1 mixture of diastereoisomers at the 4′-centre of the target **5**. While this lack of selectivity was disappointing, we have not as yet explored any of the myriad methods that could offer a more selective reduction at this final step, or indeed attempting the hydrogenation at an earlier step in which the ring is much more sterically crowded by protecting groups which would greatly improve this final step in the synthesis.

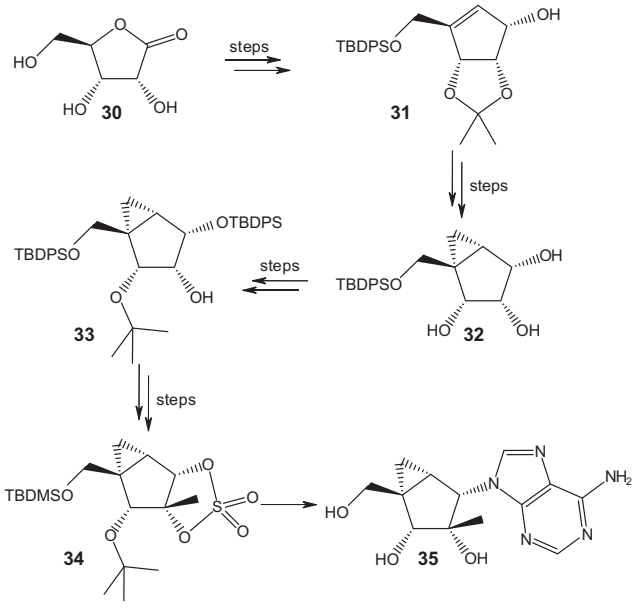
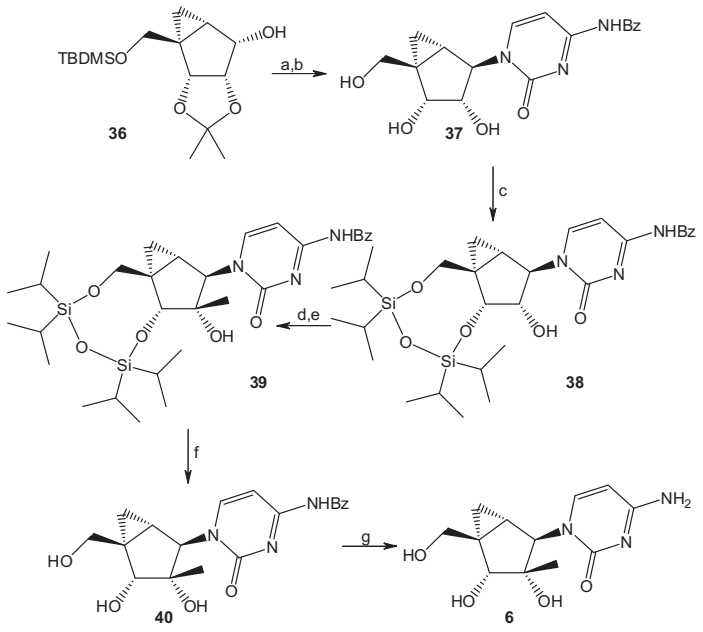



**Figure 5.** The route by Lee et al. route to 2′-*C*-methyl cyclopropyl fused cyclopentanes.

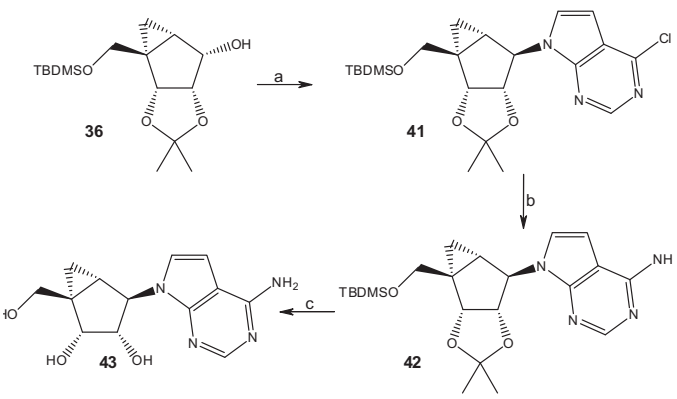
Another way to bias a ribose analogue towards the northern 3′-*endo* conformation is to fuse the cyclopentane ring to a cyclopropane ring at the 4′/6′ positions.[15] We were interested in combining this structural feature with the 2′-*C*-Me insertion described above to access target compounds of structure **6**.

Few methods of making targets of this type are known in the literature. Lee et al.[16] described a method of preparing the adenine analogue **34** in 2006 as shown in Figure 5.

This method started from the commercially available ribonolactone **30**, and followed a similar route to that described in Scheme 3 above in that a cyclopentenol **31** was also targeted, and the olefin used to insert the cyclopropane ring in **32** using a Simmons–Smith reaction. Protecting group manipulation led to **33**, from which a cyclic sulfate **34** was constructed, and then used as a leaving group to insert the adenine base and yield the final target nucleoside **35** after deprotection.




**Scheme 4.** An expeditious route to 2′-*C*-Me cyclopentane/cyclopropane fused carbanucleosides. Reagents and conditions: (a) 4-*N*-benzoyl-cytosine, DIAD, $PPh_3$, THF, 0 °C, 70%; (b) AcOH, water, 70 °C, 64%; (c) tetra-*iso*propyl-dichloro-siloxane, imidazole, DMF, 76%; (d) Dess–Martin periodinane, dichloromethane, rt, 82%; (e) MeLi, THF, −78 °C, 69%; (f) TBAF, THF, rt, 82%; (g) MeOH, $NH_3$, rt, 32%.




**Scheme 5.** An expeditious route to cyclopentane/cyclopropane fused carbanucleosides. Reagents and conditions: (a) 4-chloro-7*H*-pyrrolo[2,3-*a*]pyrimidine, DIAD, $PPh_3$, THF, 0 °C, 16 h, 79%; (b) MeOH, $NH_3$, 100 °C, 24 days, 90%; (c) AcCl, MeOH, rt, 5 h, 85%.

Our initial route sought to cyclopropanate intermediates similar to **24** and **25** as a simple entry into the desired ring system. All these attempts failed, presumably due to steric encumbrance of the olefin. Our next route initially followed a very similar path to that of Lee. The cyclopentane **36**[17] was built using the same chemistry, but at this stage our route diverged in order to shorten and simplify the synthesis. We chose to insert the base directly onto **36** which proceeded well to give the nucleoside analogue **37**. The 3′ and 5′ hydroxys were then protected using a tetra-*iso*propyl-disiloxane group that favours the protection of 1,3-diols. This created a single free alcohol group in **33** that was oxidised and methylated to give a single diastereoisomer **39**. Siloxane deprotection gave **40**, and final benzoyl deprotection gave the final target **6**.

The alcohol intermediate **36** is of course a highly versatile intermediate, in which the first step illustrated in Scheme 4 could easily incorporate any number of base analogues to generate a diverse set of nucleosides.

As an illustration (Scheme 5), **36** was treated with the commercially available 4-chloro-7*H*-pyrrolo[2,3-*a*]pyrimidine under similar Mitsunobu conditions to give the coupled material **41** in good yield. Ammonia displacement to **42** and deprotection gave a straightforward alternative synthesis[18] of the final nucleoside **43**.

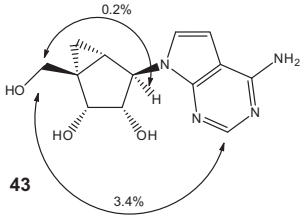



**Figure 6.** NOE data for compound **43**.

Confirmation of the *cis*-stereochemistry was provided by the NOE analysis on **43** (Fig. 6).

Throughout this Letter, we have described robust synthetic routes to install carbon substitution in a range of different locations around a ribose, or the ribose ring analogues. The methodology described herein could be adapted to further expand the range of substitution available to create yet more nucleoside diversity.

## Supplementary data

Supplementary data (experimental procedures and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.074.

## References and notes

1. *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1994; Vol. 3,.
2. For a recent review, see: Mathé, C.; Périgaud, C. *Eur. J. Org. Chem.* **2008**, 1489.
3. Gnann, J. W., Jr.; Barton, N. H.; Whitley, R. J. *Pharmacotherapy.* **1983**, *3*, 275.
4. Saag, M. S. *Clin. Infect. Dis.* **2006**, *42*, 126.
5. Pierra, C.; Amador, A.; Benzaria, S.; Cretton-Scott, E.; D'Amours, M.; Mao, J.; Mathieu, S.; Moussa, A.; Bridges, E. G.; Standring, D. N.; Sommadossi, J.-P.; Storer, R.; Gosselin, G. *J. Med. Chem.* **2006**, *49*, 6614.
6. (a) Bobek, M.; Farkas, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 1684; (b) Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 5563; (c) Scremin, C. L.; Boal, J. H.; Wilk, A.; Phillips, L. R.; Beaucage, S. L.

*Biorg. Med. Chem. Lett.* **1996**, *6*, 207; (d) Winkley, M. W. *Carbohydr. Res.* **1973**, *31*, 245.
7. For some elegant, more recent methods towards 1′-homonucleosides, see: (a) Busca, P.; McCort, I.; Prangé, T.; Merrer, Y. L. *Eur. J. Org. Chem* **2006**, 2403; (b) Lamberth, C. *Org. Prep. Proc. Int.* **2002**, *34*, 149.
8. Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, L. M.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.
9. Jeong, L. S.; Schinazi, R. F.; Beach, W.; Kim, H. O.; Nampalli, S.; Shanmuganathan, K.; Alves, A. J.; McMillan, A.; Chu, C. K.; Mathis, R. *J. Med. Chem.* **1993**, *36*, 181.
10. Eldrup, A. B.; Prhavc, M.; Brooks, J.; Bhat, B.; Prakash, T. P.; Song, Q.; Bera, S.; Bhat, N.; Dande, P.; Cook, P. D.; Bennett, F.; Carroll, S. S.; Ball, R. G.; Bosserman, M.; Burlein, C.; Colwell, L. F.; Fay, J. F.; Flores, O. A.; Getty, K.; LaFemina, R. L.; Leone, J.; MacCoss, M.; McMasters, D. R.; Tomassini, J. E.; Von Langen, D.; Wolanski, B.; Olsen, D. B. *J. Med. Chem.* **2004**, *47*, 5284.
11. Li, H.; Lee, W.; Yoo, J. C.; Hong, J. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2039.
12. Liao, X.; Butora, G.; Olsen, D. B.; Carroll, S. S.; McMasters, D. R.; Leone, J. F.; Stahlhut, M.; Doss, G. A.; Yang, L.; MacCross, M. *Tetrahedron Lett.* **2008**, *49*, 4149.
13. Booth, K. V.; da Cruz, F. P.; Hotchkiss, D. J.; Jenkinson, S. F.; Jones, N. A.; Weymouth-Wilson, A. C.; Clarkson, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2417.
14. Shiozaki, M.; Arai, M.; Kobayashi, Y.; Kasuya, A.; Miyamoto, S.; Furukawa, Y.; Takayama, T.; Haruyama, H. *J. Org. Chem.* **1994**, *59*, 4450.
15. Marquez, V. E.; Choi, Y.; Comin, M. J.; Russ, P.; George, C.; Huleihel, M.; Ben-Kasus, T.; Agbaria, R. *J. Am. Chem. Soc.* **2005**, *127*, 15145.
16. (a) Lee, J. A.; Kim, H. O.; Tosh, D. K.; Moon, H. R.; Kim, S.; Jeong, L. S. *Org. Lett.* **2006**, *8*, 5081; (b) Jeong, L. S.; Lee, J. A.; Kim, H. O.; Tosh, D. K.; Moon, H. R.; Lee, S. J.; Lee, K. M.; Sheen, Y. Y.; Moon, W. C. *Nucleosides, Nucleotides, Nucleic Acids* **2007**, *26*, 1021.
17. Michel, B. Y.; Strazewski, P. *Chem. Eur. J.* **2009**, *15*, 6244.
18. Jacobsen, K. A.; Mackman, R. L.; Joshi, B. V. *Chem. Abstr.* **2006**, *145*, 272000.