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Studies on 2′-α-*C*-carboxyalkyl nucleosides and their application to a stereocontrolled nucleobase exchange process

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The ability of 2′-α-*C*-carboxyalkyl nucleosides to undergo an unusual two-step stereocontrolled nucleobase exchange process has been investigated. Upon silylation a protected 2′-deoxy-2′-α-*C*-(carboxymethyl)uridine derivative can undergo intramolecular displacement of the uracil base, by the 2′-carboxylic acid group, to form a pentofuranosyl γ-lactone. Under identical conditions the homologous 2′-deoxy-2′-α-*C*-(carboxyethyl)uridine derivative does not yield the corresponding δ-lactone, but undergoes elimination of uracil to give the corresponding glycal. The pentofuranosyl γ-lactone is a good substrate for nucleoside synthesis by the Vorbrüggen procedures and undergoes completely stereoselective ring opening with either pyrimidine or purine silylated nucleobases to give novel 2′-*C*-carboxymethyl β-nucleosides in moderate to high yield.

Introduction

The functionalisation of RNA/DNA is becoming established as a means to confer novel and beneficial properties on nucleic acids. For example, recent studies have shown that the catalytic repertoire of nucleic acids can be expanded by preparing nucleic acid catalysts that carry a greater diversity of chemical functional groups.[1,2] Thus it has been possible to select RNA enzymes that can catalyse either amide bond formation or a Diels–Alder cycloaddition reaction by the inclusion of C-5 substituted uridines that contain either an imidazole[1] or a pyridine[2] group, respectively. Functionalisation of the 2′-position has been investigated through the synthesis of RNA/DNA oligomers containing 2′-deoxy-2′-amino nucleosides,[3] 2′-thiouridine,[4–6] 2′-α-*C*-hydroxymethylthymidine[7] and 2′-*O*-carbamoylmethylribonucleosides.[8] 2′-Deoxy-2′-amino nucleosides have been used to generate nuclease resistant aptamers against basic fibroblast growth factor[9] and human IFN gamma.[10] In other cases these modifications have been investigated with the aim of developing oligomers with improved antisense properties. As an example, Sproat and coworkers have shown that oligonucleotides functionalised with 2′-primary amide groups, through incorporation of 2′-*O*-carbamoylmethylribonucleosides **1** (Fig. 1), have substantially increased affinity for their

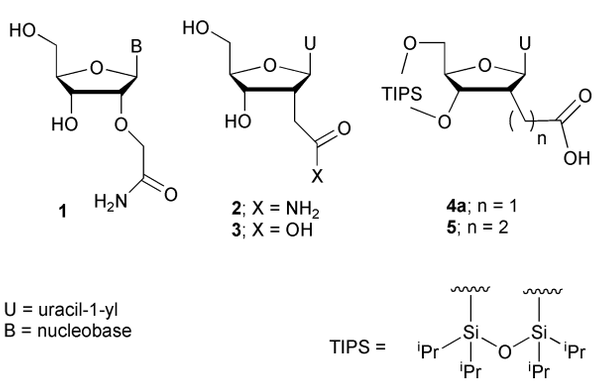


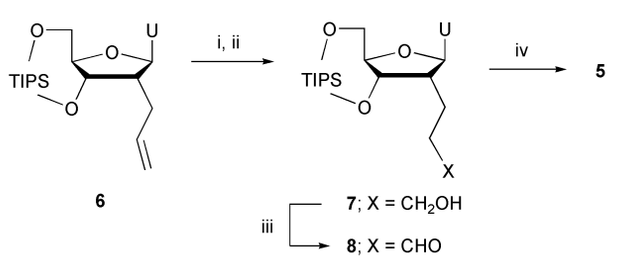
Fig. 1 Structures of 2′-functionalised nucleosides.

complementary RNA sequence, relative to the unmodified oligomer.[8] Previously we have described the synthesis of the related *C*-branched nucleosides 2′-deoxy-2′-α-*C*-(carbamoylmethyl)uridine **2** and 2′-deoxy-2′-α-*C*-(carboxymethyl)uridine **3** (Fig. 1).[11,12] These compounds are attractive functionalised 2′-*C*-branched nucleosides as they are readily prepared and the 2′-*C*-carboxymethyl group can be freely manipulated. To facilitate the synthesis of a diverse range of 2′-*C*-branched nucleosides we have examined the capacity of 2′-α-*C*-carboxyalkyl uridine derivatives (**4a** and **5**, Fig. 1) to undergo a useful nucleobase exchange process, which enables the uracil base to be replaced by either a purine or another pyrimidine base in a stereocontrolled manner. This two-step exchange process was based on the presumption that the 2′-carboxylic acid group could participate in the displacement of the uracil base and the resulting *cis*-fused anomeric-lactone would be susceptible to attack on the β-face by another nucleobase. We now describe the detailed results of this study, some parts of which have already been published in a preliminary form.[13]

Results and discussion

Synthesis of 2′-α-*C*-carboxyalkyluridine derivatives

We have previously established that the 3′,5′-tetraisopropyldisiloxanediyl (TIPS)-protected allyl nucleoside **6** is easily converted to the corresponding carboxymethyluridine derivative **4a** through oxidative cleavage of the allylic side chain.[11,12] An equally facile route to the homologous carboxyethyl nucleoside appeared to be available from the same allyl nucleoside through hydroboration and subsequent oxidation of the organoborane (Scheme 1). Hydroboration of the allyl nucleoside with a large



Scheme 1 *Reagents and conditions*: i, BH_3·SMe_2, THF, 0 °C to rt; ii, Me_3NO·$2H_2O$, 60 °C; iii, dicyclohexylcarbodiimide, $Cl_2CHCOOH$, Me_2SO; iv, $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *tert*-butyl alcohol.

excess of borane dimethyl sulfide was initially followed by oxidation with the routinely used alkaline hydrogen peroxide. However, under these conditions, considerable decomposition of the product occurred due to hydrolytic removal of the TIPS group.

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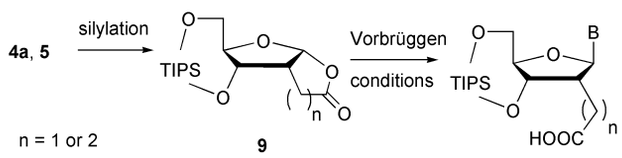
A variety of milder reagents were examined for their suitability in performing the oxidation step including: trimethylamine *N*-oxide[14] (TMAO), sodium perborate[15] and an *N*-methylmorpholine *N*-oxide–tetra-*n*-propylammonium peruthenate[16] (TPAP) procedure to give the aldehyde **8** directly. The best results were obtained using TMAO (5 equiv.) as oxidant and under these conditions the alcohol **7** was isolated in up to 63% yield, following chromatography. It should be noted that yields for this reaction were not consistently reproducible and yields below 50% were occasionally obtained.

Although diverse methods were considered to effect the oxidation of the alcohol **7** through to the corresponding acid **5**, a simple two-step procedure proceeding through the isolated aldehyde **8** proved most successful (Scheme 1). Thus, aldehyde **8** was obtained in 74% yield by a Pfitzner–Moffat oxidation, performed with DCC and dichloroacetic acid in DMSO.[17,18] For comparison, significantly lower yields were obtained when either the Dess–Martin or Swern method was used. Subsequent oxidation to the desired carboxyethyl nucleoside **5** was achieved using sodium chlorite, in a procedure analogous to that previously described for carboxymethyl uridine **4a**.[11] Spectroscopic data for the carboxyethyl nucleoside were fully consistent with its proposed structure, in particular the ^{13}C NMR spectrum showed the acid carbonyl absorbance at 175.13 ppm compared to 175.15 ppm for the carboxymethyl derivative.

Elimination of nucleobases from 2′-α-*C*-carboxyalkyl nucleosides

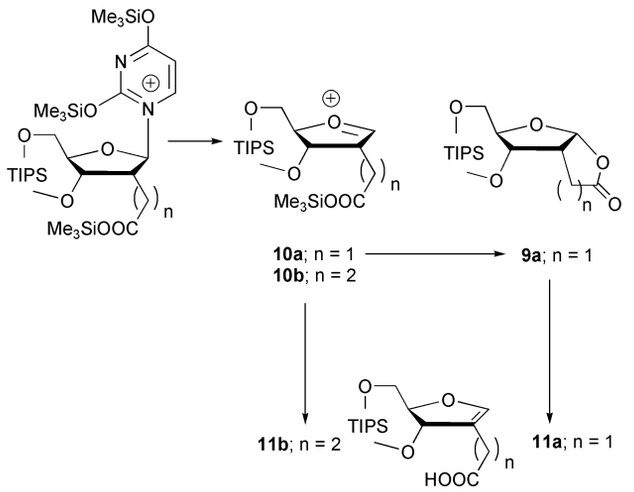
The two-step nucleobase exchange process is outlined in Scheme 2 and was based on the assumption that under the



Scheme 2 Two-step nucleobase exchange process.

appropriate conditions, 2′-α-*C*-carboxyalkyl nucleosides could potentially undergo intramolecular displacement of the nucleobase to give lactones **9**. This reaction is directly analogous to the reverse of nucleoside synthesis by the Vorbrüggen procedure and would produce lactones that are glycosyl donors correctly configured for the stereospecific synthesis of β-nucleosides. Pedersen and co-workers have previously established that furanoid glycals can be efficiently prepared by elimination of the nucleobase from thymidine on treatment with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate at reflux.[19] It is presumed that on silylation, the nucleobase is converted to a good leaving group and the resulting oxocarbenium ion loses a proton to give the glycal. In the case of 2′-α-*C*-carboxyalkyl uridine derivatives the oxocarbenium ion **10** could then be intramolecularly quenched by the carboxylic acid group to give lactones **9** (Scheme 3).

As had been hoped for, treatment of the carboxymethyl nucleoside **4a** with HMDS for 4 h, under the Pedersen conditions, gave the desired γ-lactone **9a** in 57% yield, after chromatography. However, prolonging the reaction for 16 h gave the furanoid glycal **11a** in 82% yield. These two isomeric compounds were readily distinguished by their spectroscopic data: γ-lactone **9a** was shown to have a characteristic carbonyl stretch IR absorption (1785 cm^{-1}) whilst the corresponding stretch for the glycal carboxylic acid was at 1711 cm^{-1}. The ^{1}H NMR spectrum for γ-lactone **9a** revealed H1 to be the expected doublet 5.97 ppm (*J* 5.8 Hz), whilst in glycal **11a**, H1 was shown to be the anticipated singlet (6.41 ppm). When the carboxyethyl nucleoside **5** was treated under the same conditions with

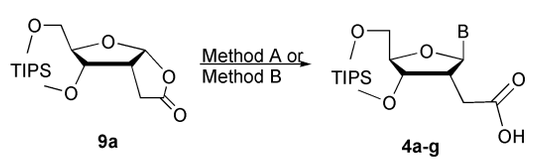


Scheme 3 Fate of 2′-α-*C*-carboxyalkyluridine derivatives when treated with hexamethyldisilazane and ammonium sulfate at reflux.

reaction times varying from 2–30 h, none of the corresponding δ-lactone **9b** was detected and the only product isolated was the glycal **11b**. As expected, spectroscopic data for glycal **11b** were very similar to those of the previously discussed homologue **11a**. As summarised in Scheme 3, it appears that once the oxocarbenium ion **10a** is formed, it is rapidly quenched by the carboxylate group to give the γ-lactone **9a**. In contrast, formation of the δ-lactone **9b** from oxocarbenium ion **10b** appears to be unfavourable in comparison to elimination and thus the glycal is obtained as the sole product.

Nucleoside synthesis

The most widely used approach to nucleoside synthesis has been developed by Vorbrüggen and involves the reaction between a 1-*O*-acyl furanoside and a silylated base in the presence of a Lewis acid.[20] As the lactone **9a** is essentially a 1-*O*-acyl furanoside, we chose to use this approach. Uracil was initially selected as the nucleobase as the synthesis would regenerate compound **4a** and unambiguously establish the integrity of the product. Uracil was silylated by heating to reflux in HMDS in the presence of a catalytic quantity of ammonium sulfate. An acetonitrile solution of the lactone **9a** was treated with an excess (~5 equiv.) of bis-trimethylsilyl (TMS) uracil in the presence of a Lewis acid. Although a variety of Lewis acids [BF_3·Et_2O, $ZnCl_2$, $SnCl_4$, trimethylsilyl triflate (TMSOTf)] were investigated, significant quantities of nucleoside product were only obtained using tin(IV) chloride and optimal yields of the nucleoside syntheses were obtained with 2 equivalents of tin(IV) chloride, as described for Method A (Scheme 4 and Experimental). Using this procedure the carboxymethyl uridine derivative **4a** was obtained in 48% yield and was identical to an original sample. In particular, it showed the characteristic doublet ($J_{1'-2'}$ 2.5 Hz) for H1′ in the ^{1}H NMR spectrum, confirming the expected β-configuration at the anomeric centre. When this procedure was applied to other nucleobases the most efficient synthesis was achieved with thymine, 69% yield (entry 2, Table 1); a low yield (17%) was achieved with N^4-benzoylcytosine (entry 5).



Scheme 4 Method A, CH_3CN, bis(trimethylsilylated) nucleobase, $SnCl_4$ (2.3 equiv.), rt; Method B, CH_3CN, nucleobase, hexamethyldisilazane, Me_3SiCl, $Me_3SiOSO_2CF_3$, 0 °C to rt.

Table 1 2′-α-*C*-carboxymethyl nucleosides prepared from **9a**

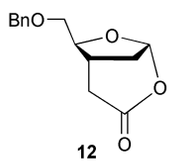
Entry	Nucleobase used	Compound	Method A % yield	Method B % yield
1	Uracil	**4a**	48	64
2	Thymine	**4b**	69	79
3	5-Bromouracil	**4c**	46	69
4	5-Fluorouracil	**4d**	—	47
5	N^4-Benzoylcytosine	**4e**	17	58
6	2,6-Dichloropurine	**4f**	47	62
7	Adenine	**4g**	21	37

In an attempt to improve both the simplicity of the procedure and yield of the reaction, the Vorbrüggen *in situ* silylation strategy[21] was investigated and once again a variety of Lewis acids were investigated. In this one-pot procedure the lactone, nucleobase, HMDS, chlorotrimethylsilane and TMSOTf were initially mixed in dry acetonitrile at 0 °C and then allowed to react at room temperature for 18 h. Unexpectedly, whilst the use of tin(IV) chloride gave yields that were comparable with Method A, the use of trimethylsilyl triflate now gave significantly higher yields (see Scheme 4). Thus, using this one-pot procedure as described under Method B (Scheme 4 and Experimental) a wide range of nucleobases could be used to open lactone **9a** and in all cases a single nucleoside product was isolated that was identical to that obtained by Method A. Table 1 shows that for each nucleobase, the yields are significantly higher than those obtained by presilylation of the nucleobase and the reaction proceeded in moderate yield even with 5-fluorouracil.

With the purine nucleosides there exists the possibility of N7 and N9 regioisomers. NMR data for a wide range of nucleosides have consistently shown that N7 and N9 isomers are differentiated by characteristic upfield chemical shifts in the anomeric 1′-H and the purine 8-H resonances of the N9 isomer relative to those of the N7 isomer.[22,23] Whilst the exact same 2′-carboxymethylpurine nucleosides reported here have not been previously prepared, we were able to compare ^{1}H NMR data for adenine derivative **4f** (8-H and 1′-H at 8.11 and 5.99 ppm respectively) with those reported for the closely related 2′-allyl nucleoside[24] (8-H and 1′-H at 8.32 and 5.96 ppm respectively). The very close proximity of the H1′ chemical shifts and the upfield shift for 8-H in **4f** relative to its position in the allyl derivative are fully consistent with **4f** having the glycosidic bond to N9. In addition, nucleoside **4f** also showed the characteristic UV spectrum of an N^9-adenine nucleoside (ε 260 nm = 15190). It should be noted that N7 and N9 isomers also show characteristic changes in the purine carbon chemical shifts although in practice, ^{13}C NMR literature data are generally less useful as the spectra are often not assigned.[25]

In conclusion, we have shown that the 2′-deoxy-2′-α-*C*-(carboxymethyl)uridine **4a** and the corresponding carboxyethyl derivative **5** behave very differently upon silylation. In particular, 2′-deoxy-2′-α-*C*-(carboxymethyl)uridine undergoes cyclisation to yield the *cis*-fused pentofuranosyl γ-lactone **9a**. Lactone **9a** is a good substrate for nucleoside synthesis using Vorbrüggen procedures and undergoes completely stereoselective ring opening with silylated nucleobases to give novel 2′-*C*-carboxymethyl β-nucleosides in moderate to high yield. The procedure is applicable to both purine and pyrimidine nucleobases and provides a very useful route to a diverse range of *C*-branched nucleosides.

It is interesting to note that very recently, Wendeborn *et al.* have reported that the δ-lactone **12** showed only marginal β/α selectivity in nucleoside synthesis using Vorbrüggen-type conditions.[26] Exclusive formation of the β-nucleoside was only achieved when the sterically demanding Lewis acid methylaluminium bis(2,6-di-*tert*-4-methylphenoxide) was used. This is in contrast to the current results with the closely related γ-lactone **9a**, and illustrates the different behaviour of 5- and 6-membered ring systems.



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Experimental

FAB mass spectra were recorded on a VG Analytical 7070E mass spectrometer operating with a PDP 11/250 data system and an Ion Tech FAB ion gun working at 8 kV. High resolution FAB mass spectra were obtained on either the above instrument or a VG ZAB/E spectrometer at the EPSRC Mass Spectrometry Service Centre (Swansea, UK). 3-Nitrobenzyl alcohol was used as a matrix unless stated otherwise. Where chemical ionisation (CI) was used ammonia was used as the carrier gas. NMR spectra were recorded at the field strength indicated and chemical shifts are given in ppm downfield from an internal standard of tetramethylsilane. Coupling constants (*J*-values) are reported in Hz. IR spectra were recorded as nujol mulls in the range 4000–600 cm^{-1} using a Perkin Elmer Paragon 1000 FT-IR spectrometer. Nucleosides were visualised either as a black spot by spraying with a solution of 5% (v/v) sulfuric acid and 3% (w/v) phenol in ethanol and charring at 120 °C or with the reagent indicated. Acetonitrile, dichloromethane and toluene were dried by heating to reflux over calcium hydride for 2–3 h and were then distilled under atmospheric pressure. THF and diethyl ether were dried by heating to reflux with sodium benzophenone until the purple colouration persisted and then distilled under atmospheric pressure. Dimethyl sulfoxide was purchased anhydrous from Aldrich in Sure-seal™ bottles. Petroleum ether fractions were distilled prior to use.

2′-Deoxy-2′-α-*C*-(3-hydroxypropyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine 7

To a stirred solution of 2′-deoxy-2′-α-*C*-(2-propenyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine **6** (6.82 g, 13.4 mmol) in dry THF (100 cm^3), under a nitrogen atmosphere, a 2.0 M solution of borane dimethyl sulfide in dry THF (46.9 cm^3, 93.8 mmol, 7 equiv.) was added dropwise at 0 °C and the reaction maintained at this temperature. After 1 h the reaction was allowed to warm to room temperature and stirring continued for a further 2.5 h. Trimethylamine-*N*-oxide dihydrate (7.5 g, 67.0 mmol, 5 equiv.) was then added and the mixture heated at 60–70 °C for 16 h, by which point tlc (50% petroleum ether (40–60)–50% ethyl acetate) showed the reaction to be complete. The volatile material was removed *in vacuo* and the resultant white solid diluted with ethyl acetate, washed with brine and dried ($MgSO_4$). The solvents were removed *in vacuo* to yield a white foam. Column chromatography on silica gel (CH_2Cl_2 with an increasing amount of MeOH, 0–4%) afforded the pure product **7** as a white foam, 4.45 g, 63%. δ_H 300 MHz [$CDCl_3$] 1.01–1.10 (28H, m, 4 × ^{i}Pr), 1.51–1.66 (2H, m, H6′, H6″), 1.77–1.98 (2H, m, H7′, H7″), 2.21–2.27 (1H, m, H2′), 3.65–3.73 (2H, m, H8′, H8″), 3.88–4.01 (2H, m, H4′, H5′), 4.21 (1H, d, H5″, *J* 13.1 Hz), 4.46 (1H, t, H3′, *J* 8.0 Hz), 5.72 (1H, d, H5, *J* 8.1 Hz), 5.78 (1H, s, H1′), 7.90 (1H, d, H6, *J* 8.1 Hz), 9.55 (1H, br s, NH); δ_C 75.5 MHz [$CDCl_3$] 12.54–13.42

(4 × Me_2CH), 16.93–17.49 (8 × CH_3), 22.01 (C6′), 30.35 (C7′), 48.44 (C2′), 60.18 (C8′), 62.67 (C5′), 68.16 (C3′), 82.95 (C4′), 89.44 (C1′), 101.93 (C5), 139.66 (C6), 150.70 (C2), 163.66 (C4); *m*/*z* (FAB^+) 551 ($M + Na^+$), 529 ($M + H^+$), 417 (M − uracil); HRMS (FAB^+) 529.2769 ($C_{24}H_{45}N_2O_7Si_2$ ($M + H^+$) requires 529.2765).

2′-Deoxy-2′-α-*C*-(3-oxopropyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine 8

To a solution of alcohol **7** (1.20 g, 2.27 mmol) in dry DMSO (30 cm^3) under a nitrogen atmosphere, DCC (1.87 g, 9.08 mmol) was added at rt followed by dichloroacetic acid (0.09 cm^3, 1.13 mmol). After stirring the reaction for 1 h, tlc (95% CH_2Cl_2–5% MeOH) showed the appearance of a new component which stained bright yellow with 2,4-dinitrophenylhydrazine. Brine (30 cm^3) and ethyl acetate (40 cm^3) were added and the reaction stirred for a further 1 h. The solution was filtered through Celite®, washing with ethyl acetate (50 cm^3) and the filtrate was subsequently washed with saturated sodium bicarbonate solution (2 × 50 cm^3). The organic layers were collected and dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield the crude aldehyde as a white gum. Column chromatography on silica gel (60% petroleum ether (40–60)–40% ethyl acetate) yielded the product aldehyde as a white foam (0.88 g, 74% yield). δ_H 300 MHz [$CDCl_3$] 0.97–1.10 (28H, m, 4 × ^iPr), 1.70–1.75 (1H, m, H6′), 2.22–2.26 (2H, m, H2′, H6″), 2.82–2.87 (2H, m, H7′, H7″), 3.88–4.04 (2H, m, H4′, H5′), 4.21 (1H, d, H5″, *J* 13.3 Hz), 4.48 (1H, t, H3′, *J* 7.8 Hz), 5.67 (1H, d, H5, *J* 8.1 Hz), 5.69 (1H, s, H1′), 7.89 (1H, d, H6, *J* 8.2 Hz), 9.22 (1H, br s, NH), 9.86 (1H, s, H8′); δ_C 75.5 MHz [$CDCl_3$] 12.53–13.43 (4 × Me_2CH), 17.03–17.85 (8 × CH_3), 29.66 (C6′), 41.43 (C7′), 48.07 (C2′), 60.05 (C5′), 67.98 (C3′), 82.89 (C4′), 88.86 (C1′), 101.68 (C5), 139.52 (C6), 150.28 (C2), 163.37 (C4), 201.78 (C8′); *m*/*z* (CI) 544 ($M + NH_4^+$), 527 ($M + H^+$), 415 (M − uracil$^+$); HRMS (CI) 527.2605 ($C_{24}H_{43}N_2O_7Si_2$ ($M + H^+$) requires 527.2609).

2′-Deoxy-2′-α-*C*-carboxyethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine 5

To a solution of aldehyde **8** (400 mg, 0.76 mmol) and 2-methylbut-2-ene (0.31 cm^3, 2.92 mmol) in *t*-BuOH (3 cm^3) was added an aqueous solution of sodium chlorite and potassium dihydrogen orthophosphate [0.2 g, 2.19 mmol; 0.2 g, 1.46 mmol respectively in water (2 cm^3)]. After stirring the reaction vigorously for 2 h at rt, tlc (99% ethyl acetate–1% AcOH) showed the reaction to be complete. Volatiles were removed *in vacuo* and the resultant residue was diluted with ethyl acetate (10 cm^3), washed with saturated sodium bicarbonate solution (2 × 5 cm^3), water (2 × 5 cm^3), brine (2 × 10 cm^3) and dried ($MgSO_4$). The solvents were removed *in vacuo* to afford the product as a white foam. Column chromatography on silica gel (50% petroleum ether (40–60)–49% ethyl acetate–1% AcOH) afforded the product acid as a white foam (295 mg, 72% yield). δ_H 300 MHz [$CDCl_3$]1.03–1.10 (28H, m, 4 × ^iPr), 2.43–2.51 (2H, m, H6′, H6″), 2.71–2.86 (3H, m, H2′, H7′, H7″), 3.93–4.03 (2H, m, H4′, H5′), 4.24 (1H, d, H5″, *J* 13.2 Hz), 4.48 (1H, t, H3′, *J* 7.7 Hz), 5.74 (1H, d, H5, *J* 8.1 Hz), 5.78 (1H, s, H1′), 7.95 (1H, d, H6, *J* 8.1 Hz), 10.6 (1H, br s, NH); δ_C 75.5 MHz [$CDCl_3$] 11.57–12.50 (4 × Me_2CH), 15.94–16.52 (8 × CH_3), 23.92 (C6′), 32.87 (C7′), 48.33 (C2′), 59.07 (C5′), 66.89 (C3′), 82.09 (C4′), 88.17 (C1′), 100.90 (C5), 138.83 (C6), 150.17 (C2), 163.01 (C4), 175.13 (C8′); *m*/*z* (FAB^-) 541 ($M - H^-$), 111 (uracil$^-$); HRMS (FAB^-) 541.2405 ($C_{24}H_{41}N_2O_8Si_2$ ($M - H^-$) requires 541.2402).

(1*R*,2*R*)-Tetrahydro-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-*erythro*-pentofuranoso][1,2-*b*]furan-2-one 9a

A solution of the carboxymethyl nucleoside (2.44 g, 4.62 mmol), ammonium sulfate (0.46 g, 3.4 mmol) and hexamethyldisilazane (30 cm^3) were heated at reflux for 4 h under argon. The hexamethyldisilazane was then removed *in vacuo* and the resulting oil was diluted with ethyl acetate (100 cm^3), washed with aqueous $NaHSO_4$ (30 cm^3) and aq. $NaHCO_3$ (30 cm^3). The organic phase was then dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (hexane–ethyl acetate 2 : 1 v/v) gave the product as a colourless oil (1.1 g, 57%). $[a]_D^{22}$ = +19.8 (*c* = 1.012, chloroform); ν_{max} (nujol)/cm^{-1} 1785 (C=O); δ_H 300 MHz [$CDCl_3$] 0.96–1.05 (28H, m, 4 × ^iPr), 2.43 (1H, dd, *J* 9.0, 19.0, H6), 3.02 (1H, d, *J* 18.7, H6′), 3.20 (1H, m, H2), 3.67 (1H, dd, *J* 3.0, 8.4, H4), 3.99 (2H, m, H5, H5′), 4.35 (1H, *pseudo* t, *J* 8.5, H3), 5.97 (1H, d, *J* 5.8, H1); δ_C 75.5 MHz [$CDCl_3$] 12.7–13.6 (4 × $CH(CH_3)_2$), 16.9–17.4 (3 × CH_3), 27.2 (C6), 41.8 (C-2), 61.0 (C5), 70.5 (C3), 80.3 (C4), 105.7 (C1), 175.6 (C7); *m*/*z* (FAB^+) 439 ($M + Na^+$), 417 ($M + H^+$), HRMS (FAB^+) 439.1938 ($C_{19}H_{36}O_6Si_2Na$ ($M + Na^+$) requires 439.1948).

Furanoid glycals 11a and 11b

Procedure as described for synthesis of **9a**, but heating continued for 16–24 h. Products purified by column chromatography on silica gel (CH_2Cl_2 containing an increasing amount of MeOH, 0–10%).

1,4-Anhydro-3,5-bis-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-2-*C*-carboxymethyl-D-*erythro*-pent-1-enitol 11a

Pale brown oil, 82%; ν_{max} (nujol)/cm^{-1} 1711 (C=O); δ_H 200 MHz [$CDCl_3$] 1.03–1.09 (28H, m, 4 × ^iPr), 3.10 (1H, d, *J* 17.6, H6), 3.25 (1H, d, *J* 17.3, H6), 4.11 (2H, m, H5), 4.48 (1H, m, H4), 5.26 (1H, d, *J* 3.6, H3), 6.49 (1H, s, H1); δ_C 75.5 MHz [$CDCl_3$] 12.56–13.59 (4 × Me_2CH), 16.74–17.38 (8 × CH_3), 29.99 (C6), 63.93 (C5), 79.73 (C3), 88.88 (C4), 107.83 (C2), 146.47 (C1), 174.60 (C7); *m*/*z* (FAB^-) 415 ($M - H^-$), 153 ($M - C_{12}H_{31}O_2Si_2^-$); HRMS ($FAB^-$) 415.1978 ($C_{19}H_{35}O_6Si_2$ ($M - H^-$) requires 415.1972).

1,4-Anhydro-3,5-bis-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-2-*C*-carboxyethyl-D-*erythro*-pent-1-enitol 11b

Yellow glass, 52%; ν_{max} (nujol)/cm^{-1} 1714 (C=O); δ_H 300 MHz [$CDCl_3$] 1.00–1.10 (28H, m, 4 × ^iPr), 2.47 (2H, t, *J* 7.6, 2 × H7), 2.59 (2H, *pseudo* t, *J* 7.6, 2 × H6), 3.62 (1H, t, *J* 11.1, H5), 4.14 (1H, dd, *J* 4.7, 11.1, H5), 4.46 (1H, ddd, *J* 4.4, 4.7, 11.1, H4), 5.14 (1H, d, *J* 3.6, H3), 6.19 (1H, br s, H1); δ_C 75.5 MHz [$CDCl_3$] 12.55–13.73 (4 × Me_2CH), 16.84–17.59 (8 × CH_3), 29.69 (C6), 33.01 (C7), 64.10 (C5), 79.69 (C3), 88.75 (C4), 114.03 (C2), 143.38 (C1), 177.49 (C8); *m*/*z* (FAB^+) 453 ($M + Na^+$), 431 ($M + H^+$), 261 ($C_{12}H_{28}O_2Si_2^+$).

General procedure for nucleoside synthesis

Method A: A suspension of the nucleobase (3 mmol), hexamethyldisilazane (10 cm^3) and a catalytic amount of ammonium sulfate or trimethylsilyl chloride was heated at reflux until the nucleobase was completely dissolved. The heating was continued for a further 1 h and the excess hexamethyldisilazane then removed under reduced pressure. After a subsequent coevaporation with dry toluene (5 cm^3) the remaining silylated nucleobase was dissolved in dry acetonitrile (7 cm^3) and this solution was filtered into a solution of lactone **9a** (0.6 mmol) in dry acetonitrile (3 cm^3). The resulting solution was stirred at room temperature and treated with an ethereal solution of $SnCl_4$ (1.4 cm^3, 1 M).

The solution was diluted with ethyl acetate (100 cm^3) and washed twice with aq. $NaHCO_3$ (30 cm^3) and brine (30 cm^3). After drying (Na_2SO_4) of the organic phase the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (chloroform containing an increasing gradient of methanol from 0–10%).

Method B: To a stirred suspension of lactone **9a** (0.6 mmol) and a nucleobase (0.9 mmol) in dry acetonitrile (10 cm^3) at 0 °C were added hexamethyldisilazane (0.72 mmol), chlorotrimethylsilane (0.72 mmol) and trimethylsilyl trifluoromethanesulfonate (2.0 mmol). The reaction mixture was allowed to warm up to room temperature and was stirred for a further 18 hours. Then the clear solution was diluted with ethyl acetate (100 cm^3) and washed twice with aq. $NaHCO_3$ (30 cm^3) and brine (30 cm^3). After drying (Na_2SO_4) of the organic phase the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (chloroform containing an increasing gradient of methanol from 0–10%).

2′-Deoxy-2′-α-*C*-carboxymethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (4a)

White amorphous solid; δ_H 200 MHz [$CDCl_3$] 1.02–1.08 (28H, m, 4 × ^{i}Pr), 2.45 (1H, dd, *J* 12.1, 19.8, H6′), 2.79–2.86 (2H, m, 2′-H, H6″), 3.89 (1H, m, H4′), 4.07 (2H, m, H5′, H5″), 4.49 (1H, *pseudo* t, *J* 7.2, H3′), 5.76 (1H, d, *J* 8.2, H5), 5.93 (1H, d, *J* 2.5, H1′), 7.66 (1H, d, *J* 7.6, H6), 10.05 (br s, 1H, NH); δ_C 50 MHz [$CDCl_3$] 12.4–13.2 (4 × *C*H[CH_3]$_2$), 16.7–17.2 (8 × CH_3), 30.6 (C6′), 45.3 (C2′), 61.1 (C5′), 69.2 (C3′), 83.6 (C4′), 88.3 (C1′), 102.2 (C5), 139.5 (C6), 150.8 (C2), 164.0 (C4), 175.2 (C-7′); *m*/*z* (FAB^+): 551 (*M* + Na^+), 529 (*M* + H^+); HRMS (FAB^+): 529.2393 ($C_{23}H_{41}N_2O_8Si_2$ (*M* + H^+) requires 529.2401); ε (262 nm) = 9970 in MeOH.

2′-α-*C*-Carboxymethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)thymidine (4b)

White amorphous solid; δ_H 300 MHz [$CDCl_3$] 0.97–1.09 (28H, m, 4 × ^{i}Pr), 1.93 (3H, s, CH_3), 2.46 (1H, dd, *J* 11.5, 15.0, H6′), 2.72–2.78 (2H, m, H2′, H6″), 3.86 (1H, ddd, *J* 7.8, 2.9, 3.6, H4′), 4.03 (1H, dd, *J* 2.9, 12.9, H5′), 4.11 (1H, dd, *J* 3.6, 12.9, H5″), 4.51 (1H, *pseudo* t, *J* 7.8, H3′), 5.93 (1H, d, *J* 3.4, H1′), 7.41 (1H, s, H6), 10.88 (1H, s, NH); δ_C 75 MHz [$CDCl_3$] 12.5 (CH_3), 12.6–13.4 (4 × CH[*C*H_3]$_2$), 16.9–17.4 (8 × CH_3), 31.5 (C6′), 45.9 (C2′), 60.4 (C5′), 69.1 (C3′), 83.6 (C4′), 88.4 (C1′), 111.5 (C5), 134.9 (C6), 151.4 (C2), 164.7 (C4), 175.0 (C7′); *m*/*z* (FAB^+): 565 (*M* + Na^+), 543 (*M* + H^+); HRMS (FAB^+): 565.2373 (*M* + Na^+), $C_{24}H_{42}N_2O_8Si_2$ requires 565.2377; ε (266 nm) = 9850 in MeOH.

5-Bromo-2′-deoxy-2′-α-*C*-carboxymethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (4c)

White amorphous solid; δ_H 300 MHz [$CDCl_3$] 0.97–1.26 (28H, m, 4 × ^{i}Pr), 2.49 (1H, dd, *J* 10.7, 14.9, H6′), 2.73–2.86 (2H, m, H2′, H6″), 3.89 (1H, ddd, *J* 7.7, 2.9, 3.6, H4′), 4.03 (1H, dd, *J* 2.9, 13.0, H5′), 4.12 (1H, dd, *J* 3.6, 13.0, H5″), 4.52 (1H, *pseudo* t, *J* 7.7, H3′), 5.9 (1H, d, *J* 3.0, H1′), 7.89 (1H, s, H6), 10.79 (1H, s, NH); δ_C 75 MHz [$CDCl_3$] 12.6–13.4 (4 × CH[CH_3]$_2$), 17.0–17.4 (8 × CH_3), 31.1 (C6′), 45.9 (C2′), 60.7 (C5′), 68.9 (C3′), 83.9 (C4′), 89.0 (C1′), 97.5 (C5), 138.8 (C6), 150.6 (C2), 159.9 (C4), 175.4 (C7′); *m*/*z* (FAB^+): 629 (*M* + Na^+), 607 (*M* + H^+); HRMS (FAB^+): 607.1506 ($C_{23}H_{40}N_2O_8Si_2{}^{79}Br$ (*M* + H^+) requires 607.1510); ε (278 nm) = 8550 in MeOH.

2′-Deoxy-2′-α-*C*-carboxymethyl-5-fluoro-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (4d)

White amorphous solid; δ_H 300 MHz [$CDCl_3$] 1.00–1.12 (28H, m, 4 × ^{i}Pr), 2.53 (1H, dd, *J* 10.6, 15.4, H6′), 2.7–2.85 (2H, m, H2′, H6″), 3.91 (1H, m, H4′), 4.05–4.07 (2H, m, H5′, H5″), 4.52 (1H, *pseudo* t, *J* 7.3, H3′), 5.91 (1H, d, *J* 2.2, H1′), 7.69 (1H, d, $J_{6,F}$ 5.6, H6), 10.9 (1H, br s, NH); δ_F 235 MHz [$CDCl_3$] −163.8 (d, 1F, $J_{6,F}$ 5.6); δ_C 75 MHz [$CDCl_3$] 12.6–13.4 (4 × CH[CH_3]$_2$), 16.8–17.4 (8 × CH_3), 31.1 (C6′), 45.7 (C2′), 61.2 (C5′), 69.6 (C3′), 84.2 (C4′), 88.6 (C1′), 123.4 (d, 1C, $J_{6,F}$ 35.0, C6), 141.0 (d, 1C, $J_{5,F}$ 240, C-5), 150.0 (C2), 157.2 (d, 1C, $J_{4,F}$ 27.0, C4), 175.7 (C7′); *m*/*z* (FAB^+): 569 (*M* + Na^+), 547 (*M* + H^+); HRMS (FAB^+): 569.2090 ($C_{23}H_{39}FN_2O_8Si_2Na$ (*M* + Na^+) requires 569.2127); ε (268 nm) = 8430 in MeOH.

N^4-Benzoyl-2′-deoxy-2′-α-*C*-carboxymethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)cytidine (4e)

White amorphous solid; δ_H 300 MHz [$CDCl_3$] 0.84–1.11 (28H, m, 4 × ^{i}Pr), 2.64–2.84 (3H, m, H2′, H6′, H6″), 3.97–4.07 (2H, m, H4′, H5′), 4.13 (1H, dd, *J* 3.8, 12.8, H5″), 4.53 (1H, *pseudo* t, *J* 6.9, H3′), 5.95 (1H, d, *J* 2.3, H1′), 7.41–7.6 (5H, m, Ph), 7.99 (1H, d, *J* 7.4, H6), 8.09 (1H, d, H5); δ_C 75 MHz [$CDCl_3$] 12.7–13.3 (4 × *C*H[CH_3]$_2$), 16.8–17.5 (8 × CH_3), 31.4 (C6′), 45.7 (C2′), 61.3 (C5′), 69.7 (C3′), 84.1 (C4′), 89.7 (C1′), 96.8 (C6), 128.3, 128.8, 133.1 (Ph), 144.5 (C5), 154.5 (C2), 163.0 (C4), 167.4 (C7), 175.8 (C7′); *m*/*z* (FAB^+) 632 (*M* + H^+); HRMS (FAB^+) 632.2814 ($C_{39}H_{46}N_3O_8Si_2$ (*M* + H^+) requires 632.2823); ε (260 nm) = 23150; ε (304 nm) = 9920 in MeOH.

2,6-Dichloro-9-[2-deoxy-2-α-*C*-carboxymethyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*erythro*-pentofuranosyl]purine (4f)

Off-white amorphous solid; δ_H 300 MHz [$CDCl_3$] 0.95–1.16 (28H, m, 4 ^{i}Pr), 2.63 (1H, dd, *J* 9.5, 17.1, 6′-H), 2.97 (1H, dd, *J* 5.8, 17.1, H6″), 3.22–3.31 (1H, m, H2′), 3.97–4.07 (3H, m, H4′, H5′, H5″), 5.04 (1H, *pseudo* t, *J* 7.2, H3′), 6.05 (1H, d, *J* 2.2, H1′), 8.33 (1H, s, H8); δ_C 75 MHz [$CDCl_3$] 12.7–13.3 (4 × CH[CH_3]$_2$), 17.0–17.3 (8 × CH_3), 31.1 (C6′), 44.6 (C2′), 62.6 (C5′), 71.6 (C3′), 84.4 (C4′), 88.7 (C1′), 131.3, 145.2, 152.2; *m*/*z* (FAB^+): 605 (*M* + H^+); HRMS (FAB^+) 605.1769 ($C_{24}H_{38}N_4O_6Si_2Cl_2$ (*M* + H^+) requires 605.1785); ε (274 nm) = 8600 in MeOH.

2′-Deoxy-2′-α-*C*-carboxymethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine (4g)

Off-white amorphous solid; δ_H 300 MHz [THF-d_8] 0.93–1.22 (28H, m, 4 × ^{i}Pr), 2.47 (1H, dd, *J* 7.1, 16.8, H6′), 2.85 (1H, dd, *J* 7.3, 16.8, H6″), 3.4 (1H, m, H2′), 4.02 (3H, m, H4′, H5′, H5″), 5.29 (1H, m, H3′), 5.99 (1H, d, *J* 3.9, H1′), 6.85 (NH_2), 7.99 (1H, s, H2), 8.11 (1H, s, H8); δ_C 75 MHz [THF-d_8] 13.9–14.4 (4 *C*H[CH_3]$_2$), 17.7–18.1 (8 × CH_3), 31.6 (C6′), 45.8 (C2′), 65.2 (C5′), 74.7 (C3′), 85.8 (C4′), 89.0 (C1′), 121.3 (C5), 140.6 (C8), 150.5 (C4), 153.6 (C6), 157.5 (C2), 174.3 (C7′); *m*/*z* (FAB^+): 552 (*M* + H^+); HRMS (FAB^+) 552.2686 ($C_{24}H_{42}N_5O_6Si_2$ (*M* + H^+) requires 552.2674); ε (260 nm) = 15190 in MeOH.

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