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Bicyclic nucleosides; stereoselective dihydroxylation and 2′-deoxygenation †

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A series of polyhydroxylated bicyclic nucleoside derivatives is approached applying stereoselective dihydroxylation reactions. Three out of four isomeric and protected products were obtained after the stereoselectivity of dihydroxylation has been completely inverted comparing a bicyclic nucleoside with a tricyclic furanose substrate. A corresponding 2′-deoxynucleoside derivative has been obtained after an optimized deoxygenation procedure.

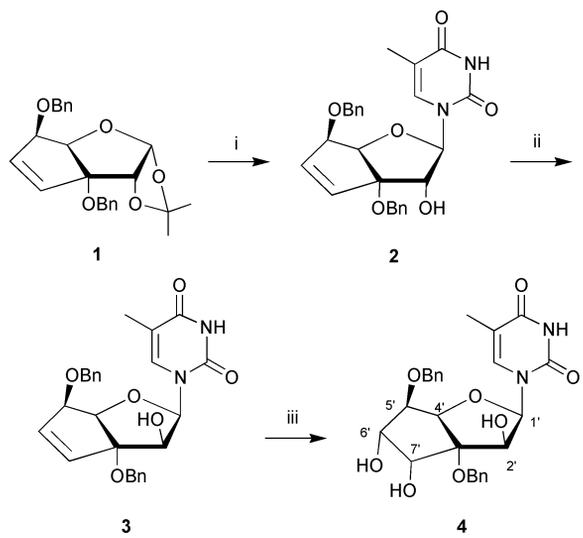
Introduction

The design of conformationally restricted nucleosides is a very important approach towards potentially antiviral agents[1] and monomers in conformationally restricted oligonucleotides for potential antisense therapeutic and diagnostic purposes.[2] Prime examples of such nucleic acid analogues with the carbohydrate moieties strongly restricted in bicyclic systems[3] are the pioneering bicycloDNA[4] and LNA (locked nucleic acids).[5] In LNA, the nucleosides are locked in N-type conformations[6] by an oxymethylene linkage between the C2′ and the C4′ positions,[5] whereas in bicycloDNA, 2′-deoxynucleosides are restricted towards S-type conformations by an ethylene linkage between the C3′ and the C5′ positions.[4] In a previous paper, we reported the synthesis of bicyclic nucleoside analogues which are *ribo*-configured analogues of the bicycloDNA monomers containing an unsaturated C3′–C5′ linkage.[7] These nucleosides were constructed *via* a convergent synthetic strategy applying a Ring-Closing Metathesis (RCM) reaction as the key step.[7]An intriguing advantage of these unsaturated bicyclic nucleoside analogues is the opportunity for further derivatisation of the double bond. In this paper we report the results obtained with 2′-deoxygenation as well as dihydroxylation of these nucleosides and of a corresponding furanose derivative.

Results

In the original construction of our bicyclic nucleosides, the tricyclic furanose derivative **1** (Scheme 1) was synthesised from D-glucose.[7] Subsequent standard transformations afforded the bicyclic *ribo*-configured nucleoside derivative **2** (Scheme 1),[7] which was converted in two easy steps to its *arabino*-configured epimer **3**.[8] *En route* to a tricyclic nucleoside analogue, **3** was treated with osmium tetraoxide and dihydroxylated to give **4** in a high yield but after a long reaction time (six days) (Scheme 1).[8] Obviously, this dihydroxylation reaction has proceeded exclusively from the less hindered convex face of the bicyclic system. The configuration of **4** has been proven indirectly, as a tricyclic nucleoside obtained from **4** in two simple conversions was examined by X-ray crystallography.[8] For further comparison, however, the ^{1}H NMR data of **4** are given in Table 1 and discussed below.

In our program for the construction of functionalised conformationally restricted nucleoside analogues, the *ribo*-configured bicyclic nucleoside **2** was also treated with osmium tetraoxide using the same conditions as used with **3** (Scheme 2). However, the reaction was slow even at elevated temperature (50 °C) affording only the product **5** in a low 22% yield as well as a bis-dihydroxylated product **6** in 23% yield. When the



Scheme 1 *Reagents and conditions*: i, Ref. 7, 4 steps, 75%; ii, Ref. 8, 2 steps, 82%; iii, Ref. 8, OsO_4, NMO, THF, H_2O, 50 °C, 83%.

Table 1 ^{1}H NMR data of the hydroxylated bicyclic nucleosides[a]

	4[c]	**5**	**11**	**18**
H1′	5.98	5.97	5.92	6.17
H2′	4.29	3.96	4.65	1.82/2.72
H4′	4.29	4.42	4.38	4.37
H5′	3.98	3.89	3.77	3.92
H6′	4.13	4.22	4.12	4.19
H7′	4.09	4.09	4.12	3.98
OH2′	5.98	5.78	5.41	—
OH6′	5.05	5.13	5.31	5.13
OH7′	4.91	5.05	5.24	5.03
$^3J_{H1'H2'}$	5.7	8.8	8.3	5.3/9.6
$^3J_{H4'H5'}$	6.6/7.5	6.9	5.5	7.1
$^3J_{H5'H6'}$		7.7	3.8	8.4
$^3J_{H6'H7'}$	ND[b]	4.2	ND[b]	4.1

[a] All data obtained at 300 MHz in DMSO-d_6. Chemical shifts in ppm relative to TMS and coupling constants in Hz. Numbering follows standard nucleoside rules continued in the carbocyclic ring as depicted in Scheme 1 for **4**. [b] Not determined due to spectral overlap. [c] Ref. 8.

† Electronic supplementary information (ESI) available: ^{13}C NMR spectra for compounds **7**, **8** and **17** as well as ^{1}H NMR data spectra for compounds **5**, **11** and **18**. See http://www.rsc.org/suppdata/ob/b2/b210439c/

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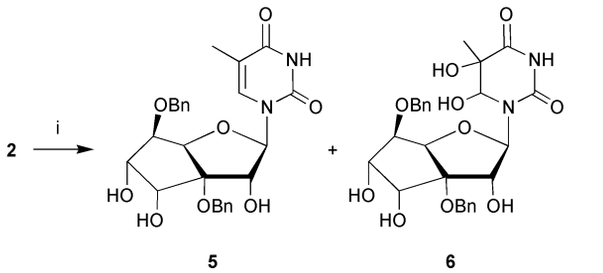
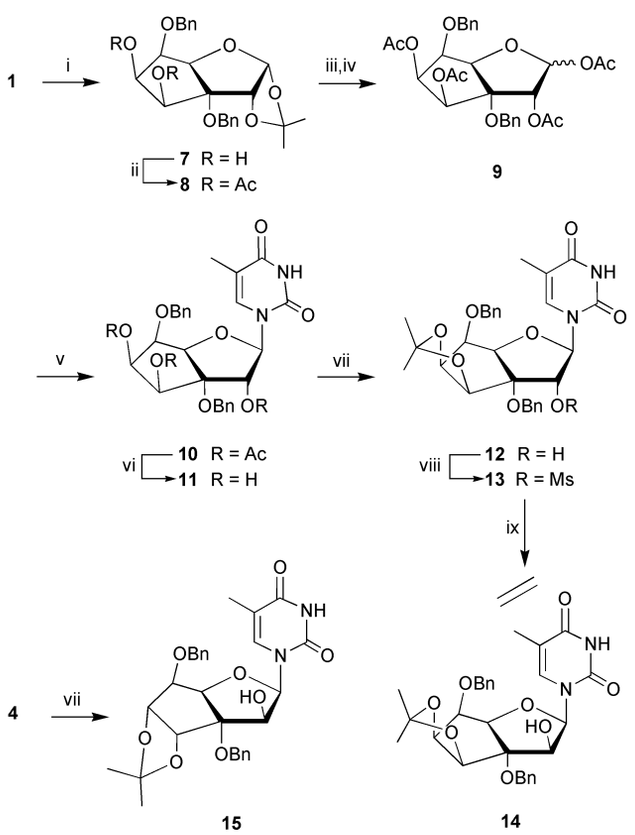


Scheme 2 *Reagents and conditions*: i, OsO_4, NMO, THF, H_2O, rt, 33% **5** and 22% **6**.

reaction was accomplished at room temperature for nine days, the yield of **5** was elevated to 33% in addition to 22% of **6** and recovery of 10% of **2**. Even though a dihydroxylation of a thymine moiety by nearly similar reaction conditions has been demonstrated before,[9] the formation of **6** was unexpected. Thus, other thymidine analogues containing unsaturated substituents have been used in dihydroxylation reactions to give vicinal diols without notably affecting the nucleobase[10] as has been exemplified also in the preparation of **4**.

In order to develop a better strategy towards the trihydroxylated bicyclic thymidine derivative **5**, we decided to perform the dihydroxylation reaction before the nucleobase coupling reaction, as outlined in Scheme 3. Thus, **1** was treated with osmium tetraoxide to give the diol **7** in a high 86% yield and after a much shorter reaction time, only four hours. The exact configuration of **7** was not elucidated at this stage, and **7** was protected as the diester **8** and converted to the diastereomeric mixture of tetraacetates **9** in 60% overall yield. These were coupled to thymine using standard Vorbrüggen-type conditions to give exclusively the β-configured bicyclic nucleoside **10** which after a standard transesterification afforded the tri-



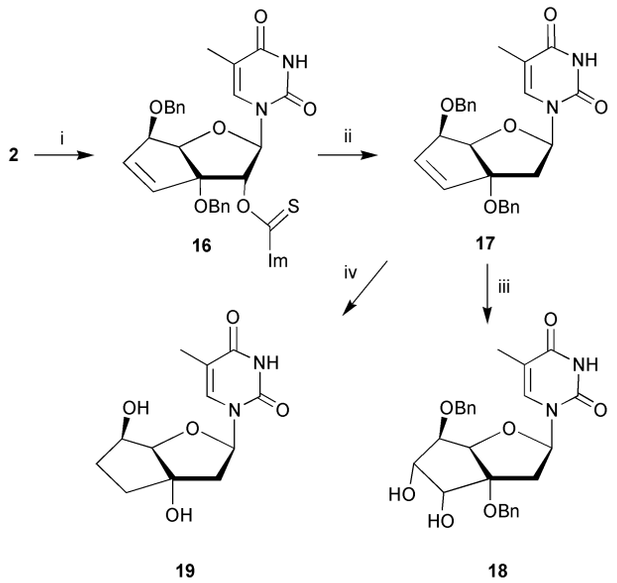
Scheme 3 *Reagents and conditions*: i, OsO_4, NMO, THF, H_2O, 60 °C, 86%; ii, Ac_2O, pyridine, 76%; iii, 80% AcOH; iv, Ac_2O, pyridine, 79% (2 steps); v, thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMS–OTf, CH_3CN, 65%; vi, $NaOCH_3$, CH_3OH, 95%; vii, $(CH_3O)_2C(CH_3)_2$, *p*-TsOH, acetone, 66% **12**, 70% **15**; viii, MsCl, pyridine, 80%; ix, NaOH, EtOH, H_2O, 0%.

hydroxylated nucleoside derivative **11** in 62% yield from **9**. To our surprise, **11** was not identical to **5** and after an NMR-spectroscopic analysis of the products (*vide infra*), the configuration of **11** was proven to be a result of a dihydroxylation from the more hindered concave face of the substrate **1**. However, it was first attempted to prepare the *arabino*-configured isomer of **11** through the same anhydro approach as used in the conversion of **2** to **3**. Thus, this conversion might in the case of a product identical to **4** disprove the determined configuration of **5**. On the other hand, it would complete the set of four isomeric nucleoside derivatives. Thus, **11** was protected as its acetonide **12** and converted to a methanesulfonic ester **13**. However, standard basic treatment afforded not the target **14** but a complex mixture of compounds including **12**. This might be explained by the acetonide sterically preventing the nucleobase from forming the anhydro intermediate. Finally and in order to fulfil a more comprehensive NMR analysis of the different isomeric products, also **4** was converted to its acetonide **15** (Scheme 3).

In Table 1 are given all ^{1}H NMR data for the three isomeric trihydroxylated bicyclic nucleosides **4**, **5** and **11**. Several observations confirm the determination of the three configurations. Thus, the large coupling constant $^3J_{H5'H6'}$ = 7.7 Hz observed for **5** suggests the *trans* positioning of H5′ and H6′ whereas the smaller $^3J_{H5'H6'}$ = 3.8 Hz observed for **11** suggests a smaller torsion angle and a *cis* positioning of these two hydrogen atoms. Simple modelling suggests that the cyclopentane rings of nucleosides **4** and **5** adopt envelope conformations in which the C6′ takes an *endo*-position (*i.e.* pointing towards the furanose ring), as this conformation would allow favourable *gauche* interactions between all oxygen substituents. This is the same conformation observed in both the parent bicycloDNA thymidine monomer[4] and its *ribo*-configured analogue.[7] In both **4** and **5** this results in a perfect *anti* positioning of H5′ and H6′ in full agreement with the observed coupling constants. Furthermore, the $^3J_{H4'H5'}$ and $^3J_{H5'H6'}$coupling constants for **4** are more like the ones observed for **5** than the ones observed for **11** (Table 1), and the configuration of **4** has been exclusively determined before (*vide supra*).[8] For both **5** and **11** the large $^3J_{H1'H2'}$coupling constants confirm the nucleosides to be β-*ribo*-configured and restricted in S-type conformations.

The large difference in chemical shift for H2′ observed between the three isomers can also be explained. Thus, the H2′ for **11** is in close proximity to the hydroxyl functionalities of C6′ and C7′ and hereby deshielded explaining the high shift at 4.65 ppm observed for **11**. The H2′ of **4** is likewise deshielded by the C3′-oxygen explaining the slightly higher shift observed in this case compared to H2′ of **5**. Finally, the chemical shifts of the hydroxyl groups also confirm the determinations of configuration as higher shifts are observed for the hydroxyl protons of C6′ and C7′ in **11** as these are in closer proximity to the C5′- and C4′-oxygens as well as the nucleobase. NOE difference spectroscopy has also been applied. Thus, a mutual contact was observed in **12** between one of the methyl groups of the acetonide and the H6 of the nucleobase. A similar contact was not observed for **15**, and the different configurations of C6′ and C7′ in **11** compared to **4** are hereby further confirmed.

In order to obtain bicyclic nucleoside derivatives more suitable for oligodeoxynucleotide sequences we decided to study also the 2′-deoxygenated bicyclic nucleoside analogue as a substrate for a dihydroxylation reaction. We have earlier reported a preliminary deoxygenation strategy,[7] which is hereby optimised (Scheme 4). Thus, **2** was converted to an imidazolethiocarboxylate derivative **16** in 84% yield, and subsequently, a careful treatment with standard Barton–McCombee conditions afforded the product **17** in 61% yield as well as 32% of the starting alcohol material **2**, *i.e.* a combined yield over the two steps of 74% based on the recovery of starting material. When **17** was treated with osmium tetraoxide, the expected product **18** was obtained in a moderate 34% yield



Scheme 4 *Reagents and conditions*: i, $(Im)_2CS$, CH_3CN, toluene, 85%; ii, AIBN, Bu_3SnH, CH_3CN, 61%; iii, OsO_4, NMO, THF, H_2O, 34%; iv, H_2, $Pd(OH)_2/C$, EtOH, 75%. Im = *N*-imidazolyl.

in addition to 17% starting material and trace amounts of the bis-dihydroxylated product. The ^{1}H NMR data of **18** (Table 1), especially the coupling constants $^3J_{H4'H5'}$ and $^3J_{H5'H6'}$, confirmed the configuration of this compound and thereby the dihydroxylation from the convex face of the bicyclic system. Furthermore, NOE difference spectra revealed strong mutual contacts between H2″ and H6′/H7′.

As a last outcome of the significant optimisation of the 2′-deoxygenation strategy, the synthesis of the bicycloDNA thymidine monomer should now be comparable to the parent synthesis developed by Tarköy and Leumann.[4a] Thus, compound **17** was readily deprotected and hydrogenated to give this target compound **19** in 74% yield (Scheme 4) and the present RCM-based synthetic strategy[7] afforded hereby **19** in 16 steps and 20% overall yield from diacetone-D-glucose avoiding troublesome separations of isomers, whereas in the original strategy,[4a] **19** was obtained in 11 steps but only 6% overall yield from another simple starting material and after separation of isomers.

Discussion

The dihydroxylation results described herein deserves some discussion. Several factors determine the stereospecific outcome of dihydroxylations such as steric or stereoelectronic factors in the substrates *e.g.* from allylic alkoxy groups.[11] It has been demonstrated that the conformational behaviour of cyclopentene substrates strongly influences the stereoselectivity of dihydroxylations.[12] Thus, dihydroxylation from the more hindered face *cis* to the 3- and 5-substituents of cyclopentenes has been observed [12,13] and explained by the Cieplak effect,[14] *i.e.* stabilisation of the more hindered transition state by electron donation from an antiperiplanar C–H bond to the antibonding orbital of the incipient bond.[12] Thus, if **1** adopts a conformation allowing the H5 to be pseudoaxial, *i.e.* a 4-*endo*-conformation of the cyclopentene corresponding to a C3-*endo* conformation of the furanose moiety, the Cieplak activity explains the observed exclusive dihydroxylation from the more hindered face of the double bond. This conformation seems reasonable though not to be proved from the experimental coupling constants.[7] On the other hand, the bicyclic nucleoside **2** (or rather its debenzylated analogue) has been demonstrated from molecular modelling to adopt the opposite C2′-*endo* conformation,[7] with the cyclopentene ring in a 4′-*exo* conformation and hereby the H5′ in a pseudoequatorial position. This excludes the possibility of a Cieplak effect from this C–H bond and, thereby, only dihydroxylation from the less hindered face is observed. The same conformation seems very likely for both **17** and **3**, as C2′-*endo* conformations should be even more favoured due to the lack of, or opposite direction of, the O2′–O4′ *gauche* effect, respectively. A simple steric hindrance from the nucleobase, however, cannot be excluded as the explanation for the preferred stereoselectivity of the dihydroxylations on **2**, **3** and **17**. Nevertheless, the reason why dihydroxylation of the nucleobase is seen with **2**, to a lesser degree with **17** and not at all with **3** might be found in smaller conformational and stereoelectronic differences.

Conclusions

Three out of the four possible diastereomeric trihydroxylated 3′,5′-di-*O*-protected bicyclic nucleoside derivatives have been obtained in addition to one of the two possible 2′-deoxygenated analogues. We expect these nucleosides to be readily deprotected and to be used as conformationally restricted nucleoside models in structure–activity studies on nucleoside/nucleotide accepting enzymes and receptors or as building blocks in the development of DNA and RNA recognising nucleic acid analogues.

Experimental

All commercial reagents were used as supplied. 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 Varian Gemini 2000 spectrometer. FAB mass spectra were recorded in positive ion mode on a Kratos MS50TC spectrometer, and MALDI mass spectra were recorded on an Ionspec Ultima Fourier Transform mass spectrometer. Assignments of NMR spectra when given are based on 2D spectra and follow standard carbohydrate and nucleoside style; *i.e.* the carbon atom next to a nucleobase is assigned C-1′; the numbering continues in the additional ring following C-5 (or C-5′) to C-6 (C-6′) and C-7 (C-7′) as depicted in Scheme 1. However, compound names for bi- and tricyclic compounds are given according to the von Baeyer nomenclature.

(1*R*,3*R*,4*R*,5*R*,6*R*,7*R*,8*R*)-5,8-Dibenzyloxy-4,6,7-trihydroxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]octane 5

To a solution of **2** (125 mg, 0.27 mmol) in THF (4 cm^3) and H_2O (4 cm^3) was added *N*-methylmorpholine *N*-oxide (145 mg, 1.24 mmol) and osmium tetraoxide (2.5% in t-BuOH, 0.4 cm^3, 0.046 mmol) and the mixture was stirred at room temperature for 9 days. An aqueous solution of $Na_2S_2O_5$ (20%, 10 cm^3) was added and the solvent was partly evaporated under reduced pressure. The mixture was extracted with ethyl acetate (3 × 20 cm^3) and the organic phase was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (3–8% MeOH in CH_2Cl_2) to give the product **5** (44 mg, 33%) as well as the by-product **6** (32 mg, 22%) and the starting material **2** (13 mg, 10%). **5**: δ_H (300 MHz; DMSO-d_6; Me_4Si) 1.62 (3H, s, CH_3), 3.89 (1H, dd, *J* 7.7, 6.9, H-5′), 3.96 (1H, dd, *J* 5.4, 8.8, H-2′), 4.09 (1H, dd, *J* 4.3, 4.2, H-7′), 4.22 (1H, m, H-6′), 4.42 (1H, d, *J* 6.9, H-4′), 4.49 (1H, d, *J* 11.7, CH_2Ph), 4.59 (1H, d, *J* 11.7, CH_2Ph), 4.90 (1H, d, *J* 11.6, CH_2Ph), 5.05 (1H, d, *J* 4.3, OH-7′), 5.09 (1H, d, *J* 11.6, CH_2Ph), 5.13 (1H, d, *J* 6.6, OH-6′), 5.78 (1H, d, *J* 5.4, OH-2′), 5.97 (1H, d, *J* 8.8, H-1′), 7.40–7.25 (10H, m, Ph), 7.54 (1H, s, H-6), 11.41 (1H, s, NH); *m*/*z* (FAB) 519 (M + Na), 497 (M + H). **6**: δ_H (300 MHz; DMSO-d_6; Me_4Si) 1.13 (3H, s, CH_3), 3.85 (1H, t, *J* 7.7, H-5′), 3.96 (1H, dd, *J* 5.8, 8.5, H-2′), 4.01 (1H, m, H-7′), 4.08 (1H, m, H-6′), 4.31 (1H, d, *J* 6.6, H-4′), 4.45 (1H, d, *J* 12.1, CH_2Ph), 4.62 (1H, d,

J 12.1, CH_2Ph), 4.76 (1H, d, *J* 4.9, OH-6), 4.89 (1H, d, *J* 11.8, CH_2Ph), 5.02 (1H, d, *J* 3.0, OH-7′), 5.05 (1H, d, *J* 4.7, OH-6′), 5.06 (1H, d, *J* 11.8, CH_2Ph), 5.47 (1H, d, *J* 5.8, OH-2′), 5.52 (1H, s, OH-5), 5.81 (1H, d, *J* 8.5, H-1′), 6.43 (1H, d, *J* 4.9, H-6), 7.21–7.44 (10H, m, Ph), 10.37 (1H, s, NH).

(1*R*,3*R*,7*R*,8*R*,9*S*,10*S*,11*R*)-8,11-Dibenzyloxy-9,10-dihydroxy-5,5-dimethyl-2,4,6-trioxatricyclo[6.3.0.0^{3,7}]undecane 7

To a solution of **1** (650 mg, 1.65 mmol) in THF (15 cm^3) and H_2O (15 cm^3) was added *N*-methylmorpholine *N*-oxide (386 mg, 3.29 mmol) and osmium tetraoxide (2,5% in t-BuOH, 0.3 cm^3, 0.035 mmol) and the mixture was stirred at 60 °C for 4 h. After cooling to room temperature an aqueous solution of $Na_2S_2O_5$ (20%, 30 cm^3) was added and the solvent was partly evaporated under reduced pressure. The mixture was extracted with ethyl acetate (3 × 40 cm^3) and the organic phase was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0–2% MeOH in CH_2Cl_2) to give the product **7** (606 mg, 86%) as a white solid material: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.40 (3H, s, CH_3), 1.59 (3H, s, CH_3), 3.12 (1H, d, *J* 6.6, OH-7), 3.33 (1H, d, *J* 7.0, OH-6), 3.97 (1H, dd, *J* 5.3, 3.7, H-5), 4.21 (1H, dd, *J* 6.6, 6.2, H-7), 4.31 (1H, m, H-6), 4.57 (1H, d, *J* 3.7, H-4), 4.58 (1H, d, *J* 10.8, CH_2Ph), 4.65 (1H, d, *J* 11.8, CH_2Ph), 4.71 (1H, d, *J* 11.8, CH_2Ph), 4.78 (1H, d, *J* 10.8, CH_2Ph), 5.07 (1H, d, *J* 3.9, H-2), 5.82 (1H, d, *J* 3.9, H-1), 7.40–7.24 (10H, m, Ph); δ_C (75 MHz; $CDCl_3$; Me_4Si) 137.8, 137.1 (2 × Ph), 128.5, 128.3, 128.1, 128.0, 127.7, 127.7 (Ph), 113.2 (*C*$(CH_3)_2$), 107.1 (C-1), 94.4 (C-3), 85.2, 79.2, 77.0, 74.9, 72.0, 71.4, 67.5 (C-2, C-4, C-5, C-6, C-7, 2 × *C*H_2Ph), 27.2, 27.0 (2 × CH_3); *m*/*z* (FAB) 451 (M + Na), 429 (M + H).

(1*R*,3*R*,7*R*,8*R*,9*S*,10*S*,11*R*)-9,10-Diacetyloxy-8,11-dibenzyloxy-5,5-dimethyl-2,4,6-trioxatricyclo[6.3.0.0^{3,7}]undecane 8

To a solution of **7** (303 mg, 0.707 mmol) in anhydrous pyridine (15 cm^3) was added acetic anhydride (5 cm^3) and the mixture was stirred at room temperature for 16 h. The mixture was diluted with H_2O (15 cm^3) and extracted with CH_2Cl_2 (3 × 30 cm^3). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (1% MeOH in CH_2Cl_2) to give the product **8** (275 mg, 76%) as a colourless oil: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.48 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.13 (3H, s, $COCH_3$), 2.15 (3H, s, $COCH_3$), 3.97 (1H, t, *J* 4.6, H-5), 4.33 (1H, d, *J* 10.4, CH_2Ph), 4.62 (2H, s, CH_2Ph), 4.63 (1H, d, *J* 4.6, H-4), 4.69 (1H, d, *J* 10.4, CH_2Ph), 5.02 (1H, d, *J* 4.0, H-2), 5.43 (1H, d, *J* 4.9, H-7), 5.60 (1H, m, H-6), 6.12 (1H, d, *J* 4.0, H-1), 7.40–7.26 (10H, m, Ph); δ_C (75 MHz; $CDCl_3$; Me_4Si) 169.8, 168.9 (C=O), 137.3, 137.2 (2 × Ph), 128.5, 128.3, 128.0, 127.9, 127.9, 127.7 (Ph), 113.9 (*C*$(CH_3)_2$), 108.5 (C-1), 90.8, 86.5, 80.6, 74.6, 74.6, 71.9, 71.7, 71.4, 67.9 (C-2, C-3, C-4, C-5, C-6, C-7, 2 × *C*H_2Ph), 27.9, 27.3 (2 × CH_3), 20.7, 20.6 (CO*C*H_3); *m*/*z* (FAB) 512 (M + H), 453 (M − OAc).

(3*RS*,1*R*,4*R*,5*R*,6*S*,7*S*,8*R*)-3,4,6,7-Tetraacetyloxy-5,8-dibenzyloxy-2-oxabicyclo[3.3.0]octane 9

Compound **8** (234 mg, 0.457 mmol) was dissolved in 80% acetic acid (10 cm^3) and stirred at 90 °C for 16 h. The solvent was evaporated under reduced pressure and the residue was co-evaporated with anhydrous ethanol (3 × 10 cm^3), toluene (3 × 10 cm^3) and pyridine (10 cm^3). The crude intermediate was redissolved in anhydrous pyridine (5 cm^3) and acetic anhydride (1 cm^3) was added. After stirring for 16 h the mixture was diluted with H_2O (10 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (0–1% MeOH in CH_2Cl_2) to give the product **9** (200 mg, 79%) as a colourless oil which was used without further purification in the next step: *m*/*z* (FAB) 497 (M − OAc).

(1*R*,3*R*,4*R*,5*R*,6*S*,7*S*,8*R*)-4,6,7-Triacetyloxy-5,8-dibenzyloxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]octane 10

A mixture of **9** (115 mg, 0.207 mmol) and thymine (78 mg, 0.619 mmol) was dried and dissolved in anhydrous MeCN (5 cm^3). The mixture was treated with *N*,*O*-bis(trimethylsilyl)-acetamide (0.25 cm^3, 1.02 mmol) and stirred under reflux for 15 min. After cooling of the mixture to 0 °C, trimethylsilyl triflate (0.1 cm^3, 0.55 mmol) was added dropwise and the solution was stirred at 50 °C for 16 h. The reaction mixture was quenched with an ice-cold saturated aqueous solution of $NaHCO_3$ (10 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (1–2% MeOH in CH_2Cl_2) to give the product **10** (84 mg, 65%) as a white solid material which was used without further purification in the next step: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.73 (1H, d, *J* 1.2, CH_3), 2.05 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 2.17 (3H, s, $COCH_3$), 4.09 (1H, dt, *J* 5.7, 4.6, H-5′), 4.61 (1H, d, *J* 5.7, H-4′), 4.72–4.61 (3H, m, CH_2Ph), 4.81 (1H, d, *J* 11.2, CH_2Ph), 5.44 (1H, d, *J* 5.1, H-7′), 5.62 (1H, dd, *J* 5.1, 4.6, H-6′), 5.97 (1H, d, *J* 8.3, H-2′), 6.39 (1H, d, *J* 8.3, H-1′), 7.35–7.24 (10H, m, CH_2Ph), 7.58 (1H, d, *J* 1.2, H-6), 9.24 (1H, br s, NH); *m*/*z* (FAB) 623 (M + H).

(1*R*,3*R*,4*R*,5*R*,6*S*,7*S*,8*R*)-5,8-Dibenzyloxy-4,6,7-trihydroxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]octane 11

To a solution of **10** (70 mg, 0.113 mmol) in anhydrous methanol (3 cm^3) was added sodium methoxide (55 mg, 1.02 mmol) and the mixture was stirred at room temperature for 16 h. The reaction mixture was neutralised with aqueous HCl and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 cm^3) and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (3–7% MeOH in CH_2Cl_2) to give the product **11** (53 mg, 95%) as a white solid material: δ_H (300 MHz; DMSO-d_6; Me_4Si) 1.71 (1H, d, *J* 1.1, CH_3), 3.77 (1H, dd, *J* 5.5, 3.8, H-5′), 4.12 (2H, m, H-6′, H-7′), 4.38 (1H, d, *J* 5.5, H-4′), 4.58 (2H, s, CH_2Ph), 4.65 (1H, dd, *J* 8.3, 6.6, H-2′), 4.78 (1H, d, *J* 11.9, CH_2Ph), 4.96 (1H, d, *J* 11.9, CH_2Ph), 5.24 (1H, d, *J* 5.5, OH-7′), 5.31 (1H, d, *J* 2.5, OH-6′), 5.41 (1H, d, *J* 6.6, OH-2′), 5.92 (1H, d, *J* 8.3, H-1′), 7.24–7.35 (10H, m, Ph), 7.75 (1H, d, *J* 1.1, H-6), 11.34 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6; Me_4Si) 163.6 (C-4), 150.9 (C-2), 139.5, 138.3, 137.1 (C-6, 2 × Ph), 128.7, 128.5, 128.4, 128.1, 128.0, 127.7 (2 × Ph), 109.4 (C-5), 89.4, 87.6, 83.1, 75.8, 74.1, 73.2, 73.1, 70.3, 66.9 (C-1′, C-2′, C-3′, C-4′, C-5′, C-6′, C-7′, 2 × *C*H_2Ph), 12.3 (CH_3).

(1*R*,2*S*,6*S*,7*R*,8*R*,10*R*,11*R*)-1,7-Dibenzyloxy-4,4-dimethyl-11-methylsulfonyloxy-10-(thymin-1-yl)-3,5,9-trioxatricyclo-[6.3.0.0^{2,6}]undecane 13

Compound **11** (66 mg, 0.133 mmol) was dissolved in acetone (4 cm^3) and 2,2-dimethoxypropane (0.4 cm^3, 3.25 mmol), and *p*-TsOH·H_2O (5 mg, 0.026 mmol) were added. The mixture was stirred at room temperature for 16 h and the solvent was evaporated under reduced pressure. The residue was redissolved in CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (1–2% MeOH in CH_2Cl_2) to give the intermediate product **12** (47 mg, 66%) as a colourless oil. The compound **12** (45 mg, 0.084 mmol) was dissolved in anhydrous pyridine (2 cm^3) and methanesulfonyl chloride (0.05 cm^3, 0.65 mmol) was added dropwise at 0 °C. The reaction

mixture was stirred for 16 h at room temperature, quenched with H_2O (3 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 cm^3) and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was co-evaporated with toluene (2 × 10 cm^3) and then purified by silica gel column chromatography (1–2% MeOH in CH_2Cl_2) to give the product **13** (41 mg, 62%) as a colourless oil which was used without further purification in the next step: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.40 (1H, s, CH_3), 1.64 (1H, s, CH_3), 1.70 (1H, s, CH_3), 3.00 (1H, s, SO_2CH_3), 3.98 (1H, t, *J* 5.5, H-5′), 4.54 (1H, d, *J* 5.5, H-4′), 4.70–4.93 (6H, m, H-6′, H-7′, 2 × C*H*$_2$Ph), 5.63 (1H, d, *J* 7.8, H-2′), 6.48 (1H, d, *J* 7.8, H-1′), 7.24–7.47 (10H, m, Ph), 7.74 (1H, s, H-6), 8.42 (1H, s, NH); *m/z* (FAB) 615 (M + H).

(1*R*,2*R*,6*R*,7*R*,8*R*,10*R*,11*S*)-1,7-Dibenzyloxy-4,4-dimethyl-11-hydroxy-10-(thymin-1-yl)-3,5,9-trioxatricyclo[6.3.0.0^{2,6}]-undecane 15

Same procedure as for the synthesis of **12** using **4** (32 mg, 0.0645 mmol), 2,2-dimethoxypropane (0.3 cm^3, 0.24 mmol), *p*-TsOH·H_2O (5 mg, 0,026 mmol) and acetone (4 cm^3). Purification by silica gel column chromatography (1–2% MeOH in CH_2Cl_2) gave the product **15** (24 mg, 70%) as a colourless oil: δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.40 (1H, s, CH_3), 1.62 (1H, s, CH_3), 1.72 (1H, s, CH_3), 4.03 (1H, dd, *J* 8.1, 2.6, H-5′), 4.44 (1H, d, *J* 8.1, H-4′), 4.57–4.80 (7H, m, H-2′, H-6′, H-7′, 2 × C*H*$_2$Ph), 5.27 (1H, br s, OH-2′), 6.12 (1H, d, *J* 2.6, H-1′), 7.27–7.48 (10H, m, Ph), 7.78 (1H, s, H-6), 11.21 (1H, br s, NH); *m/z* (FAB) 537 (M + H).

(1*R*,3*R*,4*R*,5*R*,8*R*)-5,8-Dibenzyloxy-4-(*N*-imidazolylthiocarbonyloxy)-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]oct-6-ene 16

The bicyclic nucleoside **2** (529 mg, 1.14 mmol) was coevaporated with anhydrous CH_3CN (2 × 5 cm^3) and dissolved in a 1 : 1 mixture of CH_3CN and toluene (8 cm^3). Thiocarbonyldiimidazole (407 mg, 2.28 mmol) was added, and the mixture was stirred under at 80 °C for 3 h. The mixture was cooled and the solvent evaporated under reduced pressure. The residue was dissolved in 15 cm^3 DCM and washed with a 5% aqueous solution of HCl (2 × 15 cm^3) and water until neutrality of the aqueous phase (4 × 15 cm^3) and then washed with brine (2 × 30 cm^3). The organic phase was dried (Na_2SO_4) and concentrated under redused pressure. The residue was purified by silica gel column chromatography (0–2% MeOH in CH_2Cl_2) to give the product **16** (549 mg, 84%) as a white solid material which was used without further purification in the next step: mp 78–80 °C; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.59 (3H, s, CH_3), 4.37 (1H, d, *J* 11.7, C*H*$_2$Ph), 4.46 (1H, d, *J* 11.7, C*H*$_2$Ph), 4.60–4.66 (2H, m, C*H*$_2$Ph, H-5′), 4.74–4.78 (2H, m, C*H*$_2$Ph, H-4′), 5.78 (1H, d, *J* 6.3, H-2′), 6.22 (1H, d, *J* 6.2, H-7′), 6.27 (1H, d, *J* 6.2, H-6′), 6.65 (1H, d, *J* 6.3, H-1′), 7.02 (1H, s, C=CH(Im)), 7.13–7.40 (10H, m, 2 × Ph), 7.59 (1H, s), 7.62 (1H, s) (C=CH(Im), H-6), 8.35 (1H, s, N=CH(Im)), 8.38 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 183.2 (C=S), 163.1 (C-4), 150.2 (C-2), 137.4, 137.3, 134.9, 133.5, 131.2, 128.7, 128.4, 128.3, 128.2, 127.9, 127.9 (2 × Ph, C-6, C-6′, C-7′, C(Im)), 126.8 (C(Im)), 118.1 (C(Im)), 111.9 (C-5′), 93.6 (C-3′), 88.6, 84.8, 83.8, 80.1, 72.6, 67.2 (2 × *C*H_2Ph, C-1′, C-2′, C-4′, C-5′), 12.1 (CH_3); *m/z* (MALDI) 595 (M + Na^+).

(1*R*,3*R*,5*R*,8*R*)-5,8-Dibenzyloxy-3-(thymin-1-yl)-2-oxabicyclo-[3.3.0]oct-6-ene 17[7]

The thiocarboxylate **16** (460 mg, 0.80 mmol) was coevaporated with anhydrous CH_3CN (2 × 5 cm^3) and redissolved in anhydrous CH_3CN (10 cm^3). The mixture was degassed with N_2 for 30 min and added AIBN (33 mg, 0.20 mmol) and Bu_3SnH (0.43 cm^3, 1.61 mmol). The reaction mixture was stirred under reflux at 80 °C for 22 h and then cooled. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (0–2% MeOH in CH_2Cl_2) to give the product **17** (220 mg, 61%) as a white solid as well as the starting alcohol **2** (119 mg, 32%). **17**: mp 132–134 °C; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.58 (3H, s, CH_3), 2.17 (1H, dd, *J* 7.1, 13.6, H-2′$_b$), 2.80 (1H, dd, *J* 6.2, 13.6, H-2′$_a$), 4.37 (1H, d, *J* 11.3, C*H*$_2$Ph), 4.44 (1H, d, *J* 11.3, C*H*$_2$Ph), 4.57 (1H, d, *J* 11.2, C*H*$_2$Ph), 4.64 (2H, br s, H-4′, H-5′), 4.77 (1H, d, *J* 11.2, C*H*$_2$Ph), 6.04 (2H, br s, H-6′, H-7′), 6.48 (1H, t, *J* 6.4, H-1′), 7.28–7.41 (10H, m, 2 × Ph), 7.73 (1H, s, H-6), 9.18 (1H, br s, NH), δ_C (75 MHz; $CDCl_3$; Me_4Si) 164.0 (C-4), 150.4 (C-2), 137.8, 137.6 (2 × Ph), 136.3 (C-6), 135.0, 134.5 (C-6′, C-7′), 128.5, 128.4, 128.0, 127.8, 127.3 (2 × Ph), 110.5 (C-5), 96.7 (C-3′), 88.0 (C-1′), 84.0, 81.0 (C-4′, C-5′), 72.6 (*C*H_2Ph), 67.1 (*C*H_2Ph), 44.1 (C-2′), 12.1 (CH_3); *m/z* (MALDI) 469 (M + Na^+).

(1*R*,3*R*,5*R*,6*R*,7*R*,8*R*)-5,8-Dibenzyloxy-6,7-dihydroxy-3-(thymin-1-yl)-2-oxabicyclo[3.3.0]octane 18

Compound **7** (70 mg, 0.16 mmol) was dissolved in a 1 : 1 mixture of THF and water (3 cm^3) and added *N*-methylmorpholine *N*-oxide (19 mg, 0.19 mmol) and osmium tetraoxide (2.5% in t-BuOH, 79 μL, 6.3 μmol) and the reaction mixture was stirred at 50 °C for 3 h. An aqueous solution of $Na_2S_2O_5$ (5%, 1 cm^3) was added and the mixture was stirred for another 30 min. The solvent was partly evaporated under reduced pressure and the residue was extracted with EtOAc (4 × 5 cm^3). The combined organic phases were dried (Na_2SO_4) and then evaporated under reduced pressure. The residue was purified by silica gel column chrmatography (1–2% MeOH in CH_2Cl_2) to give the product **18** (26 mg, 34%) as a white solid as well as starting material **17** (12 mg, 17%). **18**: mp 182–183 °C; δ_H (300 MHz; DMSO-d_6; Me_4Si) 1.53 (3H, s, CH_3), 1.82 (1H, dd, *J* 9.6, 14.3, H-2′$_b$), 2.71 (1H, dd, *J* 5.3, 14.3, H-2′$_a$), 3.92 (1H, dd, *J* 7.1, 8.4, H-5′), 3.98 (1H, dd, *J* 4.1, 4.7, H-7′), 4.19 (1H, m, H-6′), 4.37 (1H, d, *J* 7.1, H-4′), 4.51 (1H, d, *J* 1.7, C*H*$_2$Ph), 4.59 (1H, d, *J* 11.7, C*H*$_2$Ph), 4.63 (1H, d, *J* 11.7, C*H*$_2$Ph), 4.70 (1H, d, *J* 11.7, C*H*$_2$Ph), 5.03 (1H, d, *J* 4.7, OH-7′), 5.13 (1H, d, *J* 7.0, OH-6′), 6.17 (1H, dd, *J* 5.3, 9.6, H-1′), 7.25–7.42 (10H, m, 2 × Ph), 7.70 (1H, s, H-6), 11.35 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6; Me_4Si) 163.6 (C-4), 150.3 (C-2), 138.9, 138.3 (2 × Ph), 135.7 (C-6), 128.1, 128.1, 127.7, 127.4, 127.2 (2 × Ph), 109.5 (C-5), 90.4 (C-3′), 84.7 (C-1′), 83.3 (C-4′), 80.7 (C-5′), 75.0 (C-6′), 71.3 (C-7′), 71.0 (*C*H_2Ph), 65.7 (*C*H_2Ph), 38.5 (C-2′), 12.0 (CH_3), HR MALDI FT-MS *m/z* 503.1771. Calc. 503.1788 (M + Na^+).

(1*R*,3*R*,5*R*,8*R*)-5,8-Dihydroxy-3-(thymin-1-yl)-2-oxabicyclo-[3.3.0]octane 19[4a]

Compound **17** (29 mg, 0.066 mmol) was dissolved in anhydrous methanol (1 cm^3) and added $Pd(OH)_2$–C (16 mg). The reaction mixture was bubbled with H_2 for 10 min and then stirred under an atmosphere of H_2 for 20 h. The mixture was filtered through a layer of celite and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (2–5% MeOH in CH_2Cl_2) to give the product **19** (14 mg, 75%) as a white solid: All data were in accordance with the literature.[4a]

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