ARTICLE

OBC
www.rsc.org/obc

Conversion of 2-deoxy-D-ribose into 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine, 2′-deoxypseudouridine, and other *C*-(2′-deoxyribonucleosides)

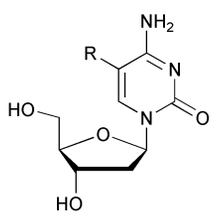
Colin B. Reese* and Qinpei Wu
Department of Chemistry, King's College London, Strand, London, UK WC2R 2LS.
E-mail: colin.reese@kcl.ac.uk; Fax: +44 (0)20 7848 1771

Received 5th June 2003, Accepted 28th July 2003
First published as an Advance Article on the web 18th August 2003

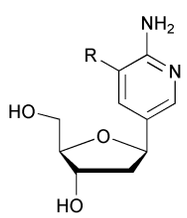
The synthesis of 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine **2a**, 2-amino-5-(2-deoxy-α-D-ribofuranosyl)-pyridine **23**, 2-amino-5-(2-deoxy-β-D-ribofuranosyl)-3-methylpyridine **2b**, 2-amino-5-(2-deoxy-α-D-ribofuranosyl)-3-methylpyridine **29** and 5-(2-deoxy-β-D-ribofuranosyl)-2,4-dioxopyrimidine [2′-deoxypseudouridine] **30a** is described. These *C*-nucleosides are prepared either from 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15** or from 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribono-1,4-lactone **16**, which are themselves prepared from 2-deoxy-D-ribose **13**. The sugar derivatives are first allowed to react with the appropriate 5-lithio-pyridine or 5-lithio-pyrimidine derivatives, which are prepared from 5-bromo-2-(dibenzylamino)pyridine **12a**, 5-bromo-2-[bis(4-methoxybenzyl)amino]pyridine **12b**, 5-bromo-2-dibenzylamino-3-methylpyridine **25** and 5-bromo-2,4-bis(4-methoxybenzyloxy)pyrimidine **33**. The products from the reactions between the lithio-derivatives and the lactol **15** are cyclized under Mitsunobu conditions; the products from the reactions between the lithio-derivatives and the lactone **16** are first reduced with L-Selectride before cyclization, also under Mitsunobu conditions. In all cases, the β-anomers of the protected *C*-nucleosides are the predominant products. Finally, the separation of the α- and β-anomers and the removal of all of the protecting groups are described.

Introduction

The antigene approach[1,2] to oligonucleotide-based chemotherapy involves the targeting of a specific sequence of a DNA duplex with the intention of forming a triplex. The third strand, which is a single-stranded oligonucleotide or oligonucleotide analogue derived from 10–20 pyrimidine nucleotides, is targeted at a sequence of an equal number of contiguous purine 2′-deoxyribonucleotides in the duplex. The third strand has a parallel orientation to the purine strand of the duplex and hybridises with it *via* Hoogsteen hydrogen bonds. This presents no problem as far as targeting AT base pairs is concerned. Thus it can be seen from Fig. 1a that H-3 of a third strand thymine residue can hydrogen bond with N-7 of a duplex adenine residue and a 6-amino proton of the same adenine residue can hydrogen bond with O-4 of the single strand thymine residue. However, it can be seen from Fig. 1b that Hoogsteen base-pairing between a cytosine residue in the third strand and a guanine residue in the duplex requires that the cytosine residue should be protonated on N-3. This would be expected to cause a problem at the physiological pH as the pK_a of 2′-deoxycytidine (dC) is only 4.3.[3] Therefore the dC residues in the third strand would be expected to be largely unprotonated on N-3 at pH 7. In order to overcome this problem, two groups of workers[4,5] independently suggested the replacement of 2′-deoxycytidine **1a** by the structurally closely related *C*-nucleoside, 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine (β-ADRP) **2a** (pK_a 6.26,[4] 5.93[5]) in third strand oligonucleotides. The hydrogen bonds assumed to be involved in the triplex derived from the hybridisation of protonated β-ADRP [C*(H^+)] with a GC duplex are illustrated in Fig. 1c. It was clearly demonstrated by means of several techniques[4–7] that this modification led to enhanced triplex stability, especially at higher pHs. For this reason, the availability of a convenient synthesis of β-ADRP **2a** has become a matter of considerable interest.



1 a; R=H
b; R=Me



2 a; R=H
b; R=Me

To the best of our knowledge, there are two previously published reports relating to the synthesis of β-ADRP **2a**. In 1995, Hsieh and McLaughlin reported[8] that bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] and tris(pentafluorophenyl)phosphine catalysed the addition of the iodo-compound **3** to the unsaturated sugar derivative **4** (Scheme 1a, step i). Following the removal of the *tert*-butyldiphenylsilyl protecting group, reduction of the resulting keto function and finally ammonolytic removal of the benzoyl protecting group, β-ADRP **2a** was obtained in *ca.* 14% overall yield. Although there is no reason to doubt the identity of the final product, no evidence was provided for the anomeric configuration of the coupling product **5** or for the configuration at C-3′ in the final product **2a**. In 1996, Hildbrand and Leumann reported[4] a second synthesis of β-ADRP **2a** (Scheme 1b). Particular features of the latter synthesis worth mentioning are (a) that the pyridine 2-amino function was protected as a 2,2,5,5-tetramethyl-2,5-disilacyclopentane derivative (as in the lithio-pyridine derivative **7**) in the coupling step (step vii) and (b) that the 2′-deoxygenation of an intermediate *C*-ribofuranoside derivative **9** was involved. However, the main problem with this approach is that it involves a large number of steps. In order to decrease the number of steps involved, we decided to base our approach to the synthesis of β-ADRP **2a** on 2-deoxy-D-ribose, which is a commercially available starting material.

DOI: 10.1039/b306341k

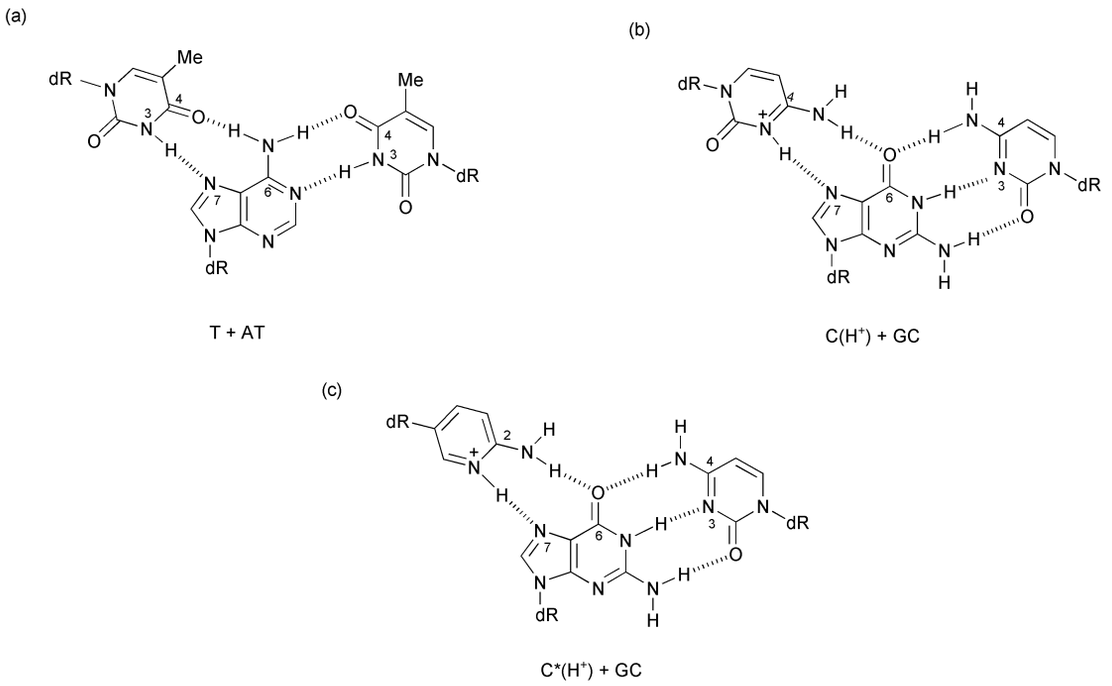
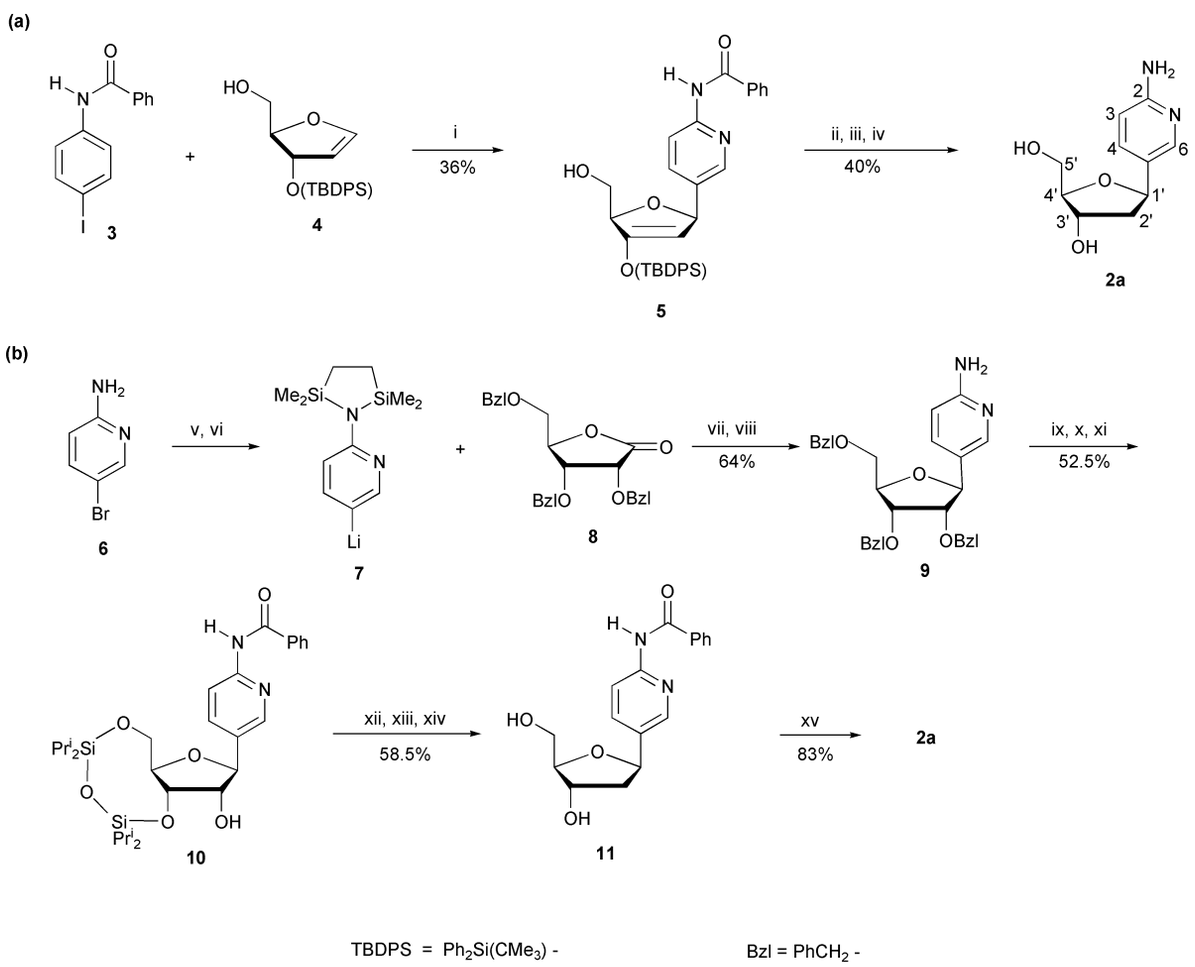


Fig. 1 Triplex hydrogen bonds

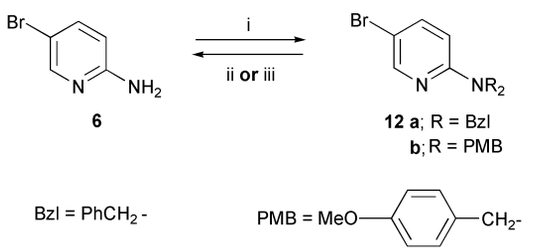


Scheme 1 *Reagents and conditions*: i, $P(C_6F_5)_3$, $Pd(dba)_2$, nBu_3N, MeCN; ii, nBu_4NF, AcOH, THF; iii, $NaBH(OAc)_3$, AcOH, MeCN; iv, conc. aq. NH_3, 55 °C, 72 h; v, $Me_2Si(Cl)CH_2CH_2Si(Cl)Me_2$, *n*BuLi, THF, −75 °C; vi, *n*BuLi, THF, −75 °C; vii, THF, −75 °C to 0 °C; viii, Et_3SiH, Et_2O–BF_3, CH_2Cl_2, −75 °C to rt; ix, PhCOCl, C_5H_5N, CH_2Cl_2, rt; x, BBr_3, CH_2Cl_2, −75 °C; xi, $Pr^i_2Si(Cl)OSi(Cl)Pr^i_2$, C_5H_5N, rt; xii, 4-$MeC_6H_4OC(S)Cl$, DMAP, MeCN, rt; xiii, azoisobutyronitrile, nBu_3SnH, PhMe, 80 °C; xiv, $nBuN_4F$, THF, rt; xv, aq. $MeNH_2$, 70 °C.

Results and discussion

We first addressed the matter of how the 2-amino function of the pyridine moiety should be protected. As we proposed to use a lithio-pyridine derivative in the coupling step, an acyl protecting group was clearly unsuitable. We were also very reluctant to use the disilyl protecting group (as in **7**), as it appeared to be too labile to survive the coupling and deoxygenation steps

(Scheme 1b, steps vii and viii) in Leumann's synthesis.[7] In the event, we decided to look into the possibility of protecting the 2-amino function either with two benzyl (Bzl, as in **12a**) or two 4-methoxybenzyl (PMB as in **12b**) groups (Scheme 2). At the outset, we were uncertain of what would be the best way of removing 2-*N*-benzyl protecting groups towards the end of the synthesis. However, by analogy with the procedures used to unblock (4-methoxybenzyl)-protected hydroxy functions,[9] it seemed likely that it would be possible to remove 2-*N*-(4-methoxybenzyl) groups either with ammonium cerium(IV) nitrate (CAN) or with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



Scheme 2 *Reagents and conditions*: i, Bzl–Br **or** PMB–Cl, NaH, DMA, 0 °C; ii, (for **12a**) CAN, MeCN–H_2O (9 : 1 v/v), rt, 30 min; iii (for **12b**) CF_3CO_2H–CH_2Cl_2 (9 : 1 v/v), rt, 5 h.

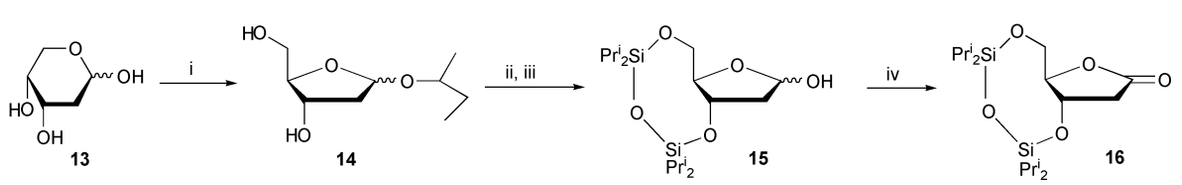
5-Bromo-2-(dibenzylamino)pyridine **12a** was readily prepared (Scheme 2, step i) by treating 2-amino-5-bromopyridine **6** with benzyl bromide and sodium hydride in *N*,*N*-dimethylacetamide (DMA) and was isolated as a crystalline solid in 91% yield. In the same way, 5-bromo-2-[bis(4-methoxybenzyl)-amino]pyridine **12b** was obtained in 89% yield following the alkylation of 2-amino-5-bromopyridine **6** with 4-methoxybenzyl chloride. Other workers[10,11] had previously reported that *N*-debenzylation of *tertiary* but not of *secondary* amines could be effected by treatment with CAN. We were therefore pleasantly surprised to find that when the dibenzylamino compound **12a** was treated with an excess of CAN in acetonitrile–water (9 : 1 v/v) at room temperature (Scheme 2, step ii), *both* benzyl protecting groups were readily removed and 2-amino-5-bromopyridine **6** was obtained in high yield. Following a slight modification of a very recently reported procedure,[12] when a solution of the bis(4-methoxybenzyl)-amino compound **12b** in trifluoroacetic acid (TFA)–dichloromethane (1 : 9 v/v) was allowed to stand at room temperature (Scheme 2, step iii), both 4-methoxybenzyl protecting groups were removed and 2-amino-5-bromopyridine **6** was again obtained in high yield.

We then undertook the preparation of 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribono-1,4-lactone **16**, the sugar component that we initially selected for our proposed *C*-nucleoside synthesis. We found that the four-step procedure, outlined in Scheme 3, for the conversion of 2-deoxy-D-ribose **13** into the lactone **16** to be both more convenient and much faster to carry out than the previously reported two-step procedure,[13] the first step of which (*i.e.* the oxidation of unprotected 2-deoxy-D-ribose **13**) requires a reaction time of 5 days. First, 2-deoxy-D-ribose **13** was treated with hydrogen chloride in butan-2-ol solution (Scheme 3, step i) to give the ribofuranoside **14**. Reaction between this product, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[14] and imidazole in THF solution, followed by hydrolysis with TFA in wet dichloromethane solution (steps ii and iii) gave the lactol[15] **15**, which was isolated in 90% overall yield. The intermediate isobutyl glycoside **14** was chosen in preference to the corresponding methyl glycoside in order to facilitate[16] the acid-catalyzed hydrolysis reaction (step iii). Oxidation of the lactol **15** with pyridinium chlorochromate in dichloromethane solution (step iv) gave the lactone **16** in 85% isolated yield.

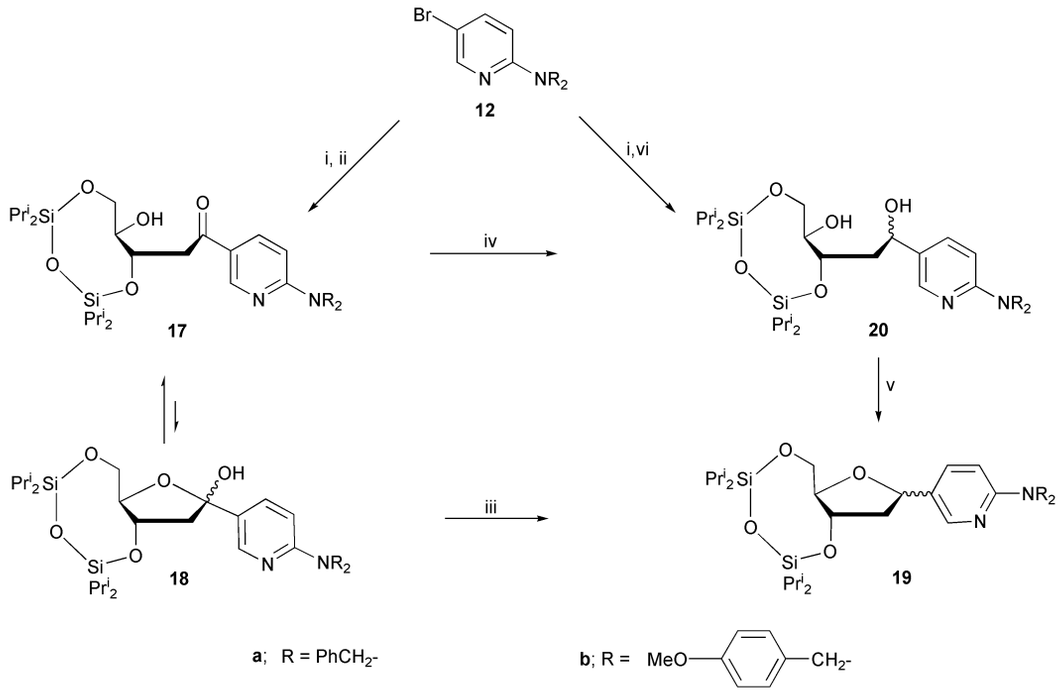
2-(Dibenzylamino)-5-bromopyridine **12a** was treated with *n*-butyllithium and the resulting lithio-derivative was allowed to react with the lactone **16** at −78 °C (Scheme 4, steps i and ii) to give the hydroxy-ketone **17a**. Spectroscopic evidence supported the assignment of the open-chain rather than the cyclic tautomeric structure **18a** of this product. First, a band at 1666 cm^{-1} in the IR spectrum may be assigned to the absorption of the carbonyl group. Secondly, in the COSY NMR spectrum of compound **17a**, a cross-peak is observed between the resonance signal of the hydroxy proton (at δ 4.99) and H-4′ (at δ 3.31). Finally, the signal at δ 196.24 in the ^{13}C NMR spectrum of compound **17a** may be assigned to the resonance of the carbonyl carbon atom (*i.e.* C-1′). However, when the hydroxy-ketone **17a** was treated with triethylsilane and boron trifluoride diethyl etherate[17] in dichloromethane solution (step iii), a mixture of the α- and β-anomers (α : β ratio, 1 : 3) of the desired product **19a** was obtained but only in *ca.* 30% yield. The anomeric assignments are based on NOESY NMR data (see below) in respect of the fully-unblocked *C*-nucleosides (**2a** and its α-anomer **23**).

Much better yields of the combined α- and β-anomers **19a** were obtained by first reducing the hydroxy-ketone **17a** to a mixture of the diastereoisomeric diols **20a**. Initially, reduction (step iv) was carried out by treatment with sodium borohydride in methanol solution. The resulting diol mixture **20a** was cyclized by treatment with diethyl azodicarboxylate (DEAD) and triphenylphosphine[18] in THF solution (step v) to give the desired products **19a** (β : α ratio, *ca.* 2 : 1) in 68% isolated yield for the two steps (or *ca.* 46% overall yield for the three steps, starting from the lactone **16**). Evidence that the Mitsunobu reaction[18] proceeded, as perhaps would be expected, by the attack of the 4′-hydroxy function on C-1′, rather than by the attack of the 1′-hydroxy function on C-4′, was provided by comparing the NMR spectra of the fully-unblocked β-anomer **2a** (see below) with corresponding spectra in the literature. The β : α anomeric ratio was increased to *ca.* 7 : 1 by carrying out the reduction of the hydroxy-ketone **17a** (step iv) with lithium tri-*sec*-butyl borohydride (L-Selectride)[19] in THF. Following Mitsunobu cyclization with DEAD and triphenylphosphine in THF (step v), the desired products were obtained in 44% overall yield for the three steps (ii, iv and v), starting from the lactone **16**.

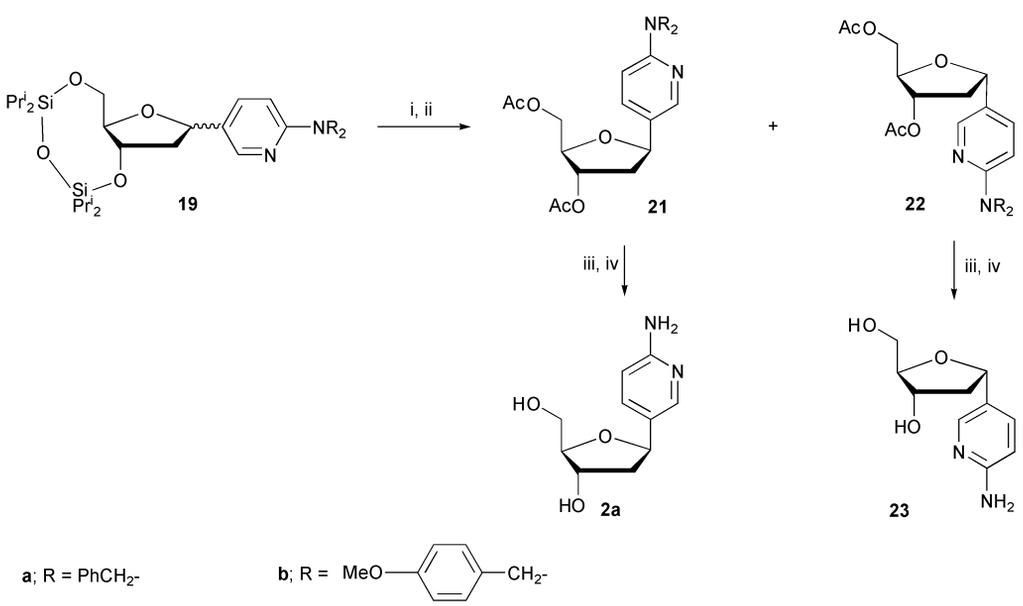
A β-rich mixture of the fully-protected *C*-nucleosides **19a** was then obtained in two fewer steps overall by treating the *lactol* **15** with the lithio-pyridine derivative (Scheme 4, steps i and vi) and then cyclizing the resulting diol mixture **20a** with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (step v). In this way, the desired products **19a** (β : α ratio, *ca.* 5 : 1) were obtained in 51% overall yield for the two steps (*i.e.* steps vi and v), starting from the lactol **15**. Although the products **19a** were slightly poorer in the β-anomer (*i.e. ca.* 83% rather than *ca.* 87%) than those obtained above in the procedure involving L-Selectride reduction, we believe that the



Scheme 3 *Reagents and conditions*: i, butan-2-ol, HCl, rt, 25 min; ii, $Pr^i_2Si(Cl)OSi(Cl)Pr^i_2$, imidazole, THF, rt, 90 min; iii, TFA, H_2O, CH_2Cl_2, −15 °C, 20 min; iv, pyridinium chlorochromate, CH_2Cl_2, rt, 16 h.



Scheme 4 *Results and conditions*: i, *n*BuLi, *n*-hexane, THF, −78 °C, 40 min; ii, lactone **16**, THF, −78 °C, 4 h; iii, Et_3SiH, Et_2O–BF_3, CH_2Cl_2, −78 °C to −10 °C, 6 h; iv, $NaBH_4$, MeOH, 0 °C, 2 h **or** L-Selectride, THF, −78 °C to rt; v, diethyl **or** diisopropyl azodicarboxylate, Ph_3P, THF, 0 °C, 3 h; vi, lactol **15**, THF, −78 °C, 1 h and then −78 °C to 0 °C over 3 h.



Scheme 5 *Reactions and conditions*: i, Et_4NF, MeCN, rt, 90 min; ii, Ac_2O, 1-methylimidazole, C_5H_5N, rt; iii, a (for **21a** and **22a**), CAN, MeCN–H_2O (98 : 2 v/v), rt, 25 min **or** b (for **21b**) TFA–CH_2Cl_2 (1 : 1 v/v), reflux, 90 min; iv, $MeNH_2$, EtOH, rt, 16 h.

lactol-based approach may be regarded as the synthetic method of choice in the present context. A similar result was obtained, starting from 5-bromo-2-[bis(4-methoxybenzyl)amino]pyridine **12b**. In the same way, the pyridine derivative **12b** was lithiated and then allowed to react with the lactol **15** (Scheme 4, steps i and vi). Following Mitsunobu cyclization with DIAD and triphenylphosphine, the fully-protected *C*-nucleosides **19b** (β : α ratio, *ca*. 5.5 : 1) were obtained in 55% overall yield for the two steps (*i.e.* steps vi and v).

Unfortunately, the chromatographic separation of the α- and β-anomers in both of the fully-protected *C*-nucleoside mixtures **19a** and **19b** did not prove to be feasible. However, when the mixture of dibenzylamino-compounds **19a** was treated first with tetraethylammonium fluoride in acetonitrile solution and then with acetic anhydride in pyridine (Scheme 5, steps i and ii), the mixture of 3′,5′-diacetates **21a** and **22a** thereby obtained could be separated by short column chromatography. In this way, the pure β- and α-anomers (**21a** and **22a**) were obtained in 76 and 15% isolated yields, respectively. The anomeric mixture of [bis(4-methoxybenzyl)]-compounds **19b** was also converted by this two-step procedure into a separable mixture of 3′,5′-diacetates: the pure anomers **21b** and **22b** were thereby obtained in 63 and 12% isolated yields, respectively. Treatment of the diacetate **21a** first with ammonium cerium(IV) nitrate (CAN) in wet acetonitrile and then with alcoholic methylamine (Scheme 5, steps iiia and iv) gave 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine (β-ADRP) **2a**, which was isolated as a colourless oil in 69% yield. Treatment of the [bis(4-methoxybenzyl)]-protected diacetate **21b** first with TFA in dichloromethane and then with alcoholic methylamine (steps iiib and iv) gave β-ADRP **2a** in 68% isolated yield. The unblocking of the dibenzyl-protected α-anomer **22a**, which was carried out in the same way as the corresponding β-anomer **21a** (*i.e.* by steps iiia and iv), gave α-ADRP **23** in 53% isolated yield. None of the

Table 1 ^{1}H NMR spectra [$(CD_3)_2SO$] of 2-amino-5-(2-deoxy-β-(and α)-D-ribofuranosyl)pyridines **2a** and **23**

Compound	H-1′	H-2′(α)	H-2′(β)	H-3′	H-4′	H-5′	H-3	H-4	H-6
β-ADRP **2a**	4.83 dd	1.93 m	1.80 m	4.17 m	3.71 m	3.42 m	6.41 d	7.37 dd	7.85 d
α-ADRP **23**	4.75 dd	1.73 m	2.41 m	4.17 m	3.76 m	3.40 dd, 3.50 dd	6.42 d	7.42 dd	7.84 d

yields obtained has so far been optimised. If the factors of stereoselectivity and the overall yield of fully-unblocked β-ADRP **2a** are taken into account, no clear preference for the protection of the 2-amino function (either with benzyl or 4-methoxybenzyl groups) is clearly discernable from the present results.

The ^{1}H and ^{13}C NMR spectra of β-ADRP **2a** were similar to the corresponding spectra reported[7] in the literature, allowing for the fact that the latter spectra were measured in methanol-d_4 rather than in DMSO-d_6 solution. Relevant ^{1}H NMR spectroscopic data relating to compounds **2a** and **23** are listed in Table 1 and through space proton–proton interactions, based on NOESY spectra, are indicated in Fig. 2. The assignments in Table 1 are mainly based on two-dimensional ^{1}H–^{1}H COSY spectra. It is apparent that H-2′(β) resonates at a higher field than H-2′(α) in the β-anomer **2a** and that H-2′(α) resonates at a higher field than H-2′(β) in the α-anomer **23**. However, the assignment of the H-2′ resonance signals is not based on the apparent shielding effect of the aglycone on the proton *cis* to it. In the NOESY spectrum of the β-anomer **2a**, H-4 and H-5′ interact with H-2′(β) and not with H-2′(α), whereas H-4′ interacts with H-2′(α) and not with H-2′(β). Furthermore, H-1′ interacts more strongly with H-2′(α) than with H-2′(β). In the NOESY spectrum of the α-anomer **23**, H-4, H-6 and H-4′ interact with H-2′(α) and not with H-2′(β), whereas H-1′ and H-3′ interact more strongly with H-2′(β) than with H-2′(α). We believe that these NOESY spectroscopic data provide strong support for the anomeric configurational assignments that have been made.

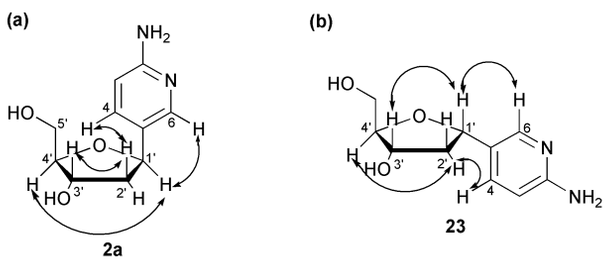


Fig. 2 Through space proton–proton interactions indicated by the NOESY spectra of (a) β-ADRP **2a** and (b) α-ADRP **23**.

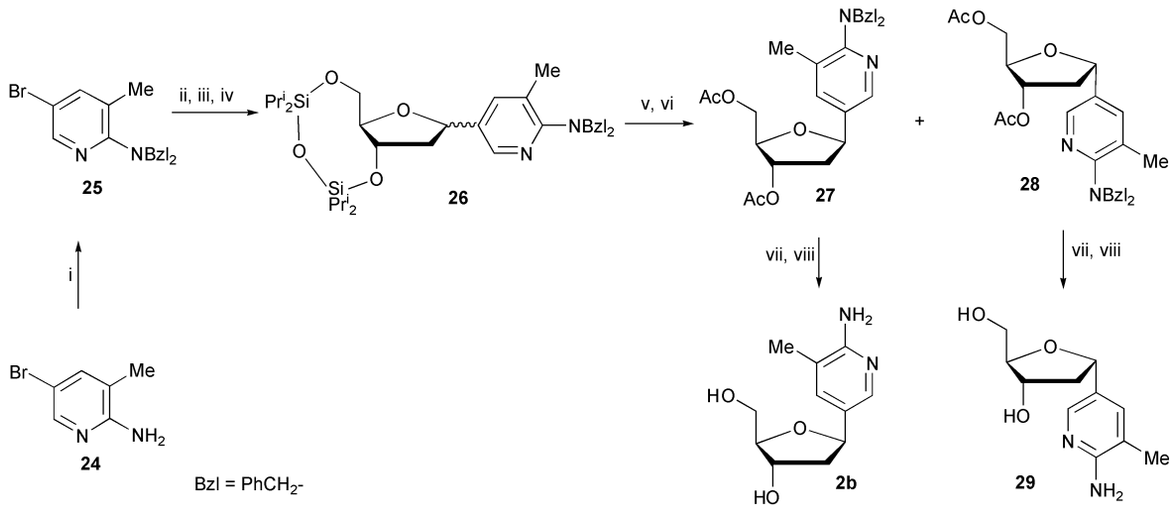
Although there is very little difference in the pK_a values of 2′-deoxycytidine **1a** and 2′-deoxy-5-methylcytidine **1b**, third strand oligonucleotides in which cytosine are replaced by 5-methylcytosine residues appear[20] to hybridise more readily with the contiguous purine strands of duplexes. For this reason, Leumann and his coworkers[7] also undertook the synthesis of 2-amino-5-(2-deoxy-β-D-ribofuranosyl)-3-methylpyridine (β-D-ADRMP) **2b** by essentially the same procedure that they used (Scheme 1b) in the synthesis of β-ADRP **2a**. In the event, these workers found that third strand oligonucleotides in which 2′-deoxycytidine **1a** were replaced by β-ADRMP **2b** residues hybridised with the purine strands of duplexes only marginally better than the corresponding oligonucleotides in which deoxycytidine were replaced by β-ADRP **2a** residues. We nevertheless decided to undertake the synthesis of β-ADRMP **2b** by the relatively short route, starting from 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15**, used in the preparation of β-ADRP **2a** (Scheme 4, steps i, vi and v, and Scheme 5, steps i, ii, iiia and iv).

5-Bromo-2-dibenzylamino-3-methylpyridine **25** was prepared by allowing 2-amino-5-bromo-3-methylpyridine[21] **24** to react with benzyl bromide and sodium hydride (Scheme 6, step i). This compound, which was isolated as a colourless oil in high yield, was lithiated in the usual way (step ii) and the product was allowed to react with the lactol **15** (step iii). Following Mitsunobu cyclization of the resulting mixture of diols (step iv), the fully-protected target *C*-nucleoside mixture **26** (β : α ratio *ca*. 1.5 : 1) was obtained and isolated as a colourless oil in 41.5% overall yield for the three steps (steps ii, iii and iv). In order to separate this mixture into pure anomers, it was again necessary first to convert it into the corresponding 3′,5′-diacetate mixture (**27** + **28**) by the now standard two-step procedure (Scheme 6, steps v and vi; see also Scheme 5, steps i and ii). In this way, the pure β- and α-anomers (**27** and **28**) were isolated in 47 and *ca*. 7% yield, respectively, after chromatography. Unblocking of the β- and α-anomers was then carried out by the two-step procedure (steps vii and viii) used in the preparation of β- and α-ADRP (Scheme 5, steps iiia and iv) to give β-ADRMP **2b** and α-ADRMP **29** in 58 and 46% isolated yield, respectively. None of these yields has yet been optimised. The chemical shifts and multiplicities of the H-2′ resonance signals in the ^{1}H NMR spectra of β- and α-ADRMP were virtually identical to the corresponding resonance signals in the ^{1}H NMR spectra of β- and α-ADRP (**2a** and **23**; Table 1). Unfortunately, the anomeric mixture **26** obtained in the Mitsunobu cyclization reaction (Scheme 6, step iv) was much poorer in the β-anomer than the corresponding mixture of anomers **19a** obtained in the preparation of β- and α-ADRP by the same route (Scheme 4, steps i, vi and v). We are not able at present to offer an explanation for this result. However, we believe that it may be possible to obtain an anomeric mixture **26** much richer in the β-anomer by starting from the protected lactone **16** and by reducing the putative intermediate hydroxyketone (corresponding to compound **17a**, Scheme 4) with L-Selectride before carrying out the Mitsunobu cyclization reaction.

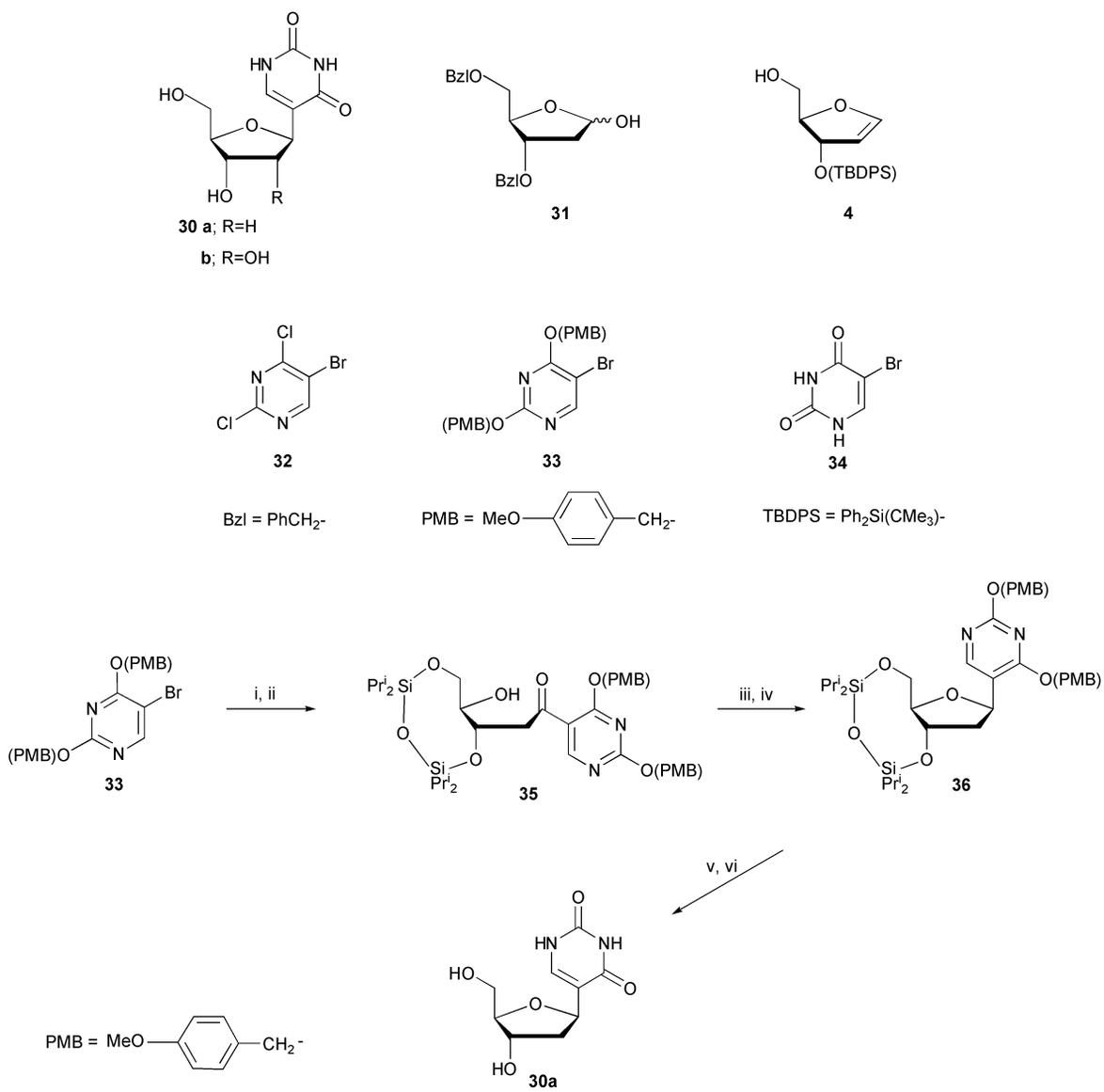
In an attempt to establish the generality of the present approach to 2′-deoxyribofuranose *C*-nucleosides, starting either from 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribono-1,4-lactone **16** or 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15**, we decided to undertake the synthesis of 5-(2-deoxy-β-D-ribofuranosyl)uracil **30a**. There are several reports[22–25] in the literature relating to the preparation of this compound, which is usually referred to as 2′-deoxypseudouridine. While 5-(β-D-ribofuranosyl)uracil [pseudouridine] **30b**[22,23] has been a convenient starting material, preparations starting from 3,5-di-*O*-benzyl-D-ribose[24] **31** and 1,4-anhydro-2-deoxy-3-*O*-(*tert*-butyldiphenylsilyl)-D-*erythro*-pent-1-enitol[25] **4** have also been reported.

The PMB group was found to be satisfactory for the protection of the 1,2- and 3,4-lactam functions of uracil. When the commercially-available 5-bromo-2,4-dichloropyrimidine **32** was treated with 4-methoxybenzyl alcohol and sodium hydride in THF at 0 °C, 5-bromo-2,4-bis(4-methoxybenzyloxy)pyrimidine **33** was obtained and isolated as a crystalline solid in 92% yield. The PMB protecting groups proved to be readily removable under conditions that were unlikely to promote anomeric interconversion. When the bis(4-methoxybenzyl) compound **33** was allowed to stand in TFA–dichloromethane (1 : 9 v/v) at room temperature for 15 min, it was quantitatively converted into 5-bromouracil **34**, which was isolated as a colourless solid in good yield.

2,4-Bis(4-methoxybenzyloxy)-5-lithiopyrimidine, which was prepared by treating the corresponding 5-bromo-compound



Scheme 6 *Reactions and conditions*: i, Bzl–Br, NaH, DMA, THF; ii, *n*BuLi, *n*-hexane, THF, −78 °C, 40 min; iii, lactol **15**, THF, −78 °C, 1 h and then −78 °C to 0 °C over 3 h; iv, diisopropyl azodicarboxylate, Ph_3P, THF, 0 °C, 3 h; v, Et_4NF, MeCN, rt, 90 min; vi, Ac_2O, 1-methylimidazole, C_5H_5N, rt; vii, CAN, MeCN–H_2O (98 : 2 v/v), rt, 25 min; viii, $MeNH_2$, EtOH, rt, 16 h.



Scheme 7 *Reactions and conditions*: i, *n*-BuLi, THF, hexane, −100 °C, 30 min; ii, lactone **16**, THF, −100 °C to −78 °C, 3 h; iii, L-Selectride, −78 °C to rt; iv, diisopropyl azodicarboxylate, Ph_3P, THF, rt, 3 h; v, Et_4NF, MeCN, rt, 1 h; vi, TFA–CH_2Cl_2 (1 : 9 v/v), rt, 15 min.

33 with *n*-butyllithium in THF–hexane at −100 °C (Scheme 7, step i), proved to be unstable at the higher temperature required for the coupling reaction with 2-deoxy-3,5-*O*-(1,1,3,3-tetra-isopropyldisiloxan-1,3-diyl)-D-ribose **15** to occur. However, the lithio-pyrimidine reacted readily with the corresponding lactone **16** at −100 °C (step ii) to give the hydroxy-ketone **35**.

The latter compound was reduced with L-Selectride (step iii) and the diol mixture obtained was cyclized under Mitsunobu conditions (step iv) to give the required fully-protected target compound **36** in *ca*. 43% overall yield for the three steps (steps ii, iii and iv), starting from the lactone **16**. Very little α-anomer was obtained. If it is assumed that the Mitsunobu reaction[18] was stereospecific, it follows that L-Selectride reduction (step iii) was highly stereoselective. In any case, any contaminating α-anomer was removed in the course of the chromatographic purification of the β-anomer **36**. Following unblocking by treatment first with tetraethylammonium fluoride (step v) in acetonitrile and then with trifluoroacetic acid in dichloromethane (step vi), 2′-deoxypseudouridine **30a** was obtained and isolated as a colourless crystalline solid in 78% yield. The anomeric configuration of this product was based on its NOESY spectrum (see Experimental section) and on the fact that its ^{13}C NMR spectrum was virtually identical to that recently reported by Ramzaeva *et al.*[26] It is particularly noteworthy that the latter workers[26] prepared their 2′-deoxypseudouridine **30a** by the 2′-deoxygenation of pseudouridine **30b**.

In conclusion, we believe that we have developed a convenient and perhaps general method for the synthesis of *C*-(β-D-2′-deoxyribofuranosides) derived from pyridine and pyrimidine aglycones. It is possible that it will also be applicable to the synthesis of *C*-(β-D-2′-deoxyribofuranosides) derived from other aglycones.[27]

Experimental

Mps were measured with an Electrothermal melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 360 MHz with a Bruker AM 360 spectrometer. ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane, and *J*-values are given in Hz. Mass spectra were measured with a JEOL AX 505W spectrometer. Infrared spectra were measured with a Perkin-Elmer model 1600 FTIR spectrometer. Merck silica gel 60 F_{254} plates (Art 5715 and 5642) were used for thin layer chromatography (TLC) and were developed either in petroleum spirit (bp 40–60 °C)–ethyl acetate or dichloromethane–methanol mixtures. Merck silica gel 60 (Art 7729) was used for short-column chromatography. Tetrahydrofuran (THF) was dried by heating, under reflux, over sodium and benzophenone and was then distilled; acetonitrile and pyridine were dried by heating, under reflux, over calcium hydride and were then distilled; diethyl ether was dried over sodium wire and was then distilled; *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) were dried by heating with calcium hydride at *ca*. 40 °C and were then distilled under reduced pressure.

5-Bromo-2-(dibenzylamino)pyridine 12a

Sodium hydride (60% dispersion in mineral oil; 3.47 g, 87 mmol) was added to a stirred solution of 2-amino-5-bromopyridine **6** (5.00 g, 28.9 mmol) and benzyl bromide (8.68 cm^3, 73.0 mmol) in dry *N*,*N*-dimethylacetamide (20 cm^3) at 0 °C (ice–water bath). After 1 h, methanol (10 cm^3) was cautiously added and the products were concentrated under reduced pressure. Dichloromethane (60 cm^3) was added to the residue and the resulting mixture was washed with water (2 × 30 cm^3). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Crystallization of the residue from petroleum spirit (bp 40–60 °C) gave the *title compound* **12a** (Found: C, 64.7; H, 4.75; N, 7.9. $C_{19}H_{17}BrN_2$ requires: C, 64.60; H, 4.85; N, 7.93%) as colourless crystals (9.30 g, 91%), mp 76–77 °C; δ_H[$CDCl_3$] 4.79 (4 H, s), 6.38 (1 H, d, *J* 8.9), 7.15–7.40 (10 H, m), 7.45 (1 H, dd, *J* 2.5 and 9.0), 8.23 (1 H, d, *J* 2.2); δ_C[$CDCl_3$] 51.59, 107.05, 107.80, 127.38, 127.52, 129.05, 138.26, 140.05, 148.94, 157.56.

5-Bromo-2-[bis(4-methoxybenzyl)amino]pyridine 12b

Sodium hydride (60% dispersion in mineral oil; 3.45 g, 86 mmol) was added to a stirred solution of 2-amino-5-bromopyridine **6** (6.00 g, 34.7 mmol) and 4-methoxybenzyl chloride (11.5 cm^3, 85 mmol) in dry *N*,*N*-dimethylacetamide (25 cm^3) at 0 °C (ice–water bath). After 1 h, methanol (5 cm^3) was cautiously added and the products were concentrated under reduced pressure. Dichloromethane (40 cm^3) was added to the residue and the resulting mixture was washed with water (2 × 20 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure. Crystallization of the residue from petroleum spirit (bp 60–80 °C) gave the *title compound* **12b** (Found: C, 61.2; H, 5.0; N, 6.8. $C_{21}H_{21}BrN_2O_2$ requires: C, 61.03; H, 5.12; N, 6.78%) as colourless crystals (12.8 g, 89%), mp 84.5–85 °C; δ_H[$CDCl_3$] 3.70 (6 H, s), 4.58 (4 H, s), 6.26 (1 H, d, *J* 9.0), 6.26 (1 H, d, *J* 9.0), 6.75 (4 H, d, *J* 8.7), 7.04 (4 H, d, *J* 8.6), 7.32 (1 H, dd, *J* 2.5 and 9.0), 8.12 (1 H, d, *J* 2.4); δ_C[$CDCl_3$] 50.83, 55.68, 106.83, 107.92, 114.44, 128.69, 130.26, 139.98, 148.88, 157.58, 159.17.

5-Bromo-2-dibenzylamino-3-methylpyridine 25

Sodium hydride (60% dispersion in mineral oil; 3.22 g, 80.5 mmol) was added to a stirred solution of 2-amino-5-bromo-3-methylpyridine **24** (6.00 g, 32.1 mmol) and benzyl bromide (9.53 cm^3, 80.1 mmol) in dry THF–*N*,*N*-dimethylacetamide (2 : 1 v/v; 60 cm^3) at 0 °C (ice–water bath). After 16 h, triethylamine (10 cm^3, 72 mmol) was added and, after a further period of 30 min, methanol (10 cm^3) was cautiously added. The products were then concentrated under reduced pressure. Dichloromethane (60 cm^3) was added to the residue and the resulting mixture was filtered. The filtrate was washed with water (2 × 30 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60 °C)–ethyl acetate (9 : 1 v/v), were concentrated under reduced pressure to give the *title compound* **25** (HRMS Found: $(M + H)^+$, 367.0822. $^{12}C_{20}{}^1H_{20}{}^{79}Br^{14}N_2$ requires $(M + H)^+$, 367.0810) as a colourless oil (11.1 g, 94%); δ_H[$CDCl_3$] 2.43 (3 H, s), 4.39 (4 H, s), 7.26–7.45 (10 H, m), 7.58 (1 H, d, *J* 2.0), 8.23 (1 H, d, *J* 2.5); δ_C[$CDCl_3$] 19.14, 54.86, 113.66, 127.38, 127.80, 128.64, 128.72, 139.05, 142.08, 146.29, 160.40.

Removal of benzyl protecting groups from 5-bromo-2-(dibenzylamino)pyridine 12a

Ammonium cerium(IV) nitrate (8.04 g, 14.7 mmol) was added to a stirred solution of 5-bromo-2-(dibenzylamino)pyridine **12a** (1.05 g, 3.0 mmol) in acetonitrile–water (9 : 1 v/v; 30 cm^3) at room temperature. After 30 min, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added and the products were filtered through Celite. The residue was washed with ethyl acetate (3 × 20 cm^3). The combined filtrate and washings were separated, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Following the fractionation of the residue by short column chromatography, 2-amino-5-bromopyridine **6** (0.45 g, 87%) was obtained as a pale yellow crystalline solid, identical (mp, ^{1}H and ^{13}C NMR) to authentic material.

Removal of 4-methoxybenzyl protecting groups from 5-bromo-2-[bis(4-methoxybenzyl)amino]pyridine 12b

Trifluoroacetic acid (2.0 cm^3, 26 mmol) was added to a stirred solution of 5-bromo-2-[bis(4-methoxybenzyl)amino]pyridine **12b** (0.82 g, 2.0 mmol) in dichloromethane (18 cm^3) at room temperature. After 5 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added cautiously. The products were concentrated and then extracted with ethyl acetate (3 × 30 cm^3). The combined organic layers were dried ($MgSO_4$) and evapor-

ated under reduced pressure. Following fractionation of the residue by short column chromatography, 2-amino-5-bromopyridine **6** (0.31 g, 90%) was obtained as a pale yellow crystalline solid, identical (mp, ^{1}H and ^{13}C NMR) to authentic material.

2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose 15

A 4.0 M solution of hydrogen chloride in 1,4-dioxane (1.59 cm^3, 6.4 mmol) was added to a stirred solution of 2-deoxy-D-ribose **13** (5.00 g, 37.28 mmol) in dry butan-2-ol (95 cm^3) at room temperature. After 25 min, triethylamine (1.0 cm^3, 7.2 mmol) was added. The products were then concentrated under reduced pressure. The residue was dissolved in acetonitrile (20 cm^3) and the solution was evaporated under reduced pressure. After this process had been repeated twice more, the residue was dissolved in THF (120 cm^3) and imidazole (7.62 g, 0.112 mol) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (13.10 cm^3, 41.0 mmol) was added to the stirred solution at room temperature. After 1.5 h, saturated aqueous sodium hydrogen carbonate was added and the products were concentrated under reduced pressure. Dichloromethane (50 cm^3) was added and the resulting mixture was washed with saturated aqueous sodium hydrogen carbonate (3 × 30 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane, were concentrated under reduced pressure to give a colourless oil (15.0 g). Trifluoroacetic acid (17.8 cm^3, 0.23 mol) and water (1.0 cm^3) were added to a stirred solution of this material (5.0 g) in dichloromethane (190 cm^3) at −15 °C (ice–salt bath). After 25 min, triethylamine (34 cm^3, 0.24 mol) was added and the products were washed with saturated aqueous sodium hydrogen carbonate (3 × 100 cm). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60 °C)–ethyl acetate (9 : 1 v/v), were combined and evaporated under reduced pressure to give the *title compound* **15** (HRMS Found: $(M - H)^+$, 375.2030. $^{12}C_{17}{}^1H_{35}{}^{16}O_5{}^{28}Si_2$ requires $(M - H)^+$, 375.2023) as a colourless oil (4.20 g, 90%, based on D-ribose); $\delta_H[(CD_3)_2SO]$ 0.80–1.20 (28 H, m), 1.70 (0.5 H, m), 1.94 (0.5 H, m), 2.09 (0.5 H, m), 2.46 (0.5 H, m), 3.63 (0.5 H, m), 3.76 (1.5 H, m), 3.92 (1 H, m), 4.23 (0.5 H, m), 4.61 (0.5 H, m), 5.26 (1 H, m), 6.30 (1 H, m); $\delta_C[(CD_3)_2SO]$ 12.33, 12.40, 12.58, 12.94, 13.02, 13.10, 13.13, 17.10, 17.14, 17.18, 17.24, 17.29, 17.40, 17.43, 17.53, 17.57, 17.68, 17.75, 42.34, 42.99, 62.92, 66.44, 72.67, 74.34, 81.11, 83.77, 96.04, 96.57.

2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribono-1,4-lactone 16

Pyridinium chlorochromate (4.28 g, 19.9 mmol) was added to a stirred solution of 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15** (3.00 g, 7.97 mmol) in dichloromethane (100 cm^3) at room temperature. After 16 h, 3 M triethylammonium phosphate buffer (pH 9.0, 30 cm^3) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and then evaporated under reduced pressure. The residual oil was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60 °C)–ethyl acetate (9 : 1 v/v), were combined and concentrated under reduced pressure to give the *title compound* **16** (HRMS Found: $(M + H)^+$, 375.2008. $^{12}C_{17}{}^1H_{35}{}^{16}O_5{}^{28}Si_2$ requires $(M + H)^+$, 375.2023) as a colourless oil (2.55 g, 85%); ν_{max}^{film} 1790 cm^{-1}; $\delta_H[CDCl_3]$ 0.85–1.30 (28 H, m), 2.72 (1 H, dd, *J* 9.2 and 17.3), 2.86 (1H, dd, *J* 8.0 and 17.3), 3.93 (1H, dd, *J* 6.6 and 12.3), 4.14 (1 H, dd, *J* 3.5 and 12.3), 4.22 (1 H, m), 4.64 (1H, m); $\delta_C[CDCl_3]$ 13.34, 13.67, 13.97, 14.11, 17.65, 17.70, 17.83, 18.00, 18.15, 18.27, 38.67, 63.17, 70.51, 85.65, 173.81.

5-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-(dibenzylamino)pyridines 19a

(a) *n*-Butyllithium (1.6 M in hexane; 19.95 cm^3, 31.9 mmol) was added to a stirred solution of 5-bromo-2-(dibenzylamino)-pyridine **12a** (11.27 g, 31.9 mmol) in THF (150 cm^3) at −78 °C (acetone–dry ice bath). After 40 min, a pre-cooled (to −78 °C) solution of 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15** (5.00 g, 13.3 mmol) in THF (50 cm^3) was added. After a further period of 1 h, the products were allowed to warm up to 0 °C. After 3 h, dry ice (3 g) and then saturated aqueous sodium hydrogen carbonate (10 cm^3) were added and the products were concentrated to a small volume under reduced pressure. The residual mixture was partitioned between dichloromethane (100 cm^3) and saturated aqueous sodium hydrogen carbonate (30 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (30 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60 °C)–ethyl acetate (4 : 1 v/v), were concentrated under reduced pressure to give a colourless oil (6.81 g). Diisopropyl azodicarboxylate (5.35 cm^3, 27.2 mmol) was added dropwise to a stirred solution of this material (6.81 g) and triphenylphosphine (7.13 g, 27.2 mmol) in dry THF (100 cm^3) at 0 °C (ice–water bath). After 3 h, a 0.5 M solution of iodine in dichloromethane was added dropwise until the iodine coloration just persisted. Saturated aqueous sodium hydrogen carbonate (50 cm^3) and then saturated aqueous sodium thiosulfate (20 cm^3) were added. The products were then concentrated under reduced pressure. The residue was partitioned between dichloromethane (100 cm^3) and saturated aqueous sodium hydrogen carbonate (100 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60 °C)–ethyl acetate (9 : 1 v/v), were combined and concentrated under reduced pressure to give the *title compounds* **19a** (β : α ratio *ca.* 5 : 1) (HRMS Found: M^+, 632.3463. $^{12}C_{36}{}^1H_{52}{}^{14}N_2{}^{16}O_4{}^{28}Si_2$ requires: M^+, 632.3466) as a colourless oil (4.30 g, 51% overall yield); $\delta_H[CDCl_3]$ includes the following signals (for the β-anomer): 0.8–1.15 (28 H, m), 2.12 (1 H, m), 2.28 (1 H, m), 3.79 (1 H, dd, *J* 8.3 and 11.2), 3.87 (1 H, m), 4.09 (1H, dd, *J* 3.5 and 11.3), 4.54 (1 H, m), 4.78 (4 H, s), 4.98 (1 H, dd, *J* 6.6 and 8.3), 6.44 (1 H, d, *J* 8.8), 7.26 (10 H, m), 7.38 (1 H, dd, *J* 2.4 and 8.8), 8.16 (1 H, d, *J* 2.3); $\delta_C[CDCl_3]$ includes the following signals (for the β-anomer): 12.51, 13.00, 13.40, 13.51, 16.98, 17.07, 17.13, 17.29, 17.40, 17.44, 17.58, 42.35, 50.92, 63.96, 74.02, 77.37, 86.43, 105.76, 124.54, 126.95, 127.03, 128.55, 135.91, 138.29, 146.64, 158.49.

(b) *n*-Butyllithium (1.6 M in hexane; 3.5 cm^3, 5.6 mmol) was added to a stirred solution of 5-bromo-2-(dibenzylamino)-pyridine **12a** (1.98 g, 5.6 mmol) in dry THF (30 cm^3) at −78 °C (acetone–dry ice bath). After 40 min, the products were added to a stirred solution of 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribono-1,4-lactone **16** (1.50 g, 4.0 mmol) in dry THF at −78 °C. After 4 h, solid carbon dioxide (1.0 g) and then saturated aqueous sodium hydrogen carbonate (10 cm^3) were added. The products were concentrated under reduced pressure and the residual mixture was partitioned between dichloromethane (60 cm^3) and saturated aqueous sodium hydrogen carbonate (20 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column

chromatography on silica gel: the appropriate fractions, which were eluted with light petroleum (bp 40–60 °C)–ethyl acetate (85 : 15 v/v), were combined and concentrated under reduced pressure to give a colourless oil (1.77 g); ν_{max}^{film} 1666 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 0.7–1.05 (28 H, m), 2.94 (1 H, dd, *J* 8.1 and 15.0), 3.31 (2 H, m), 3.73 (1 H, d, *J* 10.8), 4.01 (1 H, d, *J* 10.1), 4.38 (1 H, m), 4.88 (4 H, br), 4.99 (1 H, d, *J* 5.9), 6.64 (1 H, d, *J* 9.1), 7.27 (10 H, m), 7.95 (1 H, dd, *J* 2.3 and 9.1), 8.78 (1 H, d, *J* 2.2); $\delta_C[(CD_3)_2SO]$ 12.41, 12.48, 12.83, 13.13, 13.24, 13.66, 17.28, 17.29, 17.38, 17.47, 17.53, 17.56, 17.66, 43.96, 51.21, 62.93, 68.64, 74.50, 105.76, 122.64, 127.21, 127.32, 128.80, 137.47, 138.02, 150.93, 160.18, 196.24.

Lithium tri-*sec*-butyl borohydride (L-Selectride, 1.0 M solution in THF, 4.6 cm^3, 4.6 mmol) was added dropwise over a period of 10 min to a stirred solution of this material (2.00 g, from two batches) in dry THF (20 cm^3) at −78 °C. The reactants were allowed to warm up to room temperature and saturated aqueous sodium hydrogen carbonate (5 cm^3) was added. The products were concentrated under reduced pressure and the residue was partitioned between dichloromethane (50 cm^3) and saturated aqueous sodium hydrogen carbonate (20 cm^3). The organic layer was separated, washed with saturated sodium hydrogen carbonate (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with light petroleum (bp 40–60 °C)–ethyl acetate (75 : 25 v/v) were combined and evaporated under reduced pressure to give a colourless oil (2.00 g). Diethyl azodicarboxylate (1.17 cm^3, 7.4 mmol) was added to a stirred solution of this material (2.00 g) and triphenylphosphine (1.94 g, 7.4 mmol) in dry THF (20 cm^3) at 0 °C (ice–water bath). After 3 h, a 0.5 M solution of iodine in dichloromethane was added dropwise until the iodine coloration just persisted. The products were then concentrated under reduced pressure. The residue was partitioned between dichloromethane (60 cm^3) and saturated aqueous sodium hydrogen carbonate (20 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography, as in (a) above to give the *title compounds* **19a** (β : α ratio *ca*. 7 : 1) as a colourless oil (1.27 g, 44% overall yield). Apart from the slightly different β : α ratio, the ^1H and ^{13}C NMR spectra of this material were virtually identical to the corresponding spectra indicated in (a) above.

(c) Instead of being reduced with L-Selectride, the product (0.20 g), obtained as in (b) above by allowing 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribono-1,4-lactone **16** to react with 2-(dibenzylamino)-5-lithiopyridine, was treated with sodium borohydride (0.034 g, 0.4 mmol) in methanol solution at 0 °C (ice–water bath). After 2 h, the products were worked up and chromatographed as above to give an oil (*ca*. 0.2 g). This material was treated with diethyl azodicarboxylate (0.12 cm^3, 0.76 mmol) and triphenylphosphine (0.20 g, 0.76 mmol) in THF (5 cm^3) at 0 °C. After 3 h, the products were worked up as above and chromatographed to give the *title compounds* **19a** (β : α ratio *ca*. 2 : 1) as a colourless oil (0.14 g, *ca*. 68% for the two steps). Taking into account the different β : α ratio, the ^1H and ^{13}C NMR spectra of this material were clearly similar to the corresponding spectra indicated in (a) and (b) above.

(d) Triethylsilane (1.36 cm^3, 8.5 mmol) was added to a stirred solution of the product (1.10 g), obtained as in (b) above by allowing 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribono-1,4-lactone **16** to react with 2-(dibenzylamino)-5-lithiopyridine, in dichloromethane (40 cm^3) at −78°(acetone–dry ice bath). Boron trifluoride diethyl etherate (1.05 cm^3, 8.3 mmol) was then added and the reactants were allowed to warm up to −10 °C. After 6 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added. The organic layer was then separated, washed with saturated aqueous sodium hydrogen carbonate (3 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Following fractionation of the products by short column chromatography, the *title compounds* **19a** (β : α ratio *ca*. 3 : 1) were obtained as a colourless oil (0.34 g, *ca*. 30%). Taking into account the different β : α ratio, the ^1H and ^{13}C NMR spectra of this material were closely similar to the corresponding spectra indicated in (a) and (b) above.

5-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-[bis(4-methoxybenzyl)amino]pyridine 19b

n-Butyllithium (1.6 M in hexane; 7.50 cm^3, 12.0 mmol) was added to a stirred solution of 5-bromo-2-[bis(4-methoxybenzyl)amino]pyridine **12b** (4.96 g, 12.0 mmol) in dry THF (60 cm^3) at −78 °C (acetone–dry ice bath). After 40 min, a pre-cooled (to −78 °C) solution of 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15** (1.88 g, 5.0 mmol) in dry THF (20 cm^3) was added. After a further period of 1 h, the products were allowed to warm up to 0 °C. After 3 h, dry ice (2 g) and then saturated aqueous sodium hydrogen carbonate (10 cm^3) were added, and the products were worked up and fractionated, according to the procedure described above in the corresponding reaction between 2-(dibenzylamino)-5-lithiopyridine and 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15**, to give a colourless oil (2.90 g). Diisopropyl azodicarboxylate (2.18 cm^3, 11.1 mmol) was added dropwise to a stirred solution of this material (2.90 g) and triphenylphosphine (2.90 g, 11.1 mmol) in dry THF (40 cm^3). After 3 h, a 0.5 M solution of iodine in dichloromethane was added dropwise until the iodine coloration just persisted. The products were then worked up and fractionated according to the procedure described above for the preparation of the corresponding dibenzylamino derivatives **19a** from 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15** to give the *title compounds* **19b** (β : α ratio *ca*. 5.5 : 1) (HRMS Found: M^+, 692.3655. $^{12}C_{38}{}^1H_{56}{}^{14}N_2{}^{16}O_6{}^{28}Si_2$ requires: M^+, 692.3677) as a colourless oil (1.90 g, 55% overall yield); $\delta_H[CDCl_3]$ includes the following signals (for the β-anomer): 0.9–1.15 (28 H, m), 2.13 (1 H, m), 2.28 (1 H, m), 3.77 (6 H, s), 3.81 (1 H, m), 3.89 (1 H, m), 4.10 (1 H, dd, *J* 3.4 and 11.3), 4.54 (1 H, m), 4.68 (4 H, s), 4.97 (1 H, dd, *J* 6.6 and 8.3), 6.44 (1 H, d, *J* 8.8), 6.82 (4 H, m), 7.13 (4 H, d, *J* 8.6), 7.37 (1 H, dd, *J* 2.4 and 8.8), 8.16 (1 H, d, *J* 2.3); $\delta_C[CDCl_3]$ includes the following signals (for the β-anomer): 12.93, 13.43, 13.92, 13.93, 17.41, 17.50, 17.56, 17.71, 17.83, 17.87, 18.00, 42.77, 50.54, 55.66, 64.39, 74.45, 77.81, 86.84, 106.26, 114.33, 124.77, 128.71, 130.70, 136.27, 147.01, 158.94, 159.04.

5-(2-Deoxy-3,5-di-*O*-acetyl-β(α)-D-ribofuranosyl)-2-(dibenzylamino)pyridines 21a and 22a

A 1.0 M solution of tetraethylammonium fluoride in acetonitrile (10 cm^3, 10 mmol) was added to a stirred solution of 5-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-(dibenzylamino)pyridine **19a** (1.60 g, 2.53 mmol), prepared from 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15**), in acetonitrile (2 cm^3) at room temperature. After 1.5 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added and the products were extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was evaporated from pyridine solution (3 × 10 cm^3) and was redissolved in pyridine (20 cm^3). 1-Methylimidazole (0.60 cm^3, 7.5 mmol) and acetic anhydride (1.75 cm^3, 18.4 mmol) were then added to the stirred solution at room temperature. After 1.5 h, methanol (2 cm^3) was added and, after a further period of 10 min, the products were concentrated under reduced pressure. The residue was partitioned between dichloromethane (20 cm^3) and

saturated aqueous sodium hydrogen carbonate (20 cm^3). The organic layer was separated, washed with water (2 × 5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography into two components, which were both eluted with dichloromethane–methanol (99.5 : 0.5 v/v). Fractions containing the first eluted major component were combined and evaporated under reduced pressure to give *5-(2-deoxy-3,5-di-O-acetyl-β-D-ribofuranosyl)-2-(dibenzylamino)pyridine* **21a** (0.91 g, 76%) (HRMS Found: M^+, 474.2125. $^{12}C_{28}{}^{1}H_{30}{}^{14}N_2{}^{16}O_5$ requires M^+, 474.2155) as a colourless oil; δ_H[$CDCl_3$] 2.08 (3 H, s), 2.10 (1 H, m), 2.12 (3 H, s), 2.25 (1 H, m), 4.21 (2 H, m), 4.32 (1 H, dd, *J* 3.9 and 11.5), 4.79 (4 H, s), 5.00 (1 H, dd, *J* 5.0 and 10.9), 5.22 (1 H, m), 6.47 (1 H, d, *J* 8.8), 7.15–7.35 (10 H, m), 7.40 (1 H, dd, *J* 2.4 and 8.8), 8.17 (1 H, d, *J* 2.2); δ_C[$CDCl_3$] 21.31, 21.53, 40.75, 51.37, 64.94, 77.03, 79.20, 82.72, 106.32, 123.52, 127.40, 128.99, 136.19, 138.58, 147.21, 159.17, 171.01, 171.14.

Later fractions containing the minor component were combined and evaporated to give *5-(2-deoxy-3,5-di-O-acetyl-α-D-ribofuranosyl)-2-(dibenzylamino)pyridine* **22a** (0.18 g, 15%) as a colourless oil; δ_H[$CDCl_3$] 2.05 (3 H, s), 2.08 (1 H, m), 2.10 (3 H, s), 2.74 (1 H, m), 4.23 (2 H, m), 4.34 (1 H, m), 4.80 (4 H, s), 5.04 (1 H, m), 5.21 (1 H, m), 6.47 (1 H, d, *J* 8.8), 7.2–7.35 (10 H, m), 7.46 (1 H, dd, *J* 2.4 and 8.8), 8.17 (1 H, d, *J* 2.2); δ_C[$CDCl_3$] 21.34, 21.41, 39.95, 51.39, 64.34, 76.07, 78.54, 81.52, 106.21, 124.77, 127.41, 128.97, 136.34, 138.63, 147.08, 158.95, 171.07, 171.22.

5-(2-Deoxy-3,5-di-*O*-acetyl-β(α)-D-ribofuranosyl)-2-[bis-(4-methoxybenzyl)amino]pyridine 21b and 22b

A 1.0 M solution of tetraethylammonium fluoride in acetonitrile (11 cm^3, 11 mmol) was added to a stirred solution of 5-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-[bis(4-methoxybenzyl)amino]pyridine **19b** (1.90 g, 2.74 mmol) in acetonitrile (4 cm^3) at room temperature. After 1.5 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added and the products were extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was evaporated from pyridine solution (3 × 10 cm^3) and was redissolved in pyridine (30 cm^3). 1-Methylimidazole (0.64 cm^3, 8.0 mmol) and acetic anhydride (1.87 cm^3, 19.8 mmol) were then added to the stirred solution at room temperature. After 1.5 h, methanol (2 cm^3) was added and, after a further period of 10 min, the products were concentrated under reduced pressure. The residue was partitioned between dichloromethane (20 cm^3) and concentrated aqueous sodium hydrogen carbonate (20 cm^3). The organic layer was separated, washed with water (2 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography into two components, which were both eluted with dichloromethane–methanol–THF (99 : 0.5 : 0.5 v/v). Fractions containing the first eluted major component were combined and evaporated under reduced pressure to give *5-(2-deoxy-3,5-di-O-acetyl-β-D-ribofuranosyl)-2-[bis(4-methoxybenzyl)amino]pyridine* **21b** (0.93 g, 63%) (HRMS Found: $(M + H)^+$, 535.2450. $^{12}C_{30}{}^{1}H_{34}{}^{14}N_2{}^{16}O_7$ requires: $(M + H)^+$, 535.2444); δ_H[$CDCl_3$] 2.02 (3 H, s), 2.05 (3 H, s), 2.17 (1 H, dd, *J* 5.5 and 13.5), 3.71 (6 H, s), 4.11 (1 H, m), 4.16 (1 H, dd, *J* 4.6 and 11.6), 4.25 (1 H, dd, *J* 4.0 and 11.5), 4.63 (4 H, s), 4.92 (1 H, dd, *J* 5.0 and 10.9), 5.15 (1 H, m), 6.40 (1 H, d, *J* 8.8), 6.76 (4 H, m), 7.06 (4 H, d, *J* 8.6), 7.32 (1 H, dd, *J* 2.4 and 8.8), 8.10 (1 H, d, *J* 2.3); δ_C[$CDCl_3$] 19.82, 20.04, 39.24, 49.09, 54.19, 63.45, 75.58, 77.73, 81.21, 104.92, 112.87, 121.82, 127.18, 129.07, 134.64, 145.67, 157.58, 157.72, 169.53, 169.67.

Later fractions containing the minor component were combined and evaporated to give *5-(2-deoxy-3,5-di-O-acetyl-α-D-ribofuranosyl)-2-[bis(4-methoxybenzyl)amino]pyridine* **22b** (0.18 g, 12%) as a colourless oil; δ_H[$CDCl_3$] 1.98 (3 H, s), 2.00 (1 H, m), 2.03 (3 H, s), 2.66 (1 H, m), 3.70 (6 H, s), 4.15 (2 H, m), 4.25 (1 H, m), 4.62 (4 H, s), 4.95 (1 H, t, *J* 7.5), 5.13 (1 H, m), 6.39 (1 H, d, *J* 8.8), 6.75 (4 H, m), 7.05 (4 H, m), 7.37 (1 H, dd, *J* 2.5 and 8.8), 8.10 (1 H, d, *J* 2.4); δ_C[$CDCl_3$] 21.33, 21.41, 39.94, 50.60, 55.67, 64.34, 76.08, 78.55, 81.50, 106.31, 114.34, 124.57, 128.68, 130.62, 136.28, 147.03, 158.98, 159.06, 171.07, 171.21.

2-Amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine 2a

(a) Ammonium cerium(IV) nitrate (4.43 g, 8.1 mmol) was added to a stirred solution of 5-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-2-(dibenzylamino)pyridine **21a** (0.91 g, 1.9 mmol) in acetonitrile–water (98 : 2 v/v; 20 cm^3) at room temperature. After 25 min, the products were basified (to pH 9) by adding 0.4 M aqueous sodium hydroxide, and were then filtered through a bed of Celite. The filtrate was extracted with dichloromethane (3 × 10 cm^3) and the residue was washed with dichloromethane (4 × 10 cm^3). The combined extracts and washings were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane–methanol (9 : 1 v/v), were combined and evaporated under reduced pressure. The residue was dissolved in ethanol (2 cm^3) and an 8 M solution of methylamine in ethanol (1.95 cm^3, 15.6 mmol) was added to the stirred solution at room temperature. After 16 h, the products were concentrated under reduced pressure and the residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane–methanol (4 : 1 v/v) were combined and evaporated under reduced pressure to give the *title compound* **2a** (0.28 g, 69%) (HRMS Found: M^+, 210.0998. $^{12}C_{10}{}^{1}H_{14}{}^{14}N_2{}^{16}O_3$ requires: M^+, 210.1004) as a colourless oil; δ_H[$(CD_3)_2SO$] 1.80 (1 H, m), 1.93 (1 H, m), 3.42 (2 H, m), 3.71 (1 H, m), 4.17 (1 H, m), 4.75 (1 H, br), 4.83 (1 H, dd, *J* 5.3 and 10.5), 5.03 (1 H, br), 5.87 (2 H, br s), 6.41 (1 H, d, *J* 8.5), 7.37 (1 H, dd, *J* 2.3 and 8.5), 7.85 (1 H, d, *J* 1.5); δ_C [$(CD_3)_2SO$] 43.11, 62.84, 72.84, 77.69, 87.82, 108.05, 125.22, 136.01, 146.39, 159.74. In the NOESY spectrum of 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine **2a**: (a) a strong cross-peak is observed between the lower field (presumed α) H-2′ (δ 1.93) and H-1′ (δ 4.83) resonance signals; (b) a cross-peak is observed between the higher field (presumed β) H-2′ (δ 1.80) and the H-4 (δ 7.37) resonance signals; (c) a stronger cross-peak is observed between the H-3′ (δ 4.17) resonance signal and the higher field rather than the lower field H-2′ resonance signal; (d) a cross-peak is observed between the resonance signals of H-1′ and H-4′ (δ 3.71).

(b) Trifluoroacetic acid (1.58 cm^3) was added to a stirred solution of 5-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-2-[bis(4-methoxybenzyl)amino]pyridine **21b** (0.55 g, 1.03 mmol) in dichloromethane (1.6 cm^3) and the resulting solution was heated, under reflux. After 1.5 h, the cooled products were concentrated under reduced pressure. The residue was partitioned between dichloromethane (10 cm^3) and saturated aqueous sodium hydrogen carbonate (10 cm^3). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane–methanol (9 : 1 v/v) were evaporated under reduced pressure to give a colourless oil (0.27 g). A solution of this material (0.20 g) in ethanol (0.8 cm^3) was treated as in (a) above with 8 M ethanolic methylamine (0.84 cm^3, 6.7 mmol). Following work-up and short column chromatography, the *title compound* **2a** (0.11 g, 68%) was obtained as a colourless oil. This material was identical (^{1}H, ^{13}C NMR) to that described in (a) above.

2-Amino-5-(2-deoxy-α-D-ribofuranosyl)pyridine 23

Ammonium cerium(IV) nitrate (1.60 g, 2.9 mmol) was added to a stirred solution of 5-(2-deoxy-3,5-di-*O*-acetyl-α-D-ribofuranosyl)-2-(dibenzylamino)pyridine **22a** (0.35 g, 0.74 mmol) in acetonitrile–water (98 : 2 v/v; 6 cm^3) at room temperature. After 25 min, the products were worked-up and chromatographed as in the preparation of the β-isomer **2a** (see (a) above) to give a residual oil (0.15 g). A solution of this material (0.20 g, from two batches) in ethanol (0.8 cm^3) was treated as above with 8 M ethanolic methylamine (0.84 cm^3, 6.7 mmol) at room temperature. After 16 h, the products were worked-up and chromatographed as in the preparation of the β-isomer (see (a) above) to give the *title compound* **23** (0.11 g, 53%) (HRMS Found: $(M + H)^+$, 211.1082. $^{12}C_{10}{}^{1}H_{14}{}^{14}N_2{}^{16}O_3$ requires: $(M + H)^+$, 211.1083) as a colourless oil; $\delta_H[(CD_3)_2SO]$ 1.73 (1 H, m), 2.41 (1 H, m), 3.40 (1 H, dd, *J* 5.4 and 11.6), 3.50 (1H, dd, *J* 3.8 and 11.6), 3.76 (1 H, m), 4.17 (1 H, m), 4.69 (1 H, br), 4.75 (1 H, dd, *J* 6.5 and 8.9), 5.05 (1 H, br), 5.86 (2 H, br s), 6.42 (1 H, d, *J* 8.5), 7.42 (1 H, dd, *J* 2.4 and 8.5), 7.84 (1 H, d, *J* 2.1); $\delta_C[(CD_3)_2SO]$ 43.16, 62.09, 72.02, 77.10, 86.29, 108.09, 126.43, 136.03, 146.22, 159.56. In the NOESY spectrum of 2-amino-5-(2-deoxy-α-D-ribofuranosyl)pyridine **23**: (a) cross-peaks are observed only between the higher field (presumed α) H-2′ (δ 1.73) and the H-4 (δ 7.42) and H-6 (δ 7.84) resonance signals; (b) strong cross peaks are observed between the lower field (presumed β) H-2′ (δ 2.41) and the H-1′ (δ 4.75) and H-3′ (δ 4.17) resonance signals; (c) the cross-peak between the H-1′ and H-3′ resonance signals is stronger than that between the H-1′ and H-4′ (δ 3.76) resonance signals; (d) a cross-peak is observed between only the higher field H-2′ resonance signal and that of H-4′.

5-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-dibenzylamino-3-methylpyridines 26

n-Butyllithium (1.6 M in hexane, 15.7 cm^3, 25.1 mmol) was added to a stirred solution of 5-bromo-2-dibenzylamino-3-methylpyridine **25** (9.25 g, 25.2 mmol) in dry THF (100 cm^3) at −78 °C (acetone–dry ice bath). After 40 min, a pre-cooled (to −78 °C) solution of 2-deoxy-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-D-ribofuranose **15** (3.39 g, 9.00 mmol) in THF (40 cm^3) was added. The reactants were stirred at −78 °C for 1 h, and were then allowed to warm up to 0 °C over a period of 3 h. The products were then worked up and chromatographed as in the above preparation of 5-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-(dibenzylamino)pyridines **19a** to give a colourless oil (3.95 g). Diisopropyl azodicarboxylate (2.92 cm^3, 14.8 mmol) was added dropwise to a stirred solution of this material and triphenylphosphine (3.90 g, 14.9 mmol) in THF (60 cm^3) at 0 °C (ice–water bath). After 3 h, a 0.5 M solution of iodine in dichloromethane was added dropwise until the iodine coloration just persisted. The products were then worked-up and fractionated as in the above preparation of 5-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-(dibenzylamino)pyridine **19a** to give the *title compounds* **26** as a colourless oil (2.42, 41.5% overall yield; β : α ratio *ca.* 1.5 : 1) (HRMS Found: $(M + H)^+$, 647.3681. $^{12}C_{37}{}^{1}H_{55}{}^{14}N_2{}^{16}O_4{}^{28}Si_2$ requires: $(M + H)^+$, 647.3700); $\delta_H[CDCl_3]$ 0.99 (28 H, m), 2.05 (1 H, m), 2.23 (0.6 H, m), 2.31 (1.8 H, s), 2.33 (1.2 H, s), 2.51 (0.4 H, m), 3.81 (2 H, m), 3.96 (0.4 H, dd, *J* 2.5 and 10.8), 4.02 (0.6 H, dd, *J* 2.2 and 10.2), 2.34 (4 H, s), 4.49 (1 H, m), 4.84 (0.4 H, dd, *J* 5.9 and 10.0), 4.95 (0.6 H, t, *J* 7.2), 7.14 (10 H, m), 7.34 (0.6 H, d, *J* 2.1), 7.45 (0.4 H, d, *J* 2.1), 7.99 (1 H, s); $\delta_C[CDCl_3]$ 12.94, 12.99, 13.29, 13.39, 13.74, 13.84, 13.91, 17.37, 17.43, 17.46, 17.52, 17.56, 17.67, 17.72, 17.79, 17.83, 17.86, 17.94, 17.97, 19.21, 19.25, 42.93, 43.01, 54.84, 63.75, 64.05, 73.95, 74.20, 76.68, 77.34, 84.00, 86.85, 125.85, 127.15, 128.58, 128.63, 131.30, 131.86, 137.88, 139.43, 143.77, 161.50.

5-(2-Deoxy-3,5-di-*O*-acetyl-β(α)-D-ribofuranosyl)-2-dibenzylamino-3-methylpyridines 27 and 28

A 1.0 M solution of tetraethylammonium fluoride in acetonitrile (15 cm^3, 15 mmol) was added to a stirred solution of 5-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β(α)-D-ribofuranosyl]-2-dibenzylamino-3-methylpyridines **26** (2.42 g, 3.74 mmol) in acetonitrile (5 cm^3) at room temperature. After 1.5 h, the products were worked up as in the above preparation of 5-(2-deoxy-3,5-di-*O*-acetyl-β(α)-D-ribofuranosyl-2-(dibenzylamino)pyridines **21a** and **22a** to give a colourless oil. This material was evaporated from pyridine (3 × 10 cm^3) solution and was then redissolved in pyridine (20 cm^3). 1-Methylimidazole (0.89 cm^3, 11.2 mmol) and acetic anhydride (2.12 cm^3, 22.5 mmol) were added to the stirred solution at room temperature. After 1.5 h, methanol (3 cm^3) was added and, after a further period of 10 min, the products were concentrated under reduced pressure. The residue was partitioned between dichloromethane (50 cm^3) and saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure. The residue was fractionated by short column chromatography into two components which were both eluted with dichloromethane–methanol (99.5 : 0.5 v/v). Fractions containing the first eluted major component were combined and evaporated under reduced pressure to give *5-(2-deoxy-3,5-di-O-acetyl-β-D-ribofuranosyl)-2-dibenzylamino-3-methylpyridine* **27** (0.86 g, 47%) (HRMS Found: $(M + H)^+$, 489.2402. $^{12}C_{29}{}^{1}H_{33}{}^{14}N_2{}^{16}O_5$ requires: $(M + H)^+$, 489.2389) as a colourless oil; $\delta_H[CDCl_3]$ 1.99 (1 H, m), 2.01 (3 H, s), 2.04 (3 H, s), 2.21 (1 H, dd, *J* 5.1 and 13.7), 2.33 (3 H, s), 4.13 (1 H, m), 4.19 (1 H, m), 4.26 (4 H, s), 4.29 (1 H, dd, *J* 3.8 and 11.5), 4.95 (1 H, dd, *J* 5.0 and 10.9), 5.15 (1 H, d, *J* 6.5), 7.16 (10 H, m), 7.35 (1 H, d, *J* 2.1), 8.01 (1 H, d, *J* 2.2); $\delta_C[CDCl_3]$ 19.35, 21.26, 21.48, 41.11, 54.78, 64.84, 76.97, 78.86, 82.95, 125.81, 127.20, 128.58, 128.61, 129.75, 137.86, 139.34, 143.85, 161.82, 170.96, 171.08.

Later fractions containing the minor component were combined and evaporated under reduced pressure to give *5-(2-deoxy-3,5-di-O-acetyl-α-D-ribofuranosyl)-2-dibenzylamino-3-methylpyridine* **28** (0.14 g, 7.7%) (HRMS Found: $(M + H)^+$, 489.2363) as a colourless oil; $\delta_H[CDCl_3]$ 1.93 (3 H, s), 2.01 (1 H, m), 2.04 (3 H, s), 2.34 (3 H, s), 2.69 (1 H, m), 4.17 (2 H, m), 4.26 (4 H, s), 4.31 (1 H, m), 5.01 (1 H, t, *J* 7.3), 5.14 (1 H, m), 7.15 (10 H, m), 7.40 (1 H, d, *J* 2.1), 8.02 (1 H, d, *J* 2.3); $\delta_C[CDCl_3]$ 18.94, 20.95, 20.98, 39.84, 54.50, 63.99, 75.70, 77.92, 81.47, 125.40, 126.83, 128.22, 128.25, 130.69, 137.60, 139.03, 143.32, 161.16, 170.63, 170.81.

2-Amino-5-(2-deoxy-β-D-ribofuranosyl)-3-methylpyridine 2b

Ammonium cerium(IV) nitrate (2.88 g, 5.25 mmol) was added to a stirred solution of 5-(2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)-2-dibenzylamino-3-methylpyridine **27** (0.86 g, 1.76 mmol) in acetonitrile–water (98 : 2 v/v, 20 cm^3) at room temperature. After 25 min, the products were worked up and fractionated as in the above preparation of 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine **2a** to give a colourless oil (0.41 g). This material was dissolved in ethanol (1.6 cm^3) and an 8 M solution of methylamine in ethanol (1.62 cm^3, 13.0 mmol) was added to the stirred solution at room temperature. After 16 h, the products were worked up and chromatographed as in the above preparation of 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine **2a** to give the *title compound* **2b** (0.23 g, 58%) (HRMS Found: M^+, 224.1156. $^{12}C_{11}{}^{1}H_{16}{}^{14}N_2{}^{16}O_3$ requires: M^+, 224.1161) as a colourless glass; $\delta_H[(CD_3)_2SO]$ 1.81 (1 H, m), 1.94 (1 H, m), 2.03 (3 H, s), 3.42 (2 H, m), 3.70 (1 H, m), 4.17 (1 H, m), 4.75 (1 H, br), 4.82 (1 H, dd, *J* 5.3 and 10.5), 5.03 (1 H, br), 5.66 (2 H, br s), 7.23 (1 H, d, *J* 1.4), 7.73 (1 H, d, *J* 2.0); $\delta_C[(CD_3)_2SO]$ 17.42, 43.16, 62.84, 72.82, 77.64, 87.83, 115.94, 125.84, 135.86, 143.65, 158.23.

2-Amino-5-(2-deoxy-α-D-ribofuranosyl)-3-methylpyridine 29

Ammonium cerium(IV) nitrate (0.49 g, 0.86 mmol) was added to a stirred solution of 5-(2-deoxy-3,5-di-*O*-acetyl-α-D-ribofuranosyl)-2-dibenzylamino-3-methylpyridine **28** (0.14 g, 0.29 mmol) in acetonitrile–water (98 : 2 v/v, 10 cm^3) at room temperature. After 25 min, the products were worked up and fractionated as in the above preparation of 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine **2a** to give a colourless oil (0.062 g). This material was dissolved in ethanol (0.25 cm^3) and an 8 M solution of methylamine in ethanol (0.25 cm^3, 2.0 mmol) was added to the solution at room temperature. After 16 h, the products were worked up and chromatographed as in the above preparation of 2-amino-5-(2-deoxy-β-D-ribofuranosyl)pyridine **2a** to give the *title compound* **29** (0.030 g, 46%) (HRMS Found: $(M + H)^+$, 225.1230. $^{12}C_{11}{}^{1}H_{16}{}^{14}N_2{}^{16}O_3$ requires: $(M + H)^+$, 225.1239) as a colourless glass; $\delta_H[(CD_3)_2SO]$ 1.73 (1 H, m), 2.04 (3 H, s), 2.41 (1 H, m), 3.39 (1 H, m), 3.49 (1 H, m), 3.76 (1 H, m), 4.16 (1 H, m), 4.69 (1 H, m), 4.75 (1 H, dd, *J* 6.5 and 8.9), 5.06 (1 H, d, *J* 4.8), 5.73 (2 H, br s), 7.31 (1 H, s), 7.71 (1 H, s); $\delta_C[(CD_3)_2SO]$ 16.99, 42.75, 61.62, 71.54, 76.53, 85.80, 115.73, 126.63, 135.61, 142.57, 157.45. In the NOESY spectrum of 2-amino-5-(2-deoxy-α-D-ribofuranosyl)-3-methylpyridine **29** (a) cross-peaks are observed only between the higher field (presumed α) H-2′ (at δ 1.73) and the H-4 (at δ 7.31) and to a lesser extent the H-6 (at δ 7.71) resonance signals; (b) strong cross-peaks are observed between the lower field (presumed β) H-2′ (at δ 2.41) and the H-1′ (at δ 4.75) and H-3′ (at δ 4.16) resonance signals; (c) a strong cross-peak is observed between the H-1′ and H-3′, but not between the H-1′ and H-4′ (at δ 3.76) resonance signals; (d) a medium intensity cross-peak is observed between the H-4′ and only the higher field H-2′ resonance signal.

5-Bromo-2,4-bis(4-methoxybenzyloxy)pyrimidine 33

Sodium hydride (60% dispersion in mineral oil; 2.45 g, 61 mmol) was added in portions to a stirred solution of 5-bromo-2,4-dichloropyrimidine **32** (5.60 g, 24.6 mmol) and 4-methoxybenzyl alcohol (8.46 g, 61 mmol) in dry THF (100 cm^3) at 0 °C (ice–water bath). After 1.5 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added cautiously and the products were then concentrated under reduced pressure to a small volume. The residual mixture was extracted with dichloromethane (50 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. Crystallization of the resulting solid residue from petroleum spirit (bp 40–60 °C) gave the *title compound* **33** (9.76 g, 92%) (HRMS Found: $(M + H)^+$, 431.0595. $^{12}C_{20}{}^{1}H_{19}{}^{79}Br^{14}N_2{}^{16}O_4$ requires: $(M + H)^+$, 431.0606), mp 69.5–70.5 °C; $\delta_H[CDCl_3]$ 3.83 (6 H, s), 5.35 (2 H, s), 5.42 (2 H, s), 6.92 (4 H, m), 7.41 (4 H, m), 8.34 (1 H, s); $\delta_C[CDCl_3]$ 55.69, 69.44, 69.88, 98.75, 114.24, 114.35, 127.97, 128.63, 130.09, 130.39, 159.76, 159.98, 160.06, 164.00, 166.67.

Removal of the 4-methoxybenzyl protecting groups from 5-bromo-2,4-bis(4-methoxybenzyloxy)pyrimidine 33

Trifluoroacetic acid (0.26 cm^3, 3.4 mmol) was added to a stirred solution of 5-bromo-2,4-bis(4-methoxybenzyloxy)pyrimidine **33** (0.30 g, 0.70 mmol) in dichloromethane (2.4 cm^3) at room temperature. After 15 min, the products were concentrated under reduced pressure. The residue was redissolved in methanol (2 cm^3) and triethylamine (0.5 cm^3) was added. The solution was re-evaporated under reduced pressure and the residue was triturated with dichloromethane (2 × 10 cm^3) to give 5-bromouracil **34** (0.112 g, 84%) as a colourless solid, identical (^1H and ^{13}C NMR) to authentic material.

5-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl]-2,4-[bis(4-methoxybenzyloxy)]pyrimidine 36

n-Butyllithium (1.6 M in hexane; 9.38 cm^3, 15.0 mmol) was added to a stirred solution of 5-bromo-2,4-bis(4-methoxybenzyloxy)pyrimidine **33** (6.48 g, 15.7 mmol) in dry THF (100 cm) at −100 °C (acetone–liquid nitrogen bath). After 30 min, the products were added to a stirred solution of 2-deoxy-3,5-*O*-(tetraisopropyldisiloxan-1,1,3,3-diyl)-D-ribono-1,4-lactone **16** (4.50 g, 12.0 mmol) in dry THF at −100 °C. The reactants were allowed to warm up to −78 °C (acetone–dry ice bath). After 3 h, solid carbon dioxide (2.0 g) and then saturated aqueous sodium hydrogen carbonate (20 cm^3) were added. The products were concentrated under reduced pressure and the residual mixture was partitioned between dichloromethane (100 cm^3) and saturated aqueous sodium hydrogen carbonate (50 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was co-evaporated with dry toluene (4 × 15 cm^3), dissolved in dry THF (80 cm^3) and the stirred solution was cooled to −78 °C. Lithium tri-*sec*-butyl borohydride (L-Selectride, 1.0 M solution in THF, 18.0 cm^3, 18.0 mmol) was added and the reactants were allowed to warm up to room temperature. Saturated aqueous sodium hydrogen carbonate was then added and the products were concentrated under reduced pressure. The residual mixture was partitioned between dichloromethane (100 cm^3) and saturated aqueous sodium hydrogen carbonate (50 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3), dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60 °C)–ethyl acetate (9 : 1 to 7 : 3 v/v), were combined and concentrated under reduced pressure to give a mobile oil (5.20 g). Diisopropyl azodicarboxylate (3.51 cm^3, 17.8 mmol) was added to a stirred solution of this material (5.20 g) and triphenylphosphine (4.68 g, 17.8 mmol) in dry THF (70 cm^3) at room temperature. After 3 h, a 0.5 M solution of iodine in dichloromethane was added dropwise until the iodine coloration just persisted. Saturated aqueous sodium hydrogen carbonate (20 cm^3) and saturated aqueous sodium thiosulfate (15 cm^3) were then added, and the products were concentrated under reduced pressure. The residual mixture was partitioned between dichloromethane (80 cm^3) and saturated aqueous sodium hydrogen carbonate (20 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60 °C), were combined and evaporated under reduced pressure to give the *title compound* **36** (3.72 g, 43.6% overall yield) (HRMS Found: M^+, 710.3415. $^{12}C_{37}{}^{1}H_{54}{}^{14}N_2{}^{16}O_8{}^{28}Si_2$ requires: M^+, 710.3419) as a colourless oil; $\delta_H[CDCl_3]$ 0.85–1.2 (28 H, m), 2.09 (1 H, m), 2.36 (1 H, m), 3.79 (7 H, m), 3.90 (1 H, dd, *J* 6.4 and 11.8), 4.10 (1 H, dd, *J* 3.3 and 11.8), 4.43 (1 H, dd, *J* 6.1 and 13.8), 5.16 (1 H, t, *J* 7.1), 5.37 (2 H, s), 5.39 (2 H, s), 6.90 (4 H, m), 7.39 (2 H, m), 7.43 (2 H, m), 8.36 (1 H, s); $\delta_C[CDCl_3]$ 12.96, 13.32, 13.67, 13.82, 17.39, 17.46, 17.52, 17.66, 17.79, 17.81, 17.83, 17.96, 41.14, 55.62, 63.47, 68.38, 69.23, 72.84, 72.90, 85.72, 114.15, 114.28, 116.39, 128.62, 129.18, 129.93, 130.40, 156.24, 159.85, 159.93, 164.50, 167.80.

5-(2-Deoxy-β-D-ribofuranosyl)uracil 30a

A 1.0 M solution of tetraethylammonium fluoride in acetonitrile (20.9 cm^3, 20.9 mmol) was added to a stirred solution of 5-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl]-2,4-[bis(4-methoxybenzyloxy)]pyrimidine **36** (3.72 g, 5.23 mmol) in acetonitrile (10 cm^3) at room temperature. After 1 h, saturated aqueous sodium hydrogen carbonate (10 cm^3) was added and the products were concentrated under reduced pressure. The residual mixture was partitioned between

dichloromethane (50 cm^3) and saturated aqueous sodium hydrogen carbonate (20 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was co-evaporated with dry toluene (3 × 10 cm^3) and was then dissolved in dichloromethane (18 cm^3). Trifluoroacetic acid (2.0 cm^3) was added to the stirred solution at room temperature. After 15 min, the products were concentrated under reduced pressure (bath temperature at or below room temperature). The residue was dissolved in methanol (5 cm^3) and triethylamine (2.0 cm^3) was added. The basified products were evaporated under reduced pressure and the residue was triturated with diethyl ether (20 cm^3). The solid thereby obtained was collected by filtration and washed with diethyl ether (3 × 10 cm^3) to give the *title compound* **30a** (Found, in material recrystallized from a mixture of methanol and ethanol and dried *in vacuo*: C, 46.0; H, 5.3; N, 11.8. Calc. for $C_9H_{12}N_2O_5 \cdot 0.5H_2O$: C, 45.75; H, 5.55; N, 11.86%) as a colourless solid (0.94 g, 78%), mp 220–222 °C; $\delta_H[(CD_3)_2SO]$ 1.75 (1 H, m), 2.00 (1 H, m), 3.40 (2 H, m), 3.68 (1 H, m), 4.11 (1 H, m), 4.73 (1 H, m), 4.79 (1 H, dd, *J* 5.7 and 9.7), 4.96 (1 H, d, *J* 3.1), 7.37 (1 H, s), 10.82 (1 H, br), 11.09 (1 H, br); $\delta_C[(CD_3)_2SO]$ 41.16, 62.52, 72.42, 73.52, 87.37, 113.50, 138.11, 151.52, 163.80. In the NOESY spectrum of 5-(2-deoxy-β-D-ribofuranosyl)uracil **30a**, strong cross-peaks are observed between (a) H-1′ (δ 4.79) and H-2′(α) (δ 2.00); (b) H-2′(α) and H-4′ (δ 3.68); (c) H-2′(β) (δ 1.75) and H-3′ (δ 4.11) and H-6 (δ 7.37).

Acknowledgements

One of us (Q. W.) thanks the K. C. Wong Foundation for the award of a scholarship.

References

1 V. J. Soyfer and V. N. Potamen, *Triple-Helical Nucleic Acids*, Springer, New York, Berlin and Heidelberg, 1995, pp. 274–283.
2 P. S. Miller in *Bioorganic Chemistry: Nucleic Acids*, ed. S. M. Hecht, Oxford University Press, New York and London, 1996, pp. 352–360.
3 *Handbook of Biochemistry and Molecular Biology, Nucleic Acids,*, Vol. I, 3rd edn., ed. G. D. Freeman, CRC Press, Cleveland, 1975, p. 142.
4 S. Hildbrand and C. Leumann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1968–1970.
5 P. J. Bates, C. A. Laughton, T. C. Jenkins, D. C. Capaldi, P. D. Roselt, C. B. Reese and S. Neidle, *Nucleic Acids Res.*, 1996, **24**, 4176–4184.
6 S. A. Cassidy, P. Slickens, J. O. Trent, D. C. Capaldi, P. D. Roselt, C. B. Reese, S. Neidle and K. R. Fox, *Nucleic Acids Res.*, 1997, **25**, 4891–4898.
7 S. Hildbrand, A. Blaser, S. P. Parel and C. J. Leumann, *J. Am. Chem. Soc.*, 1997, **119**, 5499–5511.
8 H.-P. Hsieh and L. W. McLaughlin, *J. Org. Chem.*, 1995, **60**, 5356–5359.
9 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edn., Wiley-Interscience, New York, 1999, pp. 86–91.
10 B. Hungerhoff, S. S. Samanta, J. Rolls and P. Metz, *Synlett*, 2000, 77–79.
11 S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3765–3774.
12 M. Sollogoub, K. R. Fox, V. E. C. Powers and T. Brown, *Tetrahedron Lett.*, 2002, **43**, 3121–3123.
13 U. Wichai and S. A. Woski, *Org. Lett.*, 1999, **1**, 1173–1175.
14 W. T. Markiewicz, *J. Chem. Res. (S)*, 1979, 24–25; W. T. Markiewicz, *J. Chem. Res. (M)*, 1979, 181–197.
15 M. Yokoyama, T. Ikuma, N. Obara and H. Togo, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3243–3247.
16 C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Bell, London, 1953, p. 334.
17 U. Wichai and S. A. Woski, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3465–3468.
18 O. Mitsunobu, *Synthesis*, 1981, 1–28.
19 H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, 1972, **94**, 7159–7161.
20 L. E. Xodo, G. Manzini, F. Quadrifoglio, G. A. van der Marel and J. H. van Boom, *Nucleic Acids Res.*, 1991, **19**, 5625–5631.
21 K. S. Huang, M. J. Haddadin, M. M. Olmstead and M. J. Kurth, *J. Org. Chem.*, 2001, **66**, 1310–1315.
22 A. Matsuda, C. K. Chu, U. Reichman, K. Pankiewicz, K. A. Watanabe and J. J. Fox, *J. Org. Chem.*, 1981, **46**, 3603–3609.
23 K. Pankiewicz, A. Matsuda and K. A. Watanabe, *J. Org. Chem.*, 1982, **47**, 485–488.
24 S. D. Bridges, D. M. Brown and R. C. Ogden, *J. Chem. Soc., Chem. Commun.*, 1977, 460–461.
25 H.-C. Zhang and G. D. Daves, *J. Org. Chem.*, 1992, **57**, 4690–4696.
26 N. Ramzaeva, H. Rosemeyer, P. Leonard, K. Mühlegger, F. Bergmann, H. von der Eltz and F. Seela, *Helv. Chim. Acta*, 2000, **83**, 1108–1126.
27 M. Yokoyama, H. Toyoshima, M. Shimizu and H. Togo, *J. Chem. Soc., Perkin Trans. 1*, 1997, 29–33.