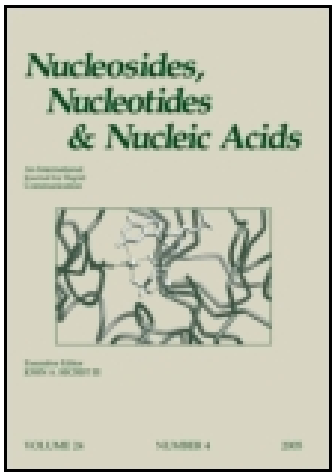


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# SYNTHESIS AND NMR-ANALYSIS OF TRICYCLIC NUCLEOSIDES

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# SYNTHESIS AND NMR-ANALYSIS OF TRICYCLIC NUCLEOSIDES

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## ABSTRACT

Two anomeric tricyclic nucleosides have been synthesised from diacetone-D-glucose using oxidation, stereoselective Grignard-addition of a vinyl-group, a stereoselective dihydroxylation followed by a tandem ring closing reaction, and finally a nucleobase coupling. The main $\beta$-configured product was examined and its configuration confirmed using NMR-spectroscopy in connection to *ab initio* calculations. The preferred conformation of this tricyclic nucleoside was described.

Conformationally restricted nucleosides have been intensively investigated as potential antiviral agents and in oligonucleotide analogues (1). Thus, bi- and tricyclic nucleosides have been constructed and further developed into nucleic acid analogues with very promising abilities in the recognition of complementary nucleic acid sequences (2–6). As an example, the bicyclic nucleoside **1** (Scheme 1) has been synthesised and incorporated into oligodeoxynucleotides (2). A fully modified sequence demonstrated moderately enhanced affinity towards complementary RNA. The furanose ring in **1** has been shown to prefer an O4′-endo conformation as demonstrated by an X-ray crystallographic study of **1** incorporated in a DNA dodecamer duplex (7) as well as by a corresponding NMR-study (8).

In order to improve the properties of **1**, we decided to introduce further conformational restriction into this bicyclic structure by the synthesis of tricyclic nucleosides (Scheme 1). As a convenient and cheap starting material,

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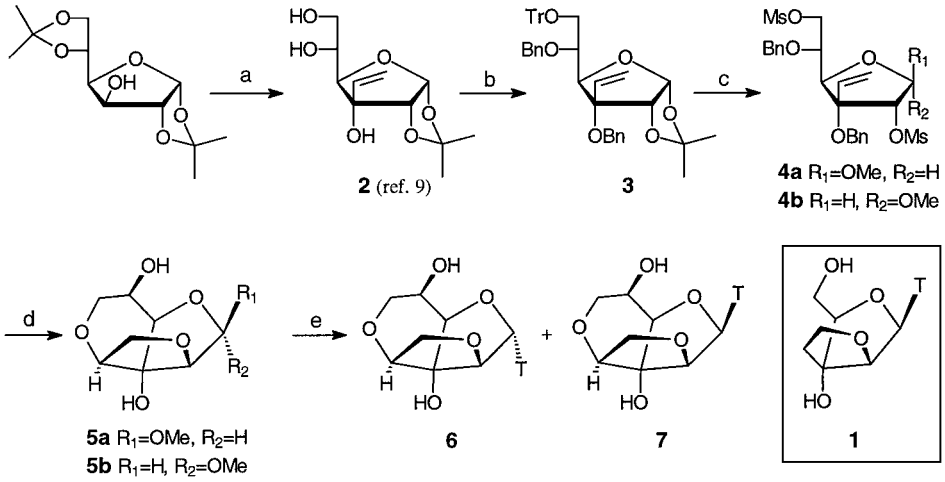


***Scheme 1.*** a) i. $CrO_3$, $Ac_2O$, Pyridine, $CH_2Cl_2$, ii. VinylMgBr, Ether, THF, iii. 80% AcOH (75%); b) i. TrCl, Pyridine, ii. BnBr, NaH, DMF (63%); c) i. 20% HCl in MeOH, $H_2O$ (76%), ii. MsCl, Pyridine (95%); d) i. $OsO_4$, NMO, $H_2O$, Pyridine, *t*-BuOH, ii. NaH, DMF (48/42%); e) i. Thymine, BSA, TMS-Tf, $CH_3CN$ (52%), ii. $H_2$, $Pd(OH)_2$-C, EtOH (73%). T = thymin-1-yl.

diacetone-D-glucose was chosen and stereoselectively converted to the 3′-*C*-vinyl compound **2** using a slightly changed literature method (9). Reprotection to give **3**, acidic treatment and mesylation gave the separable anomers **4a** and **4b**. Dihydroxylation of **4a** followed by a base-induced tandem ring closure afforded only one major product **5a**. The exact configuration of **5a** was not elucidated at this stage. However, MS-data and NMR strongly suggested the formation of a tricyclic structure. In a similar sequence, **4b** afforded the other anomer **5b**. A nucleobase coupling of either of the two anomers gave the same inseparable anomeric mixture of nucleosides which after deprotection were separated to give the two tricyclic nucleoside products **6** and **7** in a 1:3 ratio.

The exact configurations of **6** and **7** could only partly be confirmed by NOE-spectroscopy due to spectral overlap. Thus, an NOE-contact between H1′ and H4′ was only seen for the major product (**7**) confirming its $\beta$-configuration. However, the exact $^3J_{HH}$ coupling constants were measured for both compounds as shown for **7** in Table 1. Subsequently, *ab initio* calculations were performed for **7** as well as for three alternative tricyclic structures **A**, **B** and **C**, which from a synthetic point of view had to be considered (Fig. 1). The torsional angles were calculated as shown in Table 1. Furthermore, the Karplus relationships (10) between $J_{H1'H2'}$ and the pseudorotation angle P of the furanose ring (11) as well as between the other $^3J_{HH}$ coupling constants listed in Table 1 and the corresponding dihedral angles were derived. From these Karplus curves (not shown), the dihedral angles allowed by the experimental coupling constants could be found. In none of the calculations performed on **A**–**C**, a geometry was obtained in which all torsional angles could fit all the measured coupling constants simultaneously. Even though calculations were

***Table 1.*** Exp.[1]H-NMR Data[a] for **7** and Calc. Data[b] for the Theoretically Possible $\beta$-Nucleosides[c]

| $\delta$/ppm | $^3J_{HH}$/Hz | | **7** | **A** | **B** | **C** |
|---|---|---|---|---|---|---|
| H1′ 6.11 | H1′H2′ 4.7 | P | 85° | 39° | 175° | 85° |
| H2′ 4.39 | | $\Phi_{max}$ | 37° | 22° | 23° | 38° |
| H4′ 4.04 | H4′H5′ 3.1 | $\theta_{H4'H5'}$ | 55° | −26° | −42° | −23° |
| H5′ 4.22 | H5′H6′ 7.7 | $\theta_{H5'H6'}$ | −23° | 54° | 84° | 83° |
| H6′ 4.02 | | $\theta_{H5'H6''}$ | −141° | −65° | −39° | −39° |
| H6″ 3.72 | H5′H6″ 8.0 | $\theta_{H7'H8'}$ | 38° | 44° | −55° | −69° |
| H7′ 3.90 | H7′H8′ 3.2 | $\theta_{H7'H8''}$ | −85° | 172° | 62° | 165° |
| H8′ 4.01 | | $\gamma$ | 178° | 92° | 81° | 95° |
| H8″ 3.95 | H7′H8″ <1.5 | | | | | |

[a]$CD_3OD$ at 500 MHz.
[b]Performed at the 3–21G level.
[c]For definitions on P, $\Phi_{max}$ and $\gamma$ see ref. 11.

performed in which some of the angles were constrained in allowed angles (not shown), other angles did not fit the experimental data. Thus, we conclude that **7** is the only possible structure fitting our experimental NMR-data and the configuration of **7** is hereby confirmed.

Since no change in the coupling constants of **7** was observed in the temperature range from −50 to 50°C, the nucleoside is believed to exist in only one conformation. This conformation is described by the torsional angles obtained from the unconstrained geometry optimisation (Table 1) and is shown in Figure 1. The furanose ring of this tricyclic nucleoside prefers the O4′-endo conformation as in the bicyclic nucleoside **1**. This is an unusual and high-energy conformation in unmodified nucleosides (11). However, this conformation might be favourable for nucleic acid recognition as found for oligodeoxynucleotides containing **1** (2), its smaller analogue with a four-membered ring (3), or the 2′F-arabinodeoxynucleoside analogues (7,12). On the other hand, the C4′-C5′ torsional angel $\gamma$ of **7** is found to be in the $+ap$ range which is probably unfavourable for Watson-Crick type duplex formation (6).

In conclusion, the alternative epimer **A** seems to be restricted in a more favourable conformation than **7** and the synthesis of this nucleoside as well as the

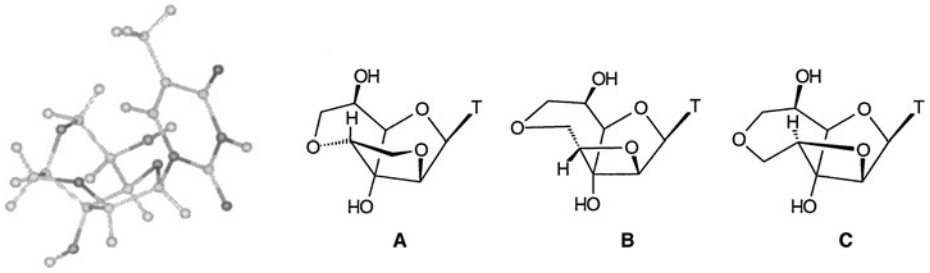


***Figure 1.*** The determined conformation of **7**, and the possible alternative structures.





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incorporation of both epimers into oligonucleotide sequences will be performed in due course.

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