Synthesis of bicyclic nucleosides by ring-closing metathesis

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The ring-closing metathesis method is applied in the construction of conformationally restricted bicyclic nucleosides. From diacetone-D-glucose, the unsaturated bicyclic carbohydrate derivative **11** is efficiently obtained through two vinyl group Grignard additions, subsequent metathesis of the double bonds, and resolution of the stereochemistry by an oxidation/reduction reaction sequence. Two separate routes differing in the 3-*O*-protecting group are compared. Thus, an additional protecting step improves the yields significantly. Standard conversions of **11** give the bicyclic nucleoside **22** containing an olefinic moiety with a high potential for further functionalisation. As examples, two simple bicyclic *ribo*-nucleoside analogues **4** and **5**, which are restricted to the unusual South-type conformations, are synthesised.

Introduction

The natural nucleosides of DNA and RNA are known to exist in an equilibrium between two major conformers, the North (*N*) and the South (*S*) types (Fig. 1).[1] This conformational behaviour forms the basis of the two major double-helical structures, the A- and B-forms. The *N*-type (3′-*endo*) conformations are preferred by the *ribo*-nucleosides found in RNA and result in A-form duplexes, whereas the *S*-type (2′-*endo*) conformations give B-form duplexes as adopted by the 2′-deoxynucleosides found in most DNA sequences.[1] Furthermore, this conformational equilibrium of nucleosides is considered as essential for many other biological functions including the binding to nucleoside/nucleotide-converting enzymes.[1,2]

Conformational restriction of nucleosides has received considerable attention during the last few years.[3–5] In particular, nucleoside analogues with bicyclic carbohydrate moieties have been designed as potential antiviral agents[3] and as the monomers in conformationally restricted oligonucleotide sequences.[4,5] Due to the decrease in conformational freedom introduced by the bicyclic nucleosides, these oligonucleotides have displayed very promising results as compounds with improved recognition of complementary RNA and DNA sequences.[4,5] As a pioneer example, the bicyclic nucleosides **1** (Fig. 1) were synthesised by Leumann and co-workers and incorporated into oligonucleotides.[6–9] The nucleoside structure **1** is known to prefer an *S*-type conformation,[6] but the torsion angle γ describing the C-4′–C-5′ bond[1] is found to prefer the $+ac/+ap$ range,[6] which is not the preferred range in A- and B-type duplex structures.[1] Thus, oligomers containing exclusively **1** are found to prefer Hoogsteen base-pairing over the normal Watson–Crick base-pairing.[8] In general, the binding affinities towards complementary nucleic acid sequences were slightly improved compared to unmodified oligodeoxynucleotides but very dependent on the nucleotide sequences.[7,8] Improved binding affinities have been introduced with a tricyclic analogue of **1** in which γ is restricted into the less unfavourable $+ac$ range.[10]

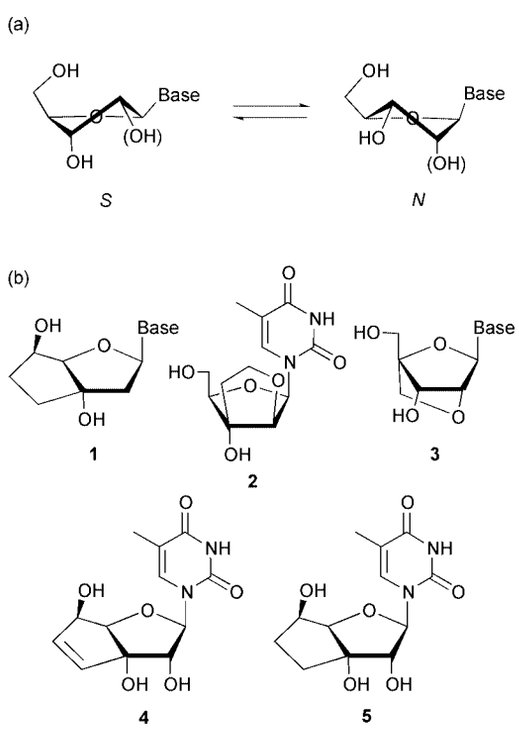

Fig. 1 (a) Conformational equilibrium of nucleosides. (b) Examples of bicyclic nucleosides.

After the introduction of **1**, several bicyclic nucleoside analogues have been synthesised and investigated as building blocks in oligonucleotide sequences.[5] The best results concerning the hybridisation with complementary RNA have been obtained with nucleoside analogues restricted to *N*-type conformations.[4,5] As a prime example, oligonucleotides containing the nucleosides **3** (Fig. 1) are known as LNA (Locked Nucleic Acids) and display very strong recognition of both RNA and DNA.[11] As other examples, two different bicyclic carbocyclic nucleosides, the so-called methanocarba nucleosides, restricted to either *S*- or *N*-type conformations have been presented and used in several studies on oligonucleotides[12] as well as on the conformational preferences of the substrates in nucleoside/nucleotide-converting enzymes and nucleoside-recognising receptors.[13]

Also, bi- and tricyclic nucleosides with conformations in between *N*- and *S*-type conformations have been presented.[14–16] As an example, nucleoside **2** (Fig. 1) has been incorporated into oligonucleotides displaying enhanced affinity towards RNA in a fully modified sequence.[14] This nucleoside has been suggested to prefer an O-4′-*endo*, East (*E*) type[1] conformation,[16] which

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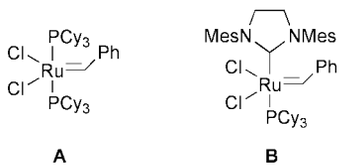
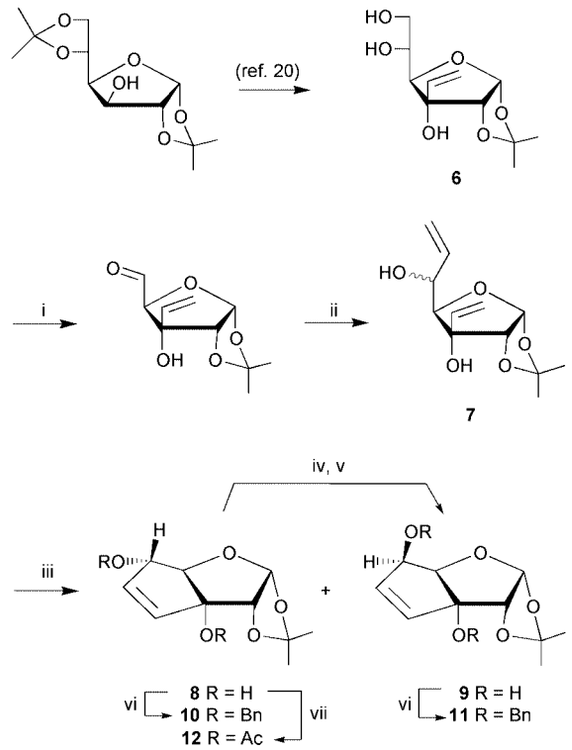
has been further confirmed by X-ray[17] as well as NMR studies on duplex structures containing **2**.[18]

Here we present a simple synthesis of new bicyclic nucleosides taking advantage of a ring-closing metathesis (RCM) reaction. This technology has recently achieved considerable attention for its convenient and widespread synthetic applications.[19] In particular, the introduction of Grubbs' catalyst **A** as a very stable, efficient and functional group-tolerant



A **B**

catalyst[19] prompted us to investigate the use of the RCM reaction in the construction of bicyclic nucleosides containing olefinic moieties. Thus, we hereby introduce a conformational restriction into the natural nucleoside structure by incorporating an unsaturated bridge between C-3′ and C-5′. A protected bicyclic nucleoside intermediate **22** is synthesised and considered as a key compound in the construction of other functionalised bi- or tricyclic nucleosides for potential applications in oligonucleotide sequences or as antiviral compounds. As the first examples, the simple bicyclic nucleosides **4** and **5**, which are conformationally restricted *ribo*-nucleoside analogues and close derivatives of the first bicyclic 2′-deoxynucleosides **1**, are hereby presented.



Scheme 1 *Reagents and conditions*: i, $NaIO_4$, aq. MeOH; ii, vinylMgBr, THF; iii, Grubbs' catalyst **A**, CH_2Cl_2; iv, PCC, CH_2Cl_2; v, $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; vi, BnBr, NaH, DMF; vii, Ac_2O, pyridine.

Results

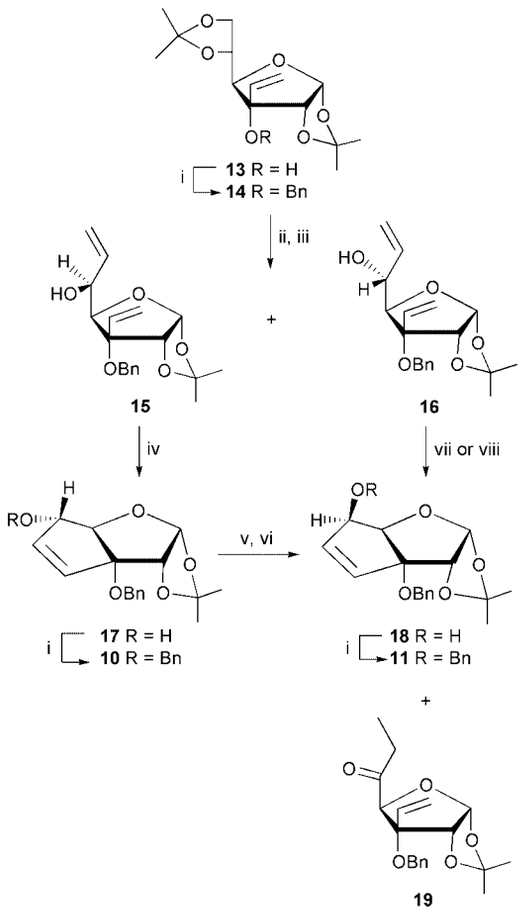
Chemical synthesis

The 3′-*C*-vinylallose derivative **6** was obtained from diacetone-D-glucose using oxidation, a stereoselective Grignard reaction and a selective deprotection following a known procedure (Scheme 1).[20] This vicinal diol was cleaved to give an aldehyde which was used without purification as a substrate in a second Grignard addition using vinylmagnesium bromide. This afforded the product **7** as an epimeric mixture in a 1 : 3 ratio and in 57% yield. The aldehyde was also obtained by *in situ* deprotection of the primary acetonide and diol oxidation using periodic acid following a protocol by Robins *et al.*[21] However, in the present example this method did not improve the overall yield of **7**. The diastereomers of **7** were not separated but used directly in an RCM reaction using Grubbs' catalyst **A**. This reaction afforded smoothly the two tricyclic compounds **8** and **9** in 24 and 67% yield, respectively, after chromatographic separation. The reaction products were not analytically pure at this stage due to remains of the ruthenium catalyst, but after a subsequent benzylation the protected analogues **10** and **11** were obtained as pure compounds and in acceptable yields (70 and 80%, respectively). Attempts to obtain analytically pure RCM products using a lead additive[22] or tris(hydroxymethyl)-phosphine[23] failed in this case.

The stereochemistry of the two epimeric compounds **10** and **11** was solved *via* ^{1}H NMR using $^3J_{HH}$ coupling constants as well as NOE experiments. Thus, in the constrained ring systems the small $^3J_{H4H5}$ coupling constants (<1 Hz and 2.5 Hz for **8** and **10**, respectively) indicate the *trans*-position of the hydrogens in accordance with torsion angles near 90°, whereas the larger $^3J_{H4H5}$ coupling constants (4.6 Hz for **9**, not determined for **11**) indicate the corresponding *cis*-position of the hydrogens in accordance with smaller torsion angles. For further confirmation of the configurations, NOE experiments were performed. Due to significant overlap of signals in both **8** and **10**, however, no useful NOE-difference spectra were obtained and, instead, the hydroxy groups of **8** were esterified to give the diacetylated compound **12**. As expected, the H-5 signal was shifted downfield and the signal overlap was decreased. From the NOE-difference spectra of **12** a weak mutual contact between H-5 and H-1 was observed, confirming the C-5 configuration. From the NOE-difference spectra of **9**, the lack of any contacts between H-5 and H-1/H-2 indicates the opposite C-5 configuration. In combination, the coupling constants and NOE experiments confirm the stereochemical determinations of compounds **8**–**12**.

Even though the major isomer **9** has the preferred C-5 configuration we converted the other isomer **8** to give **9** in two steps using a mild oxidation followed by a selective reduction using Luche conditions[24] in order to avoid any 1,4-hydride addition on the intermediate α,β-unsaturated ketone. Due to the structure of the tricyclic system the boron hydride could only approach the ketone from the convex site thereby affording **9** as the only product in 73% yield over the two steps. This further confirmed our determination of the configurations of **8** and **9**.

In the present synthesis of the key compound **11** (Scheme 1), the second Grignard addition could be considered as the yield-limiting step. Therefore, we decided to improve this by protecting the tertiary alcohol moiety of the starting material before the second Grignard reaction. Thus, compound **13**[20] was converted to the benzyl ether **14**[25] in 97% yield (Scheme 2). In this case, the combined selective cleavage/oxidation method using periodic acid[21] was superior and the subsequent Grignard addition gave the epimers **15** and **16** in a 4 : 1 ratio and a significantly higher (88%) yield over the two steps. The epimers were separated, and an RCM reaction using Grubbs' catalyst **A** and the major product **15** as the substrate afforded smoothly the product **17** in 79% yield. However, double the amount of catalyst (10 mol%) was necessary in order to finish the reaction. Benzylation of **17** afforded a product which was found to be **10**, determined beforehand to have the wrong C-5 configuration (*vide supra*). Thus, the ratio of the Grignard addition has in fact been inverted from a 1 : 3 ratio to a 4 : 1 ratio in favour of the opposite isomer by using the 3-*O*-protected starting material. Nevertheless, **17** was very efficiently converted to the



Scheme 2 *Reagents and conditions*: i, BnBr, NaH, DMF; ii, H_5IO_6, EtOAc; iii, vinylMgBr, THF; iv, Grubbs' catalyst **A**, CH_2Cl_2; v, PCC, CH_2Cl_2; vi, $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; vii, Grubbs' catalyst **A**, $ClCH_2CH_2Cl$; viii, Grubbs' catalyst **B**, CH_2Cl_2.

other and preferred epimer **18** in 93% yield using the same oxidation and selective reduction sequence as in the conversion of **8** to **9**. Subsequently, **18** was as expected easily benzylated to give the key compound **11** in 97% yield.

The observed change in the stereoselectivity between the different Grignard reactions might find some preliminary explanation from the ability of the divalent magnesium ion from the coexisting magnesium bromide to co-ordinate with two different oxygens. Thus, the magnesium ion can co-ordinate with the carbonyl oxygen as well as with either the 3-oxygen in a β-chelation or the ring oxygen in an α-chelation (Fig. 2).[26] In the former case, the carbonyl group would be orientated towards nucleophilic attack from the *re*-face, giving predominately the 5(*R*)-product as in **16**, whereas the latter chelation type would orientate the carbonyl group towards attack from the *si*-face, giving predominantly the 5(*S*)-product as in **15**. Thus, when the Grignard reaction is performed without a 3-*O*-protecting group, a 3-oxyanion is formed and a strong β-chelation involving this anion and magnesium explains the favouring of the 5(*R*)-product in **7**. With the alternative 3-benzyl ether, an α-chelation with magnesium is preferred and the 5(*S*)-product **15** is favoured.

The minor product of the last Grignard reaction, **16**, was also used in an RCM reaction using Grubbs' catalyst **A** in refluxing dichloromethane but, surprisingly, afforded a mixture of products from which only 10% of the expected product **18** was isolated. The major product was isolated in 33% yield and from NMR determined to be **19**. Thus, an ABX_3 system was identified, and chemical shifts further verified an ethyl ketone group. This isomerisation of allylic alcohols has been reported before using other ruthenium catalysts[27] and as a side reaction in metathesis reactions.[28] In an attempt to improve this

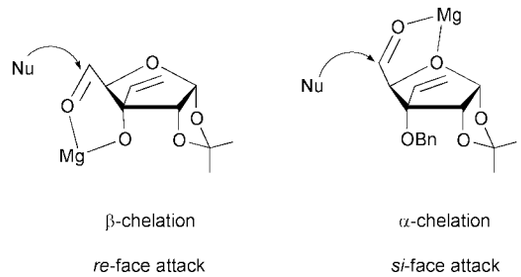
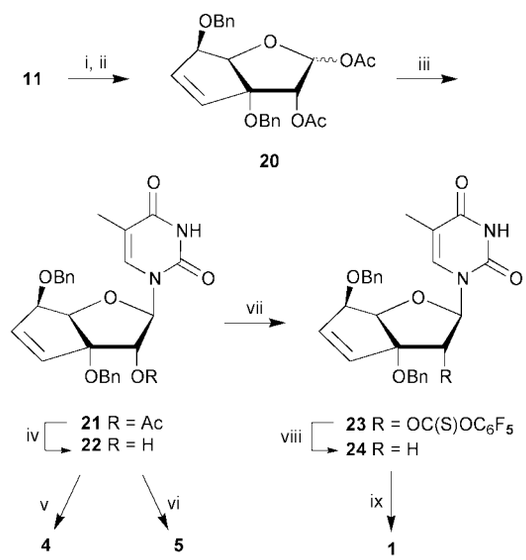


Fig. 2 Different chelations explaining the stereoselectivity in the Grignard reactions.

result, 1,2-dichloroethane was used as solvent and the reaction temperature was elevated. However, in that case only **19** was obtained, in 67% yield. Nevertheless, the recent introduction of the improved catalyst **B**,[29] *vide supra*, prompted us to use this in an improvement of the reaction. Fortunately, the reaction gave smoothly the expected product **18** in a very high (88%) yield. These results remain unexplained but confirm the reported efficiency of the improved Grubbs' catalyst **B**.[29,30] Problematic RCM reactions with terminal allylic benzyl ethers using catalyst **A** have been reported before[19] and **B** has in general been recognised as a much more reactive metathesis catalyst.[19,30]

The key intermediate **11** was hydrolysed and acetylated to give in 85% yield the anomeric mixture of **20** in a ≈1 : 1 ratio (Scheme 3). This mixture was coupled to thymine in a



Scheme 3 *Reagents and conditions*: i, 80% AcOH; ii, Ac_2O, pyridine; iii, thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMS triflate, CH_3CN; iv, MeONa, MeOH; v, BCl_3, hexane, CH_2Cl_2; vi, H_2, $Pd(OH)_2$–C, MeOH; vii, $C_6F_5OC(=S)Cl$, DMAP, CH_2Cl_2; viii, AIBN, Bu_3SnH, benzene; ix, H_2, $Pd(OH)_2$–C, cyclohexa-1,4-diene, MeOH.

modified Vorbrüggen-type nucleobase coupling reaction. Due to anchimeric assistance the β-nucleoside **21** was, as expected, obtained as the only product. This was easily deacetylated to give the bicyclic key nucleoside **22** in 88% yield from **20**. The nucleoside **22** has wide further potential for diverse and selective chemical treatments of the 2′-hydroxylic and/or the olefinic functionalities. However, the structure of **22** had to be exclusively confirmed and, therefore, we decided first to explore the obvious conversion of **22** into the original bicyclic nucleoside **1** (Base = thymine). Thus, the secondary alcohol moiety was converted to a thionocarbonate ester **23** as a precursor for a deoxygenation reaction. However, this reaction afforded only a 20% yield of the product in combination with uncharacterised side products. Nevertheless, **23** was treated with tributyltin hydride and a radical initiator to give the 2′-deoxynucleoside derivative **24** in a medium (50%) yield. As double bonds have

been reduced before with cyclohexa-1,4-diene as the hydrogen donor,[31] we treated **24** with both cyclohexadiene and hydrogen simultaneously, and the deprotected as well as saturated target compound **1** (Base = thymine) was obtained in 61% yield. The structure was confirmed by comparison of all NMR data with the corresponding literature data.[6] The present synthesis of **1** from **22** was performed in a low overall yield. However, the structure of **22** including the C-5′ configuration has been exclusively confirmed.

In order to obtain the two deprotected derivatives **4** and **5**, the bicyclic nucleoside **22** was treated with hydrogen and a palladium catalyst. This afforded smoothly the deprotected as well as saturated nucleoside **5** in 98% yield. The unsaturated deprotected bicyclic nucleoside **4** was obtained in 82% yield by the use of a strong Lewis acid for cleavage of the benzylic ethers.

Conformational behaviour

In order to study the conformational behaviour of the bicyclic nucleosides **4** and **5**, the experimental $^3J_{HH}$ coupling constants contain a fair amount of information. Thus, $^3J_{H1'H2'}$ was found to be 7.3 and 8.5 Hz for **4** and **5**, respectively. These large coupling constants prove both nucleosides to adopt (at least broadly defined) *S*-type conformations according to the Karplus relationship between $^3J_{H1'H2'}$ and the pseudorotation angle P.[1,32] Thus, for **4** the coupling constant correlates with a pseudorotation angle in either of two possible ranges 90–110° or 180–200°. For **5**, the pseudorotation angle is in the range 110–180°.[32] This is in agreement with the nucleoside **1** (Base = thymine) which, likewise, has been found to adopt an *S*-type conformation with $P = 128°$ as found by X-ray crystallography.[6] As found for **1** and other bi- and tricyclic nucleosides[6,16] we believe both **4** and **5** to exist in only one conformation each and not as dynamic equilibria between two or more conformers.

Also the $^3J_{H4'H5'}$ coupling constants contain useful information and were found to be 5.8 and 5.1 Hz for **4** and **5**, respectively. From a Karplus relationship between $^3J_{H4'H5'}$ and the torsion angle $\theta_{H4'H5'}$,[16,32] both these coupling constants comply with four different ranges of $\theta_{H4'H5'}$ of which two can be excluded due to the covalent geometry. Thus, $\theta_{H4'H5'}$ could for both nucleosides be found in the range around 30° as well as around −30° corresponding to γ of around 150° or 90°, respectively. For **1** (Base = thymine) this torsion angle γ was found from X-ray crystallography to be 149° and the coupling constant $^3J_{H4'H5'}$ was 5.3 Hz.[6] As it seems probable that the cyclopentane ring should behave similarly in both **1** and **5**, we expect γ of the *ribo*-nucleoside **5** to be in the same +*ac*/+*ap* range ($\gamma \approx 150°$) as for its 2′-deoxy analogue **1**. With the furanose in the same *S*-type (1′-*exo*)[1] conformation as for **1**,[6] both five-membered rings adopt envelope conformations as found for other bicyclic [3.3.0] nucleoside systems, *e.g.* **2**.[16]

Due to the greater constraint in the cyclopentene ring of **4** compared to the cyclopentane ring of **5**, the unsaturated nucleoside **4** is expected to be more conformationally restricted than **5**. The cyclopentene ring must take an envelope form with C-4′ flipping out of the plane. Hence, one of these flips would drive the furanose ring towards the *S*-type conformation, whereas the other could twist the furanose ring into an *E*-type or *N*-type conformation. The *E*-type is an unusual high-energy conformation in unmodified nucleosides[1] but has been found to be the preferred furanose conformation in other bicyclic, *e.g.* **2**, and tricyclic nucleoside analogues.[16] The $^3J_{H1'H2'}$ coupling constant of **4** complies with both an *E*-type conformation with P in the 90–110° range and a high *S*-type with P in the 180–200° range (*vide supra*). The former corresponds to a $\theta_{H4'H5'} \approx 30°$ and a $\gamma \approx 150°$, whereas the latter corresponds to a $\theta_{H4'H5'} \approx -30°$ and a $\gamma \approx 90°$. Thus, both of the two different conformations comply with the experimental coupling constants. However, from *ab initio* calculations using the Gaussian94 program,[33] geometry optimisations at the 3-21G* level found that the *E*-type conformation is not a low-energy conformation. Thus, the only low-energy conformation found that complies with the experimental data is a perfect *S*-type conformation with $P = 180°$, $\Phi_{max}{}^1 = 33°$ and $\theta_{H4'H5'} = -31°$ corresponding to a $\gamma \approx 89°$. Another low-energy conformation, with $P = 1°$, $\Phi_{max} = 32°$ and $\theta_{H4'H5'} = 25°$, was found. However, this *N*-type conformation can be entirely excluded from the large $^3J_{H1'H2'}$ coupling constant (*vide supra*).

Discussion

In the present synthetic work, the RCM methodology has been successfully applied to the construction of bicyclic nucleosides. As expected, the RCM method has been very efficient in the construction of the cyclopentene ring. With the more efficient catalyst **B**, the problem with an unexpected isomerisation of the substrate **16** was also solved. Thus, an unsaturated tricyclic carbohydrate derivative **11** has been efficiently obtained and converted through **20** to a bicyclic unsaturated key nucleoside **22**. Overall, **22** was obtained in high yields using either of the two synthetic routes. Thus, **22** was obtained in 11 steps and 17% yield from diacetone-D-glucose following the first route (Schemes 1 and 3) and 22% including the use of the isomer **8**. However, following the other route (Schemes 2 and 3), which includes an additional protecting step, **22** was obtained in 13 steps and 36% yield when all of the material of **18** obtained through **17** as well as through the efficient RCM reaction performed on **16** was included. The reaction sequence might, in theory, be even further improved, if the separation of **15** and **16** were avoided and the RCM reaction performed on the mixture of these using the improved catalyst **B**. Subsequently, an oxidation/reduction procedure on the mixture of **17** and **18** would give exclusively **18**. Hereby, this synthetic strategy would present a highly stereoselective route with no need for tedious separations of isomers. Of course, other nucleobases are expected to react stereoselectively with **20**. Thus, the strategy opens an obvious potential for similar bicyclic derivatives of other nucleosides.

The present synthetic strategy was not meant as an improved synthetic route towards the known and intensively investigated[6–8] bicyclic nucleosides **1**. Therefore, we did not put any effort into improving the disappointing yields of **23** and **24**. However, this might after all present an improved synthetic strategy compared to the completely different synthesis of **1** published by Leumann and co-workers[6] if the deoxygenation procedure could be significantly optimised. It might also be preferable to perform the hydrogenation of the double bond before the deoxygenation process.

In our synthetic strategy, it was a main purpose to obtain a key bicyclic nucleoside compound **22** with the potential of treating the double bond and the 2′-hydroxy group independently and without affecting the 5′- and 3′-hydroxy groups. Therefore, we did not optimise the protecting-group strategy for the specific syntheses of **4** and **5** as this, obviously, suggests the general use of, *e.g.*, acetic esters instead of benzyl ethers. The nucleoside **22** can be considered as a key compound in the development of other bi- and tricyclic nucleoside analogues. Thus, the olefinic moiety is new in the construction of bicyclic nucleosides and opens a wide potential of derivatisation, revealing, *e.g.*, alcohols and amines as well as additional ring systems. Thus, as an example the introduction of amino groups into bicyclic nucleosides and oligonucleotides as presented recently by Leumann and co-workers[9] gives the possibility of studying the hybridisation behaviour of zwitterionic oligonucleotides.

The two deprotected nucleosides **4** and **5** represent new conformationally restricted *ribo*-nucleoside analogues. Even though the conformational analysis has not been very comprehensive, our experimental data suggest the nucleoside **5** to adopt a conformation closely resembling the conformation of **1**

with γ in the $+ac/+ap$ range and the furanose ring in an *S*-type (1′-*exo*) conformation. On the other hand, the nucleoside **4** adopts a 'higher' *S*-type (2′-*endo*) conformation and with γ in the $+sc/+ac$ range. However, neither **4** nor **5** has the same degree of conformational restriction as, *e.g.*, the nucleoside **3**, which is perfectly locked in an *N*-type (3′-*endo*) conformation.[11] Nevertheless, both **4** and **5** can be considered as *ribo*-nucleoside analogues which are conformationally restricted towards the *S*-type conformations. For unmodified *ribo*-nucleosides this conformation is the less favoured in the equilibrium with the *N*-type conformations.[1] Therefore, **5** and perhaps to a higher degree **4** and/or analogues of these with other nucleobases might have interesting biological properties and might, *e.g.*, find useful applications as tools in the studies of conformational preferences and structure–activity relations in nucleoside/nucleotide-converting enzymes. On the other hand, we do not expect these *ribo*-nucleosides to improve the affinity of their corresponding oligonucleotides towards complementary nucleic acid sequences. Thus, the restriction in an *S*-type conformation demands the formation of a B-type helix but also brings the 2′-OH group towards a pseudoequatorial position which might give rise to steric interference in B-type duplex formation. However, at least for **4** the torsion angle γ prefers the $+sc/+ac$ range which is much more typically found in duplex structures compared to the $+ac/+ap$ range of **1** and **5**.[1] Thus, oligodeoxynucleotides containing the 2′-deoxy analogue of **4** might reveal significant improvements in hybridisation properties compared to the original oligomers of **1**.

Conclusions

We have developed a novel and very convenient synthetic strategy towards new bicyclic nucleosides taking advantage of stereoselective methods as well as the RCM methodology and starting from a very cheap starting material. Hereby, two bicyclic *ribo*-nucleosides **4** and **5** have been obtained. These nucleosides are expected to be useful tools as restricted analogues of the natural *ribo*-nucleosides and to display interesting biological properties. The use of the protected bicyclic nucleoside derivative **22** in the construction of other derivatised, bicyclic and/or tricyclic nucleosides as well as further applications of the RCM method in the construction of nucleoside and nucleotide derivatives are in progress in our laboratory.

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 MHz, 300 MHz or 500 MHz and ^{13}C NMR spectra were recorded at 62.5 MHz 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 **4**, **5**, **8**, **11**, **12**, **15**, **16** and **19**. ^{1}H NOE-difference spectra were recorded for compounds **9** and **12** and ^{1}H^{13}C-COSY spectra were recorded for compounds **4**, **5**, **12**, **15**, **16** and **19**. Assignments of NMR signals follow standard carbohydrate and nucleoside style. However, compound names for bi- and tricyclic compounds are given according to von Baeyer nomenclature. Fast-atom bombardment (FAB) mass spectra were recorded in positive-ion mode on a Kratos MS50TC spectrometer, and EI mass spectra were recorded on an SSQ710 Finnigan MAT spectrometer. High-resolution MALDI mass determinations were performed on an Ionspec Ultima Fourier Transform mass spectrometer. Microanalyses were performed at The Microanalytical Laboratory, Department of Chemistry, University of Copenhagen.

(5*R*/*S*)-6,7-Dideoxy-1,2-di-*O*-isopropylidene-*C*-vinyl-α-D-ribohept-6-enofuranose 7

To a solution of triol **6**[20] (3.18 g, 12.7 mmol) in MeOH (25 cm^3) and water (25 cm^3) was added $NaIO_4$ (3.0 g, 14.0 mmol) and the reaction mixture was stirred at room temperature for 30 min. The white precipitate was filtered off and the solvent was partly removed *in vacuo*. The residue was continuously extracted with CH_2Cl_2 (150 cm^3) overnight and the organic extract was dried ($MgSO_4$), and then concentrated *in vacuo*. The residue was re-dissolved in anhydrous tetrahydrofuran (THF) (100 cm^3) and the solution was cooled to 0 °C. A 1 M solution of vinylmagnesium bromide in THF (30 cm^3, 30 mmol) was added dropwise over a period of 30 min and the mixture was stirred at room temperature for 16 h. Water (250 cm^3) was added and the solution was neutralised with 4 M acetic acid. The solvent was partly removed *in vacuo* and the residue was extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 100 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 96 : 4, v/v) to give the mixture of diastereomers **7** (1.74 g, 57%, *R*/*S* 3 : 1) as a white solid (Found: C, 59.74; H, 7.62. $C_{12}H_{18}O_5$ requires C, 59.49; H, 7.49%); δ_H ($CDCl_3$) 1.38 (s, CH_3), 1.61 (s, CH_3), 2.32 (m, 5-OH), 2.77 [s, 3-OH(*S*)], 3.09 [s, 3-OH(*R*)], 3.73 (m, 4-H), 4.20 (m, 5-H), 4.26 (m, 2-H), 5.20–5.46 (m, CH=CH_2), 5.51–5.68 (m, CH=CH_2), 5.80–6.04 (m, C*H*=CH$_2$); δ_C ($CDCl_3$) 26.5, 71.0, 71.2, 81.0, 82.2, 83.4, 84.1, 84.8, 103.1, 103.5, 113.0, 116.2, 116.3, 116.6, 116.8, 134.0, 134.0, 135.2, 137.3; EI-MS *m*/*z* 242 [M$^+$].

(9*S*)- and (9*R*)-(1*R*,2*R*,6*R*,8*R*)-1,9-Dihydroxy-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 8 and 9

To a solution of **7** (1.37 g, 5.66 mmol) in anhydrous CH_2Cl_2 (60 cm^3) was added **A** (286 mg, 0.33 mmol) and the mixture was stirred at room temperature for 16 h and then at 40 °C for 3 h. The solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 96 : 4, v/v) to give the two products **8** (294 mg, 24%) and **9** (801 mg, 67%) as darkly coloured solids which were used without further purification.

(1*R*,2*R*,6*R*,8*R*,9*S*)-1,9-Dihydroxy-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 8. δ_H ($CDCl_3$) 1.40 (3H, s, CH_3), 1.62 (3H, s, CH_3), 3.76 (1H, s, OH), 3.88 (1H, s, OH), 4.29 (1H, app. s, 4-H), 4.46 (1H, app. s, 5-H), 4.46 (1H, d, *J* 3.6, 2-H), 5.71 (1H, d, *J* 3.6, 1-H), 5.81 (1H, d, *J* 5.7, 7-H), 6.08 (1H, dd, *J* 5.7 and 1.1, 6-H); δ_C ($CDCl_3$) 27.2, 27.4, 79.4, 81.4, 89.1, 90.8, 105.6, 113.0, 134.8, 137.3; EI-MS *m*/*z* 214 [M$^+$].

(1*R*,2*R*,6*R*,8*R*,9*R*)-1,9-Dihydroxy-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 9. δ_H ($CDCl_3$) 1.42 (3H, s, CH_3), 1.62 (3H, s, CH_3), 2.60 (1H, d, *J* 10.2, 5-OH), 3.12 (1H, s, 3-OH), 4.36 (1H, d, *J* 4.6, 4-H), 4.45 (1H, d, *J* 3.8, 2-H), 4.95 (1H, dd, *J* 10.2 and 4.6, 5-H), 5.68 (1H, dd, *J* 5.7 and 1.4, 6-H), 5.84 (1H, d, *J* 3.8, 1-H), 6.03 (1H, d, *J* 5.7, 7-H); δ_C ($CDCl_3$) 27.2, 27.2, 76.1, 83.2, 83.6, 89.5, 106.3, 113.5, 130.3, 141.0; EI-MS *m*/*z* 214 [M$^+$].

Alternative method for the preparation of 9

To a solution of **8** (1.75 g, 8.18 mmol) in CH_2Cl_2 (50 cm^3) was added pyridinium chlorochromate (PCC) (3.5 g, 16.2 mmol). The mixture was stirred at room temperature for 14 h and the mixture was filtered through a layer of silica. The filter was rinsed with ethyl acetate (150 cm^3), and the filtrate was concentrated by distillation under reduced pressure. The residue was

re-dissolved in MeOH (50 cm^3) and treated with $CeCl_3 \cdot 7H_2O$ (2.98 g, 8.0 mmol). This solution was cooled to 0 °C, $NaBH_4$ (405 mg, 10.7 mmol) was added in small portions, and the mixture was stirred at 0 °C for 1 h. Water (50 cm^3) was added and the solution was neutralised with 4 M acetic acid and continuously extracted with CH_2Cl_2 (150 cm^3) overnight. The organic 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 96 : 4, v/v) to give the product **9** (1.28 g, 73%) as a white solid.

(1*R*,2*R*,6*R*,8*R*,9*S*)-1,9-Diacetoxy-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 12

To a solution of **8** (149 mg, 0.696 mmol) in anhydrous pyridine (4 cm^3) was added acetic anhydride (1 cm^3), and the solution was stirred at room temperature for 16 h. The reaction mixture was quenched with water (4 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (2 × 10 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 product **12** (152 mg, 73%) as a clear oil; δ_H ($CDCl_3$) 1.37 (3H, s, CH_3), 1.53 (3H, s, CH_3), 2.08 (3H, s, $COCH_3$), 2.09 (3H, s, $COCH_3$), 4.60 (1H, s, 4-H), 4.89 (1H, d, *J* 4.0, 2-H), 5.38 (1H, d, *J* 2.5, 5-H), 5.83 (1H, d, *J* 4.0, 1-H), 6.12 (1H, ddd, *J* 5.6, 2.5 and 1.1, 6-H), 6.48 (1H, d, *J* 5.6, 7-H); δ_C ($CDCl_3$) 20.9, 20.9 ($CO\mathit{C}H_3$), 26.9, 27.6 [$C(\mathit{C}H_3)_2$], 79.9 (5-C), 80.0 (2-C), 88.1 (4-C), 93.8 (3-C), 106.4 (1-C), 112.7 [$\mathit{C}(CH_3)_2$], 135.3 (6-C), 136.0 (7-C), 169.7, 169.9 ($\mathit{C}OCH_3$).

3-*O*-Benzyl-1,2;5,6-di-*O*-isopropylidene-3-*C*-vinyl-α-D-allofuranose[25] 14

A 60% oily dispersion of sodium hydride (1.08 g, 27 mmol) was suspended in anhydrous *N*,*N*-dimethylformamide (DMF) (50 cm^3) and the mixture was cooled to 0 °C. A solution of compound **13**[20] (4.03 g, 14.08 mmol) in anhydrous DMF (10 cm^3) was added dropwise over a period of 30 min. The mixture was stirred at 50 °C for 1 h and then cooled to 0 °C. Benzyl bromide (4.7 g, 27.5 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 re-dissolved in CH_2Cl_2 (300 cm^3). The solution was washed with saturated aq. $NaHCO_3$ (2 × 100 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 (light petroleum–ethyl acetate 9 : 1, v/v) to give the product **14** (5.14 g, 97%) as a clear oil; δ_H ($CDCl_3$) 1.33 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.61 (3H, s, CH_3), 3.95 (2H, d, *J* 5.9, 6-H_2), 4.16 (1H, q, *J* 5.9, 5-H), 4.31 (1H, d, *J* 5.9, 4-H), 4.60 (1H, d, *J* 11.4, CH_2Ph), 4.62 (1H, d, *J* 3.7, 2-H), 4.68 (1H, d, *J* 11.4, CH_2Ph), 5.29 (1H, d, *J* 18.2, CH=CH_2), 5.46 (1H, d, *J* 11.3, CH=CH_2), 5.82 (1H, d, *J* 3.7, 1-H), 5.86 (1H, dd, *J* 18.2 and 11.3, C*H*=CH_2), 7.21–7.41 (5H, m, Ph); δ_C ($CDCl_3$) 138.8, 135.5, 128.0, 127.1, 126.9, 118.6, 112.9, 108.8, 104.4, 84.9, 82.1, 81.4, 74.0, 66.8, 66.3, 26.9, 26.7, 26.6, 25.3; FAB-MS *m*/*z* 377 [M + H^+].

(5*S*)- and (5*R*)-3-*O*-Benzyl-6,7-dideoxy-1,2-di-*O*-isopropylidene-3-*C*-vinyl-α-D-*ribo*-hept-6-enofuranose 15 and 16

To a solution of **14** (10.4 g, 27.6 mmol) in ethyl acetate (300 cm^3) was added periodic acid (6.5 g, 28.5 mmol) and the reaction mixture was stirred at room temperature for 1 h. The white precipitate was filtered off and the solvent was removed by distillation under reduced pressure. The residue was re-dissolved in anhydrous THF (250 cm^3) and the solution was cooled to 0 °C. A 1 M solution of vinylmagnesium bromide in THF (50 cm^3, 50 mmol) was added dropwise over a period of 30 min and the mixture was stirred at room temperature for 48 h. Water (350 cm^3) was added and the solution was neutralised with 4 M acetic acid. The solvent was partly removed by distillation under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 250 cm^3). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 300 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 (light petroleum–ethyl acetate 7 : 3, v/v) to give the two products **15** (6.38 g, 69%) and **16** (1.70 g, 19%) as clear oils.

(5*S*)-3-*O*-Benzyl-6,7-dideoxy-1,2-di-*O*-isopropylidene-3-*C*-vinyl-α-D-*ribo*-hept-6-enofuranose 15. δ_H ($CDCl_3$) 1.39 (3H, s, CH_3), 1.60 (3H, s, CH_3), 2.27 (1H, br s, OH), 4.12 (1H, d, *J* 6.7, 4-H), 4.23 (1H, dd, *J* 6.7 and 5.8, 5-H), 4.59 (1H, d, *J* 11.3, CH_2Ph), 4.65 (1H, d, *J* 3.6, 2-H), 4.67 (1H, d, *J* 11.3, CH_2Ph), 5.22 (1H, d, *J* 10.4, 7-H^b), 5.28 (1H, d, *J* 18.1, CH=CH_2), 5.39 (1H, d, *J* 17.1, 7-H^a), 5.45 (1H, d, *J* 11.2, CH=CH_2), 5.86 (1H, d, *J* 3.6, 1-H), 5.89 (1H, dd, *J* 18.1 and 11.2, C*H*=CH_2), 5.98 (1H, ddd, *J* 17.1, 10.4 and 5.8, 6-H), 7.25–7.38 (5H, m, Ph); δ_C ($CDCl_3$) 26.6, 26.9 (2 × CH_3), 66.9 ($\mathit{C}H_2$Ph), 71.0 (5-C), 81.7 (2-C), 84.2 (4-C), 84.5 (3-C), 103.9 (1-C), 113.1 [$\mathit{C}(CH_3)_2$], 116.4 (7-C), 118.1 (CH=$\mathit{C}H_2$), 126.9, 127.3, 128.2 (Ph), 135.0 ($\mathit{C}H$=CH_2), 135.8 (6-C), 138.5 (Ph); EI-MS *m*/*z* 332 [M^+].

(5*R*)-3-*O*-Benzyl-6,7-dideoxy-1,2-di-*O*-isopropylidene-3-*C*-vinyl-α-D-*ribo*-hept-6-enofuranose 16. δ_H ($CDCl_3$) 1.38 (3H, s, CH_3), 1.61 (3H, s, CH_3), 2.65 (1H, br s, OH), 3.98 (1H, d, *J* 9.0, 4-H), 4.16 (1H, dd, *J* 9.0 and 5.7, 5-H), 4.62 (1H, d, *J* 10.9, CH_2Ph), 4.66 (1H, d, *J* 3.6, 2-H), 4.70 (1H, d, *J* 10.9, CH_2Ph), 5.20 (1H, d, *J* 10.5, 7-H^b), 5.38 (1H, d, *J* 18.0, CH=CH_2), 5.38 (1H, d, *J* 17.0, 7-H^a), 5.56 (1H, d, *J* 11.5, CH=CH_2), 5.83 (1H, d, *J* 3.6, 1-H), 5.95 (1H, dd, *J* 18.0 and 11.5, C*H*=CH_2), 5.96 (1H, ddd, *J* 17.0, 10.5 and 5.7, 6-H), 7.28–7.39 (5H, m, Ph); δ_C ($CDCl_3$) 26.6, 26.7 (2 × CH_3), 67.7 ($\mathit{C}H_2$Ph), 70.8 (5-C), 80.9 (2-C), 82.2 (4-C), 86.1 (3-C), 104.3 (1-C), 113.1 [$\mathit{C}(CH_3)_2$], 116.4 (7-C), 119.0 (CH=$\mathit{C}H_2$), 127.4, 127.6, 128.3 (Ph), 134.2, 137.5 ($\mathit{C}H$=CH_2, 6-C), 137.8 (Ph); EI-MS *m*/*z* 332 [M^+].

(1*R*,2*R*,6*R*,8*R*,9*S*)-1-Benzyloxy-9-hydroxy-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 17

To a solution of **15** (5.8 g, 17.4 mmol) in anhydrous CH_2Cl_2 (200 cm^3) was added the catalyst **A** (750 mg, 0.89 mmol) and the mixture was stirred at room temperature for 48 h. At this time another portion of **A** (750 mg, 0.89 mmol) was added and the mixture was stirred for an additional 72 h. The solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (light petroleum–ethyl acetate 7 : 3, v/v) to give the product **17** (4.18 g, 79%) as a darkly coloured solid which was used without further purification in the next step; δ_H ($CDCl_3$) 1.41 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.94 (1H, br s, OH), 4.49 (1H, s, 4-H), 4.50 (1H, d, *J* 2.5, 5-H), 4.58 (1H, d, *J* 11.3, CH_2Ph), 4.61 (1H, d, *J* 3.6, 2-H), 4.69 (1H, d, *J* 11.3, CH_2Ph), 5.71 (1H, d, *J* 3.6, 1-H), 6.04 (1H, dd, *J* 5.8 and 0.5, 7-H), 6.17 (1H, ddd, *J* 5.8, 2.5 and 1.4, 6-H), 7.21–7.39 (5H, m, Ph); δ_C ($CDCl_3$) 27.5, 27.5, 67.1, 79.4, 81.3, 90.0, 94.6, 106.1, 113.5, 127.5, 127.7, 128.2, 138.5, 134.4, 138.6; FAB-MS *m*/*z* 305 [M + H^+].

(1*R*,2*R*,6*R*,8*R*,9*R*)-1-Benzyloxy-9-hydroxy-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 18

Method A, from 17. To a solution of **17** (3.65 g, 12.0 mmol) in CH_2Cl_2 (100 cm^3) was added PCC (3.1 g, 14.4 mmol) and the mixture was stirred at room temperature for 14 h. Ethyl acetate (200 cm^3) was added and the mixture was filtered through a layer of silica. The filter was rinsed with ethyl acetate (400 cm^3), and the filtrate was concentrated *in vacuo*. The residue was re-

dissolved in MeOH (100 cm^3) and treated with $CeCl_3 \cdot 7H_2O$ (4.5 g, 12.1 mmol). This solution was cooled to 0 °C and added to $NaBH_4$ (750 mg, 19.8 mmol) in small portions and the mixture was stirred at 0 °C for 30 min. Water (100 cm^3) was added and the solution was neutralised with 4 M acetic acid and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 96 : 4, v/v) to give the product **18** (3.40 g, 93%) as a white solid (Found: C, 66.92; H, 6.61. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62%); δ_H ($CDCl_3$) 1.42 (3H, s, CH_3), 1.64 (3H, s, CH_3), 2.70 (1H, d, *J* 10.5, OH), 4.41 (1H, d, *J* 11.3, CH_2Ph), 4.60 (1H, d, *J* 4.5, 4-H), 4.61 (1H, d, *J* 3.6, 2-H), 4.63 (1H, d, *J* 11.3, CH_2Ph), 4.80 (1H, ddt, *J* 10.5, 4.5 and 1.4, 5-H), 5.78 (1H, d, *J* 3.6, 1-H), 5.88 (1H, ddd, *J* 5.8, 1.8 and 0.8, 7-H), 6.13 (1H, dt, *J* 5.8 and 1.4, 6-H), 7.26–7.36 (5H, m, Ph); δ_C ($CDCl_3$) 27.3, 27.5, 67.8, 76.4, 83.2, 83.2, 94.6, 106.6, 114.2, 127.6, 127.7, 128.3, 129.4, 138.1, 142.4; FAB-MS *m*/*z* 327 [M + Na^+].

Method B, from 16. To a solution of **16** (168 mg, 0.51 mmol) in anhydrous CH_2Cl_2 (10 cm^3) was added the catalyst **B** (21 mg, 0.025 mmol) and the mixture was stirred at 40 °C for 1 h. The solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (light petroleum–ethyl acetate 7 : 3, v/v) to give the product **18** (135 mg, 88%) as a grey solid.

3-*O*-Benzyl-6,7-dideoxy-1,2-di-*O*-isopropylidene-3-*C*-vinyl-α-D-*ribo*-heptofuran-5-ulose 19

To a solution of **16** (72 mg, 0.217 mmol) in anhydrous 1,2-dichloroethane (4 cm^3) was added **A** (18 mg, 0.022 mmol) and the mixture was stirred under reflux at 83 °C for 24 h. The solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (light petroleum–ethyl acetate 4 : 1, v/v) to give the product **19** (48 mg, 67%) as a darkly colored oil; δ_H ($CDCl_3$) 1.01 (3H, t, *J* 7.3, CH_2CH_3), 1.39 (3H, s, CH_3), 1.62 (3H, s, CH_3), 2.45 (1H, dq, *J* 18.0 and 7.3, C$H_2$$CH_3$), 2.60 (1H, dq, *J* 18.0 and 7.3, C$H_2$$CH_3$), 4.62 (1H, d, *J* 11.1, CH_2Ph), 4.67 (1H, d, *J* 3.6, 2-H), 4.73 (1H, d, *J* 11.1, CH_2Ph), 4.81 (1H, s, 4-H), 5.33 (1H, d, *J* 17.6, CH=CH_2), 5.42 (1H, d, *J* 11.3, CH=CH_2), 5.67 (1H, dd, *J* 17.6 and 11.3, C*H*=CH_2), 5.97 (1H, d, *J* 3.6, 1-H), 7.25–7.34 (5H, m, Ph); δ_C ($CDCl_3$) 6.9 (CH_2CH_3), 26.6, 26.9 [C(CH_3)$_2$], 33.4 (CH_2CH_3), 67.3, 81.2 (2-C, CH_2Ph), 85.8, 85.9 (3-C, 4-C), 104.2 (1-C), 113.2 [$C(CH_3)_2$], 119.1 (2′-C), 127.1 , 127.4, 128.2 (Ph), 133.4 (1′-C), 138.0 (Ph), 206.2 (CO).

(1*R*,2*R*,6*R*,8*R*,9*R*)-1,9-Bis(benzyloxy)-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 11

Method A, from 9. Same procedure as for the preparation of **14** was used with NaH (1.1 g, 27.5 mmol), **9** (1.17 g, 5.47 mmol), benzyl bromide (4.68 g, 27.4 mmol) and DMF (45 cm^3). Purification by silica gel column chromatography (light petroleum–ethyl acetate 4 : 1, v/v) gave the product **11** (1.73 g, 80%) as a white solid.

Method B, from 18. Same procedure as for the preparation of **14** was used with NaH (915 mg, 22.9 mmol), **18** (2.23 g, 7.33 mmol), benzyl bromide (4.03 g, 23.6 mmol) and DMF (60 cm^3). Purification by silica gel column chromatography (light petroleum–ethyl acetate 4 : 1, v/v) gave the product **11** (2.80 g, 97%) as a white solid (Found: C, 72.97; H, 6.71. $C_{24}H_{26}O_5$ requires C, 73.08; H, 6.71%); δ_H ($CDCl_3$) 1.42 (3H, s, CH_3), 1.65 (3H, s, CH_3), 4.39 (1H, d, *J* 10.8, CH_2Ph), 4.51 (1H, d, *J* 11.6, CH_2Ph), 4.59 (1H, d, *J* 3.9, 2-H), 4.65 (1H, d, *J* 10.8, CH_2Ph), 4.67–4.69 (2H, m, 4-H and 5-H), 4.76 (1H, d, *J* 11.6, CH_2Ph), 5.94 (1H, d, *J* 3.9, 1-H), 5.97 (1H, dd, *J* 6.0 and 1.4, 7-H), 6.11 (1H, dt, *J* 6.0 and 1.4, 6-H), 7.25–7.40 (10H, m, Ph); δ_C ($CDCl_3$) 27.3, 27.5, 67.9, 71.8, 82.0, 82.5, 82.9, 94.9, 107.4, 113.4, 127.7, 127.8, 127.8, 128.1, 128.3, 128.4, 130.2, 137.8, 138.2, 140.7; FAB-MS *m*/*z* 395 [M + H^+].

(1*R*,2*R*,6*R*,8*R*,9*S*)-1,9-Bis(benzyloxy)-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-10-ene 10

Method A, from 8. Same procedure as for the preparation of **14** was used with NaH (25 mg, 0.63 mmol), **8** (21 mg, 0.098 mmol), benzyl bromide (106 mg, 0.62 mmol) and DMF (4 cm^3). Purification by silica gel column chromatography (light petroleum–ethyl acetate 4 : 1, v/v) gave the product **10** (27 mg, 70%) as a clear oil.

Method B, from 17. Same procedure as for the preparation of **14** was used with NaH (60 mg, 1.5 mmol), **17** (188 mg, 0.62 mmol), benzyl bromide (265 mg, 1.55 mmol) and DMF (10 cm^3). Purification by silica gel column chromatography (light petroleum–ethyl acetate 4 : 1, v/v) gave the product **10** (133 mg, 55%) as a clear oil; δ_H ($CDCl_3$) 1.41 (3H, s, CH_3), 1.62 (3H, s, CH_3), 4.28 (1H, d, *J* 2.5, 5-H), 4.55 (1H, d, *J* 12.0, CH_2Ph), 4.57 (1H, d, *J* 2.5, 4-H), 4.62 (2H, s, CH_2Ph), 4.65 (1H, d, *J* 3.6, 2-H), 4.68 (1H, d, *J* 12.0, CH_2Ph), 5.69 (1H, d, *J* 3.6, 1-H), 5.94 (1H, d, *J* 5.8, 7-H), 6.12 (1H, ddd, *J* 5.8, 2.4 and 1.3, 6-H), 7.20–7.42 (10H, m, Ph); δ_C ($CDCl_3$) 27.4, 27.6, 67.3, 71.7, 82.2, 86.5, 87.4, 94.8, 105.8, 113.6, 127.2, 127.4, 127.7, 127.7, 128.1, 128.4, 134.9, 136.5, 137.8, 138.9; FAB-MS *m*/*z* 395 [M + H^+].

(3*R*/*S*,1*R*,4*R*,5*R*,8*R*)-3,4-Diacetoxy-5,8-bis(benzyloxy)-2-oxabicyclo[3.3.0]oct-6-ene 20

A solution of **11** (3.21 g, 8.14 mmol) in 80% aq. acetic acid (50 cm^3) was stirred at 90 °C for 16 h. The solvents were removed by distillation under reduced pressure and the residue was coevaporated with anhydrous EtOH (3 × 30 cm^3), toluene (3 × 30 cm^3), and anhydrous pyridine (30 cm^3) and re-dissolved in anhydrous pyridine (30 cm^3). Acetic anhydride (20 cm^3) was added dropwise and the solution was stirred at room temperature for 16 h. The reaction mixture was quenched with ice-cold water (50 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (2 × 100 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 (light petroleum–ethyl acetate 4 : 1, v/v) to give the anomeric mixture **20** (3.03 g, 85%) as a clear oil (Found: C, 67.53; H, 5.92. $C_{25}H_{26}O_7 \cdot 1/5H_2O$ requires C, 67.79; H, 6.03%); δ_C ($CDCl_3$) 170.0, 169.9, 169.5, 169.4, 138.5, 138.4, 137.9, 137.7, 136.9, 133.2, 131.2, 128.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 126.9, 126.8, 101.1, 96.6, 95.5, 92.5, 84.5, 82.9, 81.6, 80.6, 77.8, 75.7, 72.3, 72.0, 67.6, 67.3, 21.1, 21.0, 20.7, 20.5; FAB-MS *m*/*z* 379 [M − OAc].

(1*R*,3*R*,4*R*,5*R*,8*R*)-4-Acetoxy-5,8-bis(benzyloxy)-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]oct-6-ene 21

A mixture of **20** (3.03 g, 6.91 mmol) and thymine (1.81 g, 14.4 mmol) was dried and dissolved in anhydrous CH_3CN (100 cm^3). The mixture was treated with *N*,*O*-bis(trimethylsilyl)acetamide (9.0 cm^3, 36.4 mmol) and stirred under reflux for 15 min. After cooling of the mixture to 0 °C, TMS triflate (2.5 cm^3, 13.8 mmol) was added dropwise and the solution was stirred at 50 °C for 16 h. The reaction mixture was quenched with ice-cold saturated aq. $NaHCO_3$ (100 cm^3) and extracted with CH_2Cl_2 (3 × 75 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 97 : 3, v/v) to give the product **21** (3.18 g, 91%) as a white solid material (Found: C, 66.23; H, 5.60; N, 5.39. $C_{28}H_{28}N_2O_7 \cdot 1/5H_2O$ requires C, 66.18;

H, 5.63; N, 5.51%); δ_H ($CDCl_3$) 1.60 (3H, d, *J* 1.1, 5-CH_3), 2.09 (3H, s, $COCH_3$), 4.36 (1H, d, *J* 11.4, CH_2Ph), 4.45 (1H, d, *J* 11.4, CH_2Ph), 4.57 (1H, d, *J* 11.3, CH_2Ph), 4.64 (1H, m, 5′-H), 4.70 (1H, d, *J* 5.4, 4′-H), 4.75 (1H, d, *J* 11.3, CH_2Ph), 5.04 (1H, d, *J* 6.1, 2′-H), 6.11–6.18 (2H, m, 6′-H and 7′-H), 6.16 (1H, d, *J* 6.1, 1′-H), 7.25–7.36 (10H, m, Ph), 7.54 (1H, d, *J* 1.1, 6-H), 8.44 (1H, br s, NH); δ_C ($CDCl_3$) 12.1, 20.6, 67.0, 72.6, 170.2, 78.6, 80.7, 83.4, 89.2, 93.3, 111.4, 127.0, 127.7, 127.8, 128.1, 128.4, 128.6, 133.8, 135.6, 136.8, 137.4, 137.8, 150.3, 163.4; FAB-MS *m*/*z* 505 [M + H^+].

(1*R*,3*R*,4*R*,5*R*,8*R*)-5,8-Bis(benzyloxy)-4-hydroxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]oct-6-ene 22

To a solution of **21** (3.18 g, 6.30 mmol) in anhydrous methanol (40 cm^3) was added sodium methoxide (704 mg, 13.0 mmol) and the mixture was stirred at room temperature for 16 h. The reaction mixture was neutralised with aq. HCl and extracted with CH_2Cl_2 (2 × 150 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (2 × 100 cm^3) and then dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure to give the product **22** (2.84 g, 97%) as a white solid material (Found: C, 67.88; H, 5.72; N, 6.04. $C_{26}H_{26}N_2O_6$ requires C, 67.52; H, 5.67; N, 6.06%); δ_H ($CDCl_3$) 1.54 (3H, d, *J* 1.1, CH_3), 3.20 (1H, d, *J* 8.2, 2′-OH), 4.10 (1H, dd, *J* 8.2 and 6.1, 2′-H), 4.44 (1H, d, *J* 11.1, CH_2Ph), 4.50 (1H, d, *J* 11.1, CH_2Ph), 4.58 (1H, d, *J* 11.3, CH_2Ph), 4.63 (1H, m, 5′-H), 4.71 (1H, d, *J* 5.7, 4′-H), 4.76 (1H, d, *J* 11.3, CH_2Ph), 6.07 (1H, d, *J* 6.1, 7′-H), 6.15 (1H, m, 6′-H), 6.16 (1H, d, *J* 6.1, 1′-H), 7.26–7.38 (10H, m, Ph), 7.58 (1H, d, *J* 1.1, 6-H), 8.18 (1H, br s, NH); δ_C ($CDCl_3$) 12.0, 67.1, 72.7, 78.8, 80.4, 81.9, 91.8, 93.6, 111.0, 127.7, 127.8, 128.2, 128.2, 128.6, 128.6, 133.3, 135.9, 136.7, 137.0, 137.4, 150.7, 163.5; FAB-MS *m*/*z* 463 [M + H^+].

(1*R*,3*R*,4*R*,5*S*,8*R*)-4,5,8-Trihydroxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]oct-6-ene 4

A solution of **22** (80 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (2.5 cm^3) was stirred at −78 °C and a 1 M solution of BCl_3 in hexane (0.4 cm^3, 0.4 mmol) was added dropwise. After stirring for 5 h at −78 °C the mixture was treated with methanol (2 cm^3) and water (0.1 cm^3) and stirred at room temperature for 1 h. The solvents were removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 93 : 7, v/v) to give the product **4** (40 mg, 82%) as a white solid; δ_H (DMSO-d_6) 1.82 (3H, s, CH_3), 3.85 (1H, d, *J* 7.3, 2′-H), 4.07 (1H, d, *J* 5.8, 4′-H), 4.59 (1H, d, *J* 5.8, 5′-H), 5.75–5.85 (2H, m, 6′-H and 7′-H), 5.96 (1H, d, *J* 7.3, 1′-H), 7.86 (1H, s, 6-H), 11.35 (1H, s, NH); δ_C (DMSO-d_6) 12.2 (CH_3), 72.5 (5′-C), 77.3 (2′-C), 86.1 (4′-C), 87.0 (3′-C), 90.1 (1′-C), 109.2 (5-C), 134.5, 135.8 (6′-C and 7′-C), 136.9 (6-C), 150.9 (2-C), 163.7 (4-C); HR MALDI FT-MS *m*/*z* 305.0744. Calc. 305.0744 [M + Na^+].

(1*R*,3*R*,4*R*,5*S*,8*R*)-4,5,8-Trihydroxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]octane 5

A solution of **22** (65 mg, 0.14 mmol) in methanol (3 cm^3) was added to 20% $Pd(OH)_2$–C (25 mg) and the mixture was degassed with argon and flushed with H_2 for 5 min. After stirring under an atmosphere of H_2 for 2 h the mixture was filtered through a pad of Celite and the solvent was removed by distillation under reduced pressure to give the product **5** (39 mg, 98%) as a white solid; δ_H (DMSO-d_6) 1.47 (1H, m, 7′-H), 1.72 (1H, m, 6′-H), 1.81 (3H, s, CH_3), 1.86–1.94 (2H, m, 6′-H and 7′-H), 3.81 (1H, dd, *J* 8.5 and 6.2, 2′-H), 4.92 (1H, d, *J* 5.1, 4′-H), 4.96 (1H, m, 5′-H), 4.93 (1H, d, *J* 5.3, 5′-OH), 5.04 (1H, s, 3′-OH), 5.31 (1H, d, *J* 6.2, 2′-OH), 5.81 (1H, d, *J* 8.5, 1′-H), 7.74 (1H, s, 6-H), 11.32 (1H, s, NH); δ_C (DMSO-d_6) 12.2 (CH_3), 32.0 (6′-C), 33.9 (7′-C), 70.7 (5′-C), 77.2 (2′-C), 81.9 (3′-C), 87.0 (1′-C), 88.6 (4′-C), 109.5 (5-C), 136.6 (6-C), 150.9 (2-C), 163.7 (4-C); EI-MS *m*/*z* 284 [M^+]; HR MALDI FT-MS *m*/*z* 307.0906. Calc. 307.0901 [M + Na^+].

(1*R*,3*R*,4*R*,5*R*,8*R*)-5,8-Bis(benzyloxy)-4-pentafluorophenoxythiocarbonyloxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]oct-6-ene 23

To a solution of **22** (154 mg, 0.33 mmol) in CH_2Cl_2 (3 cm^3) was added 4-(dimethylamino)pyridine (DMAP) (80 mg, 0.66 mmol) and the mixture was cooled to −20 °C. Pentafluorophenyl chlorothionoformate (0.10 cm^3, 0.62 mmol) was added dropwise and the solution was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (7 cm^3) and washed with saturated aq. $NaHCO_3$ (2 × 10 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 [0–2% (v/v) MeOH in CH_2Cl_2] to give the product **23** contaminated with a pentafluorophenyl compound as well as unidentified by-products. The product was purified by additional chromatography to give the title compound **23** (46 mg, 20%) as a clear oil, δ_H ($CDCl_3$) 1.54 (3H, d, *J* 1.1, CH_3), 4.38 (1H, d, *J* 11.5, CH_2Ph), 4.54 (1H, d, *J* 11.5, CH_2Ph), 4.58 (1H, d, *J* 11.5, CH_2Ph), 4.64 (1H, m, *J* 5.1, 5′-H), 4.75 (1H, d, *J* 11.5, CH_2Ph), 4.77 (1H, d, *J* 5.1, 4′-H), 5.69 (1H, d, *J* 5.2, 2′-H), 6.13–6.21 (2H, m, 6′-H, 7′-H), 6.49 (1H, d, *J* 5.2, 1′-H), 7.27–7.39 (10H, m, Ph), 7.60 (1H, d, *J* 1.1, 6-H), 8.90 (1H, br s, NH); δ_C ($CDCl_3$) 12.1, 67.6, 72.5, 80.8, 83.9, 87.4, 89.3, 93.4, 111.5, 127.1, 127.9, 127.9, 128.2, 128.4, 128.6, 132.5, 135.8, 137.0, 137.2, 138.2, 150.3, 164.0, 191.3; δ_F ($CDCl_3$) −152.3 (2F, m), −157.1 (2F, m), −162.5 (1F, m); FAB-MS *m*/*z* 689 (M + H^+).

(1*R*,3*R*,5*R*,8*R*)-5,8-Bis(benzyloxy)-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]octane 24

The thionocarbonate **23** (46 mg, 0.067 mmol) was dissolved in anhydrous benzene (1.0 cm^3) and azaisobutyronitrile (AIBN) (5 mg, 0.03 mmol) was added. The mixture was flushed with argon for 20 min, Bu_3SnH (0.03 cm^3, 0.11 mmol) was added, and the reaction mixture stirred at 90 °C for 16 h. The mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. Purification by silica gel chromatography [0–3% (v/v) MeOH in CH_2Cl_2] gave the product **24** (15 mg, 50%) which was used without further purification in the next step, δ_H ($CDCl_3$) 1.57 (3H, d, *J* 1.3, CH_3), 2.17 (1H, dd, *J* 13.8, 6.9, 2′-H[b]), 2.80 (1H, dd, *J* 13.8, 6.2, 2′-H[a]), 4.37 (1H, d, *J* 11.3, CH_2Ph), 4.45 (1H, d, *J* 11.3, CH_2Ph), 4.57 (1H, d, *J* 11.3, CH_2Ph), 4.65 (2H, br s, 4′-H, 5′-H), 4.77 (1H, d, *J* 11.3, CH_2Ph), 6.02–6.08 (2H, m, 6′-H, 7′-H), 6.47 (1H, dd, *J* 6.2, 6.9, 1′-H), 7.26–7.37 (10H, m, Ph), 7.76 (1H, d, *J* 1.3, 6-H), 8.52 (1H, br s, NH); δ_C ($CDCl_3$) 12.1, 44.1, 67.1, 72.6, 81.0, 84.1, 88.1, 96.8, 110.5, 127.3, 127.8, 127.9, 128.0, 128.5, 128.5, 134.5, 135.0, 136.3, 137.7, 137.8, 150.2, 163.7; FAB-MS *m*/*z* 447 (M + H^+).

(1*R*,3*R*,5*S*,8*R*)-5,8-Dihydroxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]octane 1 (Base = thymine)

A solution of **24** (15 mg, 0.034 mmol) in methanol (1.0 cm^3) was treated with 20% $Pd(OH)_2$–C (10 mg) and cyclohexa-1,4-diene (0.05 cm^3, 0.53 mmol) and the mixture was degassed with argon and flushed with H_2 for 5 min. After stirring under an atmosphere of H_2 for 16 h the mixture was filtered through a pad of Celite and the solvent was removed by distillation under reduced pressure to give the product **1** (5.5 mg, 61%) as a white solid; ^1H and ^{13}C NMR were in accordance with published data.[6]

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