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Recent Approaches in the Synthesis of Conformationally Restricted Nucleoside Analogues

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This review describes some approaches in the synthesis of conformationally restricted nucleoside analogues. The focus is on the preparation of nucleosides as monomers modified only on the pentofurano sugar moiety, with an additional linkage capable of modulating the dynamic conformational equilibrium of natural nucleosides. The results of the different structural modifications in terms of pseudorotational analysis, as well as the potential use of such conformationally restricted nucleoside analogues, are briefly presented.

1. Introduction

Over several decades, a large number of nucleoside analogues have been synthesised and some of them have demonstrated potent antiviral or antitumour activities.[1] Such compounds generally have to be metabolised by cellular kinases to their corresponding active 5′-triphosphate forms, which finally interact with viral or cellular polymerases. In order to discover new nucleoside derivatives endowed with potential biological activities, modifications both of the bases and of the sugar moieties of natural nucleosides have been attempted.[2]

Recently, the conformational behaviour of natural and modified nucleosides, especially the sugar puckering, has come to be seen as of great importance in terms both of their metabolic pathways and of their final interactions with the target polymerases.[3] The sugar puckerings of natural ribo- and deoxyribonucleosides are known to exist in dynamic equilibria between two major conformers: the North (N) and the South (S) types (Figure 1, A).[4] Conformational studies of nucleosides in solution indicate that the North/South interconversion is rapid.[5] However, when a nucleoside or a nucleotide binds to an enzyme (anabolic or catabolic) or its pharmacological target, only one conformer would be expected to be present within the active

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Christophe Mathé was born in Alès, France (1966) and studied chemistry at the University Montpellier 2, where he obtained his PhD degree in 1994 under the supervision of Dr. Gilles Gosselin working on the synthesis of L-nucleoside analogues. Dr. C. Mathé undertook two periods of postdoctoral studies. The first was performed with Prof. V. Nair at the University of Iowa, USA, while the second was carried out at the University Monptellier 2 as an ANRS postdoctoral fellow. He was appointed as an Assistant Professor at the University Montpelier 2 in 1998. His main research interests involve the design, the synthesis and the study of nucleoside analogues as potential bioactive compounds.

Christian Périgaud, born 1963 in Nimes (France), was trained in chemistry at the University of Montpellier. In 1991, he passed his Ph.D Thesis in the laboratory directed by the Prof. J.-L. Imbach under the supervision of Dr. G. Gosselin. These investigations were supported by the Synthélabo Company and were related to the synthesis of new series of nucleoside analogues. He moved as a postdoctoral fellow to the laboratory of Prof. J.-P. Sommadossi at Birmingham (University of Alabama, USA). Back at the University of Montpellier, he was appointed as associate professor in 1993 and started his work on the synthesis and the study of mononucleotide prodrugs. Nominated professor in 2001, he is nowadays the group leader of a research team mainly involved in nucleoside and nucleotide chemistry. He has co-authored about eighty publications in these fields. His scientific interests focus on the development of antiviral and antitumour agents as well as on tools for the understanding of biological processes.

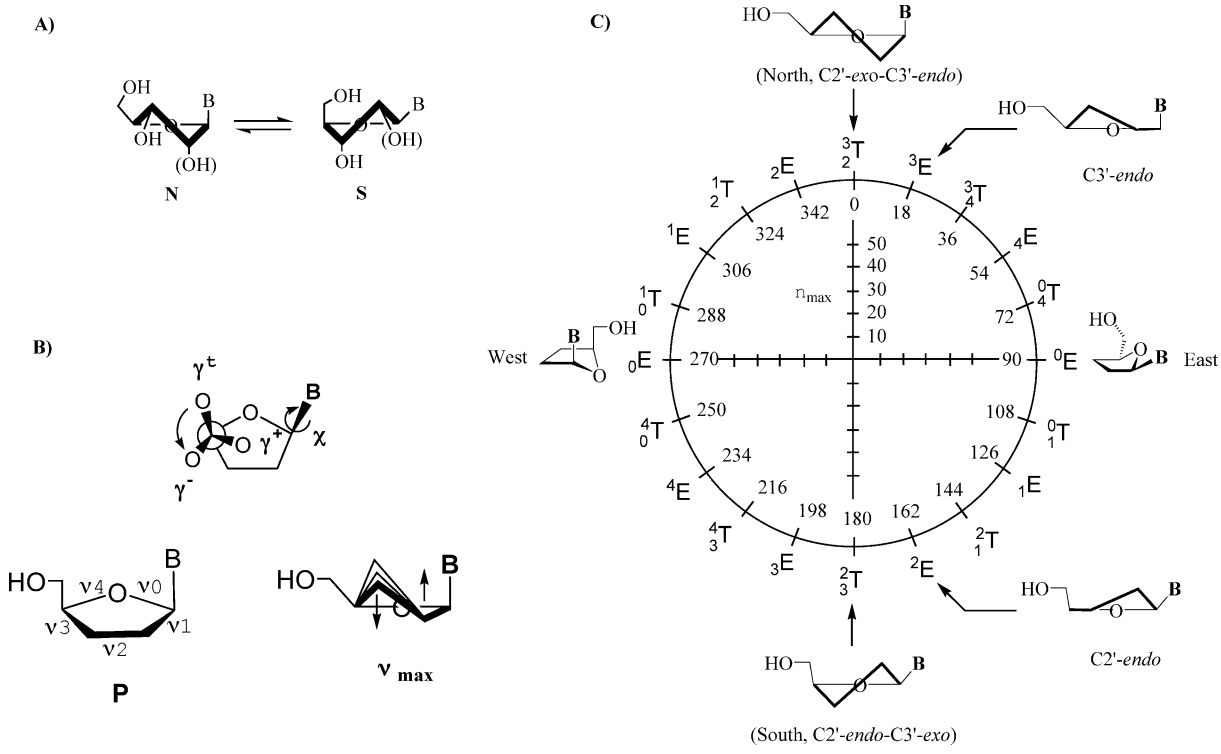


Figure 1. A) Dynamic equilibrium between North and South conformers. B) Torsion angles present in nucleosides (ν_0–ν_4, γ and χ). C) Pseudorotational cycle for nucleosides showing the characterisic North, South, East and West conformations. The radius of the cycle corresponds to ν_{max}. The units of P and ν_{max} values are degrees. Envelope (E) and twist (T) forms alternate every 18°.

site. Although the binding conformation is probably modified by the enzyme to achieve optimal fitting, any conformation–activity study would be very useful in order to identify conformational preferences of enzymes involved in the metabolism of nucleos(t)ides and to study the interactions of such compounds with their enzymatic targets. For these reasons, conformationally restricted nucleosides have attracted considerable attention since they can adopt determined conformations, which can be useful tools in such an evaluation. However, the use of conformationally restricted nucleoside analogues is not only limited to research into bioactive compounds or biological tools. Indeed, recent years have seen the development of conformationally restricted nucleotides in which the sugar moieties are locked in defined sugar puckering patterns. Such oligonucleotides, the so called LNAs[6] or BNAs,[7] showed interesting binding properties with target nucleic acids as well as nuclease resistance. The purpose of this Microreview is to survey the literature since 2000 on the synthesis of conformationally restricted nucleoside analogues as monomers with an additional linkage on the pentofuranose moiety. The consequences of the modifications on modulation of the dynamic conformational equilibria, as well as their potential uses, are also presented.

2. Conformational Parameters of Nucleosides

Briefly, the complete definition of the conformational behaviour of natural or modified nucleosides involves the determination of four structural parameters (Figure 1, B).[4] The glycosidic torsion angle χ determines the *syn* or *anti* disposition of the base relative to the sugar moiety (*syn* when the pyrimidine carbonyl C-2 or the purine N-3 lies over the sugar ring, *anti* when these atoms are oriented in the opposite direction). The torsion angle γ determines the position of the 5′-OH with respect to C-3′ as represented by the three main rotamers γ^+, γ^t and γ^-. The conformation of the furanose ring and its deviation from planarity are described by the pseudorotational phase angle P and the maximal puckering amplitude ν_{max}. The pseudorotational phase angle (P) is calculated from the endocyclic torsion angles (ν_0–ν_4)[8] as shown in Equation (1) and the maximum amplitude puckering is given by Equation (2). In cases in which ν_2 is negative, one should add 180° to the calculated value of P, while when P is negative 360° should be added.[5]

$$\tan P = \frac{(\nu_4 + \nu_1) - (\nu_3 + \nu_0)}{2 \cdot \nu_2 \cdot (\sin 36° + \sin 72°)} \quad (1)$$

$$\nu_{max.} = abs\left(\frac{\nu_2}{\cos P}\right) \quad (2)$$

The conformation of the furanose ring can be described easily when values of P in combination with ν_{max} are plotted in the pseudorational cycle (Figure 1, C).[9] Values of phase angles are given in multiple of 36° and vary from 0° to 360°. Twenty distinct twist (T) and envelope (E) confor-

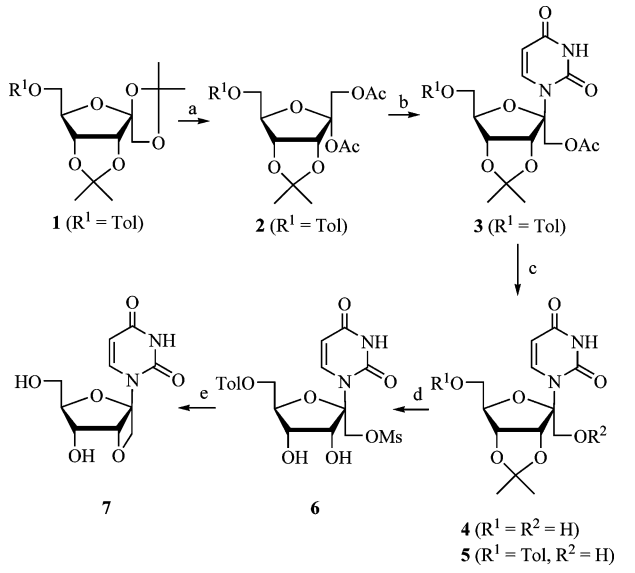
mations alternate every 18°. The T conformation is observed at even multiples of 18°, and E is found at odd multiples. By convention, a phase angle of $P = 0°$ is defined such that the torsion angle v_2 is maximally positive and corresponds to an absolute north conformation possessing a symmetrical C2′-*exo*–C3′-*endo* twist form ($^3_2$T). The mirror image is represented by $P = 180°$ and corresponds to an absolute South conformation with a symmetrical C2′-*endo*–C3′-*exo* twist form ($^2_3$T). For the great majority of natural nucleosides, the values of P are centred in the vicinity either of a North-type conformation ($P = 18°$, ^{3}E, C3′-*endo*) or a South-type conformation ($P = 162°$, ^{2}E, C2′-*endo*).[10] In both regions, the values of v_{max} are found in a range from 30° to 46°, and most of them fall around 38°.[11] While in the solid state one conformation is prevalent in relation to the other, in solution, both conformations exist in a dynamic equilibrium. The energy barrier between these two states is low (4.7 kcal mol^{-1} is observed experimentally) and a rapid transition from one to the other proceeds through the East (^{0}E, O4′-*endo*) rather than the West ($_0$E, O4′-*exo*) conformation. The relative position of the equilibrium is determined by the stereoelectronic *gauche* and anomeric effects, which are modulated by the electronegativity, steric hindrance and stereochemistry of the substituents on the furanose ring. For example, amounts of N conformers increase linearly with the electronegativities of the substituents in the 2′-positions in 2′-deoxyribonucleoside derivatives, owing to their preferential axial orientations due to the *gauche* effect.[12] In addition, the less favourable conformation in terms of steric interactions is W ($_0$E, O4′-*exo*) in which C2′- and C3′-substituents are eclipsed, while 5′-CH_2OH and the base are in axial positions. The bases have their least steric hindrance when in the pseudoequatorial positions of the S conformation, while the 5′-CH_2OH moieties have minimal hindrance in the N conformation. Lastly, the anomeric effect promotes the N conformation over the S one, where the base is in a pseudoaxial orientation.

This short survey of the conformational behaviour of nucleosides clearly shows that an infinite number of conformations are possible – varying from a particular sugar puckering to distinct rotamers – such as *syn*/*anti* orientations of the bases (*anti* is usually observed for the pyrimidines while rapid *syn*/*anti* equilibria are observed for the purines) or $\gamma^+/^-/^t$ orientations of 5′-CH_2OH. In this regard, many approaches to lock the conformations of nucleosides have been attempted, including restriction of the sugar puckering, as well as the rotation of the base or the 5′-hydroxymethyl group.

3. Nucleoside Analogues with Restricted Sugar Conformations

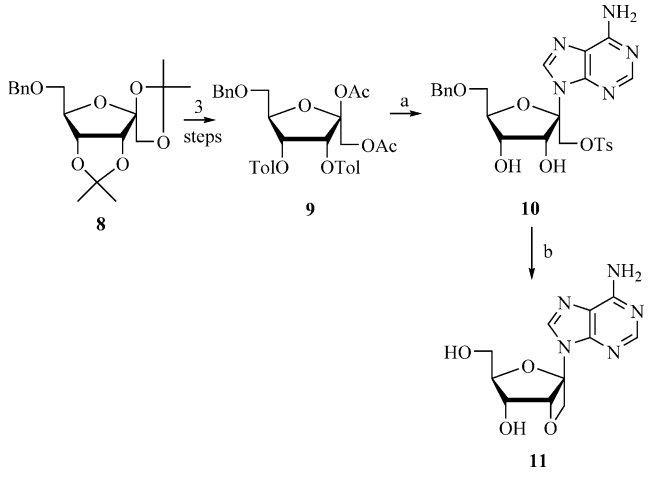
3.1. 1′,2′-, 1′,3′- and 1′,4′-Conformational Constraints[13]

In the early 2000s, syntheses of locked 1′,2′-oxetane-fused purine and pyrimidine nucleosides for incorporation into oligo-DNA or -RNA were reported.[14] Complete regioselectivity and strong enhancement of the β anomers were achieved through the coupling of 1,2-di-*O*-acetyl-3,4-di-*O*-isopropylidene-6-*O*-(4-toluoyl)-D-psicofuranose (**2**, Scheme 1) or 2-*O*-acetyl-6-*O*-benzyl-1,3,4-tri-*O*-(4-toluoyl)-D-psicofuranose (**9**, Scheme 2) with persilylated bases by the Vorbrüggen procedure.[15] Both osidic precursors were obtained from the known 1,2:3,4-di-*O*-isopropylidene-6-*O*-(4-toluoyl)-β-D-psicofuranose (**1**).[16] In the pyrimidine series, as exemplified with uracil, treatment of **1** with acetic acid, acetic anhydride and triflic acid provided the 1,2-di-*O*-acetyl-α-D-psicofuranosyl derivative **2**. The crude product was coupled with silylated base to give a mixture of α and β anomers. The predominant β anomer could be separated by simple crystallisation. The origin of the anomeric selectivity lies in the presence of a participating acetate group at C1′, giving spirocyclic 1,3-dioxolanium ions as intermediates.[17] Since a leaving group was required at C1′ in order to achieve a 1′,3′-ring closure and to complete the oxetane synthesis, treatment of **3** with methanolic ammonia gave a separable mixture of the desired compound **5** and the 1′,6′-deprotected nucleoside **4**. Compound **5** was mesylated and subjected to acid hydrolysis to give the corresponding diol **6**, which was treated with sodium bis(trimethylsilyl)amide (NaHMDS). Finally, deprotection with methanolic ammonia gave the oxetane uridine derivative **7**.

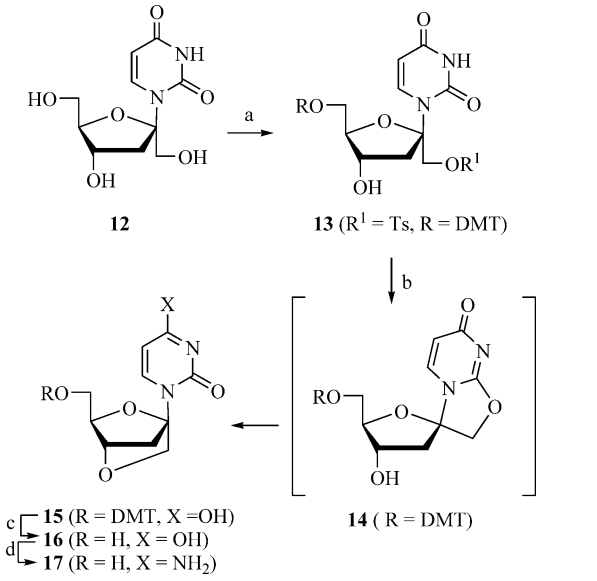


Scheme 1. *Reagents and conditions:* a) Ac_2O, AcOH, TfOH, room temp., 90%. b) i. uracil, BSA, CH_3CN, 90 °C; ii. TMSOTf, 77% (α:β, 1:9). c) 16% methanolic ammonia, room temp., 44% for **4**, 48% for **5**. d) i. MsCl, pyridine, 0 °C, 95%; ii. 90% TFA, room temp. e) i. NaHMDS, THF, 0 °C; ii. 25% methanolic ammonia, room temp., 63% from **6**.

Glycosylation reactions with **2** and protected purines (adenine and guanine) under the above conditions yielded the β anomers of psicofuranosyl nucleosides with moderate yields. However, during removal of the isopropylidene groups under acidic conditions, considerable depurination took place, so an alternative strategy using sugar **9**



Scheme 2. *Reagents and conditions:* a) i. persilylated N^6-benzoyladenine, CH_3CN, TMSOTf, 80 °C, 60% (α:β, 3:7); ii. methanolic ammonia, room temp.; iii. *p*-toluenesulfonyl chloride, pyridine, 0 °C, 45% (two steps). b) i. NaHMDS, THF, 0 °C→r.t., 90%; ii. ammonium formate, MeOH, $Pd(OH)_2$/C, 75 °C, quantitative.



Scheme 3. *Reagents and conditions:* a) i. DMTCl, pyridine, CH_2Cl_2; ii. TsCl, pyridine, CH_2Cl_2, 29% (two steps). b) NaH, DMF, 93% for **15**. c) 80% AcOH, 91%. d) nitrophenylation/ammonolysis procedure, 80%.

(Scheme 2) with base-labile protecting groups was adopted. Compound **9** was prepared in three steps from the bisketal **8**.[14] Glycosylations with the protected bases gave the corresponding purine nucleoside in good yield with the β anomer as the major compound. This was separated from the α:β anomeric mixture, after removal of the toluoyl groups and subsequent 1′-tosylation, by silica gel column chromatography. The conversion of **10** into its corresponding oxetane derivative was achieved by treatment with NaHMDS. Finally, reductive removal of the benzyl group afforded building block **11**, suitable for the preparation of oligonucleotides.

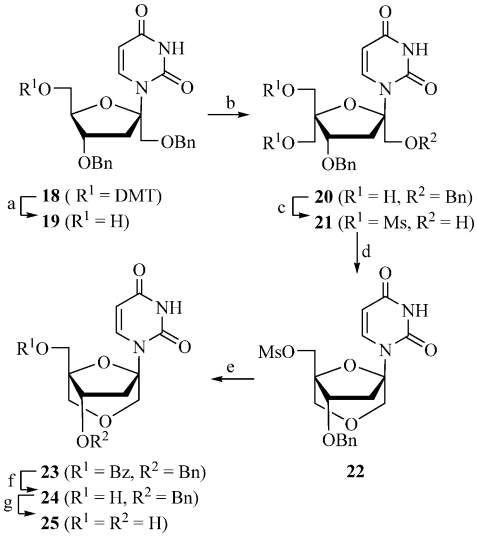
From a conformational analysis point of view, introduction of a 1′,2′-oxetane moiety restricts the conformation into a North-East-type sugar conformation (*P* centred around 41.6°, v_{max} around 35.8°). Recently, similar results were obtained with 1′,2′-azetidine-fused[18] bicyclic pyrimidine nucleosides in which the 1′,2′-aminomethyl bridge imposes a pseudorotational phase angle *P* in the range of 44.5–53.8° and a puckering amplitude (v_{max}) of 29.3–32.6°. Studies of azetidine-modified oligo-DNA/RNA heteroduplexes show that the azetidine nucleosides display improved binding affinities in relation to those of North-East constrained sugar oxetane-fused analogues.

During the same period, the synthesis of nucleoside analogues with 1′,3′- or 1′,4′-conformational constraints were reported. Both were synthesised in a few steps from the known 1-(3-deoxy-β-D-psicofuranosyl)uracil (**12**,[19] Scheme 3).

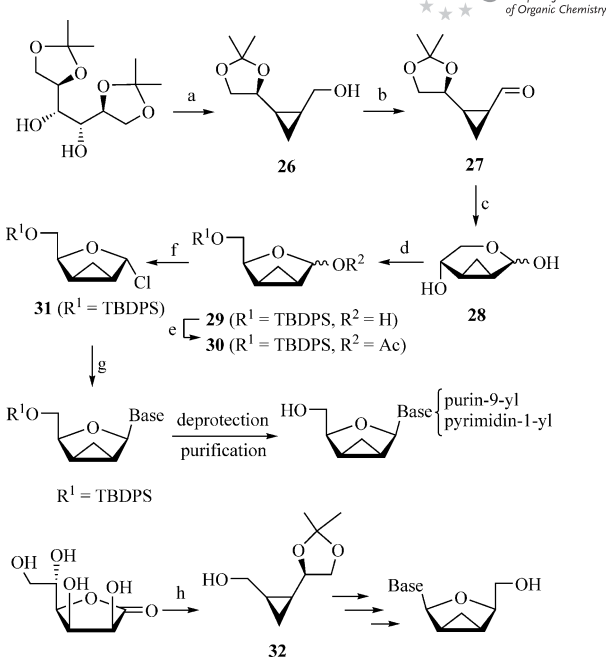
The synthesis of the cytosine and uracil nucleoside derivatives incorporating 1′,3′-conformational constraints was reported by Wightman et al.[20] Protection of the 6′-position was selectively achieved with a 4,4′-dimethoxytrityl (DMT) group (Scheme 3) and subsequent 1′-tosylation furnished the monotosyl derivative **13**. Cyclisation of **13** was accomplished by treatment with NaH in anhydrous DMF to afford the bicyclic nucleoside **15** via the 2,1′-anhydronucleoside intermediate **14**. Removal of the DMT group from **15** gave the uracil analogue **16**, which was converted into the corresponding cytosine derivative **17** by a nitrophenylation/ammonolysis procedure.[21] Conformational analysis of **16** and **17** by NOE experiments revealed that the bicyclic structures were locked in S-type furanose conformations with the nucleobases in *anti* conformations. Both nucleosides proved to be devoid of anti-HIV activity in cell culture experiments.

A similar approach was also developed for the synthesis of a uracil nucleoside derivative incorporating a 1′,4′-conformational constraint (Scheme 4). In a closely related methodology, the protected 6′-*O*-DMT and 1′,4′-di-*O*-Bn derivative **18**, readily obtained from **12**, was used. After hydrolysis of the DMT group, oxidation of the derivative **19** was accomplished with Dess–Martin periodinane. The aldehyde intermediate was not isolated, but was subjected to a tandem aldol condensation and Cannizzaro reaction to give the diol **20**. The hydroxy groups were mesylated and the primary alcohol was subsequently selectively debenzylated by hydrogenolysis in the presence of 20% $Pd(OH)_2$ as a catalyst. The cyclisation was performed by treatment of **21** with NaOH in dioxane to give **22** with no evidence of removal of the 5′-mesyl group. Consequently, a two-step procedure was applied. Firstly, a nucleophilic substitution with NaOBz in DMF gave the benzoate derivative **23**, which upon deprotection with NaOMe in MeOH yielded **24**. Finally, debenzylation of **24** with BCl_3 in CH_2Cl_2 afforded the desired nucleoside **25**.

Conformational analysis by NOE examination was not conclusive. However, an energy-minimised structure of **25** obtained by molecular mechanics supported the assumption of an O4′-*endo* (^{0}E) furanose conformation, while the 1,4-dioxane ring adopted a ring chair-like conformation.



Scheme 4. *Reagents and conditions:* a) 80% AcOH, 94%. b) i. Dess–Martin periodinane, CH_2Cl_2; ii. 37% H_2CO, 1 M NaOH, 1,4-dioxane, 78% (two steps). c) i. MsCl, pyridine; ii. H_2, 20% $Pd(OH)_2/C$, EtOH, 55% from **20**. d) 1 M NaOH, 1,4-dioxane, 64%. e) NaOBz, DMF. f) NaOMe; MeOH, 90% (two steps). g) BCl_3, CH_2Cl_2, 84%.



Scheme 5. *Reagents and conditions:* a) six steps, 55%, ref.[23]. b) Swern oxidation. c) 1% HCl/1,4-dioxane, room temp. d) TBDPSCl, pyridine, CH_2Cl_2, 0 °C, 50% from **26**. e) Ac_2O, pyridine, 87%. f) HCl/diethyl ether, –10 °C. g) Silylated pyrimidines, $CHCl_3$, 0 °C to room temp., 63–68%, or sodium salts of purines, CH_3CN or DME or DMF/THF, 0 °C to room temp., 35–66%. h) 7 steps, 61%, ref.[24]

The phosphoramidite derivative of **25** was incorporated into oligonucleotides, and thermal denaturation studies showed moderate decreases in duplex stabilities toward complementary DNA and RNA.

3.2. 2′,3′-Conformational Constraints

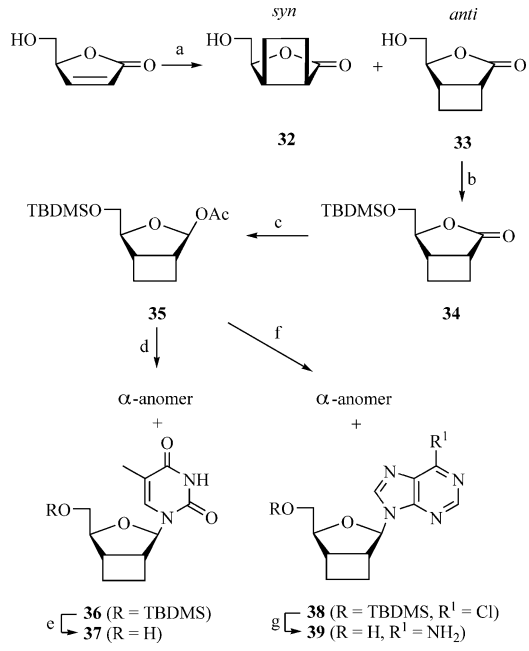
Chu et al. reported the synthesis of D- and L-2′,3′-dideoxy-2′,3′-*endo*-methylene nucleoside derivatives (Scheme 5) as potential antiviral agents.[22] To synthesise the target D-nucleosides, 1,2:5,6-di-*O*-isopropylidene-D-mannitol was used as the starting material and converted in six steps into the cyclopropyl intermediate **26**. A Swern oxidation furnished the aldehyde **27**, which was deprotected to give lactol **28**. Protection of the primary hydroxy group with TBDPSCl provided the bicyclic furanose **29**. Treatment of **29** with acetic anhydride gave the corresponding acetate **30** with an unusual anomeric ratio (α/β = 20:1, determined by NMR). Condensation of **30** with the heterocyclic bases under Vorbrüggen conditions mainly gave the undesired α anomers, probably due to the steric hindrance of the sugar β-face. To overcome the undesired stereoselectivity, the α-chloro sugar **31**, which was readily obtained from **29**, was used. S_N2-type condensations of **31** with sodium salts of purines or silylated pyrimidines gave the β anomers as major isomers. The target D-nucleosides were obtained after deprotection and purification.

To obtain the L-derivatives, the cyclopropyl intermediate **32** was prepared from L-gulonic γ-lactone. Starting from **32**, the same procedure was applied and afforded the target L-nucleosides.

Conformational analyses of the resulting nucleosides were based upon X-ray structure determination. The X-ray determination revealed that the conformation around the glycosylic bound was highly *anti* and that around the C4′–C5′ was γ^t. The conformation of the furanose ring was found an O4′-*endo* arrangement with a pseudorotational angle *P* of 91.7° (^{0}E, East-type) and a relatively large ν_{max} of 34.5°. These conformational features are the result of the steric hindrance of the β face of the sugar moiety. Such steric interactions may lead the sugar to adopt an O4′-*endo* conformation with a high amplitude of puckering. The anti-HIV activities of the corresponding D-2′,3′-dideoxy-2′,3′-*endo*-methylene nucleoside derivatives were evaluated in cell culture experiments. However, none of them showed any anti-HIV activity.

Conformationally restricted nucleoside analogues bearing cyclobutane rings, rather than cyclopropyl ones, in the 2′,3′-positions was also envisioned.[25] The synthesis of the target compounds was achieved through the preparation of the sugar precursor **35** (Scheme 6). Thus, starting from commercially available (*S*)-5-hydroxymethyl-5*H*-furan-2-one, a photochemical reaction with (*Z*)-1,2-dichloroethylene, followed by a dihydrodehalogenation reaction with Bu_3SnH and AIBN in toluene at reflux, provided the expected cyclobutanes **32** and **33** with excellent diastereoselectivity (*syn*/*anti* 1:9). After protection with a TBDMS group, the lactone **34** was reduced with DIBAL-H, and the resultant lactol was acetylated to give the β anomeric acetate **35**. Condensation of **35** with silylated thymine afforded a mixture of α and β anomers. Chromatographic purification provided the pure β anomer **36**, which after removal of the silyl group led to the desired nucleoside **37**. Coupling of N^6-

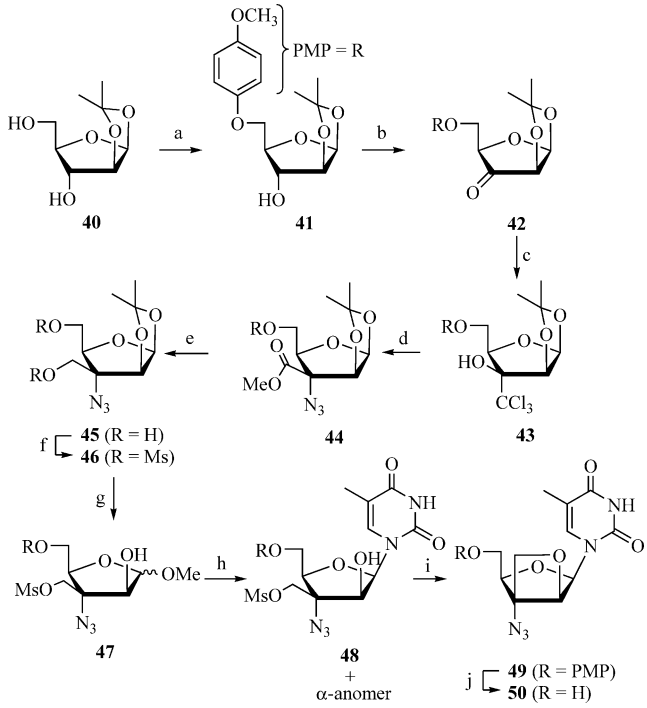
benzoyladenine with **35** gave poor *N*9/*N*7 regioselectivity, but the condensation of **35** with silylated 6-chloropurine was performed and furnished a chromatographically separable mixture of the expected *N*9 α and β anomers **38**. The adenosine analogue **39** was finally obtained by sequential treatment with TBAF and methanolic ammonia.



Scheme 6. *Reagents and conditions:* a) i. *hv*, (*Z*)-1,2-dichloroethene, CH_3CN, –40 °C; ii. Bu_3SnH, AIBN, toluene, reflux, 73% (two steps). b) TBMDSCl, imidazole, CH_2Cl_2, 93%. c) i. DIBAL-H, toluene, –78 °C; ii. Ac_2O, pyridine, 85% (two steps). d) thymine, BSA, TMSOTf, CH_3CN, 85%. e) TBAF, THF, 79%. f) 6-chloropurine, BSA, TMSOTf, CH_3CN, 67%. g) i. TBAF, THF; ii. MeOH, NH_3, 82% (two steps).

The X-ray structure analysis of compound **39** revealed that the furanose ring adopts a C4′-*endo* (^{4}E) conformation (P = 228.1°) and a ν_{max} of 22.9°. The conformation around the glycosylic bound was *anti* and the preferred rotamer around the C4′–C5′ was γ^t. No biological evaluation of these compounds has been reported so far.

Nielsen et al. reported the synthesis of a conformationally restricted nucleoside analogue of the anti-HIV drug AZT bearing a 2′,3′-fused oxetane ring (Scheme 7).[26] Treatment of the known arabinose derivative **40**[27] with *p*-methoxyphenol under Mitsunobu conditions provided the corresponding ether **41**. This was oxidised to give a quantitative yield of the keto sugar **42**, which on treatment with trichloromethyl anion afforded the substituted tertiary alcohol **43** with absolute stereoselectivity. By the modified Corey–Link procedure,[28] **43** was converted into the β-azido methyl ester **44** in high yield by treatment with NaN_3, 18-crown-6 and DBU in MeOH. A mild reduction with $NaBH_4$ efficiently gave the primary alcohol **45**. Conversion of **45** into its mesyl ester derivative **46**, followed by treatment with methanolic HCl, provided a mixture of methyl furanosides **47** in a high yield. Simultaneous trimethylsilylation of the secondary alcohol of **47** and thymine and subsequent coupling in the presence of TMSOTf gave, after separation, the anomers β-**48** and α-**48** in good yields and in an almost equimolar ratio. Finally, the bicyclic nucleoside **50** bearing a 2′,3′-fused oxetane ring was smoothly obtained after treatment with a strong base and CAN.

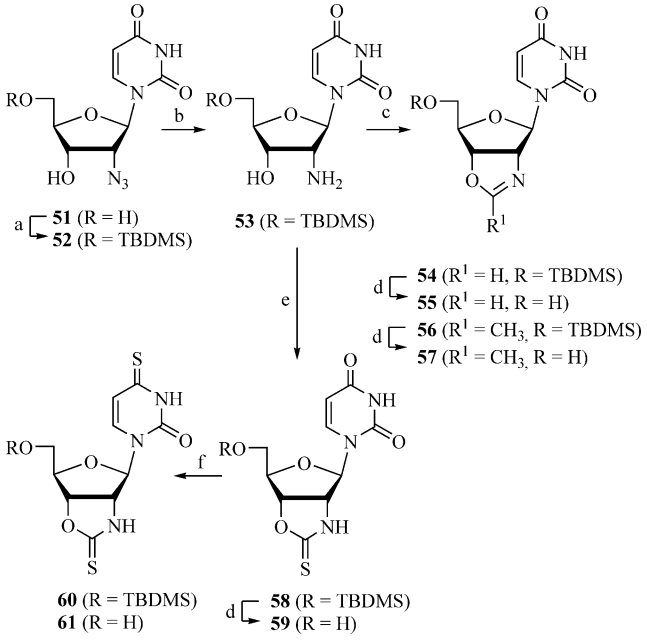


Scheme 7. *Reagents and conditions:* a) *p*-methoxyphenol, DEAD, Ph_3P THF, 63% (two steps). b) CrO_3, Ac_2O, pyridine, CH_2Cl_2, 99%. c) $CHCl_3$, LiHMDS, THF, 74%. d) NaN_3, 18-crown-6, DBU, MeOH, 87%. e) $NaBH_4$, THF, EtOH, 80%. f) MsCl, pyridine, 87%. g) AcCl, MeOH, H_2O, CH_2Cl_2, 94%. h) thymine, TMSCl, BSA, TMSOTf, CH_3CN, 32% β anomer, 35% α anomer. i) NaH, DMF, 79%. j) CAN, CH_3CN, H_2O, 96%.

Conformational analysis of nucleoside **50** was based on modelling studies and NMR analysis. Thus, a geometry optimisation by ab initio calculation revealed that the bicyclic nucleoside adopts an East-type conformation (O4′-*endo*) with P = 91.4° and a ν_{max} of 46.8°. In addition, the experimentally determined coupling constant $^3J_{H1',H2'}$ = 2.7 Hz perfectly agreed with a conformation with P ca. 90°. The nucleoside **50** did not show anti-HIV activity in cell culture experiments. Another example of a 2′,3′-fused oxetane ring nucleoside was reported by the same team.[29] Recently, an α-D-*arabino*-configured bicyclic nucleoside restricted in an East-type conformation by the same 2′,3′-conformational constraint, produced by a different synthetic strategy, was reported to improve nucleic acid recognition in mixmers with α-DNA monomers.[30]

Other examples of conformationally restrained nucleosides bearing oxazole and thiocarbamate rings at their 2′,3′-positions have been reported.[31] The synthesis was carried out from 2′-azido-2′-deoxyuridine[32] (**51**), which was selectively protected with a TBDMS group (Scheme 8). The 5′-*O*-TBDMS derivative **52** was subjected to the Staudinger reaction[33] to furnish the 2′-amino nucleoside **53**. Cycli-

sation[34] to form the 2′,3′-oxazole ring was achieved with *N*,*N*-dimethylformamide dimethyl acetal in DMF at room temperature and in good yield. Compound **54** was deprotected with TBAF to give the target imino nucleoside **55**. In a similar way, **53** was treated with *N*,*N*-dimethylacetamide dimethyl acetal to provide the 2′,3′-(2-methyloxazole) derivative **56**, which after deprotection gave the nucleoside **57**. The corresponding thiocarbamate derivative was obtained by treatment of **53** with thiocarbonyldiimidazole (Scheme 8). Deprotection of **58** with TBAF afforded **59** as the major tautomer. Furthermore, treatment of **58** with Lawesson's reagent produced the silyl-protected nucleoside **60** as well as the deprotected 4-thiouridine derivative **61**.



Scheme 8. *Reagents and conditions:* a) TBDMSCl, imidazole, DMF, 70%. b) Ph_3P, THF, H_2O, 60 °C, 87%. c) *N*,*N*-dimethylformamide dimethyl acetal, DMF, 78% for **54**, or *N*,*N*-dimethylacetamide dimethyl acetal, DMF, 60% for **56**. d) TBAF, THF, 83% for **55**, 86% for **57**, 72% for **59**. e) thiocarbonyl diimidazole, CH_2Cl_2, 94%. f) Lawesson's reagent, toluene, 80 °C, 34% for **60**, 66% for **61**.

The conformational evaluation was carried out by theoretical potential energy calculation with the Macromodel V.6.0 molecular modelling programme. The results of the conformational analysis are summarised in Table 1.

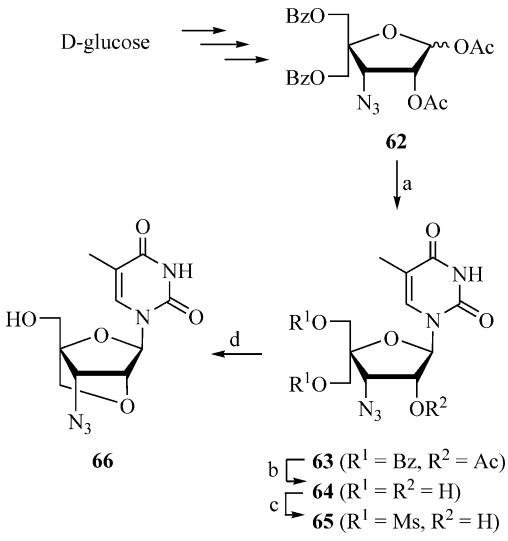
Table 1. Conformational analysis of selected nucleosides **55**, **57** and **59**.

	Bicyclic nucleoside		
	55	**57**	**59**
P value	89°	110°	73°
Sugar pucker	^{0}E	$^{1}_{0}T$	$^{4}_{0}T$
χ value	*anti*	*anti*	*anti*
γ value	t	+	t

Introduction of an oxazole or a thiocarbamate ring at its 2′,3′-positions leads the sugar ring to adopt a conformation close to an East-type conformation. The conformation around the glycosylic bound was found to be *anti*, and the values of γ were found to be in a range from γ^t to γ^+. Compounds **55**, **57**, **59** and **61** were evaluated for their inhibitory activity against a wide spectrum of viruses. None of the compounds showed activity against any of the virus strains tested, as well as no cytotoxicity.

3.4. 2′,4′-Conformational Constraints

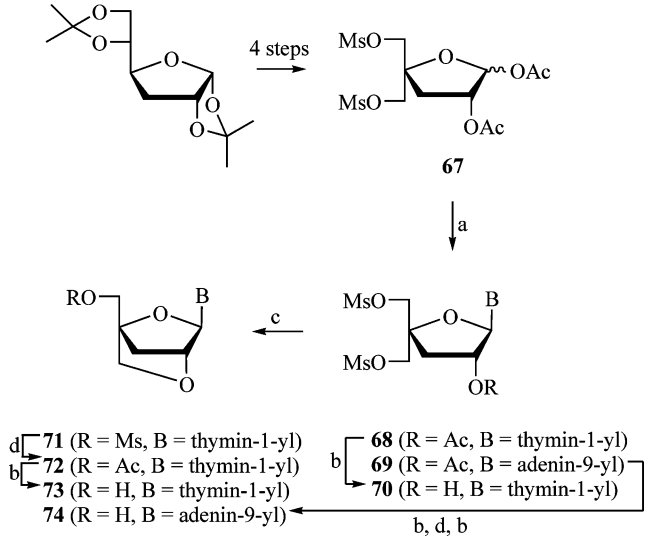
Wengel et al. reported the synthesis of a conformationally locked AZT analogue containing a 2′-*O*,4′-*C*-methylene-linked bicyclic furanose moiety.[35] The authors used the known 3-azido-3-deoxyfuranose **62**, easily obtained from D-glucose, as starting material (Scheme 9).[36] Treatment of **62** with persilylated thymine under Vörbruggen conditions proceeded stereoselectively to afford the β-D-*ribo* derivative **63** in good yield. Complete deprotection with sodium methoxide in methanol gave the nucleoside **64**. Selective mesylation of the two primary hydroxy groups provided **65**, which upon treatment with a mixture (1:1 *v*/*v*) of 1,4-dioxane and aqueous NaOH (1 M) directly yielded the target compound **66**.



Scheme 9. *Reagents and conditions:* a) BSA, thymine, TMSOTf, CH_3CN, 68%. b) MeOH, MeONa, 85%. c) MsCl, pyridine, d) NaOH, aq. 1,4-dioxane, 36% from **64**.

Evaluation of the conformation was based on molecular modelling (HyperChem™ program) and was confirmed by ^1H NMR and NOE experiments. From these studies, it turns out that introduction of a 2′-*O*,4′-*C*-methylene linkage leads the sugar to adopt a North-type (^3E, C3′-*endo*) conformation while the thymine moiety adopts an *anti* conformation. Although the sugar is locked in a North-type conformation corresponding to that of AZT triphosphate bonded with HIV-1 reverse transcriptase,[37] the nucleoside **66** did not show antiviral activity when evaluated against HIV-1 in cell culture experiments. In a similar way, the corresponding 3′-deoxy-2′-*O*,4′-*C*-methylene-linked bicyclic nucleoside analogues with locked North-type (C3′-*endo*) furanose conformations were prepared by a convergent syn-

thetic strategy.[38] The di-*O*-(methylsulfonyl)furanose key intermediate **67** was obtained in four steps from 3-deoxy diacetone-D-glucose (Scheme 10). The use of such intermediates for the synthesis of locked nucleic acid-type (LNA-type) nucleosides had been demonstrated previously.[39] Thus, coupling between **67** and thymine by the Vorbrüggen procedure stereoselectively provided nucleoside **68**. The acetyl group was removed by treatment with methanolic ammonia to give **70**, which was converted into the bicyclic nucleoside **71** with a strong base. The remaining mesyl group was replaced by an acetate group by treatment of **71** with a mixture of potassium acetate and 18-crown-6 in dioxane at reflux to give **72**, which upon treatment with methanolic ammonia provided the target bicyclic nucleoside **73**. Coupling of **67** with adenine with $SnCl_4$ in acetonitrile afforded nucleoside **69**. The target adenine derivative **74** was obtained from **69** by procedures similar to those described above for the corresponding thymine nucleoside.



Scheme 10. *Reagents and conditions:* a) BSA, thymine, TMSOTf, CH_3CN, 23% from 3-deoxy-D-glucose or adenine, $SnCl_4$, CH_3CN. b) MeOH/NH_3, 65% for **73**, 3% for **74** overall yield from 3-deoxy-D-glucose. c) NaH, DMF [B = thymin-1-yl, 64% two steps; B = adenin-9-yl]. d) AcOK, 18-crown-6, 1,4-dioxane [B = thymin-1-yl, 66%, B = adenin-9-yl].

The target nucleosides **73** and **74** did not show antiviral activity when evaluated against HIV-1 in cell culture experiments. In addition, the corresponding masked 5′-monophosphate cyclosal[40] and aryloxy phosphoramidate derivatives[41] of some 2′-*O*,4′-*C*-methylene-linked bicyclic nucleoside analogues – **66**, **73** and **74** –were synthesised (Figure 2). Such 5′-monophosphate nucleoside prodrugs have been reported to be enzymatically cleaved inside the cell, liberating the free 5′-monophosphate. However, none of these mononucleotide prodrugs demonstrated any anti-HIV activity in cell culture experiments. This result suggests, as reported earlier, either that the North-type conformation is not adapted for efficient 5′-*O*-phosphorylation in vivo[42] or that the presence of a substituent in the 2′-α position (a *ribo*-like substituent) prevents the binding of the incoming triphosphate derivative in the catalytic site of the reverse transcriptase through a repulsive interaction between a tyrosine moiety (Tyr115) and the axial 2′-C–O bond.[43]

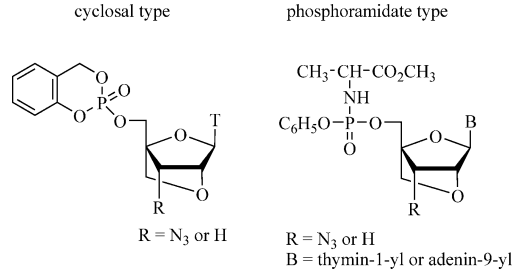
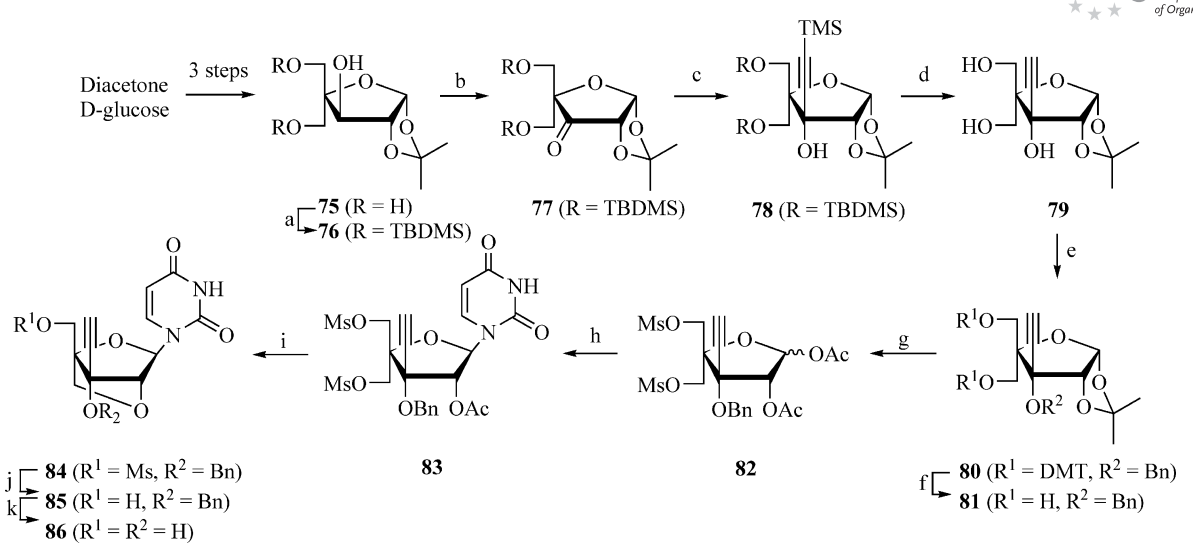


Figure 2. 5′-Monophosphate nucleosidic cyclosal-type and aryloxy phosphoramidate-type prodrugs.

The synthesis of conformationally restricted analogues of the anticancer nucleoside 3′-*C*-ethynyluridine (EUrd)[44] bearing a 2′-*O*,4′-*C*-methylene linkage (Scheme 11) was reported by Wengel et al.[45] The starting material **75**, conveniently obtained in three steps from diacetone D-glucose,[46] was converted into derivative **76** by selective TBDMS protection of the primary hydroxy groups. Oxidation of **76** to 3-ulose derivative **77** was accomplished by treatment with Dess–Martin periodinane.[47] Nucleophilic addition of lithium trimethylsilylacetylene to **77** occurred from the sterically less hindered β face to give exclusively the *ribo*-like derivative **78**. Desilylation of **78** with TBAF gave the key intermediate **79**. To prevent undesired 3′-*O*,4′-*C* ring-closure at a latter stage of the synthesis, suitable protection of the 3′-hydroxy group of **79** was required. In this regard, primary hydroxy groups of **79** were transiently protected as the 4,4′-dimethoxytrityl (DMT) ethers, and subsequent 3′-benzylation gave the fully protected derivative **80**. Removal of the DMT ethers provided furanose **81**. Next, permesylation of **81** and subsequent isopropylidene cleavage and peracetylation furnished the sugar precursor **82**. Condensation of **82** with uracil under Vorbrüggen conditions gave the β-nucleoside **83**, treatment of which with aqueous NaOH in 1,4-dioxane resulted in tandem deacetylation and ring-closure to give the LNA-type derivative **84**. Nucleophilic displacement of the remaining mesylate group with sodium benzoate required harsh conditions and resulted in partial decomposition. Nevertheless, the crude benzoate was treated with methanolic ammonia to give nucleoside **85**. Finally, debenzylation of **85** with boron trichloride afforded the EUrd-LNA-type analogue **86** without affecting the alkyne functionality.

The target nucleoside **86** was subjected to Monte-Carlo-based conformational searches using AMBER force-field and generalised Born/surface area solvation model as implemented in the Macromodel V 7.2 suite.[48] As expected, the 2′-*O*,4′-*C*-methylene linkage restricted the nucleoside **86** in a North-type conformation (P = 24°) with an extreme pucker (ν_{max} = 55°). In addition, the conformation around the glycosylic bound was found to be *anti*. Such a conformation is contrary to that observed for the unrestricted 3′-



Scheme 11. *Reagents and conditions:* a) TBDMSCl, imidazole, DMF, room temp., 71%. b) Dess–Martin periodinane, CH_2Cl_2, 0 °C to room temp., 97%. c) TMSC≡CH, *n*BuLi, THF, –78 °C, 90%. d) TBAF, THF, room temp., 74%. e) i. DMTCl, DMAP, pyridine, room temp.; ii. NaH, BnBr, Bu_4I, THF. f) 80% aq. AcOH, room temp., 55%, 3 steps from **79**. g) i. MsCl, pyridine, room temp.; ii. 80% aq. TFA, room temp.; iii. Ac_2O, pyridine, 89%, 3 steps from **81**. h) Uracil, BSA, TMSOTf, CH_3CN, 50 °C, 88%. i) 2 M NaOH, 1,4-dioxane/H_2O, room temp., 94%. j) i. NaOBz, DMF, 110–140 °C; ii. NH_3/MeOH, room temp., 62% two steps from **84**. k) BCl_3, CH_2Cl_2, hexane, –78 °C to room temp., 63%.

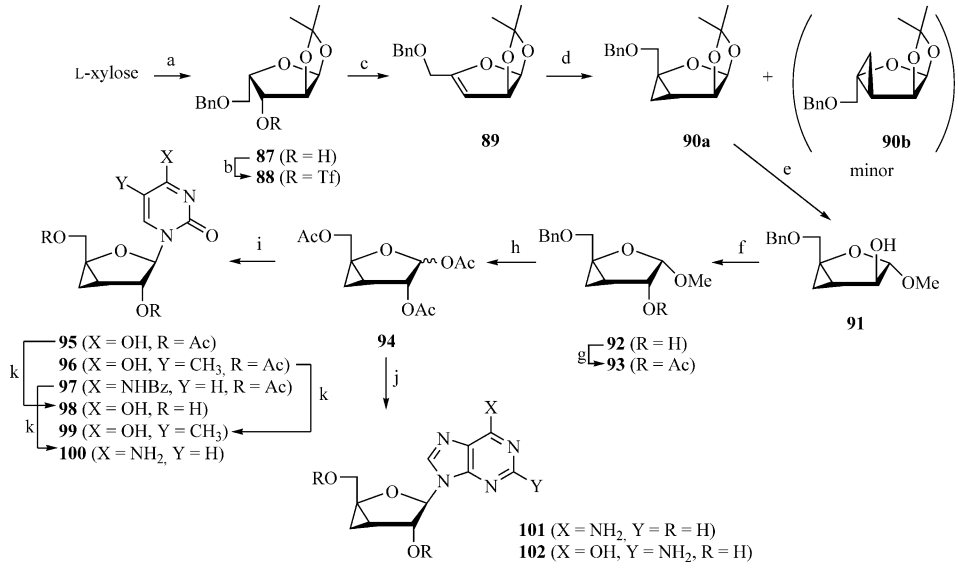
C-ethynyl ribonucleoside, which adopts a South-type conformation both in the crystalline state (P = 182°) as well as in solution.[49] When evaluated against HIV-1 in cell culture experiments (MT-4 cells), the nucleoside **86** did not present antiviral activity. A marginal cytotoxicity ($CD_{50} \geq 30$ μM), in relation to that of 3′-*C*-ethynyluridine (CD_{50} = 0.03 μM), was observed in the same cellular system. The lack of anticancer activity of nucleoside **86** may arise from opposing conformational requirements between nucleotide kinases and/or RNA polymerases and the furanose conformation of **86**, locked in a North-type form.

Recently, conformationally locked 2′,4′-carbocyclic *ribo*-thymidine nucleosides have been reported.[50] Reactions involving the hex-5-enyl or hept-6-enyl radical cyclisation of a distant double bond at C4′ and a radical centre at C2′ of ribofurano-thymidine have been used to synthesise North-type conformationally constrained *cis*-fused bicyclic five-membered and six-membered carbocyclic analogues of LNA. Their incorporation into antisense oligonucleotides (AONs) demonstrated that they enhance the T_m values of the modified AON/RNA heteroduplexes as well as their stabilities against nucleases.

3.5. 3′,4′-Conformational Constraints

Nucleoside analogues incorporating the five naturally occurring nucleic acid bases mounted on 2-oxabicyclo[3.1.0]-hexane were recently reported by us.[51] The synthesis of these conformationally restricted nucleoside analogues involved preparation of the suitable sugar **94**, bearing the 2-oxabicyclo[3.1.0]hexane scaffold (Scheme 12). L-Xylose was chosen as starting material and was converted into derivative **87** by a protocol similar to that established for the synthesis of its D counterpart.[52] Compound **87** was treated with triflic anhydride in a pyridine/dichloromethane mixture at –15 °C to provide sugar **88**, which was subjected to a β-elimination reaction in the presence of DBU in acetonitrile at reflux. A Simmons–Smith-type cyclopropanation reaction on the unsaturated sugar **89** was achieved by Furukawa's protocol[53] to afford a mixture of compounds **90a** and **90b**. Separation was accomplished by silica gel column chromatography to provide pure **90a** and **90b**, in 91% and 1.5% yields, respectively. Stereoselective control of the reaction on compound **89** was achieved thanks to the isopropylidene group, directing the methylene insertion on the less hindered α face, to provide sugar **90a**, with a D-like configuration, as a major compound. To obtain nucleosides with the β configuration, and owing to anchimeric participation of an acyl-type protective group during glycosylations, compound **90a** with an *arabino*-like configuration has to be converted into a sugar with a *ribo*-like configuration. In this regards, treatment of **90a** with HCl in a dioxane/methanol mixture afforded the α anomer of methyl furanoside **91**. A chromium-mediated oxidation of **91** provided the ketone, which was directly reduced with $NaBH_4$ to give the corresponding sugar epimer **92**. This was converted in a two-step procedure into the suitable precursor **94** after an acetylation reaction yielding intermediate **93**, which was next treated with $AcOH/Ac_2O/H_2SO_4$ to afford **94** as an anomeric mixture (α/β ratio 9:91). Glycosylation reactions with uracil, thymine or N^4-benzoyl cytosine and **94**, under Vorbrüggen conditions, gave the protected nucleosides **95**–**97**, which upon treatment with methanolic ammonia gave the target pyrimidine nucleosides **98**–**100**.

A glycosylation reaction with adenine and sugar **94** under Saneyoshi conditions[54] led, after deprotection with sodium methoxide in methanol, to nucleoside **101** (Scheme 12). A condensation reaction between 2-*N*-acetyl-



Scheme 12. *Reagents and conditions:* a) Ref.[52] b) Tf_2O, pyridine/CH_2Cl_2, –15 °C. c) DBU, CH_3CN, 80 °C, 92%. d) $ZnEt_2$, CH_2I_2, toluene, 0 °C, 91% for **90a**, 1.5% for **90b**. e) 4 N HCl/dioxane, MeOH, 0 °C, 89%. f) i. CrO_3, Ac_2O, pyridine/CH_2Cl_2, 0 °C; ii. $NaBH_4$/EtOH, room temp., 74% two steps). g) Ac_2O, pyridine, room temp., 91%. h) AcOH, Ac_2O, H_2SO_4, 0 °C to room temp., 81%. i) silylated pyrimidine, TMSOTf, CH_3CN, 0 °C, 80% for **95**, 67% for **96**, 75% for **97**. j) i. adenine, $SnCl_4$, CH_3CN, room temp. or silylated 2-*O*-acetyl-6-*O*-(diphenylcarbamoyl)guanine, BSA, toluene, 80 °C; ii. MeONa/MeOH, room temp., 37% for **101** (two steps), 20% for **102** (two steps). k) MeOH/NH_3, room temp., 64% for **98**, 88% for **99**, 85% for **100**.

6-*O*- (diphenylcarbamoyl)guanine and **94** by Robins' procedure[55] and subsequent treatment with methanolic ammonia gave nucleoside **102**.

For conformational studies, we chose compound **99** as a model. An ab initio calculation provided a geometry optimised structure close to a $^0T_1$ (C1′-*exo*, P = 107.2°) conformation with a ν_{max} = of 17.2°. In addition to this work, we also reported on the synthesis of pyrimidine nucleoside analogues constructed on the 2-oxabicyclo[3.1.0]hexane scaffold with various modifications at C2′, including methylene and azido groups and an *arabino*-like configuration (Figure 3).[56] The syntheses were achieved from their corresponding uracil and thymine parent nucleosides.

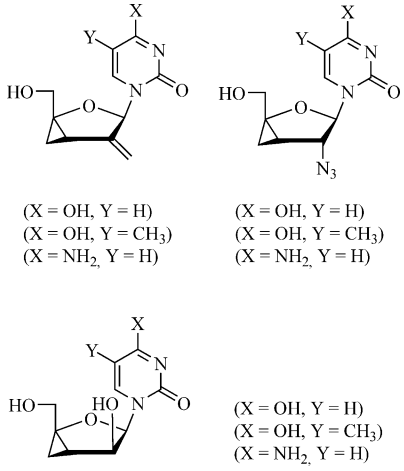
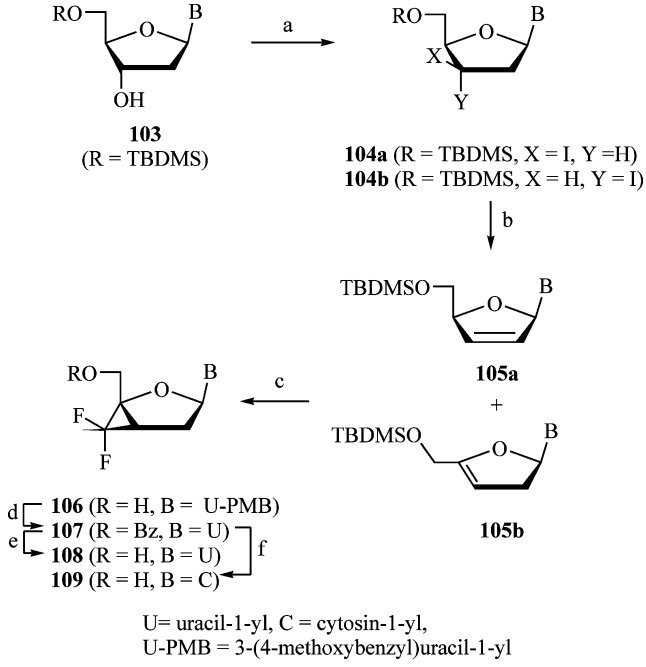


Figure 3. C2′-modified pyrimidine nucleoside analogues constructed on a 2-oxabicyclo[3.1.0]hexane scaffold.

Conformational analysis showed that the conformations of such C2′-modified nucleoside analogues were restricted in the South-East hemisphere of the pseudorational cycle (between a $^0T_1$ and a ^2E conformation). All the 2-oxabicyclo[3.1.0]hexane nucleoside analogues were tested for their effects on the replication of HIV and several RNA viruses in cell culture experiments. However, none of these compounds showed any significant antiviral activity. Nevertheless, the 2-oxabicyclo[3.1.0]hexane framework was used to determine the preferred ribose conformation at the human $P2Y_6$ receptor binding site. As previously reported, a strong preference for the South conformation was indicated, as demonstrated with the use of the 5′-diphosphate of the uridine derivative **98**.[3g]

Robins et al. reported the synthesis of 2′-deoxy nucleoside analogues with 2,2-difluorocyclopropane rings fused at C3′–C4′ (Scheme 13).[57] The synthesis was achieved by treatment of protected 2′-deoxy-3′,4′-unsaturated nucleosides with difluorocarbene generated from bis(trifluoromethyl)mercury and sodium iodide. In order to obtain the unsaturated nucleoside precursor, uridine was converted in several steps into the corresponding 2′-deoxy-5′-*O*-TBDMS derivative **103**, bearing a 4-methoxybenzyl protective group at N3. Then, treatment of **103** with Ph_3P/I_2/imidazole gave a mixture of inverted product **104a** and epimer **104b**. Formation of the doubly inverted isomer **104b** may be attributed to the participation of O2 on the uracil ring. Heating of the **104a/104b** mixture in a solution of DABCO in benzene at reflux provided a mixture of **105a** and **105b** (ratio 1:2, 99% total). No elimination was observed with the *erythro* isomer **104b**, which was recovered from the reaction mixture. Separation of **105a/105b** was not possible, and the

mixture was treated with $(CF_3)_2Hg$ and NaI in THF at 60 °C. Under these mild conditions, only the electron-rich enol ether **105b** underwent addition of difluorocarbene. Deprotection of the mixture with NH_4F/MeOH and purification allowed separation of the major adduct **106** from the unreactive derivative **105a** and other byproducts. Benzoylation of **106** and removal of the 4-methoxybenzyl group afforded compound **107**, which upon treatment with methanolic ammonia gave the 2′-deoxyuridine analogue **108**. The corresponding 2′-deoxycytidine analogue **109** was obtained from **107** via the preparation of the 4-triazolypyrimidinone derivative following ammonolysis and debenzoylation. A parallel approach was used for the synthesis of the corresponding 2′-deoxyadenosine analogue with a 2,2-difluorocyclopropane ring fused at C3′–C4′. Stereoselective α-face insertion of the difluorocarbene into the dihydrofuran ring is the result of steric hindrance by the protected β anomeric nucleobases.



Scheme 13. *Reagents and conditions:* a) Ph_3P, I_2, imidazole, 70 °C, 81% (ratio **104a/104b** 2.4:1). b) DABCO, benzene, 80 °C, 99% (ratio **105a/105b** 1:2). c) i. $(CF_3)_2Hg$, NaI, THF, 60 °C; ii. NH_4F, MeOH, 65 °C, two steps, 65%. d) i. BzCl, Et_3N, CH_2Cl_2; ii. CAN, H_2O, CH_3CN, 81%, two steps. e) MeOH, NH_3, 60 °C, 86%. f) i. $POCl_3$, 1,2,4-triazole, Et_3N, CH_3CN; ii. NH_3, H_2O, 1,4-dioxane; iii. NH_3, MeOH, 3 steps 60% as its HBr salt.

Crystals of **108** and **109**·HBr were used for the determination of the conformation by X-ray analysis. The furanose moieties in **108** and **109**·HBr were found to be in South-type conformations (P = 159.8°, close to ^{2}E conformation or P = 135.6°, close to ^{1}E conformation, respectively) with nearly planar or large puckering amplitudes (ν_{max} = 10.1° or 25.3°, respectively). The conformations around the glycosylic bound were in both cases found to be in the *anti* range. In addition to this work, the synthesis of 3′-deoxynucleoside analogues of adenosine, cytidine and uridine with 2,2-difluorocyclopropane rings fused at C3′–C4′ were also reported (Figure 4).

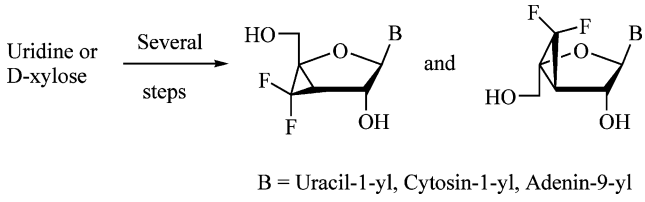
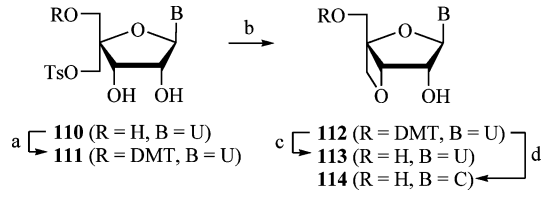


Figure 4. 3′-Deoxy nucleoside analogues with a 2,2-difluorocyclopropane ring fused at C3′–C4′.

By a similar methodology, the target nucleosides were obtained by treatment of a 2′,5′-protected-3′,4′-unsaturated derivative of uridine or of 1,2-dihydrofurans derived from D- and L-xylose with difluorocarbene. No biological evaluations of the whole series have been reported so far.

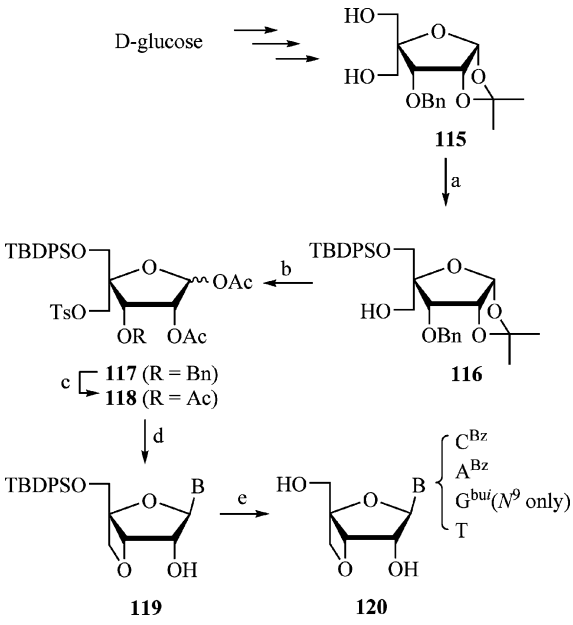
In order to develop novel 2′,5′-linked oligonucleotide analogues intended as antiviral agents and antisense/antigene oligonucleotides, Imanishi et al. reported the synthesis of 3′-*O*,4′-*C*-methyleneribonucleosides (3′,4′-BNA monomers).[58] Two synthetic pathways were used. The first methodology utilised a regioselective ring-closure reaction of the 4′-*C*-(*p*-tolylsulfonyl)oxymethyluridine[59] derivative **110**, prepared from uridine (Scheme 14). After selective protection with a DMT group in position 5′, treatment of **111** under alkaline conditions yielded the oxetane **112**. Removal of the DMT group finally gave the desired 3′,4′-BNA monomer **113**. The corresponding cytidine analogue **114** was obtained from **112** in four steps involving transformation of the nucleobase from uracil into cytosine by Sung's methodology.[60]



Scheme 14. *Reagents and conditions*: a) DMTCl, pyridine, room temp., 68%. b) NaHMDS, THF, room temp., 63%. c) 1% TCA in $Cl(CH_2)_2Cl$, room temp., 94%. d) i. Ac_2O, pyridine, room temp.; ii. 1,2,4-triazole, 4-chlorophenyl phosphorodichloridate, pyridine, room temp.; iii. aqueous NH_3, 1,4-dioxane, room temp.; iv. 1% TCA in $Cl_2(CH_2)_2Cl_2$, room temp., 4 steps, 52%.

In order to synthesise the 3′,4′-BNA monomers containing the four natural nucleobases, another synthetic pathway involving the preparation of 1,2,3-tri-*O*-acetyl-4-(*p*-tolylsulfonyl)oxymethylribofuranose derivative **118** as a condensable sugar precursor was investigated (Scheme 15). The starting material **115** was chosen and prepared from D-glucose by a multi-step procedure.[46] Selective protection of **115** with a TBDPS group was readily achieved to give the desired compound **116**. Introduction of the tosyl group, followed by removal of the isopropylidene group and acetylation, gave the diacetate **117**. The condensable sugar precursor **118** was obtained after palladium-catalysed hydro-

genolysis and treatment with acetic anhydride in pyridine. Condensation of **118** with the nucleobases was accomplished under Vorbrüggen's conditions. Removal of the acetyl groups and treatment with NaHMDS gave the oxetane derivatives **119**. Finally, removal of the TBDPS group led to the target 3′,4′-BNA monomers **120**.



Scheme 15. *Reagents and conditions:* a) TBDPSCl, Et_3N, CH_2Cl_2, room temp., 67%. b) i. TsCl, Et_3N, DMAP, CH_2Cl_2, room temp., 97%; ii. AcOH, Ac_2O, H_2SO_4, room temp., 86% c) 10% Pd-C, H_2, AcOEt, $CHCl_3$, room temp., then Ac_2O, pyridine, room temp., 91%. d) i. silylated base, TMSOTf, $Cl(CH_2)_2Cl$, room temp., 70–82%; ii. K_2CO_3, MeOH, room temp., 63–100%; iii. NaHMDS, THF, room temp., 82–100%. e) TBAF, THF, room temp., 65–78%.

The conformational analysis of the different monomers was based upon ^1H NMR measurements, X-ray analysis and molecular modelling. Results obtained from the observed coupling constant $J_{1'2'}$ values (7.3–7.6 Hz) and with the aid of the simplest equation [S(%) = 100($J_{1'2'}$-1)/6.9, because in 3′,4′-BNA monomers $J_{3'4'}$ does not exist], which predicts the probability of an S-type conformation of the ribofuranose ring,[61] indicate that the conformations of the 3′,4′-BNA monomers were restricted in an S-type conformation by the 3′-*O*,4′-*C*-methylene bridge (91% to 96%). Additionally, X-ray analysis of the 3′,4′-BNA thymine derivative revealed a *P* value of 136.3° with ν_{max} = 32.5°. Finally, a PM3 semiempirical calculation was carried out to analyse the stable conformation of the 3′,4′-BNA thymine derivative. The lowest energy state was observed for a *P* value of 130°. This result was in agreement with the X-ray analysis and demonstrated that the sugar conformations of the 3′,4′-BNA monomers were restricted in South-type arrangements (C1′-*exo*-C2′-*endo*).

3′-Amino-3′-deoxy-5-methyl-3′-*N*,4′-*C*-methyleneuridine (Figure 5) was also successfully synthesised by a similar methodology.[62] The strategy involved the preparation of an azetidine-fused furanose ring, with appropriate protecting groups, as a condensable sugar precursor, which upon glycosylation gave the corresponding 3′-amino-3′,4′-BNA monomer. A ^1H NMR experiment and a PM3 calculation revealed that the sugar moiety of the isoster of the 3′,4′-BNA monomer was restricted to an S-type conformation.

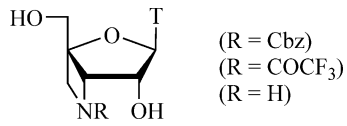
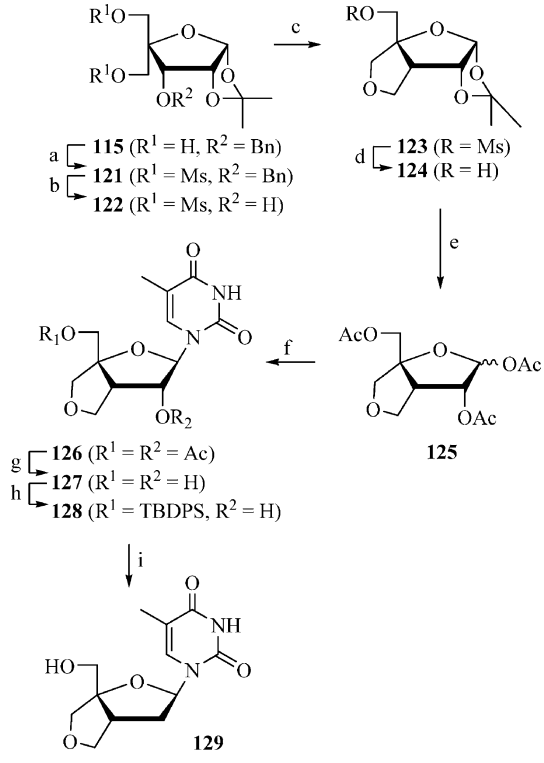


Figure 5. 3′-Amino-3′,4′-BNA monomer.

Other examples of nucleoside analogues fused with additional rings can be found in the literature. Chun et al. have reported the synthesis of thymine nucleoside analogues fused with tetrahydrofuran rings in positions 3′ and 4′.[63] The synthetic strategy was based upon the preparation of the bicyclic furo[3,4-*b*]furan derivative **125** as glycosyl donor and its condensation with the heterocyclic base (Scheme 16). Starting from **115**,[46] treatment with MsCl gave the dimesylate **121**. Removal of the benzyl group afforded **122**, which was treated with NaH to provide compound **123** through an intramolecular cyclisation. The remaining mesyl group was displaced with NaOH to give derivative **124**. Compound **124** was converted into the glycosyl



Scheme 16. *Reagents and conditions:* a) MsCl, pyridine, room temp., 73%. b) H_2, $Pd(OH)_2$, EtOH, r.t., 85%. c) NaH, THF, 55 °C, room temp. d) 0.5 N NaOH, reflux, 89% from **122**. e) i. Ac_2O, pyridine, room temp.; ii. HCO_2H, 55°; Ac_2O, pyridine, room temp., 82% from **124**. f) thymine, BSA, TMSOTf, CH_3CN, 60 °C, 70%. g) NH_4OH, MeOH, room temp., 93%. h) TBDPSCl, imidazole, DMF, room temp., 84%. i) i. PhOC(S)Cl, DMAP, Et_3N, CH_3CN, 0 °C; ii. Bu_3SnH, AIBN, toluene, 100 °C; iii. TBAF, THF, room temp., 42% from **128**.

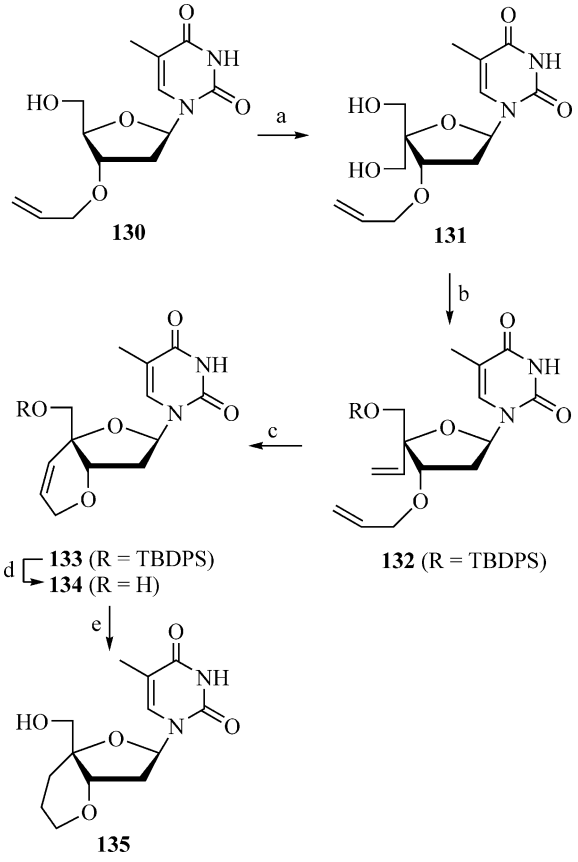
donor **125**, as an anomeric mixture, after treatment with acetic anhydride and subsequent hydrolysis and acetylation. Condensation of **125** with silylated thymine under Vorbrüggen's conditions afforded **126**, which upon deprotection gave the target compound **127**. After a selective 5′-*O*-silyl protection, compound **128** was subjected to a radical deoxygenation, and treatment with TBAF then yielded the 2′-deoxy analogue **129**.

No conformational analyses on compounds **127** and **129** were reported. Nevertheless, the large coupling constant $J_{1'2'}$ values (8 Hz for **127**) may indicate that the sugar conformation is restricted in an S-type conformation.[61] When evaluated in cell culture experiments, the thymine analogue **127** and its corresponding 2′-deoxy analogue **129** exhibited cytoxicity instead of antiviral activity.

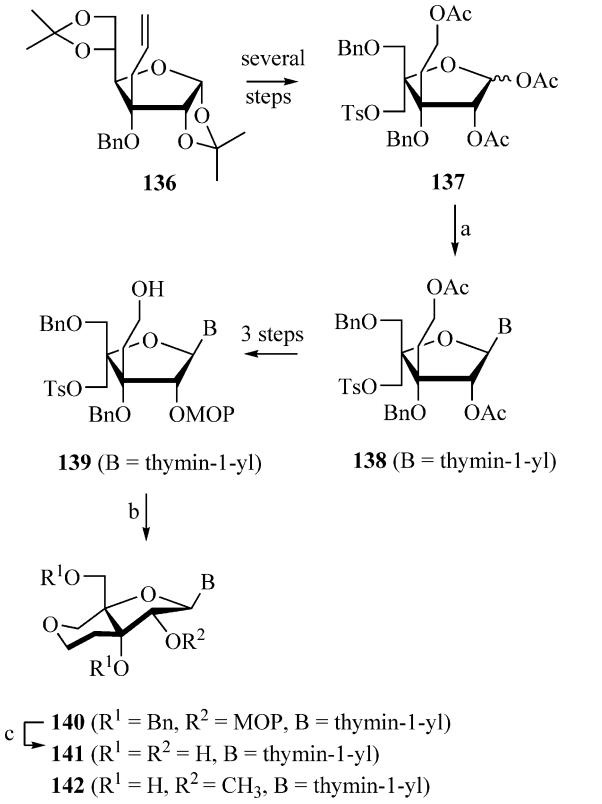
Lebreton et al. developed a route to the synthesis of bicyclic nucleoside analogues with larger fused rings (Scheme 17).[64] The synthesis of such 3′-*O*,4′-*C*-six-membered bicyclic thymidine analogues was efficiently achieved by the application of ring-closure metathesis (RCM)[65] on a diene intermediate in the presence of Grubbs catalyst. The key diene **132** was prepared from the corresponding diol **131**, which was obtained from the 3′-allyloxythymidine **130** as shown in the pathway outlined in Scheme 17. Compound **132** was subjected to a RCM reaction in dichloromethane in the presence of the Grubbs second-generation catalyst to provide the bicyclic derivative **133**. Removal of the protective group with TBAF afforded the nucleoside **134**. Reduction of the double bound in **134** was accomplished by catalytic hydrogenation on 10% Pd-C in ethanol to give the derivative **135**.

No conformational analyses on compounds **134** and **135** were reported. From the large coupling constant $J_{1'2'}$ values, however, the sugar conformation seems to be restricted in an S-type conformation. The bicyclic thymidine analogues **134** and **135** were tested in cell culture experiments against the replication of Herpes simplex virus type 1. None of these compounds was found to be active.

Other examples of 3′,4′-bicyclic nucleoside analogues can be found in the literature. Imanishi et al. reported the synthesis of a bridged nucleoside incorporating a 4,7-dioxabicyclo[4.3.0]nonane skeleton (Scheme 18).[66] The *trans*-3′,4′-BNA monomer of thymine was obtained from the known D-allofuranose derivative **136**,[67] which was converted in several steps into the condensable sugar precursor **137**. Coupling with silylated thymine gave the β anomer **138**. After protection of the 2′-position with a 2-methoxy-2-propyl (MOP) group by a two-step procedure and subsequent deacylation, a ring-closure reaction upon treatment with NaHMDS afforded compound **140**. Deprotection of the 2′-hydroxy group under acidic conditions followed by



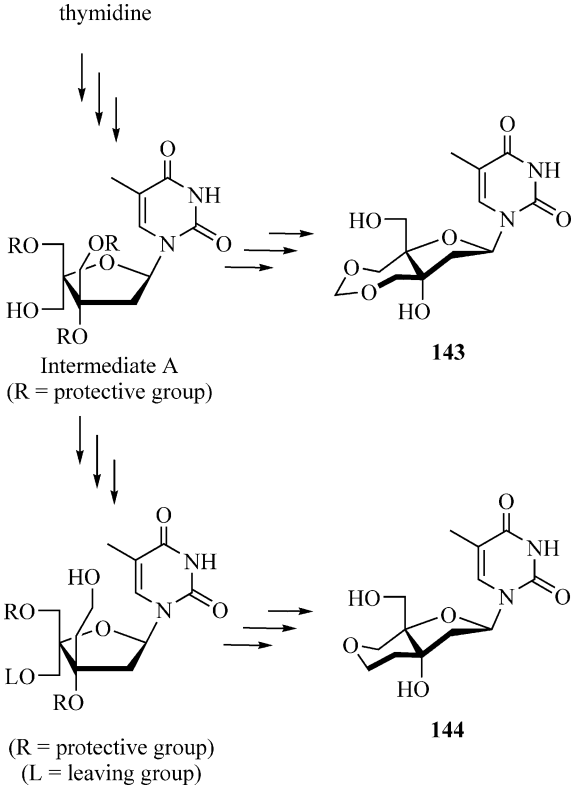
Scheme 17. *Reagents and conditions:* a) i. DCC, pyridinium trifluoroacetate; ii. HCHO, NaOH then $NaBH_4$, 33%, two steps. b) 5 steps, 37%. c) Grubbs' catalyst (2nd generation), CH_2Cl_2, room temp., 74%. d) TBAF, THF, room temp., 93%. e) H_2, P-C, EtOH, room temp., 84%.



Scheme 18. *Reagents and conditions:* a) Thymine, BSA, TMSOTf, $Cl(CH_2)_2Cl$, reflux, 87%. b) 1 M NaHMDS, THF, reflux, 73%. c) i. TsOH, H_2O, THF, MeOH, 0 °C; ii. 20% $Pd(OH)_2$, cyclohexene, EtOH, reflux, two steps, 58%.

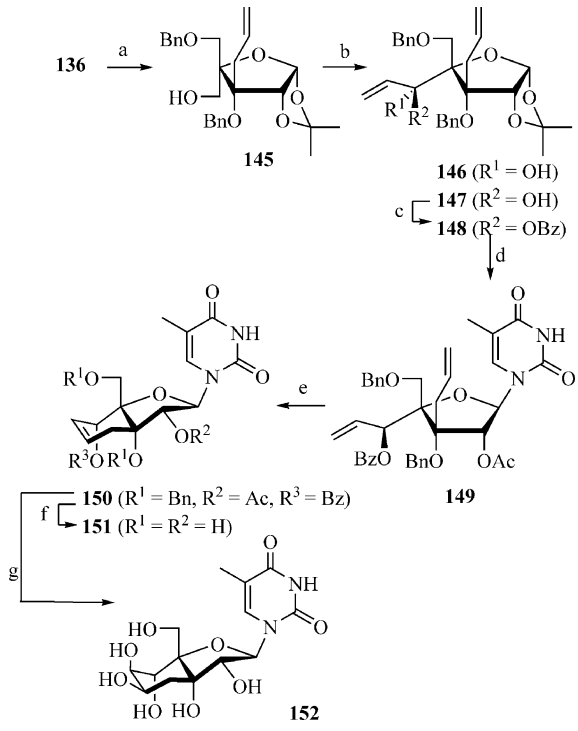
Pd-mediated hydrogenolysis yielded the ribonucleoside analogue **141**. The 2′-*O*-methyl derivative **142** was also obtained in a few steps from the nucleoside **138**. Large $J_{1'2'}$ values were observed (6.7 Hz and 7.1 Hz, respectively), meaning that the two monomers were conformationally restricted in S-type conformations. In addition, an X-ray analysis of **141** revealed a C3′-*exo* puckering mode with P = 211.4° and a large ν_{max} = of 51.9°. These compounds have been used for oligonucleotide synthesis.

Very recently, the same authors reported the synthesis of two novel *trans*-3′,4′-BNA monomers in the form of compounds **143** and **144**, one with a 3,5,8-trioxabicyclo[5.3.0]-decane structure and the other corresponding to the 2′-deoxy congener of nucleoside **141**. The synthetic strategy is outlined in Scheme 19.[68] Thymidine is used as starting material, and hydroxymethyl groups are introduced at the C3′- and C4′-positions to give the common intermediate **A** (Scheme 19). The target nucleosides can be obtained either by acetalisation or by intramolecular nucleophilic substitution. X-ray structural analysis of compounds **143** and **144** indicated that the furanose rings had typical S-type conformations with C2′-*endo* (*P* = 174°) or C3′-*exo* (*P* = 194°) sugar puckering, respectively, ring conformations very close to that observed in the B-type helical structure of DNA duplexes. The use of such nucleosides as candidates for DNA structure mimics is thus justified.



Scheme 19. Synthetic strategies for **143** and **144**.

Other examples of 3′,4′-*trans*-linked bicyclic nucleosides can be gleaned from the literature. Nielsen et al.[69] reported the synthesis of the bicyclic thymidine nucleoside **151** (Scheme 20). Starting from the C3′-allyl derivative **136** (Scheme 16), the main chemical steps involved a Cannizzaro reaction (**145**) and an oxidation step followed by a Grignard reaction, providing two epimers (**146** and **147**, ratio 1:3). After separation of the major isomer **147** and subsequent benzoylation (**148**), a Vorbrüggen-type coupling gave exclusively the β anomer **149**. Finally, the RCM reaction was performed in the presence of Grubbs' commercially available carbene precatalyst to afford compound **150**. A two-step deprotection procedure gave the target nucleoside **151**. Additionally, the cyclohexene moiety of **150** was subjected to further derivatisation. A stereoselective dihydroxylation reaction followed by deprotection provided the multihydroxylated bicyclic nucleoside **152**. The conformational behaviour of derivative **152** was determined by ^{1}H NMR spectroscopy and ab initio calculation. The furanose ring was found to be locked in a South-type conformation (C3′-*exo*, *P* ≈ 190–207°) with relatively large ν_{max} ≈ 46°). No biological evaluations have been reported so far.

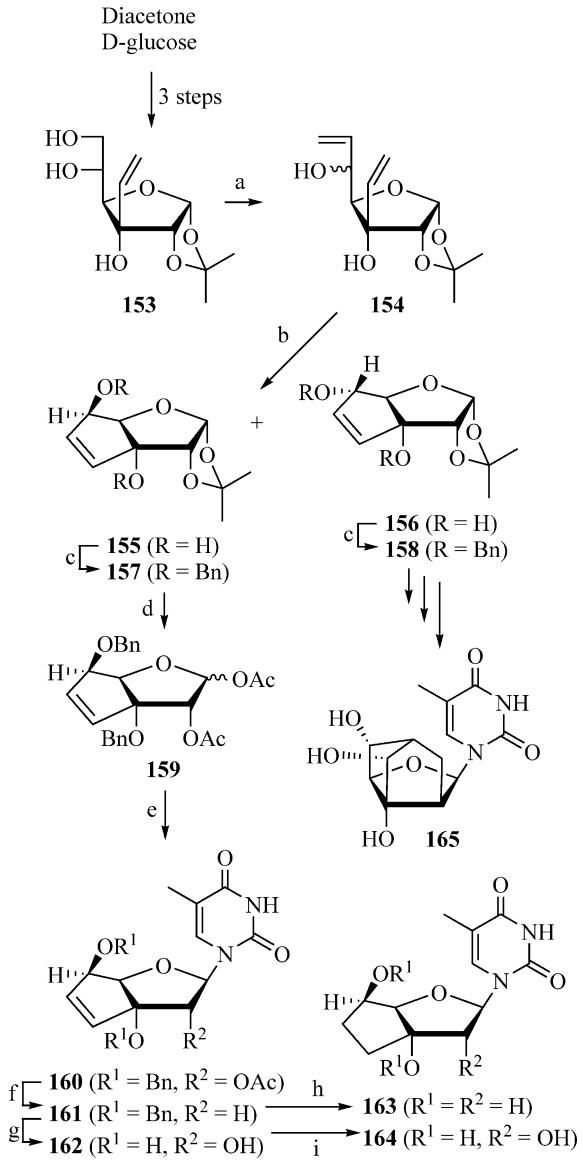


Scheme 20. *Reagents and conditions:* a) i. H_5IO_6, EtOAc; ii. HCHO, NaOH, $NaBH_4$; iii. BnBr, NaH, three steps, 45%. b) i. PCC, CH_2Cl_2, ii. vinylMgBr, THF; ii. BzCl, pyridine, 62% from **145**. c) BzCl, pyridine, 98%. d) i. 80% aq. AcOH then Ac_2O, pyrine; ii. thymine, BSA, TMSOTf, CH_3CN, two steps, 85%. e) Grubbs' catalyst, $Cl(CH_2)_2Cl$, 90%. f) i. MeONa, MeOH, reflux; ii. BCl_3, hexane, CH_2Cl_2, two steps, 41%. g) i. OsO_4, NMO, THF, H_2O; ii. MeONa, MeOH; iii. H_2, $Pd(OH)_2$, MeOH, 3 steps, 35%.

3.6. 3′,5′-Conformational Constraints

Introduction of conformational restriction into a natural nucleoside by incorporation of a bridge between the C3′ and C5′ positions has been reported by Nielsen et al.[70] These restricted nucleoside analogues have been prepared from the common diacetone D-glucofuranose, which af-

forded the C3′-vinyl allose derivative **153** after an oxidation, stereoselective Grignard reaction and a selective deprotection (Scheme 21). After cleavage of the vicinal diol, the resulting aldehyde was directly subjected to a second Grignard addition with vinyl bromide and afforded **154** as a mixture of diastereoisomers. The mixture was not separated but was directly used in a RCM reaction and smoothly provided the tricyclic compounds **155** and **156** in 67 and 24% yields, respectively. Due to the presence of ruthenium catalyst, these compounds were not isolated in pure form, but required subsequent benzylation in order to isolate pure compounds **157** and **158**. Next, compound **157** was converted, in two steps, into the condensable sugar precursor **159**, which was coupled with thymine under Vorbrüggen conditions. The β-nucleoside **160** was subjected to a radical reductive process to yield the 2′-deoxy derivative **161**. Finally, **161** was either deprotected to give **162** or subjected to reduction of the double and subsequently deprotected to afford the target nucleosides **163** and **164**. In addition, the minor compound **158** was used as a precursor for the synthesis, in several steps, of the tricyclic nucleoside thymidine derivative **165**.[71]



Scheme 21. *Reagents and conditions*: a) i. $NaIO_4$; ii. vinylMgBr, THF, two steps 57%. b) Grubb's catalyst, CH_2Cl_2. c) BnBr, NaH, DMF, 70% and 80%, respectively. d) i. 80%AcOH; ii. Ac_2O, pyridine, 85%. e) thymine, BSA, TMSOTf, CH_3CN, 91%. f) MeONa, MeOH, 97%. g) BCl_3, hexane, CH_2Cl_2. h) H_2, $Pd(OH)_2$, cyclohexa-1,4-diene, MeOH, 61%. i) H_2, $Pd(OH)_2$, MeOH, 98%.

Evaluation of the conformational behaviour of the bicyclic nucleosides **162**–**164** was based upon ^1H NMR experiments, ab initio geometry optimisation and X-ray analysis. This study revealed that the conformations of the nucleosides were locked in South-type arrangements with *P* values in the 110°–180° range. No biological evaluations have been reported so far.

Other examples of bicyclic and tricyclic nucleosides can be found in the literature. San-Félix et al. reported the synthesis of a new class of TSAO-T derivatives,[72] some of which are outlined in Figure 6.

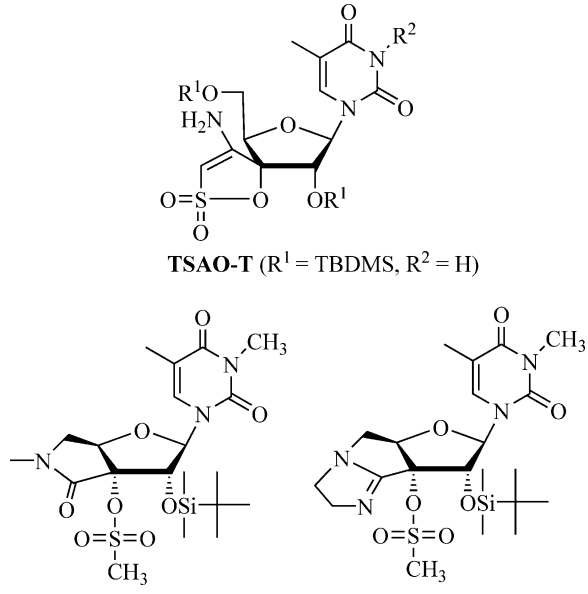


Figure 6. Bicyclic and tricyclic TSAO-T derivatives.

^1H NMR and molecular modelling studies were performed to study the conformational behaviour of these nucleosides and revealed that the conformations of such nucleosides were locked in East-type arrangements between $_4E$ (C4′-*exo*) and $_1E$ (C1′-*exo*) with *P* values in the range of 54°–126°.

4. Conclusions

Nucleic acid component analogues have been used clinically for several decades as antiviral or antitumour agents. As monomers, and in the major part of examples, these compounds have to be metabolised into their corresponding triphosphate derivatives, the active pharmaceutical forms. This metabolisation process requires discrete recognition with proteins involved in the cellular penetration (including active and/or facilitated transfer by nucleoside trans-

porters), in the metabolic pathway (including anabolic enzymes as nucleos(t)ide kinases or catabolic enzymes as adenosine deaminase) and, finally, with their target proteins (viral polymerases, DNA polymerases and/or other nucleoside metabolising enzymes). When a nucleoside or a nucleotide is activated by an enzyme or interacts with its pharmacological target, a unique conformation, probably modified by the enzyme for optimal fitting, is present at the active site. Nevertheless, any study aimed towards identification of conformational preferences of nucleos(t)ide-converting enzymes and towards study of the interactions of these compounds with their enzymatic targets could lead to a more rational approach for the discovery of new nucleoside drug candidates presenting better biological activity as a result of better affinity with respect to their targets or their activating systems. For these reason, the design, the synthesis and the study of conformationally restricted nucleoside analogues have for many years attracted considerable attention. Furthermore, a conformational restriction designed on a nucleoside analogue can be amplified by the use of oligonucleotide structures in which restricted conformations in the monomers can produce, at the macromolecular level, new oligonucleotides with interesting binding properties or resistance vs. nucleases. For all these reasons, the design, the synthesis and the use of conformationally restricted nucleosides are well warranted.

Acknowledgments

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