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Synthesis of hydroxymethyl branched [3.2.0]bicyclic nucleosides using a regioselective oxetane ring-formation

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Two [3.2.0]bicyclic nucleosides, **35** and **34**, with one and two hydroxymethyl substituents, respectively, have been efficiently synthesized. A protected (3′-*C*-vinyl-β-D-allofuranosyl)thymine derivative **28** was easily prepared from diacetone-D-glucose and the thymine moiety was protected with a BOM-group. After the introduction of a leaving group in the 2′-position, the subsequent nucleoside **31** was used as the substrate for a stereoselective dihydroxylation and a regioselective oxetane ring-formation to give after deprotection the bicyclic nucleoside **34**. The surprisingly efficient formation of an oxetane was first discovered by serendipity on a corresponding methylfuranoside derivative. The *allo*-configured bicyclic nucleoside **34** was easily shortened to a *ribo*-configured analogue **35** by a diol-cleaving reaction and subsequent reduction. Both **34** and **35** are conformationally restricted in the important intermediate O4′-*endo* conformation.

Introduction

Conformationally restricted nucleosides have been intensively investigated as building blocks for oligonucleotides (ON's) with potential therapeutic and diagnostic applications.[1,2] Especially nucleic acid analogues based on nucleoside monomers with the carbohydrate moieties strongly restricted in bi- or tricyclic systems[3] have attracted significant attention with tricyclo-DNA[4] and LNA (locked nucleic acid)[5] as prime examples. Thus, both have demonstrated improved recognition of complementary RNA, the latter with unprecedented affinity, and both have demonstrated promising *in vitro* and *in vivo* results as potential antisense therapeutics.[2,6,7] Also 2′,3′-linked bicyclic nucleosides have been investigated. Thus, the [3.3.0]bicyclic nucleoside **1**[8] and the smaller [3.2.0]bicyclic nucleoside **2**[9] (Fig. 1) were synthesised by convergent strategies and incorporated into ON's with improved recognition of complementary RNA in fully modified sequences.[8,9] Both nucleosides have been found by NMR and molecular modelling to be conformationally restricted in an O4′-*endo* conformation.[9,10] This has also been confirmed in duplex structures containing single incorporations of **1** or **2**, by NMR[11,12] as well as by X-ray crystallography.[13] The O4′-*endo* conformation is a perfect intermediate between the C2′-*endo* conformations found in archetypical B-type duplexes and the C3′-*endo* conformations found in archetypical A-type duplexes.[14] DNA:RNA duplexes can be viewed as intermediate structures in which the DNA strand possesses mixtures of C2′-*endo* and C3′-*endo* conformations.[15,16] This structural feature is regarded as pivotal for the cleavage of the RNA strand in DNA:RNA duplexes by RNase H,[16] an ability that is recognised as crucial in the development of antisense therapeutics.[2] Modified nucleic acid analogues where the nucleoside monomers are restricted in O4′-*endo* conformations can be viewed as mimics of the DNA strand in DNA:RNA duplexes.[12] As such, ON's of 2′-F-*arabino*-modified nucleosides have been found to adopt O4′-*endo* conformations when hybridised to RNA compliments, and RNase H has been found to degrade the RNA strands.[15,17] Nonetheless, this ability to recruit RNase H has not yet been found for ON's containing neither **1** nor **2**.[18]

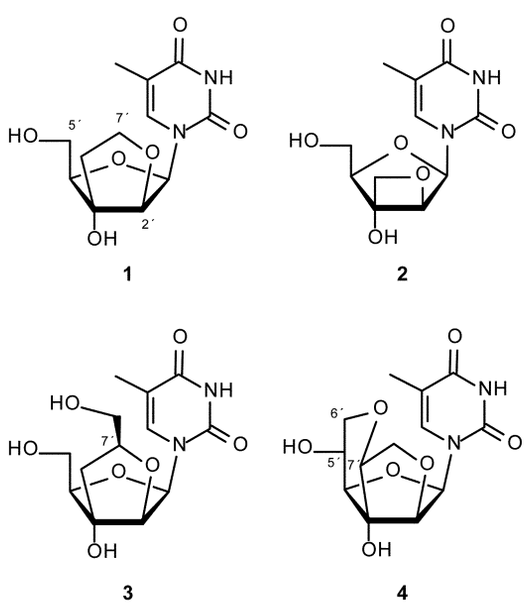

Fig. 1 2′,3′-Linked bi- and tricyclic nucleosides.

Inspired by the results with **1** and **2**, the design of nucleoside analogues containing the [3.3.0]bicyclic skeleton of **1** has been accomplished including a 2′-OMe substituted analogue of **1**[19] and a tricyclic nucleoside being conformationally locked in an S-type conformation due to an additional bond between the C-5′ and the C-7′ positions.[20] When incorporated into ON's, however, both of these demonstrated large decreases in affinity towards both DNA and RNA complements.[19,20] Also the hydroxymethyl substituted nucleoside **3**, as well as its 7′-epimer, has been conveniently obtained (Fig. 1).[21] An ON containing **3** in a fully modified sequence displays the same enhanced recognition of complementary RNA as observed for **1**, whereas the most intriguing property of the corresponding sequence of the 7′-epimer was a strong self-association.[21] Furthermore, the 7′-hydroxymethyl group of **3** has been used as a branching point for the construction of Y-shaped branched ON's,[22] and the hydroxymethyl group of the 7′-epimer has been used for the introduction of charged *N*-methylpiperazinocarbonyl moieties into the major groove of nucleic acid duplexes.[23] In another attempt to introduce further conformational restriction into **1**, we prepared the tricyclic nucleoside **4**.[10] This nucleoside

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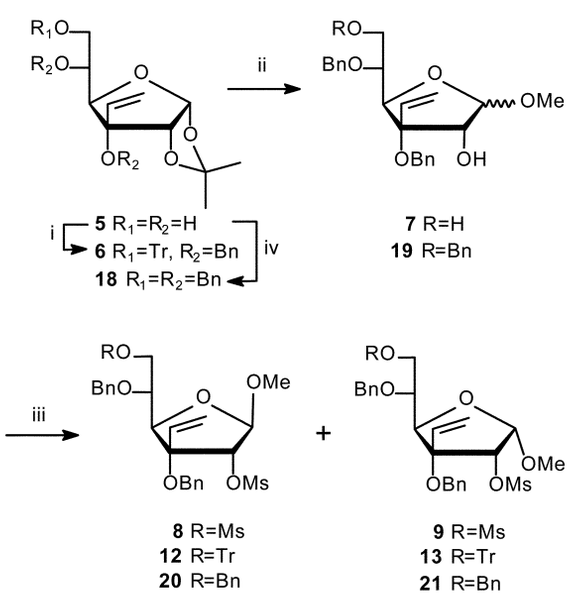
analogue was proved by NMR and molecular modelling to adopt a similar O4′-*endo* conformation but with the 5′-OH group in an unfavourable position, and it has not been incorporated into ON's.[10]

Also the bicyclic nucleoside **2** inspires the design of novel nucleoside analogues containing the same [3.2.0]bicyclic skeleton. Nevertheless, the formation of an oxetane ring demands other synthetic methods and so far, only the 3′-deoxy-3′-azido analogue of **2** has been obtained.[24] In the present paper, however, we introduce two novel hydroxymethyl substituted analogues of **2** which we expect to adopt the same O4′-*endo* conformation as found for **2**[9] as well as for its 3′-deoxy-3′-azido analogue.[24] In the synthesis, we take advantage of a stereoselective dihydroxylation and an efficient regioselective oxetane ring formation that was discovered by serendipity in the search for an improved synthesis of **4** and other tricyclic nucleoside analogues.

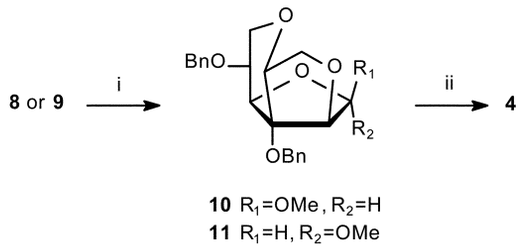
Results

1,2-Di-*O*-isopropylidene-3-*C*-vinyl-β-D-allofuranose **5** (Scheme 1) was synthesised in three steps from diacetone-D-glucose.[10,25] Thus, in our former preparation of the tricyclic nucleoside **4** and its α-anomer, **5** has been converted *via* **6** to the methylfuranoside **7**.[10] A double esterification afforded the anomeric bis-methanesulfonic esters **8** and **9**.[10] Both **8** and **9** were treated with osmium tetroxide and then, immediately, sodium hydride to give the tricyclic products **10** and **11**, respectively, as the only major products (Scheme 2).[10] These results were deduced to the preorganisation of the intermediate diol for forming first the six-membered ring from a nucleophilic attack of the secondary alcohol of C-7 to C-6 and then, after the subsequent twist in the molecule, the five-membered ring *via* a nucleophilic attack from the primary alcohol of C-8 to the secondary C-2 position.[10]



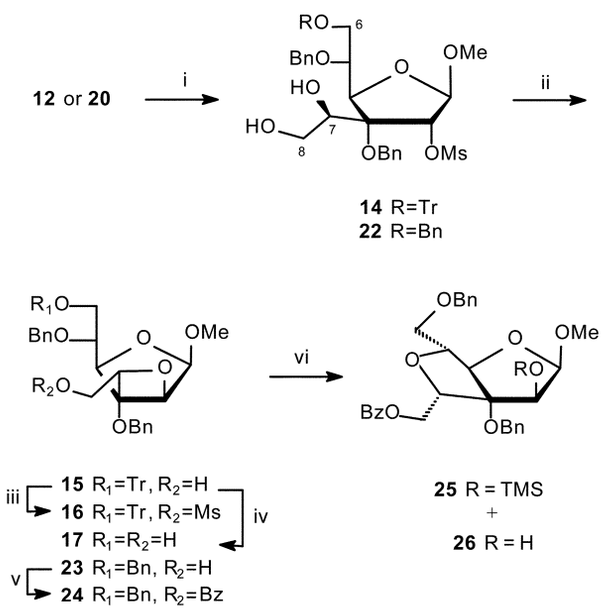
Scheme 1 *Reagents and conditions*: i, 63% (ref. 10); ii, 20% HCl in aq. MeOH, 76% **7** (ref. 10), 77% **19**; iii, 44% **8** and 39% **9** (ref. 10), TrCl *then* MsCl, pyr., 52% **12** and 31% **13**, MsCl, pyr., 55% **20** and 34% **21**; iv, NaH, BnBr, DMF, 99%.

In order to reverse this reaction sequence and improve the synthesis of the tricyclic nucleoside **4** or, alternatively, to obtain other ring-systems, *e.g.* the 7′-epimeric tricyclic nucleoside, we decided to follow a different protecting group strategy for the two alcohols of **7** and to differentiate between the two ring-closing reactions. Thus, the methylfuranoside **7** was selectively tritylated and *in situ* mesylated to give after separation the anomers **12** and **13** in a 1.6 : 1 ratio (Scheme 1). Di-



Scheme 2 *Reagents and conditions*: i, 48% **10**, 42% **11** (ref. 10); ii, 29% (two steps, ref. 10).

hydroxylation of the major anomer **12** afforded the diol **14** as the major product in a (>5 : 1) epimeric mixture (Scheme 3). The high stereoselectivity in the dihydroxylation was expected from the similar result obtained with **8** and **9**, and therefore, a resulting (*R*)-configuration of C-7 in **14** was assumed. Treatment of **14** with sodium hydride, however, did not afford a five-membered oxolane ring but instead the four-membered oxetane ring in the product **15**, which was isolated as a pure compound in a good yield after chromatographic purification. The [3.2.0]bicyclic structure was deduced from NMR. Thus, especially the OH-signal appearing as a triplet and not a duplet verified the presence of a primary alcohol. Furthermore, the $^{3}J_{H1-H2}$ coupling constant of 2.8 Hz was similar to what has been observed before for the similar [3.2.0]bicyclic system in **2** and derivatives thereof (2.3 to 2.7 Hz),[9,24] contrary to what has been observed in [3.3.0]bicyclic systems as in **1**, **10** and the tricyclic nucleoside **4** (3.7 to 4.7 Hz).[8,10] The two H-8 signals were not split, a fact consistent with an exocyclic position of C-8, and finally in ^{13}C NMR, a significant shift downfield was observed for the C-7 signals (71.5 ppm in **14** and 82.9 ppm in **15**) and not for the C-8 signals. Further evidence was obtained after esterification of **15** to give the methanesulfonic ester **16**. Thus, the H-8 signals performed a larger shift downfield than the H-7 signal. An NOE-experiment on **16**, for which the H-NMR signals were conveniently separated, showed a very clear and large mutual contact between H-5 and H-7 (9–11%) confirming the retention of the (*R*)-configuration of C-7 and a [3.2.0]bicyclic system. The trityl group of **15** was also removed using a method reported to be chemoselective for trityl ethers in the presence of other acid labile functionalities including acetals as in methylfuranosides and isopropylidene protecting



Scheme 3 *Reagents and conditions*: i, OsO_4, NMO, pyr., aq. *t*-BuOH, 77% **14**, 49% **22**; ii, NaH, DMF, 81% **15**, 91% **23**; iii, MsCl, pyr., 85%; iv, HCOOH, Et_2O, 33%; v, BzCl, pyr., 94%, vi, thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMS-OTf, CH_3CN, 35% **25** and 34% **26**.

groups.[26] However, treatment of **15** with formic acid in diethyl ether afforded the product **17** in only 33% yield.

The surprisingly regioselective ringclosure forming **15** can be rationalised from simple modelling. Thus, the free rotation around the C-3-C-7 bond in **14** is hindered by the large and bulky ring-substituent at the C-4 position (Fig. 2). Therefore, the primary hydroxy group (or the corresponding oxyanion) at C-8 cannot reach a position for possible nucleophilic attack at the C-2 position. Subsequently, only the secondary hydroxy group at C-7 can perform the ring-closing reaction. In other words, the molecule is preorganised for the formation of an oxetane ring.

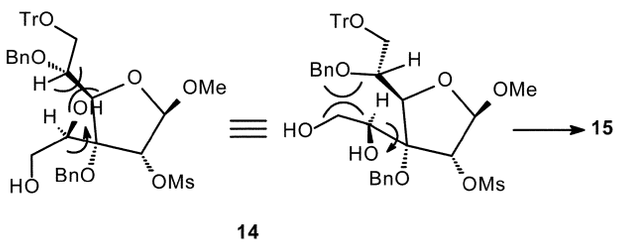
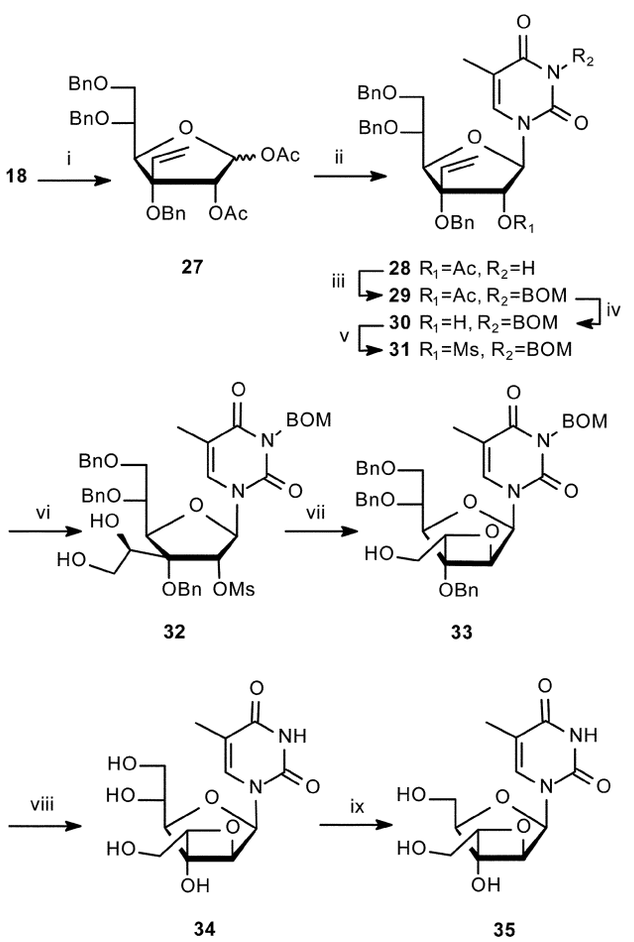


Fig. 2 Steric preorganisation for the formation of the oxetane ring.

This unexpected but very efficient route towards a constrained bicyclic system opened the possibility of constructing potentially very useful [3.2.0]bicyclic nucleosides, *i.e.* single or double hydroxymethyl substituted derivatives of **2** for potentially branched and/or functionalised ON's. However, the present synthetic strategy had to be reconsidered at this stage and, obviously, the differentiated protecting pattern of the C-5 and C-6 hydroxy functionalities was both inconvenient and unnecessary. Therefore, we decided to simply use benzyl ethers for all positions, and compound **5** was treated with an excess of sodium hydride and benzyl bromide to give **18** in a very high yield (Scheme 1). The mixture of methylfuranosides **19** was subsequently obtained and esterification afforded after separation the two anomers **20** and **21** in the same 1.6 : 1 ratio as obtained with **12** and **13**. Dihydroxylation of the major product **20** afforded again one major product **22** in a reasonable yield (Scheme 3). Also a separate minor fraction was obtained containing a small amount of the C-7 epimer, and overall, an approximately 5 : 1 ratio of the two epimers was determined. As expected, the usual basic treatment of diol **22** afforded again a product, **23**, containing on oxetane moiety. Thus, the NMR data were very similar to the data for **15** including a $^3J_{H1–H2}$ coupling constant of 2.8 Hz. In order to perform a nucleobase coupling on the bicyclic methylfuranoside skeleton, the primary alcohol at C-8 was protected as its benzoate **24**. Again, ^{1}H-NMR verified the structure, as a large shift of the H-8 signals was observed, and an NOE experiment indicated a strong mutual contact between H-5 and H-7.

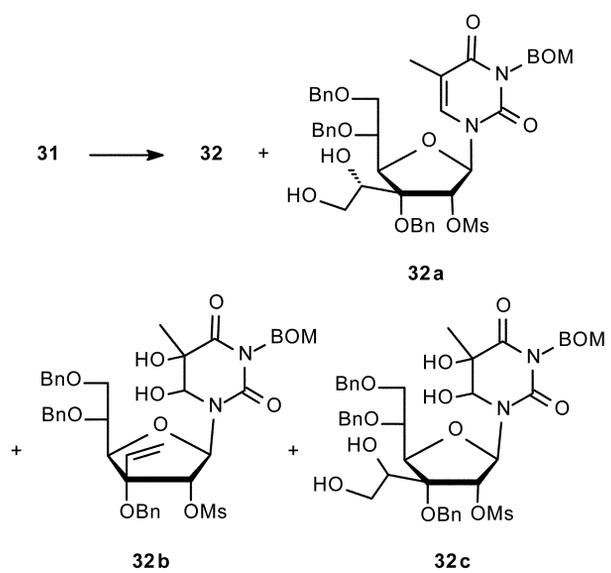
In an attempt to perform a Vorbrüggen type coupling of thymine,[27] compound **24** was treated with thymine, BSA as a silylating agent and TMS-triflate as a Lewis acid catalyst (Scheme 3). Two products **25** and **26** were obtained, the one being a trimethylsilyl protected analogue of the other. Clearly, the products were not nucleosides and the methylfuranoside structure was intact. Instead, the oxetane ring has been opened by the Lewis acid as indicated by NMR confirming a secondary 2-OH group in one of the two products, and displaying larger $^3J_{H1–H2}$ coupling constants of 5.1 and 5.6 Hz. Furthermore, only two benzyl ethers remained in the products. A reasonable mechanistic explanation would be a reaction between the C-5 oxygen atom and the C-7 carbon atom being activated by the Lewis acid and the oxetane ring strain. Subsequently, the oxetane is opened and the 5-O-benzyl bond is cleaved giving the benzylic cation and, after the aqueous work-up, benzylic alcohol, as well as the new five-membered ring in **25** and **26**. Alternatively, a six-membered ring could have been formed due to a reaction of the C-6 oxygen. However, this possibility is excluded by the NMR data. Thus, almost identical chemical shifts of the two H-6 atoms were observed indicating an exocylic position of C-6. A stronger indication was given by comparing the ^{13}C chemical shifts of the benzylic methylene groups. Thus, when comparing differently benzyl ether protected hexofuranosides such as the di- *versus* the tri-O-benzylated series of compounds presented here and in other series[28] with solely 3-O-benzylated compounds,[28] the chemical shifts for the tertiary 3-O benzyl, the secondary 5-O benzyl and the primary 6-O benzyl methylene groups were consequently near 67–68 ppm, 72 ppm and 73.5 ppm, respectively. For compounds **25** and **26**, no benzylic CH_2 signal around 72 ppm was observed.

At this stage, the strategy was reconsidered again. After all, problems performing Vorbrüggen type nucleobase couplings on constrained bicyclic carbohydrate precursors have been observed before.[29] Instead, we decided to perform the nucleobase coupling before the ring-closing reaction. This would demand a protecting group for the nucleobase during the ring-closure in order to avoid an alternative nucleophilic attack from the thymine C-2 oxygen. Nevertheless, this strategy seemed reasonable, as the stereoselective dihydroxylation as well as the regioselective ring-closure should be controlled in a similar manner on a nucleoside substrate. As the first step, tribenzylic ether **18** was converted to the anomeric mixture of acetates **27** in a high yield (Scheme 4). A standard Vorbrüggen type coupling[27] using thymine as the nucleobase afforded the β-configured nucleoside **28** as the only product, as expected due to the



Scheme 4 *Reagents and conditions*: i, a, 80% aq. AcOH, b, Ac_2O, pyr., 90%; ii, thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMS-OTf, CH_3CN, 81%; iii, BOM-Cl, pyr.; iv, MeONa, MeOH, 75% (2 steps); v, MsCl, pyr., 91%; vi, OsO_4, NMO, aq. THF, 31% (see Scheme 5); vii, NaH, DMF, 88%; viii, H_2, $Pd(OH)_2$–C, EtOH, 100%; ix, a, $NaIO_4$, aq. dioxane, b, $NaBH_4$, aq. dioxane, 89%.

anchimeric assistance of the 2-O acetyl group.[27,30] This was confirmed by the $^3J_{H1'-H2'}$ coupling constant of 7.4 Hz consistent with a β-*ribo*-configured nucleoside in a C2′-*endo* conformation.[30,31] The nucleobase was conveniently protected with the benzyloxymethyl (BOM) group to give **29** and then deacetylated to give **30**. Conversion to the methanesulfonic ester **31** revealed a new substrate for the dihydroxylation/ring-closing sequence. The dihydroxylation, however, afforded several products which were separated by chromatography (Schemes 4 and 5). As expected, **32** was isolated as the major product in a reasonable 31% yield in addition to 28% of recovered starting material **31**. Furthermore, the 7′-epimer **32a** was isolated in a 7% yield revealing a 4.5 : 1 ratio of epimers comparable to the ratio found for the dihydroxylations of **12** and **20**. In addition, dihydroxylation of the nucleobase was demonstrated. Thus, the isomeric mixtures **32b** and **32c** were isolated in 7% and 6% yields, respectively. In another experiment, the yield of **32** was slightly improved to give 37% yield after a longer reaction time. However, no starting material was re-isolated. Thus, based on this recovery of **31**, the yield of **32** following the better procedure (Scheme 5) was 43%. All attempts to improve the yield and to diminish the undesirable dihydroxylation of the nucleobase by the addition of pyridine and/or the shift of solvent mixture were unsuccessful. Osmium tetroxide mediated dihydroxylation of a thymine moiety has been seen before for comparable, though not *N*-3 protected, substrates both as the intended reaction[32] and as the cause for unintended side-products.[33] With other very similar substrates,[20,33] including the 3′-*C*-allyl ribofuranoside derivative used in the synthesis of **3**,[21] this problem was not observed.



Scheme 5 *Reagents and conditions*: (See Scheme 4) 31% **32**, 7% **32a**, 7% **32b**, 6% **32c**.

The usual treatment of **32** with sodium hydride gave in a high (88%) yield the protected bicyclic nucleoside **33** (Scheme 4). Subsequent hydrogenation removed the benzylic ethers and the BOM group to give quantitatively the functionalised bicyclic nucleoside **34**. The configuration of **33** and **34** was proven by NMR. Thus, the $^3J_{H1'-H2'}$ coupling constants of 2.1 and 2.6 Hz, respectively, were consistent with the [3.2.0]bicyclic structure and an O4′-*endo* conformation.[9,12,24] Again, the OH-signal in **33** appeared as a triplet verifying a primary alcohol on C-8′, and an NOE-experiment confirmed a large mutual contact between H-5′ and H-7′. Finally, the characteristic ^{13}C downfield shift of 11 ppm was observed when comparing the C-7′-signals of **32** and **33**. In another batch, the hydrogenation afforded a mixture of **34** and a compound with an *N*-3-hydroxymethyl moiety due to incomplete removal of the BOM group. This problem was easily solved as already described in the literature[34] by treating the mixture with concentrated sodium hydroxide to afford the pure compound **34**. Finally, this double hydroxymethyl functionalised bicyclic nucleoside was conveniently converted to a singly functionalised analogue **35** in a high yield by cleavage of the vicinal diol moiety with sodium periodate and subsequent reduction of the aldehyde with sodium borohydride. As a last experiment, also the 7′-(*S*)-configurated diol **32a** was subjected to the same reaction conditions as used in the ring-closure of **32**, but only a slow conversion and a mixture of several products was observed.

Discussion

In summary, the [3.2.0]bicyclic nucleoside **34** was conveniently obtained in 12 steps and 14% overall yield from diacetone-D-glucose. Thus, from the highly chiral carbohydrate framework given in the D-glucose, all the key reactions were performed with high stereoselectivity; the Grignard reaction,[10,25] the nucleobase-coupling and the dihydroxylation. The latter reaction, however, was the limiting step resulting in several by-products and a tedious separation. This reaction certainly deserves future improvements concerning alternative methods and/or alternative *N*-3 protecting groups.

The oxetane ring-formation was remarkably regioselective giving no detectable by-products such as the alternative five-membered oxolane ring in a [3.3.0]bicyclic product. This very efficient ring-closure was successful with the nucleoside substrate **32** as well as with the methylfuranosides **14** and **22**, and appears to rely completely on the preorganisation that is incorporated in the substrate by the large C-4 (or C-4′) ring substituent (Fig. 2). Future studies might demonstrate whether this ring-closure is also compatible with smaller C-4 substituents, or in other words, whether the derivative **35** could be obtained directly from a *ribo*-nucleoside substrate, *i.e.* a derivative of **32** without the C-6′ carbon which should be easily available. Thus, in the preparation of **2**, the 3′-*C*-vinyl substituted *ribo*-nucleoside derivative, *i.e.* **28** without the C-6′ moiety, has been easily obtained starting from 1,2-di-*O*-isopropylidine-α-D-xylofuranose.[9] It is an open question, whether the C-5 moiety as an unsubstituted CH_2OBn moiety would induce sufficient preorganisation for oxetane ring-formation. Nonetheless, the present efficient preparation of **35** from **34** does not necessitate a new parallel (and hardly better) preparation of this compound.

On the other hand, the oxetane formation seems to rely also on the substituent attached to the attacking alcohol. Thus, in another attempt on preparing **2**, oxetane ring-formation on a derivative of **14/22** without both the C-6′ and the C-8′ moieties (*i.e.* the attacking alcohol being primary) has proven impossible.[35] Thus, no sufficient preorganisation for oxetane ring-formation was given in that substrate, and instead, the oxetane ring in **2** was obtained by a nucleophilic attack from the 2′-OH group on an *arabino*-configured nucleoside towards a 3′-C-CH_2OMs moiety.[9] Thus, as is also indicated in Fig. 2, the preorganisation for oxetane ring-formation where the C-7 hydroxy function acts as the nucleophile presumably relies also on the presence of the hydroxymethyl moiety (or another substituent) on C-7. On the other hand, the formation of an oxetane ring following attack from a primary towards a secondary centre has been seen before, for example in the formation of Taxol and derivatives thereof.[36] The conclusion, however, that the present ring-closure of **32** (and of **14** and **22**) is based on a perfect preorganisation, is also confirmed by the fact that the 7′-epimer **32a** cannot efficiently form an oxetane ring. This is probably due to a significant and inconvenient steric interaction between the C-5′ and the C-7′/C-8′-diol moieties, and subsequently, a completely different conformational organisation of the reactive groups.

In the near future, the bicyclic nucleosides **34** and **35** will be

appropriately protected and incorporated into ON's. This is expected to be relatively straightforward as the necessary synthetic methods are well established for similar nucleoside derivatives containing constrained bicyclic carbohydrate moieties and/or free hydroxy groups that demand protecting groups.[9,20,21] Thus, after protection of primary hydroxy group(s) of **34** and **35**, the nucleosides will be converted to 5′-*O*-DMT protected 3′-*O* phosphoramidites for standard 3′ to 5′ incorporation of the nucleosides into ON's. The nucleic acid recognition behaviour of ON's containing **34** and/or **35** in comparison with the ON's containing the original [3.2.0]bicyclic nucleoside **2** will throw light on the possibility of influencing the hydration pattern of a DNA:RNA duplex. Thus, ON's containing the strong O4′-*endo* conformational mimic **2** demonstrated large increases in both DNA and RNA recognition, and this might be improved by the combination of O4′-*endo* conformations and additional hydrophilic groups that will be introduced by **34** and **35**. The ability of the stable hybrids between RNA sequences and ON's containing **2** to be recognised by RNase H has not yet been fully explored.[18] Thus, these hybrids should be excellent mimics of the natural DNA:RNA substrate due to the O4′-*endo* conformation mimicking the intermediate between C2′-*endo* and 3′-*endo* conformations.[12] These hybrids might therefore be recognised by RNase H in mixed sequences or in gapmers containing even very small gaps of natural 2′-deoxynucleosides.[37,38] Whether the additional hydroxymethyl groups in **34** and **35** will influence this envisioned ability of **2**, should also be explored.

Finally, **34** or **35** might be very convenient building blocks for the construction of branched ON's in the same way as formerly described with **3**.[22] Nevertheless, **35** might be a more convenient branching point than **3** being a smaller entity and more strongly conformationally restricted. The hydroxy group should be perfectly positioned in the major groove of a nucleic acid duplex. While **35** could be used for Y-shaped branched ON's, **34** might be a very useful building block for X-shaped branched ON's. Furthermore, the additional hydroxy functionalities of both **34** and **35** could be used for the incorporation of other groups as recently shown with **3** and a 4′-*C*-hydroxymethyl nucleoside,[23] or even as building blocks for DNA-templated synthesis.[39]

As an additional advantage, **35** (13 steps, 12% overall yield) and **34** are more conveniently prepared than the related derivative **3** (16 steps, 5% overall yield + 6% of the 7′-epimer).[8,21] Even more importantly, the present synthetic strategy should be useful also in the construction of the similar nucleoside analogues containing other nucleobases. Thus, in contrast to the synthesis of **1**, **2** and **3**, the present strategy does not take advantage of the so-called anhydro approach[40] where the C-2 carbonyl moiety of a pyrimidine nucleobase is used for converting the C-2′ configuration thereby changing *ribo*- to *arabino*-configured nucleosides. Therefore, also the purine analogues of **34** and **35** should be easily available.

The surprisingly efficient present synthesis of an otherwise inaccessible oxetane ring might be used in the preparation of different classes of molecules such as conformationally restricted carbohydrate derivatives related to **15**.[41] On the other hand, the original target nucleosides, *i.e.* the tricyclic nucleoside **4**, and especially its 7′-epimer, must be prepared by a different strategy.

Conclusion

A surprisingly efficient and selective oxetane ring-formation has been found by serendipity with methylfuranoside derivatives and, subsequently, used successfully on a nucleoside substrate. Hereby, two hydroxymethyl substituted [3.2.0]bicyclic nucleosides have been conveniently obtained. These are conformationally restricted in O4′-*endo* conformations and should therefore perfectly match the structure of DNA:RNA hybrids. The incorporation of the two novel bicyclic nucleosides into ON's is in progress in our laboratory. We expect these nucleic acid analogues to reveal important information about the conformational behaviour and the hydration pattern of nucleic acid duplexes, and to further establish the scopes of the crucial RNase H degradation of target RNA-sequences. Hereby, these bicyclic nucleoside monomers might demonstrate favourable properties towards the development of therapeutic ON's. Furthermore, we envision potential applications of these nucleoside monomers as branching points for the introduction of other chemical entities into nucleic acids and for the construction of novel chemical architectures thereby revealing attractive tools for nanobiotechnology.

Experimental

All commercial reagents were used as supplied. When necessary, 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, Plasma Desorption mass spectra on an Applied Biosystems BIO-ION 20R spectrometer, and MALDI mass spectra were recorded on an Ionspec Ultima Fourier Transform mass spectrometer. Microanalyses were performed at The Microanalytical Laboratory, Department of Chemistry, University of Copenhagen. Assignments of NMR spectra are based on ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-COSY and/or DEPT spectra and follow standard carbohydrate and nucleoside style; *i.e.* the carbon atom next to a nucleobase is assigned C-1′; the numbering continues from C-3 (or C-3′) to C-7 (C-7′) and C-8 (C-8′) as depicted in Scheme 3 for all compounds except **35** where the numbering continues from C-3′ to C-6′ and C-7′. However, compound names for bicyclic compounds are given according to the von Baeyer nomenclature.

Preparation of methyl 3,5-di-*O*-benzyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-3-*C*-vinyl-D-allofuranoside 12 and 13

To a stirred solution of **7** (1.00 g, 2.50 mmol) in anhydrous pyridine (7.5 cm^3) at room temperature was added trityl chloride (1.046 g, 3.75 mmol). The reaction mixture was stirred for 3 days at room temperature and then for 2 h at 40 °C. After cooling to 0 °C, methane sulfonylchloride (0.76 cm^3, 10.0 mmol) was added and the reaction mixture was stirred for 1 h at room temperature and quenched with a saturated aqueous solution of $NaHCO_3$ (75 cm^3). The mixture was extracted with dichloromethane (2 × 200 cm^3) and the combined extracts were dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with petroleum ether–ethyl acetate (85 : 15) as eluent to give the two pure products as solids;

Methyl 3,5-di-*O*-benzyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-3-*C*-vinyl-β-D-allofuranoside 12

(936 mg, 52%) (Found: C, 71.38; H, 5.75; S, 4.62. $C_{43}H_{44}O_8S$ requires C, 71.65; H, 6.15; S, 4.45%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.48–7.45 (6H, m, Ph), 7.33–7.21 (19H, m, Bn, Ph), 5.94 (1H, dd, *J* 17.6, 11.3 Hz, H-7), 5.53 (1H, d, *J* 17.6 Hz, H-8), 5.32 (1H, d, *J* 11.3 Hz, H-8), 5.10 (1H, d, *J* 4.0 Hz, H-1), 5.06 (1H, d, *J* 4.0 Hz, H-2), 4.70 (1H, d, *J* 11.0 Hz, Bn), 4.64 (2H, br s, Bn), 4.49 (1H, d, *J* 7.6 Hz, H-4), 4.42 (1H, d, *J* 11.0 Hz, Bn), 3.62 (1H, m, H-5), 3.44 (1H, dd, *J* 10.2, 3.2 Hz, H-6), 3.33 (1H, dd, *J* 10.2, 5.2 Hz, H-6), 3.23 (3H, s, OCH_3), 2.98 (3H, s, SO_2CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 144.0 (Ph), 138.9, 138.2 (Bn), 132.7 (C-7), 128.9, 128.4, 127.8, 127.8, 127.6, 127.4, 127.1, 127.0 (Bn, Ph), 118.8 (C-8), 105.9 (C-1), 86.7 (Ph_3C), 85.3 (C-3), 84.4 (C-4, C-2), 78.5 (C-5), 71.9 (Bn), 67.2 (Bn), 62.9 (C-6), 56.1 (OCH_3), 38.9 (SO_2CH_3); *m/z* (FAB) 743 (M + Na).

Methyl 3,5-di-*O*-benzyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-3-*C*-vinyl-α-D-allofuranoside 13

(556 mg, 31%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.48–7.44 (6H, m, Ph), 7.33–7.20 (19H, m, Bn, Ph), 5.91 (1H, dd, *J* 17.6, 11.2 Hz, H-7), 5.34 (1H, d, *J* 17.6 Hz, H-8), 5.28 (1H, d, *J* 11.2 Hz, H-8), 5.03 (1H, d, *J* 4.8 Hz, H-1), 4.99 (1H, d, *J* 4.8 Hz, H-2), 4.73 (1H, d, *J* 12.0 Hz, Bn), 4.68 (1H, d, *J* 11.5 Hz, Bn), 4.62 (1H, d, *J* 12.0 Hz, Bn), 4.57 (1H, d, *J* 7.3 Hz, H-4), 4.42 (1H, d, *J* 11.5 Hz, Bn), 3.62 (1H, m, H-5), 3.45 (1H, m, H-6), 3.43 (3H, s, OCH_3), 3.31 (1H, dd, *J* 10.2, 5.1 Hz, H-6), 2.99 (3H, s, SO_2CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 144.1 (Ph), 139.1, 138.3 (Bn), 135.7 (C-7), 128.9, 128.8, 128.3, 128.2, 127.8, 127.7, 127.5, 127.3, 127.2, 127.0 (Bn, Ph), 117.8 (C-8), 100.6 (C-1), 86.7 (Ph_3C), 83.1, 81.2, 79.5 (C-2, C-3, C-4), 77.9 (C-5), 71.9 (Bn), 67.2 (Bn), 62.8 (C-6), 55.7 (OCH_3), 39.0 (SO_2CH_3); *m*/*z* (FAB) 743 (M + Na).

Preparation of methyl 3,5-di-*O*-benzyl-3-*C*-(1(*R*),2-dihydroxyethyl)-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-β-D-allofuranoside 14

To a solution of **12** (596 mg, 0.827 mmol) in *tert*-butanol (9.2 cm^3) was added water (0.50 cm^3) pyridine (0.46 cm^3), *N*-methylmorpholine-*N*-oxide (673 mg, 5.80 mmol) and a 2.5 w/w-% solution of osmium tetroxide in *tert*-butanol (0.046 cm^3). The solution was stirred under reflux at 76 °C for 12 h and quenched at room temperature with a 20% aqueous solution of $Na_2S_2O_5$ (3.4 cm^3). The mixture was diluted with water (30 cm^3) and extracted with dichloromethane (2 × 100 cm^3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (75 cm^3) and then dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with dichloromethane–methanol (99 : 1) as eluent to give the product as a clear oil (482 mg, 77%) which was used without further purification in the next step; δ_H (300 MHz; $CDCl_3$; Me_4Si) (major isomer) 7.52–7.42 (6H, m, Ph), 7.33–7.21 (19H, m, Bn, Ph), 5.27 (1H, d, *J* 3.3 Hz, H-2), 5.08 (1H, d, *J* 3.3 Hz, H-1), 4.73–4.64 (4H, m, Bn, H-4), 4.31 (1H, d, *J* 10.5 Hz, Bn), 4.05 (1H, m, H-7), 3.97 (1H, m, H-5), 3.78 (1H, dd, *J* 11.8, 5.4 Hz, H-8), 3.62–3.57 (2H, m, H-6, H-8), 3.37 (1H, dd, *J* 10.4, 3.8 Hz, H-6), 3.20 (3H, s, OCH_3), 3.03 (3H, s, SO_2CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) (major isomer) 143.91 (Ph), 138.0, 137.5 (Bn), 128.9, 128.7, 128.6, 128.6, 128.4, 128.1, 128.0, 127.9, 127.6, 127.2, 127.1 (Bn, Ph), 107.4 (C-1), 87.0, 86.6 (Ph_3C, C-3), 83.9, 81.5 (C-2, C-4), 77.5 (C-5), 71.5, 71.4 (Bn, C-7), 67.7 (Bn), 63.2, 61.2 (C-6, C-8), 56.4 (OCH_3), 38.4 (SO_2CH_3); *m*/*z* (PDMS) 777 (M + Na).

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-1-benzyloxy-2-(1(*R*)-benzyloxy-2-triphenylmethoxy)ethyl-7-hydroxymethyl-4-methoxy-3,6-dioxabicyclo[3.2.0]heptane 15

A solution of **14** (458 mg, 0.608 mmol) in anhydrous DMF (1.0 cm^3) was stirred at 0 °C and a 60% oily dispersion of NaH (38 mg, 0.91 mmol) was added. The reaction mixture was stirred at room temperature for 2 days, and then quenched with a saturated aqueous solution of $NaHCO_3$ (20 cm^3) and extracted with dichloromethane (2 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica with dichloromethane–methanol (99 : 1) as eluent to give the product as a clear oil (325 mg, 80%) (Found: C, 75.20; H, 6.46. $C_{42}H_{42}O_7$, $0.5H_2O$ requires C, 75.54; H, 6.49%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.55–7.48 (6H, m, Ph), 7.35–7.23 (19H, m, Bn), 4.92 (1H, d, *J* 2.8 Hz, H-2), 4.76 (1H, d, *J* 2.8 Hz, H-1), 4.74 (1H, m, H-7), 4.71 (1H, d, *J* 11.1 Hz, Bn), 4.63 (1H, d, *J* 11.1 Hz, Bn), 4.54 (1H, d, *J* 11.4 Hz, Bn), 4.44 (1H, d, *J* 8.8 Hz, H-4), 4.40 (1H, d, *J* 11.4 Hz, Bn), 3.99 (1H, m, H-5), 3.79–3.84 (2H, m, H-8), 3.63 (1H, dd, *J* 10.4, 2.4 Hz, H-6), 3.47 (3H, s, OCH_3), 3.41(1H, dd, *J* 10.4, 4.2 Hz, H-6), 2.14 (1H, t, *J* 7.7 Hz, 8-OH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 144.0 (Ph), 138.0, 137.2 (Bn), 129.0, 128.8, 128.7, 128.4, 128.1, 127.8, 127.7, 127.6, 127.3, 127.1 (Bn, Ph), 104.1 (C-1), 86.7 (Ph_3C), 85.7 (C-3), 84.6 (C-2), 82.9 (C-7), 77.1 (C-5), 74.6 (C-4), 71.6 (Bn), 68.0 (Bn), 62.4 (C-6, C-8), 57.5 (OCH_3); *m*/*z* (FAB) 681 (M + Na).

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-1-benzyloxy-2-(1(*R*)-benzyloxy-2-triphenylmethoxy)ethyl-4-methoxy-7-methylsulfonyloxymethyl-3,6-dioxabicyclo[3.2.0]heptane 16

To a stirred solution of **15** (131 mg, 0.199 mmol) in anhydrous pyridine (1.0 cm^3) at 0 °C was added dropwise methane sulfonylchloride (0.04 cm^3, 0.5 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched with ice-cold water (15 cm^3) and extracted with dichloromethane (3 × 15 cm^3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (20 cm^3) and then dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue purified by chromatography over silica with dichloromethane–methanol (99 : 1) as eluent to give the product as an oil (124 mg, 85%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.50–7.47 (6H, m, Ph), 7.34–7.23 (19H, m, Bn), 4.97 (1H, dd, *J* 6.9, 4.0 Hz, H-7), 4.92 (1H, d, *J* 2.8 Hz, H-2), 4.75 (1H, d, *J* 2.8 Hz, H-1), 4.71 (1H, d, *J* 11.3 Hz, Bn), 4.59 (1H, d, *J* 11.3 Hz, Bn), 4.56 (1H, m, H-8), 4.53 (1H, d, *J* 11.6 Hz, Bn), 4.42 (1H, d, *J* 11.6 Hz, Bn), 4.41 (1H, d, *J* 7.2 Hz, H-4), 4.37 (1H, dd, *J* 11.6, 4.0 Hz, H-8), 3.96 (1H, m, H-5), 3.60 (1H, dd, *J* 10.4, 2.5 Hz, H-6), 3.48 (3H, s, OCH_3), 3.40 (1H, dd, *J* 10.4, 4.2 Hz, H-6), 2.80 (3H, s, SO_2CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 143.9 (Ph), 137.9, 137.0 (Bn), 128.9, 128.8, 128.6, 128.5, 128.1, 127.9, 127.8, 127.6, 127.2, 127.2 (Bn, Ph), 103.9 (C-1), 86.8 (Ph_3C), 85.1 (C-3), 84.8 (C-2), 81.0 (C-7), 77.1 (C-5), 74.4 (C-4), 71.7 (Bn), 69.3 (C-8), 67.9 (Bn), 62.3 (C-6), 57.6 (OCH_3), 37.3 (SO_2CH_3); *m*/*z* (FAB) 759 (M + Na).

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-1-benzyloxy-2-(1(*R*)-benzyloxy-2-hydroxy)ethyl-7-hydroxymethyl-4-methoxy-3,6-dioxabicyclo[3.2.0]heptane 17

A solution of **15** (90 mg, 0.137 mmol) in anhydrous diethyl ether (0.37 cm^3) was stirred at 0 °C, formic acid (0.30 cm^3) was added, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with water (5 cm^3) and neutralised with $NaHCO_3$. The mixture was extracted with diethyl ether (2 × 10 cm^3) and the combined extracts were dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by chromatography over silica with dichloromethane–methanol (97 : 3) as eluent to give the product as a clear oil (19 mg, 33%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.35–7.26 (10H, m, Bn), 4.95 (1H, d, *J* 2.8 Hz, H-2), 4.82 (1H, d, *J* 2.8 Hz, H-1), 4.79 (1H, m, H-7), 4.68 (1H, d, *J* 11.2 Hz, Bn), 4.64 (1H, d, *J* 11.2 Hz, Bn), 4.57 (1H, d, *J* 11.4 Hz, Bn), 4.52 (1H, d, *J* 11.4 Hz, Bn), 4.30 (1H, d, *J* 8.5 Hz, H-4), 4.03 (1H, m, H-6), 3.86–3.39 (4H, m, H-5, H-6, H-8), 3.58 (3H, s, OCH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 137.6, 136.9 (Bn), 128.7, 128.6, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9, 127.7, 127.7 (Bn), 104.3 (C-1), 85.6 (C-3), 83.9 (C-2), 83.0 (C-7), 77.6 (C-5), 74.2 (C-4), 71.9 (Bn), 68.4 (Bn), 62.3 (C-8), 61.0 (C-6), 57.8 (OCH_3); *m*/*z* (FAB) 439 (M + Na).

Preparation of 1,2-*O*-isopropylidene-3,5,6-tri-*O*-benzyl-3-*C*-vinyl-α-D-allofuranose 18

A 60% oily dispersion of NaH (869 mg, 21.73 mmol) was suspended in anhydrous DMF (6 cm^3) and the suspension was stirred at 0 °C. A solution of **5** (1.015 g, 4.12 mmol) in anhydrous DMF (7 cm^3) was added dropwise over 30 min. The mixture was stirred at 50 °C for 1 h and then cooled to 0 °C. Benzyl bromide (2.45 cm^3, 20.63 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 20 h. The solvent was removed by distillation under reduced

pressure and the residue was added to a saturated aqueous solution of $NaHCO_3$ (50 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica with petroleum ether–ethyl acetate (7 : 3) as eluent to give the product as a clear oil (2.105 g, 99%) (Found: C, 74.02; H, 7.15. $C_{32}H_{36}O_6$ requires C, 74.40, H; 7.02%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.35–7.15 (15H, m, Bn), 5.88 (1H, dd, *J* 11.4, 17.8 Hz, H-7), 5.80 (1H, d, *J* 3.7 Hz, H-1), 5.40 (1H, d, *J* 11.4 Hz, H-8), 5.27 (1H, d, *J* 17.8 Hz, H-8), 4.81 (1H, d, *J* 11.7 Hz, Bn), 4.71–4.53 (6H, m, H-2, 5 × Bn), 4.36 (1H, d, *J* 7.0 Hz, H-4), 3.85–3.79 (2H, m, H-5, H-6), 3.07 (1H, m, H-6), 1.60 (3H, s, CH_3), 1.38 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 139.0, 138.8, 138.7 (Bn), 135.9 (C-7), 128.4, 128.2, 128.2, 127.7, 127.7, 127.6, 127.5, 127.3, 127.2 (Bn), 118.2 (C-8), 112.9 ($C(CH_3)_2$), 104.0 (C-1), 85.6 (C-3), 81.8 (C-2), 80.8 (C-4), 77.3 (C-5), 73.3 (Bn), 72.2, 72.0 (Bn, C-6), 67.2 (Bn), 26.9, 26.7 ($C(CH_3)_2$); *m*/*z* (FAB) 539 (M + Na).

Preparation of methyl 3,5,6-tri-*O*-benzyl-3-*C*-vinyl-D-allofuranoside 19

A solution of **18** (7.31 g, 14.15 mmol) in methanol (35 cm^3) and water (10 cm^3) was stirred at 0 °C and a 20% solution of HCl in anhydrous methanol (280 cm^3) added. The reaction mixture was stirred at room temperature for 2.5 h and then quenched by the addition of $NaHCO_3$(s) and then water (800 cm^3). The mixture was extracted with dichloromethane (3 × 250 cm^3), the combined extracts were dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica with dichloromethane as eluent to give the product as a clear oil (5.359 g, 77%) as a mixture of α- and β-anomers in a 1 : 1 ratio (Found: C, 73.14; H, 7.08. $C_{30}H_{34}O_6$ requires C, 73.45; H, 6.99%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.39–7.23 (m, Bn), 6.15 (dd, *J* 17.5, 11.2 Hz, H-7), 6.06 (dd, *J* 17.5, 10.9 Hz, H-7), 5.49 (dd, *J* 17.7, 1.1 Hz, H-8), 5.42–5.30 (m, H-8), 4.91 (d, *J* 4.8 Hz, H-1α), 4.87 (d, *J* 3.2 Hz, H-1β), 4.86–4.78 (m, Bn), 4.67–4.34 (m, Bn, H-4), 4.13–4.06 (m, H-2), 3.92–3.83 (m, H-6), 3.75–3.62 (m, H-6, H-5), 3.47 (s, OCH_3), 3.41 (s, OCH_3), 3.13 (d, *J* 10.6 Hz, OH), 3.07 (d, *J* 7.5 Hz, OH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 139.4, 138.5, 138.4, 138.3, 138.3 (Bn), 135.6, 133.4 (C-7), 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.7, 127.4, 127.1, 126.8 (Bn), 117.7, 116.4 (C-8), 109.2 (C-1β), 101.7 (C-1α), 85.6, 83.0 (C-3), 81.9, 81.7 (C-4), 79.6 (C-2), 78.2, 78.0 (C-5), 76.3 (C-2), 73.5, 72.3, 71.9, 70.5, 70.0 (Bn, C-6), 66.5, 66.4 (Bn), 56.2, 55.3 (OCH_3); *m*/*z* (FAB) 513 (M + Na).

Preparation of methyl 2-*O*-methylsulfonyl-3,5,6-tri-*O*-benzyl-3-*C*-vinyl-D-allofuranoside 20 and 21

A solution of the methylfuranosides **19** (5.28 g, 10.76 mmol) in anhydrous pyridine (20 cm^3) was stirred at 0 °C. Methane sulfonylchloride (1.25 cm^3, 16.15 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 2.5 h and then at room temperature. The reaction was quenched by the addition of ice and water (100 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (200 cm^3) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was then co-evaporated with toluene (10 cm^3) and purified by chromatography over silica with petroleum ether–ethyl acetate (4 : 1) as eluent to give the two products as clear oils.

Methyl 2-*O*-methylsulfonyl-3,5,6-tri-*O*-benzyl-3-*C*-vinyl-β-D-allofuranoside 20

(3.353 g, 55%) (Found: C, 65.54; H, 6.45; S, 5.55. $C_{31}H_{36}O_8S$ requires C, 65.47; H, 6.38; S, 5.64%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.36–7.23 (15H, m, Bn), 6.04 (1H, dd, *J* 17.7, 11.2 Hz, H-7), 5.59 (1H, d, *J* 17.7 Hz, H-8), 5.42 (1H, d, *J* 11.2 Hz, H-8), 5.16 (1H, d, *J* 3.4 Hz, H-1), 5.09 (1H, d, *J* 3.4 Hz, H-2), 4.75 (1H, d, *J* 11.3 Hz, Bn), 4.65 (2H, s, Bn), 4.57 (2H, s, Bn), 4.49 (1H, d, *J* 11.3 Hz, Bn), 4.42 (1H, d, *J* 7.4 Hz, H-4), 3.82 (1H, m, H-6), 3.71–3.64 (2H, m, H-5, H-6), 3.42 (3H, s, OCH_3), 2.99 (3H, s, SO_2CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 138.7, 138.2, 138.1 (Bn), 132.9 (C-7), 128.3, 128.2, 127.7, 127.6, 127.6, 127.5, 127.2, 126.9 (Bn), 118.8 (C-8), 106.0 (C-1), 85.0 (C-3), 84.1 (C-2), 83.9 (C-4), 78.3 (C-5), 73.4, 71.9 (Bn), 69.7 (C-6), 67.1 (Bn), 56.3 (OCH_3), 38.9 (SO_2CH_3); *m*/*z* (FAB) 567 (M–H).

Methyl 2-*O*-methylsulfonyl-3,5,6-tri-*O*-benzyl-3-*C*-vinyl-α-D-allofuranoside 21

(2.073 g, 34%) (Found: C, 65.57; H, 6.64; S, 5.43. $C_{31}H_{36}O_8S$ requires C, 65.47; H, 6.38; S, 5.64%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.32–7.23 (15H, m, Bn), 6.01 (1H, dd, *J* 17.8, 11.1 Hz, H-7), 5.42 (1H, d, *J* 17.8 Hz, H-8), 5.39 (1H, d, *J* 11.1 Hz, H-8), 5.28–5.07 (2H, m, H-1, H-2), 4.81–4.50 (6H, m, Bn), 4.44 (1H, d, *J* 6.9 Hz, H-4), 3.82–3.65 (3H, m, H-5, H-6), 3.48 (3H, s, OCH_3), 3.00 (3H, s, SO_2CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 138.9, 138.3, 138.2 (Bn), 135.6 (C-7), 128.3, 128.2, 128.1, 127.6, 127.6, 127.6, 127.4, 127.2, 127.1 (Bn), 118.0 (C-8), 100.7 (C-1), 83.2 (C-3), 81.3 (C-4), 79.3 (C-2), 77.7 (C-5), 73.4, 72.1 (Bn), 70.5 (C-6), 67.2 (Bn), 55.8 (OCH_3), 39.1 (SO_2CH_3).

Preparation of methyl 2-*O*-methylsulfonyl-3-*C*-(1(*R*),2-dihydroxyethyl)-3,5,6-tri-*O*-benzyl-β-D-allofuranoside 22

A solution of the methylfuranoside **20** (3.24 g, 5.70 mmol) in *tert*-butanol (45 cm^3) and water (3 cm^3) was stirred at room temperature and pyridine (4.5 cm^3), *N*-methylmorpholine-*N*-oxide (4.69 g, 40.03 mmol) and a 2.5 w/w-% solution of osmium tetroxide in *tert*-butanol (0.40 cm^3, 1.28 mmol) were added. The reaction mixture was stirred with reflux at 76 °C for 16 h and then quenched by the addition of a 20% aqueous solution of $Na_2S_2O_5$ (50 cm^3) and then water (50 cm^3). The mixture was extracted with dichloromethane (3 × 100 cm^3) and the combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (100 cm^3) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was then co-evaporated with toluene (20 cm^3) and purified by chromatography over silica with dichloromethane–methanol (99 : 1) as eluent to give the product as a clear oil (1.318 g, 38%), which was used without further purification in the next step, as well as a fraction containing an epimeric mixture (372 mg, 11%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.39–7.26 (15H, m, Bn), 5.29 (1H, d, *J* 3.1 Hz, H-2), 5.14 (1H, d, *J* 3.1 Hz, H-1), 4.78 (1H, d, *J* 11.0 Hz, Bn), 4.70–4.55 (5H, m, H-4, Bn), 4.46 (1H, d, *J* 11.0 Hz, Bn), 4.07 (1H, m, H-7), 4.00 (1H, m, H-5), 3.90 (1H, dd, *J* 10.7, 2.4, H-6), 3.77 (1H, dd, *J* 11.6, 5.5 Hz, H-8), 3.71 (1H, dd, *J* 10.7, 3.8 Hz, H-6), 3.61 (1H, dd, *J* 11.6, 4.2 Hz, H-8), 3.43 (3H, s, OCH_3), 3.04 (3H, s, SO_2CH_3), 2.04 (1H, br s, OH), 1.65 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 138.0, 137.8, 137.3 (Bn), 128.6, 128.5, 128.4, 128.1, 128.1, 127.8, 127.7, 127.5 (Bn), 107.5 (C-1), 87.0 (C-3), 83.8 (C-2), 81.3 (C-4), 77.4 (C-5), 73.5, 71.8 (Bn), 71.5 (C-7), 68.0, 67.7 (Bn, C-6), 63.2 (C-8), 56.6 (OCH_3), 38.5 (SO_2CH_3); *m*/*z* (FAB) 625 (M + Na).

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-1-benzyloxy-2-(1(*R*),2-di(benzyloxy)ethyl)-7-hydroxymethyl-4-methoxy-3,6-dioxa-bicyclo[3.2.0]heptane 23

A solution of **22** (1.29 g, 2.15 mmol) in anhydrous DMF (10 cm^3) was stirred at 0 °C and a 60% oily dispersion of NaH (155 mg, 3.87 mmol) was added. The reaction mixture was stirred at room temperature for 6 h and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (75 cm^3). The mixture was extracted with dichloromethane (3 × 75 cm^3) and the combined extracts were dried $MgSO_4$(s). The solvent

was removed by distillation under reduced pressure and the residue was then co-evaporated with xylene (10 cm^3) and purified by chromatography over silica with dichloromethane–methanol (99 : 1) as eluent to give the pure product as a clear oil (1.011 g, 91%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.38–7.25 (15H, m, Bn), 4.93 (1H, d, *J* 2.8 Hz, H-2), 4.83–4.74 (3H, m, H-1, H-7, Bn), 4.67–4.46 (5H, Bn) 4.30 (1H, d, *J* 8.6 Hz, H-4), 4.04–3.95 (2H, m, H-5, H-6), 3.89–3.85 (2H, m, H-8), 3.76 (1H, dd, *J* 10.5, 4.2 Hz, H-6), 3.54 (3H, s, OCH_3), 2.14 (1H, t, *J* 6.8 Hz, OH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 138.2, 137.9, 137.0 (Bn), 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5 (Bn), 104.1 (C-1), 85.8 (C-3), 84.4 (C-2), 82.9 (C-7), 77.1 (C-5), 74.4 (C-4), 73.5, 72.0 (Bn), 69.5 (C-6), 67.9 (Bn), 62.4 (C-8), 57.6 (OCH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 529.2176/529.2197.

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-1-benzyloxy-7-benzoyloxymethyl-2-(1(*R*),2-di(benzyloxy)ethyl)-4-methoxy-3,6-dioxabicyclo[3.2.0]heptane 24

A solution of **23** (933 mg, 1.84 mmol) in anhydrous pyridine (5 cm^3) was stirred at 0 °C and benzoyl chloride (0.27 cm^3, 2.33 mmol) was added. The reaction mixture was stirred at room temperature for 20 min. and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (30 cm^3). The mixture was extracted with dichloromethane (3 × 30 cm^3) and the combined extracts were dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was then co-evaporated with toluene (5 cm^3) and purified by chromatography over silica with dichloromethane–methanol (99 : 1) as eluent to give the pure product as a clear oil (1.055 g, 94%) (Found: C, 72.26; H, 5.95% $C_{37}H_{38}O_8$ requires C, 72.77; H, 6.27%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.00–7.97 (2H, m, Bz), 7.52 (1H, m, Bz), 7.39–7.18 (17H, m, Bz, Bn), 5.09 (1H, dd, *J* 7.4, 3.2 Hz, H-7), 4.98 (1H, d, *J* 2.8 Hz, H-2), 4.81 (1H, d, *J* 2.8 Hz, H-1), 4.77–4.69 (2H, m, H-8, Bn), 4.64–4.52 (6H, m, H-8, Bn), 4.31 (1H, d, *J* 7.9 Hz, H-4), 4.05 (1H, ddd, *J* 7.9, 4.7, 3.0 Hz, H-5), 3.95 (1H, dd, *J* 10.7, 3.0 Hz, H-6), 3.76 (1H, dd, *J* 10.7, 4.7 Hz, H-6), 3.54 (3H, s, OCH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 166.3 (Bz), 138.2, 137.8, 137.2 (Bn), 132.9, 129.7 (Bz), 128.4, 128.3, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.3 (Bn, Bz), 104.1 (C-1), 85.2 (C-3), 84.8 (C-2), 81.5 (C-7), 76.9 (C-5), 75.0 (C-4), 73.4, 72.2 (Bn), 69.6 (C-6), 67.9 (Bn), 64.8 (C-8), 57.7 (OCH_3); *m*/*z* (FAB) 633 (M + Na).

Preparation of (1*R*,3*R*,4*S*,5*R*,6*S*,8*R*)-5-benzyloxy-8-benzyloxymethyl-6-benzoyloxymethyl-3-methoxy-4-trimethylsilyloxy-2,7-dioxabicyclo[3.3.0]octane 25 and (1*R*,3*R*,4*S*,5*R*,6*S*,8*R*)-5-benzyloxy-8-benzyloxymethyl-6-benzoyloxymethyl-4-hydroxy-3-methoxy-2,7-dioxabicyclo[3.3.0]octane 26

Compound **24** (106.3 mg, 0.174 mmol) and thymine (66 mg, 0.52 mmol) were dried and then dissolved in anhydrous acetonitrile (1.5 cm^3). The solution was stirred at room temperature and bis(trimethylsilyl)acetamide (0.4 cm^3, 1.62 mmol) added, followed by stirring with reflux at 81 °C for 15 min. The reaction mixture was cooled to 0 °C and TMS-triflate (0.13 cm^3, 0.72 mmol) was added followed by stirring at 65 °C for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (6 cm^3) and water (10 cm^3), and the mixture was extracted with dichloromethane (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$), and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica with dichloromethane–methanol (49 : 1) as eluent to give the products as clear oils as well as starting material (11 mg, 10%);

25 (36 mg, 35%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.11–8.08 (2H, m, Bz), 7.53 (1H, m, Bz), 7.43–7.23 (12H, m, Bz, Bn), 4.94 (1H, dd, *J* 8.4, 1.7 Hz, H-7), 4.83 (1H, d, *J* 5.1 Hz, H-1), 4.75 (1H, dd, *J* 12.3, 1.7 Hz, H-8), 4.65–4.60 (3H, m, H-4, Bn), 4.59–4.54 (2H, m, Bn), 4.52–4.47 (2H, m, H-2, H-8), 4.08 (1H, m, H-5), 3.69–3.67 (2H, m, H-6), 3.43 (3H, s, OCH_3), 0.14 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$; Me_4Si) 166.5 (Bz), 138.4, 138.0 (Bn), 132.7, 130.3, 129.8, 128.3, 128.3, 128.1, 127.8, 127.6, 127.3, 126.4 (Bz, Bn), 104.9 (C-1), 94.6 (C-3), 84.2 (C-5), 84.0 (C-4), 81.6 (C-7), 75.2 (C-2), 73.6 (Bn), 69.8 (C-6), 66.7 (Bn), 64.9 (C-8), 55.2 (OCH_3), −0.1 ($Si(CH_3)_3$); *m*/*z* (FAB) 615 (M + Na).

26 (31 mg, 34%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.11–8.07 (2H, m, Bz), 7.57–7.22 (13H, m, Bz, Bn), 4.98 (1H, d, *J* 5.6 Hz, H-1), 4.91 (1H, dd, *J* 12.4, 2.3 Hz, H-8), 4.79 (1H dd, *J* 8.0, 2.3 Hz, H-7), 4.72 (1H, d, *J* 12.2 Hz, Bn), 4.66–4.56 (5H, m, H-2, H-4, Bn), 4.50 (1H, dd, *J* 12.2, 8.0 Hz, H-8), 4.03 (1H, m, H-5), 3.68–3.66 (2H, m, H-6), 3.47 (3H, s, OCH_3), 3.00 (1H, d, *J* 9.9 Hz, OH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 166.9 (Bz), 138.2, 137.9 (Bn), 133.0, 129.8, 128.4, 128.4, 128.3, 127.8, 127.7, 127.4, 126.5 (Bz, Bn), 104.4 (C-1), 94.6 (C-3), 85.2 (C-4), 84.5 (C-5), 81.4 (C-7), 74.6 (C-2), 73.6 (Bn), 69.7 (C-6), 66.8 (Bn), 64.8 (C-8), 55.6 (OCH_3); *m*/*z* (FAB) 521 (M + H).

Preparation of 1,2-di-*O*-acetyl-3,5,6-tri-*O*-benzyl-3-*C*-vinyl-D-allofuranose 27

A solution of **18** (8.45 g, 16.4 mmol) in 80% aqueous acetic acid (55 cm^3) was stirred at 90 °C for 16 h. The solvent was removed under reduced pressure, and the residue was co-evaporated successively with ethanol (3 × 20 cm^3), toluene (3 × 20 cm^3) and anhydrous pyridine (3 × 25 cm^3), and then re-dissolved in anhydrous pyridine (30 cm^3). Acetic anhydride (23 cm^3) was added and the solution was stirred at room temperature for 20 h. A mixture of water and ice (20 cm^3) was added and the resulting mixture was extracted with dichloromethane (3 × 100 cm^3). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 50 cm^3) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by chromatography over silica with petroleum ether–ethyl acetate (4 : 1 v/v) as eluent to give the anomeric mixture as a clear oil (8.31 g, 90%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.32–7.25 (m, Bn), 6.39 (d, *J* 4.4 Hz, H-1), 6.17 (d, *J* 2.5 Hz, H-1), 6.07–6.01 (m, H-7), 5.62 (d, *J* 2.5 Hz, H-2), 5.56–5.36 (m, H-2, H-8), 4.82–4.77 (m, Bn), 4.62–4.44 (m, Bn, H-4), 3.83–3.64 (m, H-6, H-5), 2.08–2.04 (m, $COCH_3$); δ_C (75 MHz; $CDCl_3$; Me_4Si) 169.8, 169.4 (C=O) 138.9, 138.6, 138.3, 138.3, 138.2 (Bn), 134.3, 133.1 (C-7), 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 127.5, 127.4, 127.4, 127.2, 127.2, 126.9, 126.8 (Bn), 118.8, 118.5 (C-8), 99.1, 93.5 (C-1), 85.1, 85.0, 84.5 84.1, 78.1, 77.7, 77.6, 73.4, 73.2, 72.2, 72.0, 70.3, 67.3, 67.2 (C-2, C-3, C-4, C-5, Bn), 21.1, 21.0, 20.8, 20.5 ($CO\mathit{C}H_3$); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 583.2322/583.2302.

Preparation of 1-(2′-*O*-acetyl-3′,5′,6′-tri-*O*-benzyl-3′-*C*-vinyl-β-D-allofuranosyl)thymine 28

To a stirred solution of the anomeric mixture **27** (8.31 g, 14.8 mmol) and thymine (3.74 g, 29.6 mmol) in anhydrous acetonitrile (200 cm^3) was added bis(trimethylsilyl)acetamide (18.3 cm^3, 74.1 mmol). The reaction mixture was stirred at reflux for 30 min. and cooled to 0 °C. TMS-triflate (4.60 cm^3, 25.2 mmol) was added dropwise and the solution was stirred at 50 °C for 16 h. The mixture was allowed to cool to room temperature and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (200 cm^3) followed by extraction with dichloromethane (3 × 200 cm^3). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 200 cm^3) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by dry column vacuum chromatography[42] over silica with petroleum ether–ethyl acetate (2 : 1 v/v) as eluent to give the product as a white foam (7.51 g, 81%); (Found: C, 68.96; H, 6.08; N, 4.24. $C_{36}H_{38}N_2O_8$ requires C, 68.99; H, 6.11; N, 4.47%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.71 (1H, s, NH), 7.37–7.22 (16H,

m, Bn, H-6), 6.25 (1H, d, *J* 7.4 Hz, H-1′), 6.05 (1H, dd, *J* 17.9, 11.0 Hz, H-7′), 5.84 (1H, d, *J* 7.4 Hz, H-2′), 5.40 (1H, d, *J* 11.1 Hz, H-8′), 5.39 (1H, d, *J* 17.8 Hz, H-8′), 4.87–4.48 (6H, m, Bn), 4.45 (1H, d, *J* 5.9 Hz, H-4′), 3.90–3.85 (1H, m, H-5′), 3.79–3.70 (2H, m, H-6′), 2.09 (3H, s, $COCH_3$), 1.60 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 170.0 (C=O), 163.4 (C-4), 150.6 (C-2), 138.7, 137.8, 137.7 (Bn), 135.7 (C-6), 132.7 (C-7′), 128.5, 128.4, 128.3, 128.0, 127.7, 127.6, 127.4, 126.8, 126.8 (Bn), 119.1 (C-8′), 111.3 (C-5), 85.3, 85.0, 84.7 (C-1′, C-3′, C-4′), 79.02 (C-5′), 74.5 (C-2′), 73.4, 71.8 (Bn), 69.3 (C-6′), 67.2 (Bn), 20.7 ($COCH_3$), 12.0 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 649.2528/649.2520.

Preparation of 3-*N*-benzyloxymethyl-1-(3′,5′,6′-tri-*O*-benzyl-3′-*C*-vinyl-β-D-allofuranosyl)thymine 30

To a stirred solution of **28** (7.51 g, 12.0 mmol) in anhydrous acetonitrile (130 cm^3) was added benzyloxymethyl chloride (2.08 cm^3, 15.0 mmol) and DBU (2.24 cm^3, 15.0 mmol). After stirring at room temperature for 18 h, the solvent was removed by distillation under reduced pressure and the residue was re-dissolved in anhydrous methanol (125 cm^3). Sodium methoxide (1.29 g, 24.0 mmol) was added and the mixture was stirred at room temperature for 16 h. The mixture was neutralised with acetic acid and the solvent was partly removed by distillation under reduced pressure followed by extraction with dichloromethane (2 × 250 cm^3). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 200 cm^3) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue was purified by dry column vacuum chromatography[42] over silica with petroleum ether–ethyl acetate (3 : 1 v/v) as eluent to give the product as a white foam (6.32 g, 75%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.38–7.23 (20H, m, Bn), 7.07 (1H, d, *J* 1.0 Hz, H-6), 6.18 (1H, dd, *J* 17.6, 11.0 Hz, H-7′), 5.98 (d, *J* 7.7 Hz, H-1′), 5.52–5.41 (4H, m, H-8′, BOM), 4.87–4.49 (9H, m, Bn, H-4′), 4.30 (1H, dd, *J* 10.3, 7.7 Hz, H-2′), 3.89 (1H, m, H-5′), 3.81–3.69 (2H, m, H-6′), 2.93 (1H, d, *J* 10.3 Hz, 2′-OH), 1.64 (3H, d, *J* 1.0 Hz, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 163.2 (C-4), 151.6 (C-2), 137.9, 137.7, 137.6 (Bn), 134.7 (C-6), 132.1 (C-7′), 128.5, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.6, 127.3, 126.9 (Bn), 118.6 (C-8′), 110.6 (C-5), 88.8 (C-1′), 84.3 (C-3′), 81.7 (C-4′), 79.0 (C-5′), 76.4 (C-2′), 73.5, 72.1, 72.1 (Bn), 70.6 (BOM), 68.7 (C-6′), 66.2 (Bn), 12.7 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 727.3001/727.2990.

Preparation of 3-*N*-benzyloxymethyl-1-(2′-*O*-methylsulfonyl-3′,5′,6′-tri-*O*-benzyl-3′-*C*-vinyl-β-D-allofuranosyl)thymine 31

Compound **30** (6.28 g, 8.92 mmol) was dissolved in anhydrous pyridine (140 cm^3) and cooled to 0 °C. Methane sulfonylchloride (1.73 cm^3, 22.3 mmol) was added dropwise and the solution was stirred at room temperature for 75 min. The reaction was quenched with water and ice (200 cm^3) and the mixture was extracted with dichloromethane (3 × 400 cm^3). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (300 cm^3), dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography over silica with dichloromethane–methanol (99 : 1 v/v) as eluent to give the product as a white foam (6.37 g, 91%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.37–7.25 (20H, m, Bn), 7.16 (1H, d, *J* 1.0 Hz, H-6), 6.28 (1H, d, *J* 7.1 Hz, H-1′), 6.08 (1H, dd, *J* 17.8, 11.0 Hz, H-7′), 5.59–5.47 (5H, m, H-2′, H-8′, BOM), 4.87–4.49 (9H, m, Bn, H-4′), 3.95 (1H, m, H-5′), 3.78–3.69 (2H, m, H-6′), 2.96 (3H, s, SO_2CH_3), 1.61 (3H, d, *J* 1.0 Hz, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 163.2 (C-4), 151.3 (C-2), 138.3, 137.8, 137.6, 137.6 (Bn), 134.7 (C-6), 131.8 (C-7′), 128.6, 128.4, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 126.9, 126.7 (Bn), 120.1 (C-8′), 110.9 (C-5), 86.6 (C-1′), 84.4 (C-3′), 84.2 (C-4′), 79.5 (C-2′), 79.0 (C-5′), 73.4, 71.9, 71.8 (Bn), 70.5 (BOM), 68.8 (C-6′), 67.1 (Bn), 38.9 (SO_2CH_3), 12.7 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 805.2768/805.2765.

Preparation of 3-*N*-benzyloxymethyl-1-(2′-*O*-methylsulfonyl-3-*C*-(1(*R*),2-dihydroxyethyl)-3′,5′,6′-tri-*O*-benzyl-β-D-allofuranosyl)thymine 32

To a solution of **31** (1.982 g, 2.53 mmol) in THF and water (1 : 1 v/v, 30 cm^3) was added *N*-methylmorpholine-*N*-oxide (0.445 g, 3.80 mmol) and a 2.5 w/w-% solution of osmium tetroxide in *tert*-butanol (1.27 cm^3, 0.101 mmol) and the mixture was stirred at 50 °C for 19 h. The reaction was quenched by adding a saturated aqueous solution of sodium hydrogensulfite (6 cm^3) and the mixture was stirred for 30 min. at room temperature. The solvent was partly removed by distillation under reduced pressure followed by extraction with ethyl acetate (4 × 50 cm^3). The organic phase was dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica with dichloromethane–methanol (99.5 : 0.5 v/v) as eluent to give the starting material, the main product and three side-products. The compounds were eluted as follows:

Starting material 31

(0.554 g, 28%).

3-*N*-Benzyloxymethyl-5,6-dihydroxy-5-methyl-1-(2′-*O*-methylsulfonyl-3′,5′,6′-tri-*O*-benzyl-3′-*C*-vinyl-β-D-allofuranosyl)pyrimidine-2,4-dion 32b

(0.144 g, 7%); δ_H (300 MHz; $CDCl_3$; Me_4Si) (major isomer) 7.37–7.24 (20H, m, Bn), 6.33 (1H, d, *J* 8.2 Hz, H-1′), 6.05 (1H, dd, *J* 17.8, 11.2 Hz, H-7′), 5.63 (1H, d, *J* 17.7 Hz, H-8′), 5.51 (1H, d, *J* 11.2 Hz, H-8′), 5.40 (1H, d, *J* 8.2 Hz, H-2′), 5.35 (1H, d, *J* 10.3 Hz, BOM), 5.24 (1H, d, *J* 10.3 Hz, BOM), 4.97 (1H, d, *J* 2.2 Hz, H-6), 4.93–4.39 (9H, m, Bn, H-4′), 3.87 (1H, m, H-5′), 3.76–3.67 (2H, m, H-6′), 3.42 (1H, s, 5-OH), 3.01 (1H, d, *J* 2.2 Hz, 6-OH), 2.82 (3H, s, SO_2CH_3), 2.32 (1H, dd, *J* 7.0, 5.3 Hz, 8′-OH), 1.31 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) (major isomer) 173.7 (C-4), 151.1 (C-2), 138.7, 137.5, 137.4 (Bn), 131.7 (C-7′), 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3, 126.8, 126.7 (Bn), 120.4 (C-8′), 84.5 (C-3′), 84.1 (C-4′), 83.8 (C-1′), 80.8 (C-2′), 80.2 (C-5′), 77.3 (C-6), 73.5, 72.4 (Bn), 72.0 (C-5), 71.4 (Bn), 70.5 (BOM), 69.3 (C-6′), 67.1 (Bn), 39.0 (SO_2CH_3), 22.2 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 839.2857/839.2820.

3-*N*-Benzyloxymethyl-1-(2′-*O*-methylsulfonyl-3-*C*-(1(*S*),2-dihydroxyethyl)-3′,5′,6′-tri-*O*-benzyl-β-D-allofuranosyl)thymine 32a

(0.141 g, 7%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.37–7.23 (20H, m, Bn), 6.96 (1H, d, *J* 0.9 Hz, H-6), 6.03 (1H, d, *J* 7.1 Hz, H-2′), 5.66 (1H, d, *J* 7.1 Hz, H-1′), 5.50 (1H, d, *J* 9.9 Hz, BOM), 5.44 (1H, d, *J* 9.9 Hz, BOM), 5.06–4.48 (8H, m, Bn), 4.78 (1H, d, *J* 9.1 Hz, H-4′), 4.36 (1H, m, H-5′), 4.18 (1H, d, *J* 4.1 Hz, 7′-OH), 4.04–3.99 (1H, m, H-7′), 3.94 (1H, dd, *J* 11.0, 2.4 Hz, H-6′), 3.88–3.85 (2H, m, H-8′), 3.74 (1H, dd, *J* 11.1, 2.9 Hz, H-6′), 3.00 (3H, s, SO_2CH_3), 2.32 (1H, dd, *J* 7.0, 5.3 Hz, 8′-OH), 1.87 (3H, d, *J* 0.9 Hz, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 163.3 (C-4), 151.1 (C-2), 138.3, 138.2, 137.8 (Bn), 136.0 (C-6), 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6, 127.3 (Bn), 110.6 (C-5), 92.8 (C-1′), 85.4 (C-3′), 79.2 (C-4′), 78.4 (C-5′), 75.4 (C-2′), 73.4 (Bn), 73.0 (C-7′), 72.0, 71.7 (Bn), 70.3 (BOM), 68.2, 66.9 (C-6′, Bn), 61.9 (C-8′), 38.6 (SO_2CH_3), 12.9 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 839.2811/839.2820.

3-*N*-Benzyloxymethyl-1-(2′-*O*-methylsulfonyl-3-*C*-(1(*R*),2-dihydroxyethyl)-3′,5′,6′-tri-*O*-benzyl-β-D-allofuranosyl)thymine 32

(0.631 g, 31%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.38–7.22 (21H, m, Bn, H-6), 6.20 (1H, d, *J* 6.7 Hz, H-1′), 5.52 (2H, s, BOM), 5.45 (1H, d, *J* 6.7 Hz, H-2′), 4.88–4.55 (9H, m, Bn, H-4′), 4.34 (1H, m, H-5′), 4.27 (1H, m, H-7′), 3.89–3.71 (5H, m, H-6′, H-8′, 7′-OH), 2.83 (3H, s, SO_2CH_3), 2.13 (1H, t, *J* 6.1 Hz, 8′-OH), 1.94 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 163.2 (C-4), 151.5 (C-2), 137.8, 137.6, 137.5, 137.1 (Bn), 134.2 (C-6), 128.6, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 126.8, (Bn), 111.5 (C-5), 86.3 (C-1′), 81.9 (C-3′), 78.7 (C-4′), 77.2, 77.2 (C-2′, C-5′), 73.6, 73.4, 71.8 (Bn), 71.7 (C-7′), 70.6 (BOM), 68.4 (C-6′), 67.6 (Bn), 61.8 (C-8′), 38.6 (SO_2CH_3), 13.4 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 839.2844/839.2820.

3-*N*-Benzyloxymethyl-5,6-dihydroxy-5-methyl-1-(2′-*O*-methylsulfonyl-3-*C*-(1,2-dihydroxyethyl)-3′,5′,6′-tri-*O*-benzyl-β-D-allofuranosyl)pyrimidine-2,4-dion 32c

(0.131 g, 6%); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 873.2891/873.2875.

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-1-benzyloxy-2-(1(*R*),2-di(benzyloxy)ethyl)-7-hydroxymethyl-4-(3-*N*-(benzyloxymethyl)thymin-1-yl)-3,6-dioxabicyclo[3.2.0]heptane 33

A stirred solution of **32** (0.362 g, 0.443 mmol) in anhydrous DMF (2.5 cm^3) was cooled to 0 °C and a 60% oily dispersion of NaH (0.027 g, 0.67 mmol) was added. The mixture was stirred at room temperature for 20 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (12 cm^3) and extracted with dichloromethane (3 × 30 cm^3). The organic phase was dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography over silica with dichloromethane–methanol (99.5 : 0.5 v/v) as eluent to give the product as a white foam (0.280 g, 88%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.48 (1H, s, H-6), 7.39–7.25 (20H, m, Bn), 5.96 (1H, d, *J* 2.1 Hz, H-1′), 5.47 (2H, s, BOM), 5.19 (1H, d, *J* 2.1 Hz, H-2′), 4.94 (1H, t, *J* 5.0 Hz, H-7′), 4.85–4.52 (8H, m, Bn), 4.39 (1H, d, *J* 7.7 Hz, H-4′), 4.12 (1H, m, H-5′), 3.93–3.88 (3H, m, H-6′, H-8′), 3.73 (1H, dd, *J* 10.5, 5.0 Hz, H-6′), 2.09 (1H, t, *J* 6.8 Hz, 8′-OH), 1.88 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$; Me_4Si) 163.2 (C-4), 150.8 (C-2), 137.8, 137.7, 136.4, 136.1 (Bn, C6), 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.7, 127.6, 127.5 (Bn), 109.2 (C-5), 85.2 (C-3′), 83.9 (C-2′), 83.8 (C-1′), 83.1 (C-7′), 76.6 (C-5′), 75.3 (C-4′), 73.6, 72.6, 72.1 (Bn), 70.5 (BOM), 69.6 (C-6′), 68.2 (Bn), 62.2 (C-8′), 13.3 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 743.2918/743.2939.

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-1-hydroxy-2-(1(*R*),2-dihydroxy)ethyl-7-hydroxymethyl-4-(thymin-1-yl)-3,6-dioxabicyclo[3.2.0]heptane 34

A solution of nucleoside **33** (0.159 g, 0.221 mmol) in anhydrous degassed methanol (2.8 cm^3) was stirred at room temperature with 20% palladium hydroxide over carbon (0.054 g, 0.077 mmol). The mixture was degassed with nitrogen and placed in a hydrogen atmosphere. After stirring for 21 h at room temperature the mixture was filtered through celite and the solvent was removed by distillation under reduced pressure. The residue was dissolved in THF–water (9 : 1 v/v, 5 cm^3) and sodium hydroxide (0.026 g, 0.661 mmol) was added. The mixture was stirred at room temperature for 2 h and subsequently neutralised with 1M hydrochloric acid. The solvent was removed by distillation under reduced pressure, re-dissolved in ethanol and filtered. The solvent was removed by distillation under reduced pressure to give the product as a white solid (0.073 g, 100%); δ_H (300 MHz; CD_3OD; Me_4Si) 7.72 (1H, s, H-6), 5.88 (1H, d, *J* 2.6 Hz, H-1′), 5.00 (1H, t, *J* 4.1 Hz, H-7′), 4.86 (1H, d, *J* 2.6 Hz, H-2′), 4.02 (1H, m, H-5′), 3.92–3.86 (2H, m, H-8′), 3.76–3.71 (2H, m, H-4′, H-6′), 3.59 (1H, dd, *J* 11.7, 5.5 Hz, H-6′), 1.80 (3H, s, CH_3); δ_C (75 MHz; CD_3OD; Me_4Si) 166.3 (C-4), 152.0 (C-2), 139.9 (C-6), 110.0 (C-5), 89.7 (C-2′), 86.5 (C-7′), 85.0 (C-1′), 82.2 (C-4′), 81.6 (C-3′), 71.9 (C-5′), 65.2, 63.4 (C-6′, C-8′), 12.4 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 353.0967/353.0955.

Preparation of (1*R*,2*R*,4*R*,5*S*,7*R*)-2,7-di(hydroxymethyl)-1-hydroxy-4-(thymin-1-yl)-3,6-dioxabicyclo[3.2.0]heptane 35

To a solution of **34** (0.0125 g, 0.0378 mmol) in dioxane and water (1 : 1 v/v, 1 cm^3) was added a solution of sodium periodate (0.0081 g, 0.0378 mmol) in water (0.08 cm^3). The mixture was stirred for 50 min. at room temperature, and subsequently, ethanol was added until the precipitation of sodium iodate was observed. The solution was filtered, sodium borohydride (0.0013 g, 0.0344 mmol) was added and the mixture was stirred at room temperature for 35 min. The mixture was filtered and neutralised with 10% aqueous acetic acid, and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica with dichloromethane–methanol (95 : 5 v/v) as eluent to give the product as a white solid (0.0101 g, 89%); δ_H (300 MHz; CD_3OD; Me_4Si) 7.82 (1H, d, *J* 0.9, H-6), 5.93 (1H, d, *J* 2.8 Hz, H-1′), 4.92 (1H, d, *J* 2.8 Hz, H-2′), 4.90 (1H, t, *J* 4.2 Hz, H-6′), 4.04–3.83 (5H, m, H-4′, H-5′, H-7′), 1.88 (3H, d, *J* 0.9, CH_3); δ_C (75 MHz; CD_3OD; Me_4Si) 166.3 (C-4), 152.0 (C-2), 140.0 (C-6), 110.0 (C-5), 89.7, 86.0, 85.2, 84.3, 81.2 (C-1′, C-2′, C-3′, C-4′, C-6′), 63.2, 61.0 (C-5′, C-7′), 12.4 (CH_3); HiRes MALDI FT-MS *m*/*z* (M + Na) found/calcd. 323.0849/323.0850.

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