Tricyclic nucleosides derived from D-glucose. Synthesis and conformational behaviour

Poul Nielsen,* Michael Petersen and Jens Peter Jacobsen

Department of Chemistry, University of Southern Denmark, Odense University, 5230 Odense M, Denmark

Received (in Cambridge, UK) 27th July 2000, Accepted 15th September 2000
First published as an Advance Article on the web 31st October 2000

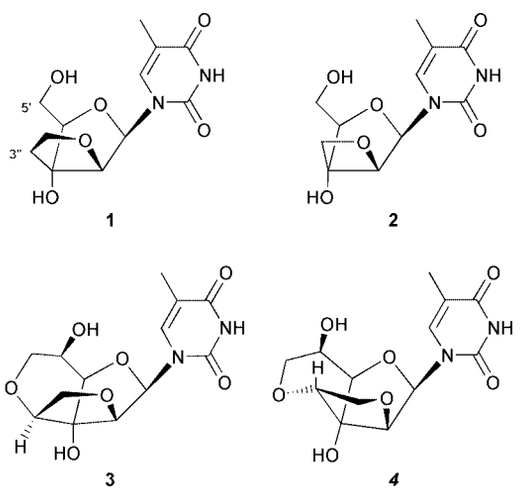
Two anomeric nucleosides with tricyclic carbohydrate moieties, **3** and **14**, are synthesised in 11 steps from diacetone-D-glucose, taking advantage of a stereoselective Grignard reaction, a stereoselective dihydroxylation and a regioselective tandem ring-closing procedure. The configuration of **3** is confirmed by measuring the $^3J_{HH}$ coupling constants in connection with molecular modelling and *ab initio* calculations, as these exclude alternative tricyclic nucleoside structures. The conformational preference for **3** is described. The furanose ring is found to be in an O-4′-*endo* conformation and the γ torsion angle in the $+ap$ range.

Introduction

Conformationally restricted nucleosides have attracted considerable attention as monomers in oligonucleotide analogues[1–8] and as potential antiviral agents.[9–12] Especially, nucleosides with bi-[2–7] and tricyclic[8] carbohydrate moieties have been synthesised in order to restrict the conformational flexibility of nucleosides into conformations which are ideal for nucleic acid recognition. As a prime example, LNA (Locked Nucleic Acid) has recently been introduced and shown to display unprecedented recognition of complementary DNA and RNA.[4] Nucleoside analogues involving the nucleobase in conformationally fixed polycyclic structures have also been reported.[13] Bicyclic nucleosides have demonstrated some activity against antiviral enzymes,[9] *e.g.* HIV reverse transcriptase,[11] and can, furthermore, serve as tools in the evaluation of conformational preferences and structure–activity relations in nucleoside/nucleotide converting enzymes.[11,12]

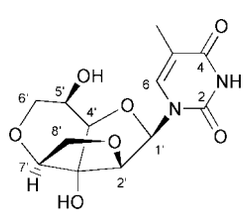
The bicyclic nucleoside **1** has been synthesised and incorporated into oligodeoxynucleotides.[2] A fully modified sequence exhibited moderately enhanced affinity towards a complementary RNA strand when compared with an unmodified oligodeoxynucleotide sequence. On the other hand a decreased affinity towards a complementary single stranded DNA strand was observed.[2] The smaller and more constrained bicyclic nucleoside **2** has also been incorporated into oligodeoxynucleotides demonstrating a slight improvement over **1** concerning affinity towards complementary RNA-sequences.[3] Furthermore, an improvement in affinity towards single stranded DNA-sequences was also observed. In a conformational study we have suggested **1** to prefer a C-1′-*exo* conformation[14] with a pseudorotation angle[14] of $P \approx 129°$ but with a slight degree of conformational freedom in the bicyclic system.[3] However, an X-ray crystallographic study of **1** in a DNA dodecamer duplex has shown that the bicyclic nucleoside residues have O-4′-*endo* conformations[14] with pseudorotation angles of $P = 94 \pm 6°$.[15] Likewise, a recent NMR study has confirmed this conformation of **1** in a duplex structure.[16] In this paper, our earlier conformational conclusions[3] are revised.

In order to induce further conformational restriction in the bicyclic structure of **1** the introduction of a 5′-CH_2–O-3″ bridge generating tricyclic nucleosides was planned. We chose a synthetic strategy potentially leading to both of the two possible β-configured tricyclic nucleosides **3** and ***4***.† However, only the (7′*R*)-isomer † **3** was obtained, and the synthesis of this as well as its α-configured anomer **14** is hereby presented. The conformation of **3** was established by use of NMR spectroscopy, molecular modelling and *ab initio* calculations.



1 **2** **3** ***4***

† In all the tricyclic nucleoside structures **3**, ***4***, **14**, ***15***, ***16*** we use the same numbering scheme as exemplified below with **3**; C-1′–C-6′ represent the atoms C-1–C-6 in the original D-glucose, and C-7′ is the new bridgehead atom connecting C-3′ and C-8′, the additional CH_2 positioned in either of the additional rings. H-6″ and H-8″ are positioned on the β-face of the nucleoside structure. Imaginary structures (compounds never synthesised) are throughout this report shown in italics. Note, however, that atom locants in the NMR spectra (Experimental section) follow the *systematic* nomenclature used for the tricycles **3**, **11**–**14**.

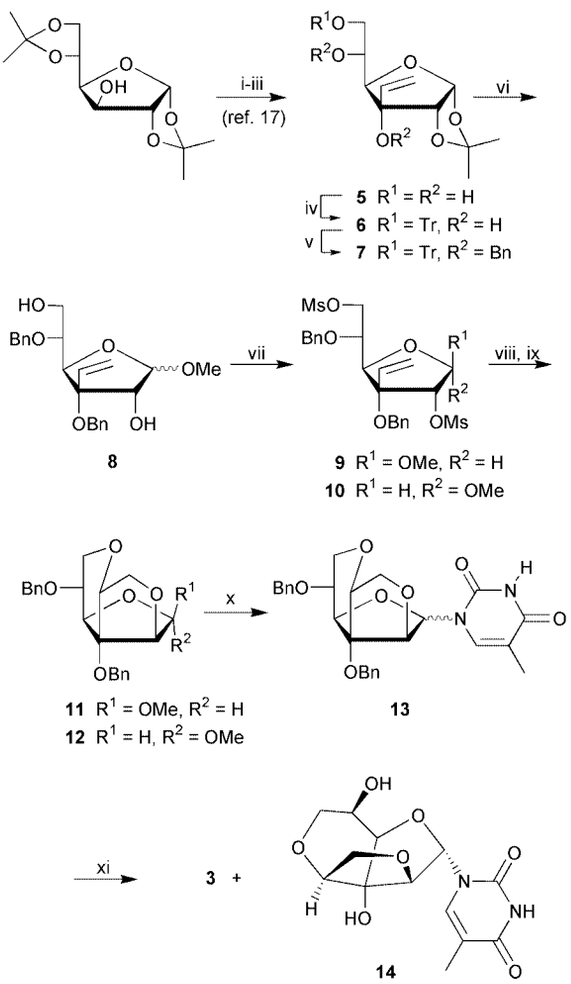


 DOI: 10.1039/b006082h

Results

Chemical synthesis

Retrosynthetic analysis of **3** and ***4***, both with D-altrose configuration, suggested D-glucose as the carbohydrate precursor possessing a convenient stereochemistry. Thus, diacetone-D-glucose was chosen as a very cheap and readily available starting material demanding conversion of the configuration at the C-2 and C-3 positions. Efficient conversion to the known 3-*C*-vinyl-D-allose derivative **5**[17] was performed in three steps and 75% overall yield using oxidation followed by a stereoselective vinylmagnesium-bromide-mediated Grignard reaction and selective deprotection of the primary acetonide (Scheme 1).



Scheme 1 *Reagents and conditions*: i, CrO_3, Ac_2O, pyridine, CH_2Cl_2; ii, vinylMgBr, ether, THF; iii, 80% AcOH; iv, TrCl, pyridine; v, BnBr, NaH, DMF; vi, 20% HCl in aq. MeOH; vii, MsCl, pyridine; viii, OsO_4, *N*-methylmorpholine *N*-oxide, aq. pyridine, *t*-BuOH; ix, NaH, DMF; x, thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMS triflate, CH_3CN; xi, H_2, $Pd(OH)_2$–C, EtOH.

Selective tritylation of the primary hydroxy group to give **6** and benzylation of the two remaining hydroxy groups to give **7** in 63% overall yield was followed by treatment with methanolic hydrochloric acid to give an anomeric mixture of detritylated methyl furanosides **8** in 76% yield. The two hydroxy groups were converted to methylsulfonic esters and the two anomers **9** and **10** were separated. A standard dihydroxylation of the double bond in the β-anomer **9** using osmium tetraoxide and *N*-methylmorpholine *N*-oxide as cooxidant did not, as expected, yield two diastereomeric diols but a more complex mixture of products. This mixture was, without further purification, treated with sodium hydride to give in 48% yield only one major product which was later determined to be the tricyclic compound **11**. Even though a tricyclic methyl furanoside structure was confirmed by NMR and MS data, the exact configuration of the new C-7′-stereocentre and the distribution of the fused ring systems were not finally solved at this stage. Using the same reaction sequence on the α-anomer **10** gave the tricyclic compound **12**. Coupling of either **11** or **12** to thymine using a modified Vorbrüggen method gave in both cases a mixture of anomeric nucleosides **13** (β:α ≈ 3:1) in 52% yield. After removal of the benzyl groups, using hydrogenation at atmospheric pressure followed by chromatographic separation, the two tricyclic nucleosides **3** and **14** were isolated in 55 and 18% yield, respectively. The major isomer was later determined to be the β-anomer **3** (*vide infra*).

The stereoselectivity observed for the dihydroxylation reactions on **9** and **10** was ascribed to control from the allylic oxygen[18] in combination with a steric effect from the large C-4 substituent (Fig. 1). Subsequently, the primary hydroxy group could not find a position for attacking either C-2 or C-6, while the secondary hydroxy group was placed in a position favourable for attacking C-6 and forming the six-membered ring in a bicyclo[4.3.0] intermediate. The remaining primary hydroxy group in this system was thereby organised towards a nucleophilic attack at C-2 forming the tricyclic methyl furanosides **11** and **12**.

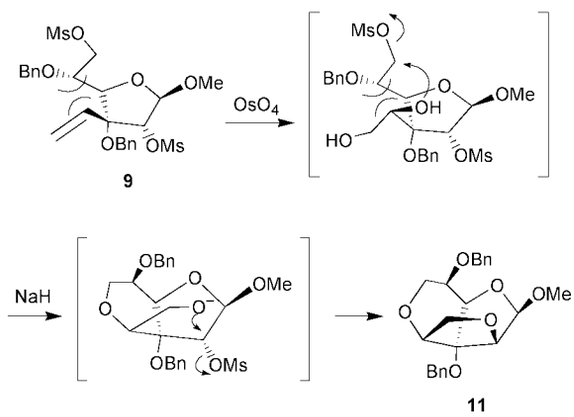


Fig. 1 Suggested mechanism explaining the formation of the tricyclic methyl furanoside **11**.

Determination of the configuration

In order to determine the exact configuration of the two synthesised anomeric tricyclic nucleosides **3** and **14**, intensive NMR investigations, molecular modelling and *ab initio* calculations were performed. ^1H and ^{13}C NMR signals were assigned using 1D- and 2D-NMR methods. This confirmed, in conjunction with MS data, tricyclic nucleoside structures. Due to a considerable signal overlap neither 1D- nor 2D-NOE experiments were able to completely elucidate the exact configurations. However, a conclusive NOE-contact between H-1′ and H-4′ confirmed the β-configuration of the major product (nucleoside **3**), and the lack of an NOE contact between H-1′ and H-4′ indicated the α-configuration of the minor product (nucleoside **14**). Furthermore, the lack of an NOE-contact between H-6 and H-7′ indicated the C-7′-configuration to be the one in **3** rather than the one in ***4***. Nevertheless, the exact configuration of the major product could not be completely assigned, and four possible tricyclic β-nucleoside structures **3**, ***4***, ***15*** or ***16*** had to be considered. However, the structure **3** seemed most likely to be identical to the major product due to preliminary NOE results as well as mechanistic arguments (*vide supra*, Fig. 1). Fortunately, measurements of $^3J_{HH}$ coupling constants in conjunction with molecular modelling did, as shown below, successfully establish the major tricyclic nucleoside product to be **3**.

Table 1 ^{1}H NMR experimental data for **3** and **14**[a]

3				**14**			
δ/ppm		$^3J_{HH}$/Hz		δ/ppm		$^3J_{HH}$/Hz	
H-1′	6.11	H-1′,H-2′	4.7	H-1′	5.68	H-1′,H-2′	1.8
H-2′	4.39			H-2′	4.72		
H-4′	4.04	H-4′,H-5′	3.1	H-4′	4.53	H-4′,H-5′	2.5
H-5′	4.22	H-5′,H-6′	7.7	H-5′	4.08	H-5′,H-6′	6.6
H-6′	4.02			H-6′	3.83		
H-6″	3.72	H-5′,H-6″	8.0	H-6″	3.69	H-5′,H-6″	9.1
H-7′	3.90	H-7′,H-8′	3.2	H-7′	3.97	H-7′,H-8′	3–5[b]
H-8′	4.01			H-8′/H-8″	≈4.05		
H-8″	3.95	H-7′,H-8″	<1.5			H-7′,H-8″	<2[b]

[a] Measured in CD_3OD at 500 MHz. [b] Coupling constants estimated from an ABX system.

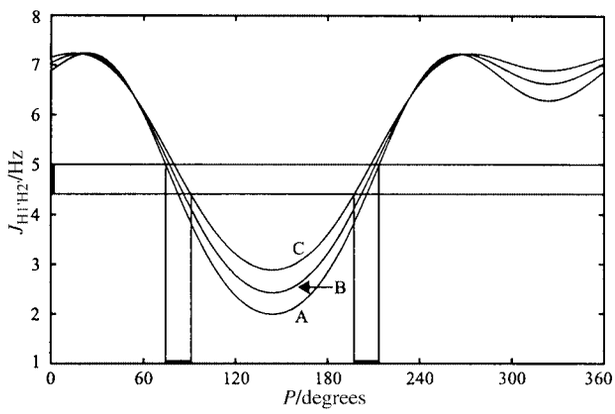
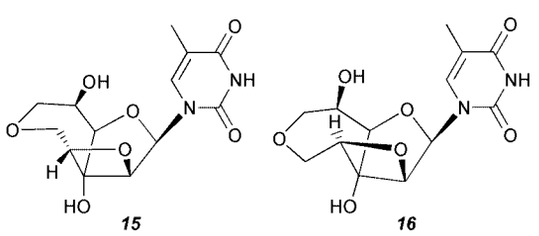


Fig. 2 $J_{H1'H2'}$ as a function of the furanose pseudorotation angle P for **3**, ***4***, ***15*** and ***16***. (A, B, C) Karplus curves calculated with puckering amplitude of 42°, 38° and 34°, respectively. It is evident that the observed coupling constant (4.7 Hz) yields two possible conformational ranges.



Measurement of $^3J_{HH}$ coupling constants and determination of allowed ranges for the torsion angles

The $^3J_{HH}$ coupling constants of **3** and **14** were determined as given in Table 1. Since no change in the coupling constants was observed for any of the nucleosides in the temperature range from −50 to +50 °C we believe that each nucleoside exists in only one conformer and not in a dynamic equilibrium between two or more conformers. All subsequent molecular modelling calculations were performed under this assumption. We derived the Karplus relationships between $J_{H1'H2'}$ and the pseudorotation angle P of the furanose ring.[19–21] Similarly, we derived the relationships between $J_{H4'H5'}$, $J_{H5'H6'}$, $J_{H5'H6''}$, $J_{H7'H8'}$ and $J_{H7'H8''}$ and the corresponding torsion angles for the four theoretically possible β-configured isomers **3**, ***4***, ***15*** and ***16***.† The Karplus dependence between $J_{H1'H2'}$ and P is identical for all these isomers and for **1** as well. Likewise, the Karplus relationships for $J_{H4'H5'}$, $J_{H5'H6'}$ and $J_{H5'H6''}$ are identical for **3**, ***4***, ***15*** and ***16***. The Karplus relationships are shown in Figs. 2–4. Since the H-6′/H-6″ and H-8′/H-8″ proton pairs are geminal, the difference in the torsion angles $\theta_{H5'H6'}$ and $\theta_{H5'H6''}$ as well as in the torsion angles $\theta_{H7'H8'}$ and $\theta_{H7'H8''}$ must be close to 120° in both cases. Thus, only a few of the regions are allowed by the experimental vicinal coupling constants. These regions are marked out in the Figures and discussed below.

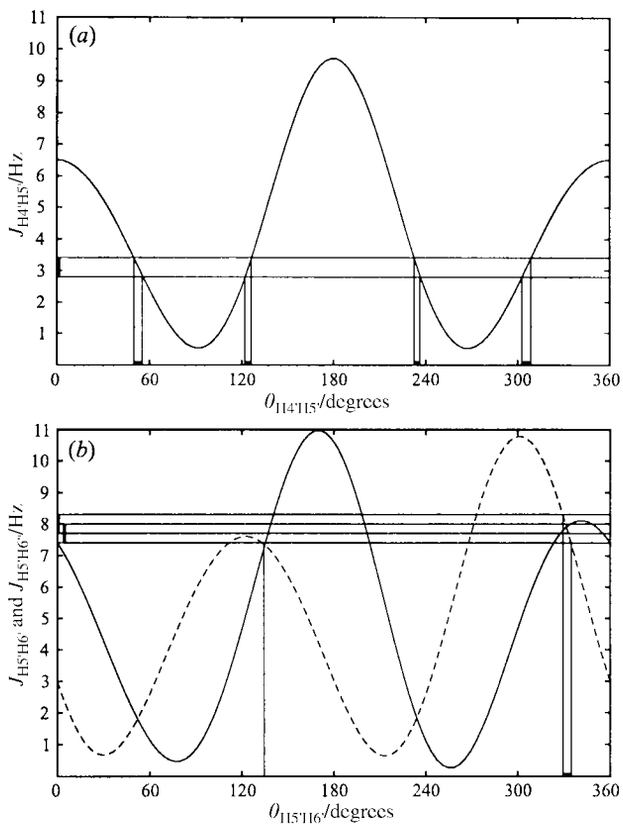


Fig. 3 (*a*) $J_{H4'H5'}$ as a function of $\theta_{H4'H5'}$ for **3**, ***4***, ***15*** and ***16***. The observed coupling constant (3.1 Hz) allows four ranges of $\theta_{H4'H5'}$. (*b*) $J_{H5'H6'}$ (——) and $J_{H5'H6''}$ (----) as functions of $\theta_{H5'H6'}$ for **3**, ***4***, ***15*** and ***16***. The observed coupling constants ($J_{H5'H6'}$ = 8.0 Hz and $J_{H5'H6''}$ = 7.7 Hz or *vice versa*) give rise to two possible geometries.

The configuration of 3

As demonstrated by Figs. 2–4, the measured three-bond coupling constants gave a fair amount of information, sufficient to establish the configuration and conformation of **3** with a high degree of confidence.

First, the alternative isomer ***4*** was considered. This is a rather strained entity as can be gauged from simple model building. Consequently, an unconstrained 3-21G* geometry optimisation yielded only one possible geometry for this configuration (Table 2). This geometry does not comply with the experimental coupling constants for the major product **3**, *e.g.* the pseudorotation angle of the furanose is 39°, yielding $J_{H1'H2'} \approx 7$ Hz (Fig. 2).

The other alternative isomers ***15*** and ***16*** represent a more complex situation since these ring systems contain more conformational freedom than does ***4***. Therefore, we carried out a number of geometry optimisations at the 3-21G* level either

Table 2 Calculated data on the four theoretically possible tricyclic β-nucleosides.[a] All angles are in degrees

	P	Φ_{max}	$\theta_{H4'H5'}$	$\theta_{H5'H6'}$	$\theta_{H5'H6''}$	$\theta_{H7'H8'}$	$\theta_{H7'H8''}$	γ[c]
3	85	37	55	−23	−141	38	−85	178[b]
	201	**38**	−53	47	−73	0	−125	62
	201	**38**	−42	16	−103	12	−113	78
4	39	22	−26	54	−65	44	172	92
15	175	23	−42	84	−39	−55	62	81
	161	18	−38	88	−35	**−38**	**85**	86
	178	24	−42	83	−40	**−64**	**60**	80
	91	30	69	**−30**	**−148**	−57	62	−163
	188	32	−12	**−30**	**−148**	**−64**	**60**	107
	171	25	−6	**−30**	**−148**	**−38**	**85**	115
16	85	38	−23	83	−39	−69	165	95
	66	36	−25	49	−68	**40**	**−82**	89
	81	39	57	−64	−178	**−112**	**126**	176
	81	44	19	**−30**	**−148**	−44	−171	137
	82	40	43	**−30**	**−148**	**−112**	**126**	166
	64	46	26	**−30**	**−148**	**40**	**−82**	146

[a] Gaussian94 geometry optimisations carried out at the 3-21G* level except [b] which was carried out at the 6-31G* level. Torsion angles constrained in a given calculation are shown in bold. [c] γ is defined as the C-3′–C-4′–C-5′–O torsion angle.

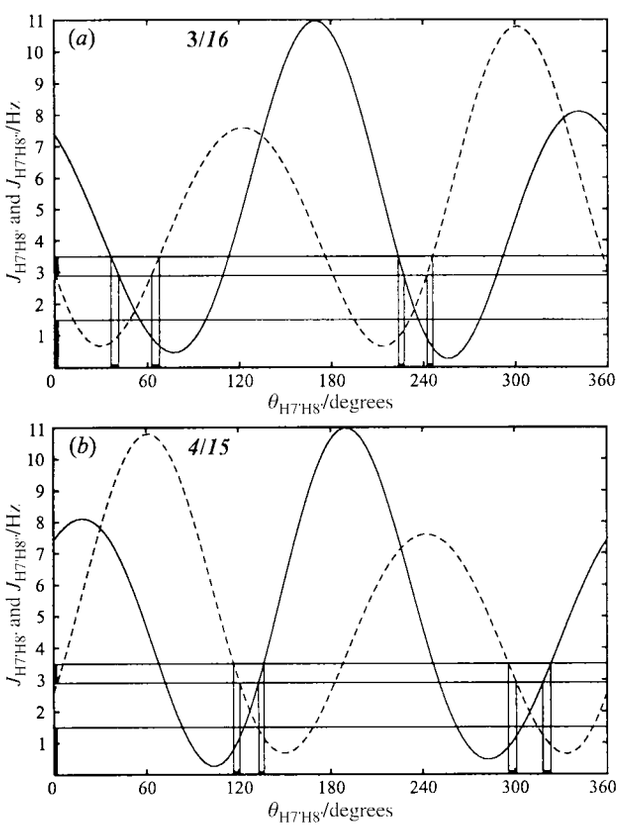


Fig. 4 (*a*) $J_{H7'H8'}$ (——) and $J_{H7'H8''}$ (----) as functions of $\theta_{H7'H8'}$ calculated for **3** and ***16***. The observed coupling constants ($J_{H7'H8'}$ = 3.2 Hz and $J_{H7'H8''}$ < 1.5 Hz or *vice versa*) give rise to four possible geometries. (*b*) $J_{H7'H8'}$ (——) and $J_{H7'H8''}$ (----) as functions of $\theta_{H7'H8'}$ calculated for ***4*** and ***15***. The observed coupling constants ($J_{H7'H8'}$ = 3.2 Hz and $J_{H7'H8''}$ < 1.5 Hz or *vice versa*) give rise to four possible geometries.

with no constraints or with one or two CH_2CH fragments constrained in the geometry allowed by the coupling constants. The situation is further complicated as we, *a priori*, cannot perform a stereoselective assignment of the geminal H-6′/H-6″ and H-8′/H-8″ proton pairs. However, as shown below the analysis of the $^3J_{HH}$ coupling constants allows stereoselective assignment.

Table 3 Torsion angles (°) allowed by Karplus analysis of the experimental coupling constants[a]

15* + *16	$\theta_{H5'H6'}$	$\theta_{H5'H6''}$	*c*
Assignment 1[b]	−30	−148	p.g.
Assignment 2	138	15	n.p.
15	$\theta_{H7'H8'}$	$\theta_{H7'H8''}$	*c*
Assignment 1[b]	136	−100	n.p.
	−38	85	p.g.
Assignment 2	−64	60	p.g.
	116	−120	n.p.
16	$\theta_{H7'H8'}$	$\theta_{H7'H8''}$	*c*
Assignment 1[b]	40	−82	p.g.
	−133	103	d.n.c.
Assignment 2	−112	126	p.g.
	63	−54	d.n.c.

[a] $\theta_{H5'H6'}$- and $\theta_{H5'H6''}$- (as well as $\theta_{H7'H8'}$- and $\theta_{H7'H8''}$-) values are derived from separate Karplus curves and, hence, do not differ by exactly 120°. [b] Assignment 1 denotes the assignment of the H-6′/H-6″ and H-8′/H-8″ proton pairs listed in Table 1, which subsequently was confirmed to be the correct assignment. [c] p.g. = possible geometry; n.p. = not possible due to covalent geometry; d.n.c. = calculation did not converge to a minimum.

The geometries allowed by Karplus analysis of the experimental coupling constants are listed in Table 3. Subsequently, we carried out Gaussian geometry optimisations with either the H-5′–H-6′/H-6″ fragment constrained, the H-7′–H-8′/H-8″ fragment constrained, or both these fragments constrained to the possible geometries listed in Table 3. The results of these calculations are included in Table 2. None of the calculations yielded a geometry which can encompass all the experimental data, *e.g.* the pseudorotational angles P found for five of the six geometries of ***15*** are in the 161–188° range which do not comply with either of the two possible conformational ranges depicted in Fig. 2. The sixth geometry of ***15***, as well as the six calculated geometries of ***16***, can be excluded by either $\theta_{H4'H5'}$, $\theta_{H5'H6'}$ and/or $\theta_{H7'H8'}$ torsion angles not complying with the possible ranges depicted in Figs. 3 and 4.

In contrast, unconstrained geometry optimisations of the structure **3** at both the 3-21G* and 6-31G* levels yielded nearly

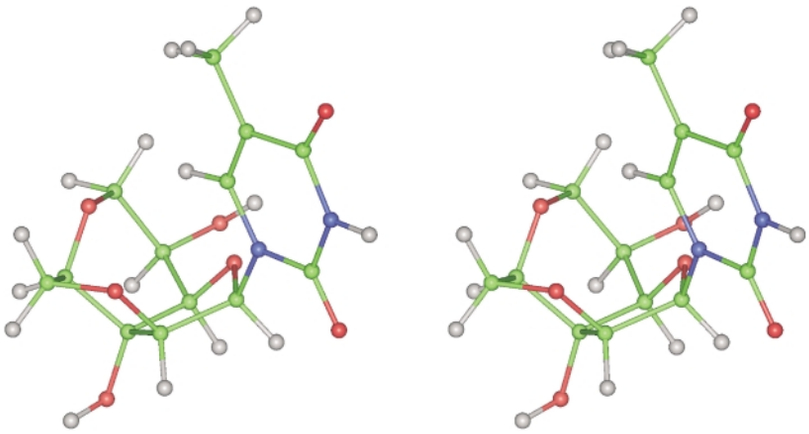


Fig. 5 A stereoview presenting the determined conformation of **3**.

identical structures (Table 2, footnote *b*) in perfect agreement with the experimental data (Table 1 and Figs. 2–4). Thus, we conclude that only the structure **3** is commensurate with our experimental data of the major tricyclic nucleoside product obtained.

The conformations of 3 (and 1 revised)

Two regions of the pseudorotation cycle are permitted by the experimental coupling constant for **3** $J_{H1'H2'} = 4.7$ Hz, one close to $P = 90°$ and one in the vicinity of $P = 200°$ (Fig. 2). The unconstrained geometry optimisations gave structures with $P \approx 90°$ (*vide supra*) and to test if the $P \approx 200°$ domain is feasible we carried out two constrained geometry optimisations with $P = 200°$ (constraining two of the *endo* cyclic torsion angles). The two starting structures were low-energy conformations from a molecular dynamics calculation. However, neither of the conformations generated (Table 2) agreed with the measured coupling constants. Therefore, we conclude that the conformation obtained by the unconstrained geometry optimisation indeed is the conformation dictated by the experimentally observed data. A view of the determined conformation is presented in stereo in Fig. 5.

We have previously studied the conformations of **1**.[3] However, this study was performed using a general Karplus equation[19] and forcefield methods.[3] To draw any conclusions on the resemblance of **1** to **3**, an analysis of this bicyclic nucleoside was performed at the same theoretical level as **3**, *i.e.* a Karplus equation parametrised for nucleotides[20] and *ab initio* quantum mechanical calculations. It is evident from Fig. 2 that two regions of the pseudorotation cycle are allowed by the experimental coupling constant $J_{H1'H2'} = 4.3$ Hz.[2] A geometry optimisation at the 3-21G* level yielded a conformation with $P \approx 90°$, in accordance with the measured coupling constant,[2] X-ray crystallographic data,[15] and an NMR high-resolution structure.[16] It is noteworthy that $P = 90°$ is a 'high-energy' O-4′-*endo* furanose conformation,[14] in this case probably driven by the propensity of the 2′,3′-fused tetrahydrofuran ring to adopt an envelope conformation.

Discussion

It has to be taken into account that all our calculations were performed as gas-phase calculations and at a restricted theoretical level. However, geometry optimisations tend to converge at a theoretically lower level than energies do.[22] Our level of calculations taken into consideration, we refrain from discussions of energies as these are prone to be inaccurate. The geometry of **3** found seems reasonable, *e.g.* the five-membered rings have puckering amplitudes of 37° and 38°, respectively. This is normally observed in furanose and tetrahydrofuran rings in general.[14,23]

Both five-membered rings of the tricyclic nucleoside **3** are in envelope conformations (as found for **1**), whereas the six-membered ring has a twisted boat conformation. The furanose ring of the tricyclic nucleoside **3** prefers the O-4′-*endo* conformation as in the bicyclic nucleoside **1**. This is an unusual and high-energy conformation in unmodified nucleosides.[14] However, this sugar conformation might be favourable for nucleic acid recognition as found for oligodeoxynucleotides containing **1**,[2] **2**,[3] or the 2′-fluoro-arabinodeoxynucleoside analogues.[15,24] On the other hand, the C-4′–C-5′ torsion angle γ is found to be in the $+ap$ range (Table 2). This is probably unfavourable for duplex formation since in both A- and B-type duplexes γ is in the $+sc$ range.[14] Bicyclic nucleosides restricting this torsion in the $+ap/+ac$ range have been studied by Leumann and coworkers[6,7] who showed that the corresponding oligodeoxynucleotides prefer Hoogsteen-association over Watson–Crick base-pairing.[7] Subsequently, the ability to recognise complementary DNA and RNA was improved with tricyclic nucleosides in which γ has been shown to be in the less unfavourable $+ac$ range.[8]

No conclusions about the torsional angle χ describing the glycosidic bond[14] can be drawn from this study. However, no factors preventing the preferable *anti* conformation are expected.

The other target tricyclic nucleoside ***4***, which was not obtained from the present synthetic strategy, seems to be more conformationally restricted than **3**. Thus, incorporation of ***4*** in oligonucleotide sequences might be more favourable for high-affinity nucleic acid recognition since our calculations (Table 2) have shown the furanose ring to prefer a C-3′-*endo* (N-type)[14] conformation. Bicyclic nucleosides restricted in this conformation have demonstrated very high affinity towards both complementary RNA and DNA.[1,4] Furthermore, the γ-torsion of ***4*** seems to be restricted in the favourable $+sc/+ac$ range.

The tricyclic α-nucleoside **14** was not intensively evaluated but the J_{HH} coupling constants (Table 1) indicate that all torsion angles seem to be in the same range as for **3**. Only the H-1′–H-2′ angle differs due to the α-configured structure.

Conclusions

We have synthesised the tricyclic nucleoside **3** as well as its α-anomer **14** using an efficient and stereoselective method. The synthesis of ***4*** demands a different synthetic strategy in which conversion of the 7′-configuration must be accomplished. However, ***4*** seems to be restricted in a more favourable conformation than does **3** concerning incorporation into nucleic-acid-recognising oligonucleotides. Therefore, efforts towards the synthesis of ***4*** and evaluation of both the conformationally restricted tricyclic nucleosides **3** and ***4*** as monomers in oligonucleotide sequences and as biologically active compounds will be performed in due course.

Experimental

All commercial reagents were used as supplied. Light petroleum refers to the fraction with distillation range 60–80 °C. All reactions were performed under an atmosphere of nitrogen. Column chromatography was carried out on glass columns using Silica gel 60 (0.040–0.063 mm). NMR spectra were obtained on a Bruker AC250, a Varian Gemini 2000 or a Varian Unity 500 spectrometer. ^{1}H NMR spectra were recorded at 250, 300 or 500 MHz and ^{13}C NMR spectra were recorded at 62.5 or 75 MHz. Values for δ are in ppm relative to tetramethylsilane as internal standard. *J*-Values are in Hz. ^{1}H–^{1}H COSY spectra were recorded for compounds **3**, **8** and **14**. ^{1}H NOE difference spectra were recorded for compounds **3** and **14** and a ^{1}H–^{13}C COSY spectrum was recorded for compound **3**. FAB mass spectra were recorded in positive-ion mode on a Kratos MS50TC spectrometer, and plasma desorption mass spectra (PDMS) on an Applied Biosystems Biopolymer Mass Analyzer BIO-ION 20R. Microanalyses were performed at The Microanalytical Laboratory, Department of Chemistry, University of Copenhagen.

1,2-*O*-Isopropylidene-3-*C*-vinyl-α-D-allofuranose[17] 5

A stirred suspension of chromium trioxide (14.8 g, 136 mmol) in anhydrous CH_2Cl_2 (228 cm^3) was cooled to 0 °C and a mixture of anhydrous pyridine (24.8 cm^3) and Ac_2O (14.8 cm^3) was added. Diacetone-D-glucose (21.0 g, 80.6 mmol) was added in small portions over a period of 30 min and the mixture was stirred for another 3 h and poured into ethyl acetate (800 cm^3). The mixture was filtered through a layer of silica, the filter was rinsed with ethyl acetate (1000 cm^3), and the filtrate was concentrated *in vacuo*. The residue was re-dissolved in anhydrous THF (500 cm^3) and this solution was cooled to 0 °C. A 1 M solution of vinylmagnesium bromide in THF (150 cm^3; 150 mmol) was added dropwise and the mixture was stirred for 42 h. Water (600 cm^3) was added and the solution was neutralised with 4 M AcOH. The solvent was partly removed *in vacuo* and the residue was extracted with ether (3 × 600 cm^3). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (800 cm^3) and then dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 99 : 1, v/v) to give the intermediate, which without further purification was re-dissolved in 80% AcOH (250 cm^3). After stirring of the solution for 16 h and concentration *in vacuo*, the residue was coevaporated with toluene (3 × 200 cm^3) and purified by silica gel column chromatography (CH_2Cl_2–MeOH 95 : 5, v/v) to give the product **5** (14.9 g, 75%) as a white solid, δ_H ($CDCl_3$) in accord with literature data;[17] δ_C ($CDCl_3$) 26.33, 26.40, 63.98, 70.36, 79.27, 80.38, 83.35, 103.46, 113.02, 116.56, 134.23.

1,2-*O*-Isopropylidene-6-*O*-triphenylmethyl-3-*C*-vinyl-α-D-allofuranose 6

To a stirred solution of **5** (2.16 g, 8.77 mmol) in anhydrous pyridine (21 cm^3) was added chloro(triphenyl)methane (3.66 g, 13.1 mmol). The reaction mixture was stirred for 2 days at room temperature and treated with another portion of triphenylchloromethane (1.22 g, 4.4 mmol), and after being stirred for 2 h the mixture was quenched with water (50 cm^3) and extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (150 cm^3) and then dried (Na_2SO_4). The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2) to give the *product* **6** (4.02 g, 94%) as a white solid (Found: C, 72.95; H, 6.65. $C_{30}H_{32}O_6 \cdot 0.25H_2O$ requires C, 73.07; H, 6.64%); δ_H ($CDCl_3$) 1.34 (3H, s, CH_3), 1.59 (3H, s, CH_3), 2.45 (1H, d, *J* 3.6, 5-OH), 3.07 (1H, br s, 3-OH), 3.29–3.32 (2H, m, 6-H_2), 3.79 (1H, m, 5-H), 4.04 (1H, d, *J* 11.3, 4-H), 4.25 (1H, d, *J* 3.6, 2-H), 5.35 (1H, dd, *J* 10.9 and 1.6, CH=C*H*H), 5.59 (1H, dd, *J* 17.3 and 1.6, CH=CH*H*), 5.73 (1H, d, *J* 3.6, 1-H), 5.87 (1H, dd, *J* 17.3 and 10.9, C*H*=CH_2), 7.19–7.46 (15H, m, ArH); δ_C ($CDCl_3$) 26.36, 26.52, 64.89, 69.77, 78.95, 80.64, 83.64, 86.61, 103.53, 112.94, 116.59, 126.95, 127.75, 128.56, 134.73, 143.64.

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-3-*C*-vinyl-α-D-allofuranose 7

A 60% oily dispersion of sodium hydride (782 mg, 19.6 mmol) was suspended in anhydrous DMF (17 cm^3) and the mixture was cooled to 0 °C. A solution of **6** (4.02 g, 8.22 mmol) in anhydrous DMF (6 cm^3) was added dropwise over a period of 45 min. The mixture was stirred at 50 °C for 1 h and then cooled to 0 °C. Benzyl bromide (2.34 cm^3, 19.6 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed by distillation under reduced pressure and the residue was treated with water (50 cm^3), neutralised with aq. HCl, and extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (150 cm^3) and then dried (Na_2SO_4). The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (light petroleum–ethyl acetate 9 : 1, v/v) to give the *product* **7** (3.87 g, 70%) as a solid (Found: C, 78.80; H, 6.66. $C_{44}H_{44}O_6$ requires C, 79.02; H, 6.63%); δ_H ($CDCl_3$) 1.37 (3H, s), 1.60 (3H, s), 3.40 (2H, d, *J* 4.4), 3.77 (1H, m), 4.42 (1H, d, *J* 6.8), 4.56 (1H, d, *J* 11.8), 4.57 (1H, d, *J* 11.0), 4.60 (1H, d, *J* 3.7), 4.69 (1H, d, *J* 11.0), 4.77 (1H, d, *J* 11.6), 5.20 (1H, d, *J* 17.9), 5.30 (1H, d, *J* 11.3), 5.74 (1H, d, *J* 3.8), 5.78 (1H, dd, *J* 18.1 and 11.5), 7.18–7.46 (25H, m); δ_C ($CDCl_3$) 26.61, 26.83, 64.33, 67.09, 71.98, 77.30, 80.79, 81.67, 85.53, 86.59, 103.90, 112.69, 117.92, 126.85, 127.14, 127.21, 127.57, 127.74, 127.81, 128.14, 128.21, 128.96, 135.95, 138.79, 139.02, 144.30; PDMS *m*/*z* 691 [M + Na^+].

Methyl 3,5-di-*O*-benzyl-3-*C*-vinyl-D-allofuranoside 8

A solution of **7** (3.87 g, 5.79 mmol) in methanolic HCl (20% w/w; 77 cm^3) and water (11 cm^3) was stirred at room temperature for 16 h. After neutralisation with $NaHCO_3$(s), the solution was extracted with CH_2Cl_2 (2 × 200 cm^3). The combined extracts were washed with water (200 cm^3) and then dried (Na_2SO_4). The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 99 : 1, v/v) to give the *anomeric mixture* **8** (1.75 g, 76%) as a clear oil (Found: C, 68.91; H, 6.78. $C_{23}H_{28}O_6$ requires C, 68.98; H, 7.05%); δ_H ($CDCl_3$) 2.12 (dd, *J* 7.7 and 5.2, 6-OH α), 2.24 (dd, *J* 8.4 and 4.9, 6-OH β), 2.98 (d, *J* 8.0, 2-OH β), 3.14 (d, *J* 10.0, 2-OH α), 3.47 (s, OCH_3 β), 3.48 (s, OCH_3 α), 3.44–3.55 (m, 5-H), 3.81–3.92 (m, 6-H), 4.08 (dd, *J* 7.9 and 3.6, 2-H β), 4.14 (dd, *J* 10.0 and 4.8, 2-H α), 4.34–4.69 (m, CH_2Ph, 4-H), 4.91 (d, *J* 3.5, 1-H α), 4.94 (d, *J* 4.7, 1-H β), 5.35–5.45 (m, CH=CH_2 α), 5.42 (dd, *J* 11.1 and 1.1, CH=C*H*H β), 5.55 (dd, *J* 17.5 and 1.2, CH=CH*H* β), 6.04 (dd, *J* 17.5 and 11.0, C*H*=CH_2 α), 6.11 (dd, *J* 17.6 and 11.2, C*H*=CH_2 β), 7.26–7.36 (m, Ph); δ_C ($CDCl_3$) 55.47, 56.74, 60.93, 61.34, 66.41, 66.52, 71.13, 71.51, 75.69, 78.01, 78.68, 79.07, 82.65, 83.01, 85.37, 101.76, 109.50, 116.99, 118.63, 126.88, 127.22, 127.48, 127.83, 127.86, 127.89, 127.94, 128.00, 128.30, 128.54, 128.57, 128.59, 132.68, 135.37, 137.70, 137.79, 138.05, 139.16; FAB-MS *m*/*z* 423 [M + Na^+].

Methyl 3,5-di-*O*-benzyl-2,6-bis(*O*-methylsulfonyl)-3-*C*-vinyl-D-allofuranoside 9 and 10

To a stirred solution of **8** (2.41 g, 6.01 mmol) in anhydrous pyridine (18 cm^3) at 0 °C was added dropwise methanesulfonyl chloride (2.28 cm^3, 30.1 mmol). The reaction mixture was stirred for 30 min at room temperature, quenched with ice-cold

water (200 cm^3), and extracted with CH_2Cl_2 (2 × 250 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (2 × 200 cm^3) and then dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2) to give three fractions as clear oils: the pure β-anomer **9** (1.464 g, 44%), the pure α-anomer **10** (1.302 g, 39%) and a mixture of anomers (0.412 g, 12%).

Methyl 3,5-di-*O*-benzyl-2,6-bis(*O*-methylsulfonyl)-3-*C*-vinyl-β-D-allofuranoside 9. δ_H ($CDCl_3$) 2.97 (3H, s), 3.01 (3H, s), 3.48 (3H, s), 3.67 (1H, m), 4.33–4.71 (7H, m), 5.08 (1H, d, *J* 3.1), 5.19 (1H, d, *J* 3.1), 5.51 (1H, d, *J* 11.8), 5.65 (1H, d, *J* 17.7), 6.05 (1H, dd, *J* 17.8 and 11.2), 7.22–7.34 (10H, m); δ_C ($CDCl_3$) 37.59, 38.92, 56.68, 67.42, 68.02, 71.75, 76.81, 83.22, 83.47, 84.79, 106.53, 119.69, 127.08, 127.52, 128.03, 128.08, 128.44, 128.57, 137.18, 137.18, 138.59; FAB-MS *m*/*z* 579 [M + Na^+].

Methyl 3,5-di-*O*-benzyl-2,6-bis(*O*-methylsulfonyl)-3-*C*-vinyl-α-D-allofuranoside 10. (Found: C, 53.82; H, 5.78. $C_{25}H_{32}O_{10}S_2$ requires C, 53.94; H, 5.79%); δ_H ($CDCl_3$) 2.92 (3H, s), 3.05 (3H, s), 3.51 (3H, s), 3.74 (1H, m), 4.31–4.74 (7H, m), 5.11 (1H, d, *J* 4.5), 5.14 (1H, d, *J* 4.3), 5.46 (1H, s, *J* 17.6), 5.51 (1H, d, *J* 11.3), 5.99 (1H, dd, *J* 17.8 and 11.1), 7.23–7.34 (10H, m); δ_C ($CDCl_3$) 37.64, 39.27, 56.22, 67.43, 68.58, 72.09, 76.07, 78.96, 80.72, 83.35, 101.27, 119.14, 127.43, 127.56, 128.17, 128.32, 128.46, 128.67, 137.43, 137.43, 138.78; FAB-MS *m*/*z* 579 [M + Na^+].

(1*R*,3*R*,4*S*,7*R*,10*R*,11*R*)-10,11-Dibenzyloxy-3-methoxy-2,5,8-trioxatricyclo[5.3.1.$0^{4,11}$]undecane 11

To a solution of **9** (1.43 g, 2.57 mmol) in *tert*-butyl alcohol (28.6 cm^3) were added *N*-methylmorpholine *N*-oxide (2.10 g, 18.1 mmol), pyridine (1.44 cm^3, 18.8 mmol), water (1.56 cm^3) and a 2.5 w/w% solution of OsO_4 in *tert*-butyl alcohol (0.144 cm^3). The solution was stirred under reflux at 80 °C for two days and quenched at room temperature with 20% aq. sodium bisulfite (10.5 cm^3). The mixture was diluted with water (100 cm^3) and extracted with CH_2Cl_2 (2 × 300 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (200 cm^3) and then dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 98 : 2, v/v) to give a clear oil (1.152 g), which was dried and dissolved in anhydrous DMF (7 cm^3). This solution was stirred at 0 °C and a 60% oily dispersion of NaH (300 mg, 7.2 mmol) was added. The mixture was stirred at room temperature for four days. The reaction mixture was quenched with water (100 cm^3), saturated with NaCl, and extracted with CH_2Cl_2 (2 × 200 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 99 : 1, v/v) to give the product **11** (490 mg, 48%) as a clear oil which was used without further purification in the next step, δ_H ($CDCl_3$) 3.66 (3H, s), 3.40–4.19 (6H, m), 4.41 (1H, d, *J* 4.2), 4.51–4.77 (5H, m), 4.92 (1H, d, *J* 4.0), 7.26–7.39 (10H, m); δ_C ($CDCl_3$) 58.02, 58.36, 67.76, 68.44, 71.21, 71.42, 73.07, 77.10, 84.15, 89.55, 104.79, 127.15, 127.92, 127.97, 128.03, 128.56, 128.62, 137.65, 137.93; FAB-MS *m*/*z* 421 [M + Na^+].

(1*R*,3*S*,4*S*,7*R*,10*R*,11*R*)-10,11-Dibenzyloxy-3-methoxy-2,5,8-trioxatricyclo[5.3.1.$0^{4,11}$]undecane 12

The same procedure as for preparation of **11** was used with precursor **10** (1.28 g, 2.29 mmol), *tert*-butyl alcohol (25.5 cm^3), *N*-methylmorpholine *N*-oxide (1.87 g, 16.1 mmol), pyridine (1.28 cm^3, 16.1 mmol), water (1.39 cm^3), a 2.5 w/w% solution of OsO_4 in *tert*-butyl alcohol (0.128 cm^3), anhydrous DMF (6 cm^3), and a 60% oily dispersion of NaH (250 mg, 6.0 mmol) to give the product **12** (382 mg, 42%) as a clear oil which was used without further purification in the next step, δ_H ($CDCl_3$) 3.43 (3H, s), 3.66–4.08 (6H, m), 4.40 (1H, m), 4.49 (1H, s), 4.52–4.67 (4H, m), 4.98 (1H, s), 7.26–7.37 (10H, m); δ_C ($CDCl_3$) 54.59, 59.48, 68.44, 68.51, 70.88, 71.09, 73.64, 78.91, 89.12, 91.01, 108.20, 127.08, 127.15, 127.81, 127.94, 128.04, 128.57, 137.83, 138.17; FAB-MS *m*/*z* 421 [M + Na^+].

(3*R*)- and (3*S*)-(1*R*,4*S*,7*R*,10*R*,11*R*)-10,11-Dibenzyloxy-3-(thymin-1-yl)-2,5,8-trioxatricyclo[5.3.1.$0^{4,11}$]undecane 13

A mixture of **11** (100 mg, 0.251 mmol) and thymine (64 mg, 0.51 mmol) was dried and dissolved in anhydrous CH_3CN (3.9 cm^3). The mixture was treated with *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) (0.38 cm^3, 1.5 mmol) and stirred under reflux for 15 min. After cooling of the mixture to 0 °C, TMS triflate (96 mm^3, 0.48 mmol) was added dropwise and the solution was stirred at room temperature for 24 h and then at 60 °C for another 24 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (10 cm^3) and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined extracts were dried (Mg_2SO_4) and the solvent was removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 98 : 2, v/v) to give the product **13** as a clear oil and a mixture of anomers (β : α ≈ 3 : 1; 64.4 mg, 52%) which was used without further purification in the next step, δ_C ($CDCl_3$) 12.10, 12.48, 63.58, 63.86, 67.16, 67.63, 70.94, 71.38, 71.52, 71.99, 72.87, 73.73, 74.53, 79.49, 80.17, 83.65, 83.70, 85.87, 92.60, 93.69, 97.75, 109.30, 110.46, 127.22, 127.37, 127.93, 128.05, 128.29, 128.31, 128.46, 128.57, 128.63, 128.70, 128.79, 136.97, 137.31, 138.01, 138.75, 139.77, 150.38, 150.49, 163.82, 164.13; FAB-MS *m*/*z* 493 [M + H^+].

(3*R*)- and (3*S*)-(1*R*,4*S*,7*R*,10*R*,11*R*)-10,11-Dihydroxy-3-(thymin-1-yl)-2,5,8-trioxatricyclo[5.3.1.$0^{4,11}$]undecane 3 and 14

A solution of **13** (62 mg, 0.13 mmol) in EtOH (1.0 cm^3) was stirred at room temperature and 20% $Pd(OH)_2$–C (50 mg) was added. The mixture was degassed with argon and placed in a H_2 atmosphere. After being stirred for 36 h the mixture was directly purified by silica gel column chromatography (CH_2Cl_2–MeOH 96 : 4, v/v) to give the two products **3** (21.8 mg, 55%) and **14** (7.1 mg, 18%) respectively.

(1*R*,3*R*,4*S*,7*R*,10*R*,11*R*)-10,11-Dihydroxy-3-(thymin-1-yl)-2,5,8-trioxatricyclo[5.3.1.$0^{4,11}$]undecane 3. δ_H (CD_3OD) 1.85 (3H, d, *J* 0.9, CH_3), 3.72 (1H, dd, *J* 11.2 and 8.0, 9-H″), 3.90 (1H, dd, *J* 3.2 and 1.2, 7-H), 3.95 (1H, d, *J* 9.8, 6-H″), 4.01 (1H, dd, *J* 10.0 and 3.2, 6-H′), 4.02 (1H, dd, *J* 10.6 and 7.6, 9-H′), 4.04 (1H, d, *J* 3.1, 1-H), 4.22 (1H, td, *J* 7.7 and 3.0, 10-H), 4.39 (1H, d, *J* 4.8, 4-H), 6.11 (1H, d, *J* 4.6, 3-H), 7.69 (1H, d, *J* 1.1, thymine 6-H); δ_C (CD_3OD) 12.44 (CH_3), 65.29 (C-10), 66.75 (C-9), 75.70 (C-6), 80.89 (C-1), 83.11 (C-7), 85.08 (C-3), 87.92 (C-11), 89.58 (C-4), 109.48 (thymine C-5), 141.06 (thymine C-6), 152.23 (thymine C-2), 166.61 (thymine C-4); FAB-MS *m*/*z* 313 [M + H^+]; FAB-HRMS Found: *m*/*z*, 313.1036. $C_{13}H_{17}N_2O_7^+$ requires *m*/*z*, 313.1031.

(1*R*,3*S*,4*S*,7*R*,10*R*,11*R*)-10,11-Dihydroxy-3-(thymin-1-yl)-2,5,8-trioxatricyclo[5.3.1.$0^{4,11}$]undecane 14. δ_H (CD_3OD) 1.88 (3H, s, CH_3), 3.69 (1H, dd, *J* 10.4 and 9.1, 9-H″), 3.83 (1H, dd, *J* 10.8 and 6.6, 9-H′), 3.97 (1H, m, 7-H), 4.04–4.07 (2H, m, 6-H_2), 4.08 (1H, m, 10-H), 4.53 (1H, d, *J* 2.5, 1-H), 4.72 (1H, d, *J* 1.7, 4-H), 5.68 (1H, d, *J* 1.9, 3-H), 7.42 (1H, d, *J* 0.8, thymine 6-H); δ_C (CD_3OD) 12.80, 65.11, 65.91, 74.04, 81.89, 85.27, 88.63, 94.25, 95.74, 111.67, 139.52, 155.10, 170.05; FAB-MS *m*/*z* 313 [M + H^+].

ab initio Calculations

All *ab initio* quantum mechanical calculations were performed using the Gaussian94 program.[25] Geometry optimisations

were carried out at either the 3-21G* or 6-31G* levels using the restricted Hartree–Fock procedure. Constrained geometry optimisations were obtained by constraining the appropriate torsion angles with the AddRedundant option. No restraints were placed upon the glycosidic linkage χ between the furanose ring and the nucleobase in any calculations.

Measurement of three-bond coupling constants

1D ^{1}H NMR spectra of the nucleosides studied were acquired on a Varian Unity 500 MHz spectrometer. The nucleosides **3** and **14** were dissolved in CD_3OD and spectra were obtained in the temperature range from −50 to +50 °C. Coupling constants were measured as the splitting of multiplet components, thereby limiting the accuracy to within 10% of the linewidth (≈0.1 Hz).

Karplus relationships

Karplus relationships correlating $^3J_{HH}$ and torsion angles were constructed employing a state-of-the-art generalised Karplus equation [eqn. (1)] for nucleosides and nucleotides developed

$$J_{HH}(\theta) = \sum_{m=0}^{3} C_m \cos(m\theta) + \sum_{n=1}^{3} S_n \sin(n\theta) \qquad (1)$$

by Altona and co-workers,[20] where the electronegativity of the HCCH-fragment substituents is accounted for in the coefficients C_m and S_n. Altona and Sundaralingam[21] have developed a simple relationship relating the five ring torsion angles of the furanose ring, θ_i, to the pseudorotation angle, P, and the puckering amplitude, Φ_{max} [eqn. (2)]. Thus, for a given

$$\theta_i = \Phi_{max} \cos[P + 144(i - 2)], \; i = 1, \ldots 5 \qquad (2)$$

value of Φ_{max}, we can deduce the value of $\theta_{H1'H2'}$ depending on P and hence the Karplus relationship between $J_{H1'H2'}$ and P.

Acknowledgements

The Danish Natural Science Research Council is thanked for financial support.

References

1 (*a*) P. Herdewijn, *Liebigs Ann.*, 1996, 1337; (*b*) P. Herdewijn, *Biochim. Biophys. Acta*, 1999, **1489**, 167.
2 (*a*) P. Nielsen, H. M. Pfundheller and J. Wengel, *Chem. Commun.*, 1997, 825; (*b*) P. Nielsen, H. M. Pfundheller, C. E. Olsen and J. Wengel, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3423.
3 N. K. Christensen, M. Petersen, P. Nielsen, J. P. Jacobsen, C. E. Olsen and J. Wengel, *J. Am. Chem. Soc.*, 1998, **120**, 5458.
4 (*a*) S. K. Singh, P. Nielsen, A. A. Koshkin and J. Wengel, *Chem. Commun.*, 1998, 455; (*b*) A. A. Koshkin, S. K. Singh, P. Nielsen, V. K. Rajwanshi, R. Kumar, M. Meldgaard, C. E. Olsen and J. Wengel, *Tetrahedron*, 1998, **54**, 3607; (*c*) S. Obika, D. Nanbu, Y. Hari, J. Andoh, K. Morio, T. Doi and T. Imanishi, *Tetrahedron Lett.*, 1998, **39**, 5401; (*d*) A. A. Koshkin, P. Nielsen, M. Meldgaard, V. K. Rajwanshi, S. K. Singh and J. Wengel, *J. Am. Chem. Soc.*, 1998, **120**, 13252; (*e*) V. K. Rajwanshi, A. E. Håkansson, M. D. Sørensen, S. Pitsch, S. K. Singh, R. Kumar, P. Nielsen and J. Wengel, *Angew. Chem., Int. Ed.*, 2000, **39**, 1656.
5 (*a*) K.-H. Altmann, R. Kesselring, E. Francotte and G. Rihs, *Tetrahedron Lett.*, 1994, **35**, 2331; (*b*) K.-H. Altmann, R. Imwinkelried, R. Kesselring and G. Rihs, *Tetrahedron Lett.*, 1994, **35**, 7625; (*c*) V. E. Marquez, M. A. Siddiqui, A. Ezzitouni, P. Russ, J. Wang, R. W. Wagner and M. D. Matteucci, *J. Med. Chem.*, 1996, **39**, 3739; (*d*) G. Wang, E. Gunic, J.-L. Girardet and V. Stoisavljevic, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1147; (*e*) V. K. Rajwanshi, R. Kumar, M. Kofod-Hansen and J. Wengel, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1407; (*f*) M. Raunkjær, C. E. Olsen and J. Wengel, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2543.
6 (*a*) M. Tarköy and C. Leumann, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1432; (*b*) M. Bolli, H. U. Trafelet and C. Leumann, *Nucleic Acids Res.*, 1996, **24**, 4660; (*c*) R. Meier, S. Grüschow and C. Leumann, *Helv. Chim. Acta*, 1999, **82**, 1813.
7 M. Bolli, J. C. Litten, R. Schütz and C. J. Leumann, *Chem. Biol.*, 1996, **3**, 197.
8 (*a*) R. Steffens and C. J. Leumann, *J. Am. Chem. Soc.*, 1997, **119**, 11548; (*b*) R. Steffens and C. J. Leumann, *J. Am. Chem. Soc.*, 1999, **121**, 3249.
9 M. A. Siddiqui, H. Ford Jr., C. George and V. E. Marquez, *Nucleosides Nucleotides*, 1996, **15**, 235.
10 (*a*) N. C. Bar, R. Patra, B. Achari and S. B. Mandal, *Tetrahedron*, 1997, **53**, 4727; (*b*) Q. Chao and V. Nair, *Tetrahedron*, 1997, **53**, 1957; (*c*) J. H. Hong, B. K. Chun and C. K. Chu, *Tetrahedron Lett.*, 1998, **39**, 225; (*d*) S. Obika, J. Andoh, T. Sugimoto, K. Miyashita and T. Imanishi, *Tetrahedron Lett.*, 1999, **40**, 6465; (*e*) H. R. Moon, H. O. Kim, M. W. Chun, L. S. Jeong and V. E. Marquez, *J. Org. Chem.*, 1999, **64**, 4733; (*f*) C. Lescop and F. Huet, *Tetrahedron*, 2000, **56**, 2995.
11 V. E. Marquez, A. Ezzitouni, P. Russ, M. A. Siddiqui, H. Ford Jr., R. J. Feldman, H. Mitsuya, C. George and J. J. Barchi Jr., *J. Am. Chem. Soc.*, 1998, **120**, 2780.
12 V. E. Marquez, P. Russ, R. Alonso, M. A. Siddiqui, S. Hernandez, C. George, M. C. Nicklaus, F. Dai and H. Ford Jr., *Helv. Chim. Acta*, 1999, **82**, 2119.
13 (*a*) M.-O. Bévierre, A. De Mesmaeker, R. M. Wolf and S. M. Freier, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 237; (*b*) H. Urata, H. Miyagoshi, T. Yumoto and M. Akagi, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1833.
14 For definitions and nomenclature of nucleoside conformations and torsions see W. Saenger, *Principles of Nucleic Acid Structure*, Springer, New York, 1984.
15 G. Minasov, M. Teplova, P. Nielsen, J. Wengel and M. Egli, *Biochemistry*, 2000, **39**, 3525.
16 L. B. Jørgensen, P. Nielsen, J. Wengel and J. P. Jacobsen, *J. Biomol. Struct. Dyn.*, 2000, **18**, 45.
17 The synthesis of the 3′-*C*-vinyl compound **5** has been reported before *via* an ethynyl Grignard addition and subsequent reduction of the corresponding 3′-*C*-ethynyl compound [(*a*) D. C. Baker, D. K. Brown, D. Horton and R. G. Nickol, *Carbohydr. Res.*, 1974, **32**, 299] followed by selective deprotection [(*b*) J. Marco-Contelles, P. Ruiz, L. Martínez and A. Martínez-Grau, *Tetrahedron*, 1993, **49**, 6669], as well as *via* a vinyl Grignard addition published without experimental details [(*c*) J. M. J. Tronchet, M. Zsely, R. N. Yazji, F. Barbalat-Rey and M. Geoffroy, *Carbohydr. Lett.*, 1995, **1**, 343].
18 J. K. Cha and N.-S. Kim, *Chem. Rev.*, 1995, **95**, 1761.
19 D. B. Davies, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1978, **12**, 135.
20 (*a*) L. A. Donders, F. A. A. M. de Leeuw and C. Altona, *Magn. Reson. Chem.*, 1989, **27**, 556; (*b*) C. Altona, J. H. Ippel, A. J. A. Westra Hoekzema, C. Erkelens, M. Groesbeek and L. A. Donders, *Magn. Reson. Chem.*, 1989, **27**, 564; (*c*) C. Altona, R. Francke, R. de Haan, J. H. Ippel, G. J. Daalmans, A. J. A. Westra Hoekzema and J. van Wijk, *Magn. Reson. Chem.*, 1994, **32**, 670.
21 C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, (*a*) 1972, **94**, 8205; (*b*) 1973, **95**, 2333.
22 F. Jensen, *Introduction to Computational Chemistry*, Wiley, Chichester, 1999.
23 B. Cadioli, E. Gallinella, C. Coulombeau, H. Jobic and G. Berthier, *J. Phys. Chem.*, 1993, **97**, 7844.
24 (*a*) H. Ikeda, R. Fernandez, A. Wilk, J. J. Barchi Jr., X. Huang and V. E. Marquez, *Nucleic Acids Res.*, 1998, **26**, 2237; (*b*) I. Berger, V. Tereshko, H. Ikeda, V. E. Marquez and M. Egli, *Nucleic Acids Res.*, 1998, **26**, 2473; (*c*) M. J. Damha, C. J. Wilds, A. Noronha, I. Brukner, G. Borkow, D. Arion and M. A. Parniak, *J. Am. Chem. Soc.*, 1998, **120**, 12976; (*d*) C. J. Wilds and M. J. Damha, *Nucleic Acids Res.*, 2000, **28**, 3625.
25 M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Comperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, Gaussian94 (Rev D.3), Gaussian Inc., Pittsburgh, PA, 1995.