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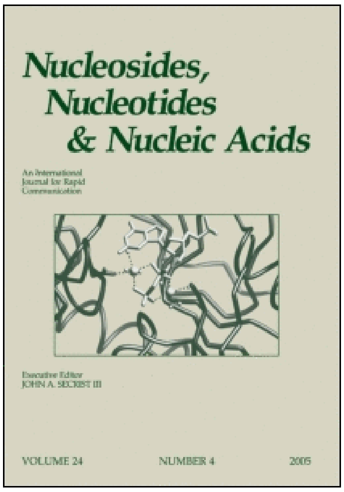

# Nucleosides, Nucleotides and Nucleic Acids

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# Synthesis of Novel 3'-*C*-Hydroxymethyl Nucleosides by a Convergent Strategy

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NUCLEOSIDES & NUCLEOTIDES, 16(7-9), 1063-1066 (1997)

# SYNTHESIS OF NOVEL 3'-*C*-HYDROXYMETHYL NUCLEOSIDES BY A CONVERGENT STRATEGY

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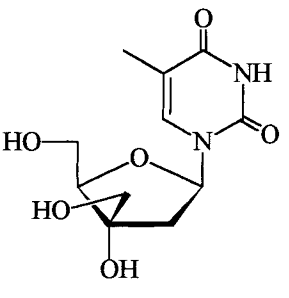
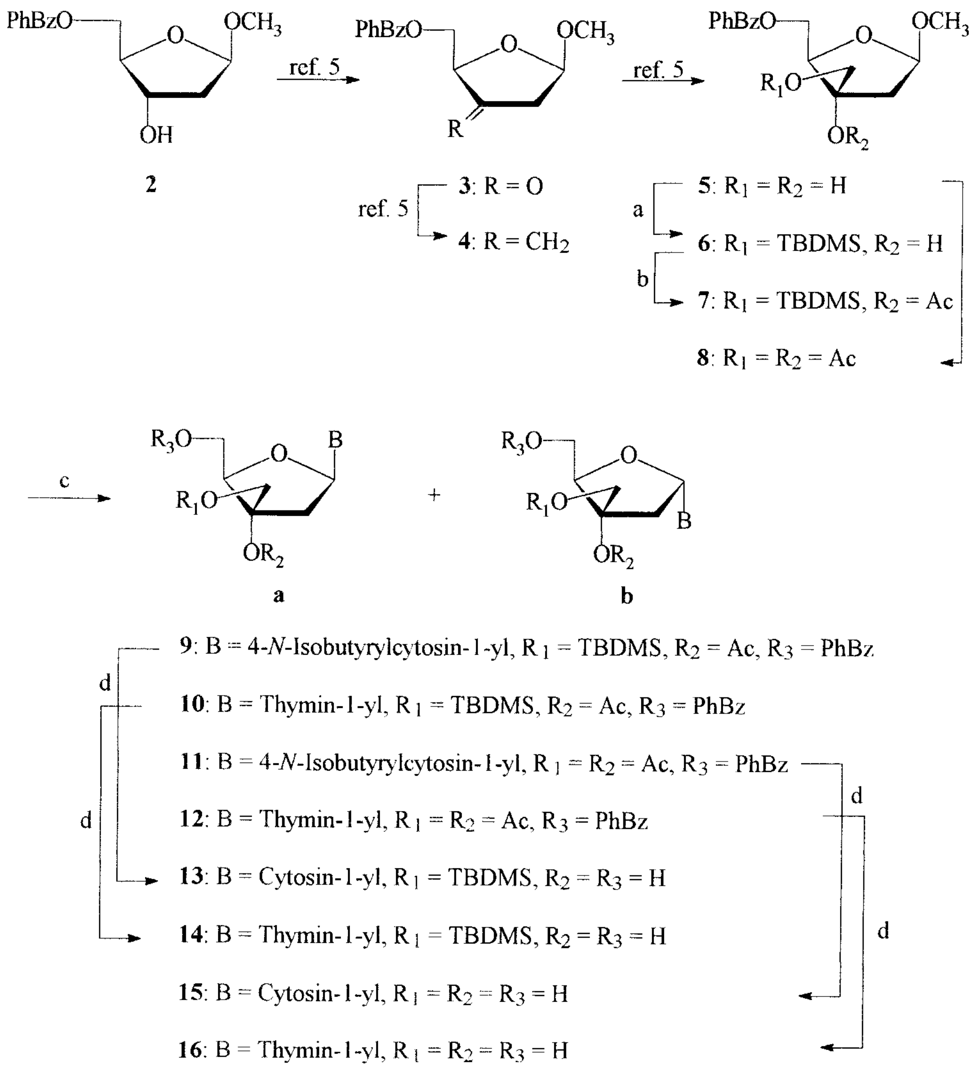
ABSTRACT: Synthesis of 1-(2-deoxy-3-*C*-hydroxymethyl-α/β-D-*erythro*-pentofuranosyl)thymine and -cytosine by a convergent strategy using the precursors **7** and **8** have been accomplished.

Previously, we have shown[2-4] that duplexes involving oligodeoxynucleotide (ODN) analogues containing 3'-*C*-hydroxymethylthymidine (**1**) exhibit excellent thermal stabilities and enhanced stability towards 3'-exonucleolytic degradation compared to unmodified ODNs. These results have promoted us to investigate the possibility of synthesising novel 3'-*C*-hydroxymethyl nucleosides by a convergent strategy.



**1**

3-*C*-Hydroxymethyl-β-D-*erythro*-pentofuranoside derivative[5] **5** was obtained from methyl 2-deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside (**2**) in four steps including stereoselective dihydroxylation[5] of 3-*C*-methylene pentofuranoside **4**. Reaction of **5** with *t*-butyldimethylsilyl chloride (TBDMSCl) in anhydrous DMF using imidazole as a catalyst gave 3-*C*-(*t*-butyldimethylsilyl)oxymethyl pentofuranoside **6** in 99% yield. Subsequent acetylation of the sterically hindered tertiary hydroxyl group, using acetic anhydride in anhydrous $CH_2Cl_2$ in the presence of pyridine and dimethylaminopyridine (DMAP), afforded methyl 2-deoxy-3-*C*-hydroxymethyl-β-D-*erythro*-pentofuranoside **7** in 94% yield. Acetylation of **5** using the same conditions as described for **6** afforded a



3: $R = O$

4: $R = CH_2$

5: $R_1 = R_2 = H$

6: $R_1 = TBDMS, R_2 = H$

7: $R_1 = TBDMS, R_2 = Ac$

8: $R_1 = R_2 = Ac$

9: $B$ = 4-*N*-Isobutyrylcytosin-1-yl, $R_1 = TBDMS, R_2 = Ac, R_3 = PhBz$

10: $B$ = Thymin-1-yl, $R_1 = TBDMS, R_2 = Ac, R_3 = PhBz$

11: $B$ = 4-*N*-Isobutyrylcytosin-1-yl, $R_1 = R_2 = Ac, R_3 = PhBz$

12: $B$ = Thymin-1-yl, $R_1 = R_2 = Ac, R_3 = PhBz$

13: $B$ = Cytosin-1-yl, $R_1 = TBDMS, R_2 = R_3 = H$

14: $B$ = Thymin-1-yl, $R_1 = TBDMS, R_2 = R_3 = H$

15: $B$ = Cytosin-1-yl, $R_1 = R_2 = R_3 = H$

16: $B$ = Thymin-1-yl, $R_1 = R_2 = R_3 = H$

**FIGURE 1.** (a) *t*-Butyldimethylsilyl chloride, imidazole, DMF; (b) $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$; (c) 4-*N*-isobutyrylcytosine or thymine, BSA, $CH_3CN$, TMS-triflate; (d) $NH_3$/MeOH.

second nucleoside precursor, namely methyl 3-*C*-acetoxymethyl-3-*O*-acetyl-2-deoxy-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside (**8**) in quantitative yield.

A direct nitrogen glycosylation reaction[6] of **7** or **8** with 4-*N*-isobutyrylcytosine and thymine, using bis(trimethylsilyl)acetamide (BSA) as silylating agent and trimethylsilyl trifluoromethanesulfonate (TMS-triflate) as Lewis acid, afforded anomeric mixtures of the four nucleosides **9a/9b** (2:1, 65% from 7), **10a/10b** (4:3, 59% from 7), **11a/11b** (2:1, 59% from **8**) and **12a/12b** (2:1, 69% from **8**). Deprotections, using a saturated solution of ammonia in methanol, afforded anomeric mixtures **13a/13b**, **14a/14b**, **15a/15b** and **16a/16b** in yields of 50-60%. We were in all cases unable to separate the anomers by neither column chromatography nor preparative HPLC.

Structural assignment of the β- and α-nucleosides in the mixtures was done by NOE and one dimensional $^1$H-NMR spectroscopy and all four coupling reactions showed predominantly β-selectivity. The β-anomers are apparently thermodynamically favored over the α-anomers as extension of the coupling time increased the β:α-ratio.

In an attempt to reduce the number of synthetic steps, other strategies were examined. It was rationalised that acetylation of **5** could be avoided by using trimethylsilyl (TMS) as temporary protection of the hydroxyl groups. Direct nitrogen glycosylation of **5** with 4-*N*-isobutyrylcytosine, using nine equivalents of BSA, afforded an anomeric mixture (2:3) of TMS diprotected nucleosides in 62% yield. Contrary to expectation, the TMS groups were stable to aqueous work up and column chromatography on silica gel. Because of the additional desilylation step, this synthetic approach was not further pursued. To avoid the protection of the hydroxyl groups, direct nitrogen glycosylation was carried out on methyl 2,3-dideoxy-3-*C*-methylene-5-*O*-(4-phenylbenzoyl)-β-D-*glycero*-pentofuranoside (**4**) with 4-*N*-isobutyrylcytosine affording an anomeric mixture (1:1) in 19% yield. The low yield and the possibility of dihydroxylation in the nucleobase in the following dihydroxylation step make this strategy less attractive.

In conclusion, universal 3-*C*-hydroxymethyl precursors have been synthesised. Direct nitrogen glycosylation reactions between silylated nucleobases and the precursors **7** and **8** were successful, affording anomeric mixtures of β- and α-nucleosides. Because of lack of stereoselectivity in the glycosylation reaction and lack of success in separating the anomeric mixtures, this strategy has only limited utility for synthesis of stereochemically pure 3'-*C*-hydroxymethyl modified ODNs. However, it provides a rapid method for obtaining anomeric mixtures of 3'-*C*-hydroxymethyl modified nucleosides for biological testing. The results of antiviral testing of the anomeric mixtures **15a/15b** and **16a/16b** will be published later.

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