Synthesis and properties of *C*-aza-2-deoxy-L-lyxonucleosides †

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'*C*-Aza-2-deoxy-L-lyxonucleosides' in which a sugar ring oxygen is replaced with a nitrogen atom are synthesized from 2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentofuranose *via* a sequential procedure of the addition of lithium salts of aromatic heterocycles, Swern oxidation and reductive aminocyclization. Their structures are determined mainly by X-ray crystallography and NMR measurements. Their bioassay is also described.

Introduction

In the view of their biological activity, structurally modified nucleosides are important synthetic targets and promising candidates for the improvement of drugs for the therapy of human diseases.[1] In particular, we have been interested in the so-called *C*-nucleosides in which the ribofuranosyl moiety is linked to the aromatic heterocycles through a carbon–carbon bond.[2] The *C*-nucleosides are similar to normal nucleosides except that they possess a more stable glycosidic bond toward hydrolysis and enzymic reaction. Accordingly, many of them can exhibit anticancer and antivirus activities.[3]

On the other hand, the azasugars in which a sugar ring oxygen is replaced with a nitrogen atom constitute an important class of natural and unnatural products because of their ability to inhibit glycohydrolases which are responsible for the cleavage of glycosidic bonds.[4] The activities of these compounds are ascribed to the charge–charge interaction and the hydrogen bonding between an enzyme and a protonated azasugar at physiological pH.[5]

Our interest is in the synthesis of potentially bioactive nucleoside analogues, wherein a furanose ring oxygen is replaced by a nitrogen atom. Some nucleosides bearing an azasugar moiety such as *C*-azanucleosides,[6] *N*-azanucleosides[7] and pyrrolidine nucleosides[8] are known, but their synthesis requires multi-step procedures.

In the course of our study on *C*-azanucleosides, the first synthesis of '*C*-aza-2-deoxy-L-lyxonucleosides' was explored by a simple and stereoselective procedure.

In this paper, we will report (1) a stereoselective synthesis of '*C*-aza-2-deoxy-L-lyxonucleosides' starting from 2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentofuranose **1**; (2) structure determination of '*C*-aza-2-deoxy-L-lyxonucleosides' mainly by using X-ray crystallography and NMR measurements; and (3) anti-HIV activity of these compounds.

Results and discussion

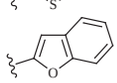
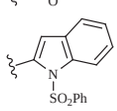
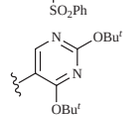
Synthesis and structures of '*C*-aza-2-deoxy-L-lyxonucleosides'

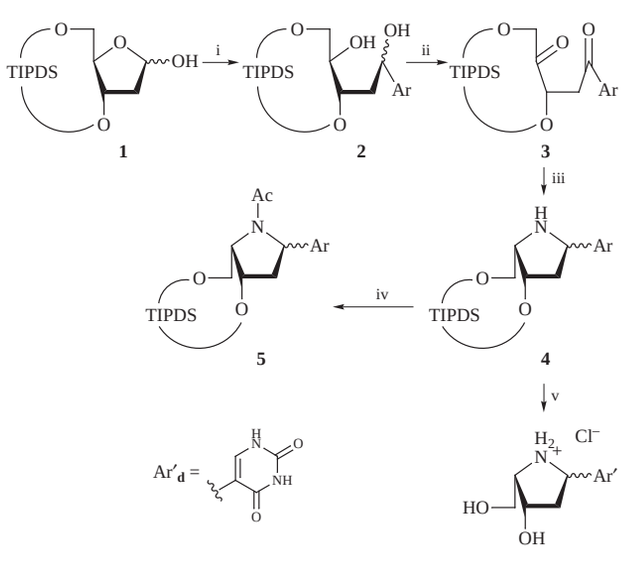
'*C*-Aza-2-deoxynucleosides' were synthesized in four steps from compound **1**, which was itself prepared from the reaction of 2-deoxy-D-ribose with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$)[9] (Scheme 1).

Compound **1** was allowed to react with organolithium reagents of thiophene, *N*-(phenylsulfonyl)indole and benzofuran to give the corresponding diol derivatives **2a**–**c** (Table 1).[2h]

† *Systematic nomenclature*: 5′-amino-2′,5′-dideoxy-L-lyxonucleosides.

Table 1 Preparation of compounds **2**, **3** and **4**

	Yields (%)		
Ar	**2** (*R*:*S*)	**3**	**4** (α:β)
a; 	88 (1:2)	64	42 (1:1)
b; 	62 (7:3)	66	30 (1:1)
c; 	97 (1:3)	69	35 (1:1)
d; 	44 (2:1)	88	27 (1:1)



Scheme 1 *Reagents and conditions*: i, Aryllithium, THF, rt, 1 h; ii, DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C to rt, 4 h; iii, HCO_2NH_4, $NaBH_3CN$, $NaBH_4$, MeOH, rt, 20 h; iv, AcCl, Et_3N, THF, 0 °C to rt, 2 h; v, 6 M HCl, MeOH, 60 °C, 30 min

These organolithium reagents were prepared *via* hydrogen–metal exchange with *n*-BuLi and were stable at 0 °C. In the case of diol **2d**, an organolithium reagent of 2,4-di(*tert*-butoxy)-pyrimidine was prepared *via* halogen–metal exchange between 5-bromo-2,4-di(*tert*-butoxy)pyrimidine and *n*-BuLi using a

Table 2 Various conditions of reductive aminocyclization from dione **3b** to azasugar **4b**

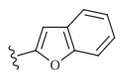
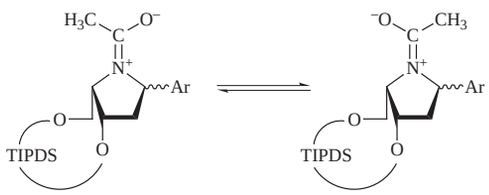
Ar	Ultrasound	Additive	Time (*t*/h)	Yield (%) (α : β)
	no	none	18	5 (1 : 1)
	)))	none	7	10 (1 : 1)
	no	$NaBH_4$	18	30 (1 : 1)
	)))	$NaBH_4$	7	31 (1 : 1)

Table 3 Rotational isomers of compound **5d**



Compounds	Temp. (*T*/°C)	Δ*G* (kJ/mol)[a]	T_c (°C)[b]	Δ$G^‡$ (kJ/mol)[c]
α	22	3.8	90	77.7
β	30	5.2	60	74.5
DMA[d]			52	50.2

[a] Δ*G*-values were calculated by $N_A/N_B = \exp(-\Delta G/RT)$. [b] The temperature at which the two singlets coalesce to a single line. [c] Δ$G^‡$-values were calculated by $\Delta G^‡ = 19.14\ T_c(9.97 + \log T_c/\delta\nu)$. [d] Ref. 11.

cannula below −78 °C, because the Li reagent decomposed instantly above −78 °C.[10]

The thus obtained diols **2a**–**d** were oxidized by Swern oxidation and then purified by column chromatography to give the corresponding diones **3a**–**d**, which were subjected to the following reaction immediately due to their lability.

Next, diones **3a**–**c** were aminated reductively and the products cyclized with ammonium formate and sodium cyanoborohydride to yield the protected '*C*-azadeoxynucleosides' **4a**–**c** in poor yields (5–30%). To improve the yield of the reductive aminocyclization, some experiments were performed with changes in the experimental conditions (ultrasound, additives) using substrate **3b** as shown in Table 2. The application of ultrasound shortened the reaction time, but did not markedly affect the yield. The yields of *C*-azanucleosides **4a**–**d** could be improved effectively by use of a secondary additive (sodium borohydride, Table 2) and then the stereoisomers of products **4a**–**d** could be separated easily by recycling HPLC (ODS column; MeOH).

The process of Swern oxidation is necessary for a simple synthesis of '*C*-aza-2-deoxynucleosides'. However, the loss of chirality in the hydroxy groups results in the formation of four stereoisomers upon the following aminocyclization. Thus, determination of their exact structures may be difficult by NMR analysis only. In the present reaction two stereoisomers of compounds **4** were formed and their structures could be determined unequivocally by X-ray crystallography.

Two experiments were carried out for X-ray crystallography. At first, the amino group of secondary amine **4d** was acetylated to give the corresponding acetamide **5d** in 78% yield. One isomer of compound **5d** could be crystallized easily by the addition of MeOH–EtOH and its structure was that of a β-type '*C*-aza-2-deoxy-L-lyxonucleoside'. However, crystallization of another isomer (α-type) of compound **5d** was difficult due to the presence of a mixture of rotational isomers which is apparent by its NMR spectrum. In the case of the β-type L-lyxonucleoside, the proton in the 6-position of pyrimidine appeared as two singlets at rt with the relative intensities of 10 : 1, while relative intensities of 5 : 1 were observed in the α-type isomer of compound **5d**. In order to verify whether compound **5d** exists as rotational isomers, NMR measurement was carried out at various temperatures. When the NMR was measured at 60 °C on the β-type isomer, the two singlets coalesced into one broad singlet. The same phenomenon was observed with the α-type isomer. Their coalescence temperatures, and values of Δ*G* and Δ$G^‡$, are shown in Table 3. The Δ$G^‡$-value of compound **5d** shows larger values than that of *N*,*N*-dimethylacetamide (DMA) perhaps because the interconversion between the two rotational isomers is hindered by intramolecular distortion of the TIPDS group. The difference between α- and β-isomers of compound **5d** may be explained by the larger steric hindrance of the α-isomer.

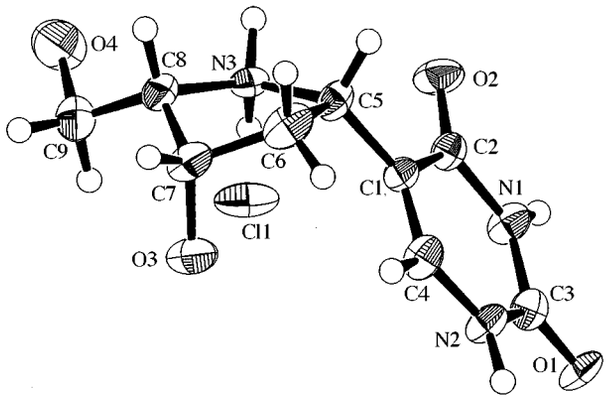


Fig. 1a X-Ray molecular structure of β-form of compound **6d** with crystallographic numbering scheme (hydrogen atoms omitted)

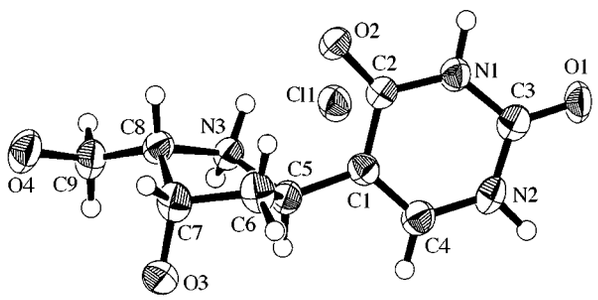


Fig. 1b X-Ray molecular structure of α-form of compound **6d** with crystallographic numbering scheme (hydrogen atoms omitted)

Next, compound **4d** was deprotected by treatment with 6 M HCl in MeOH without epimerization to give the desired two types of '*C*-aza-2-deoxynucleosides' **6d** in 98% yield as a powder of HCl salt. In one isomer of compound **6d**, a single crystal for X-ray analysis could be obtained by the addition of MeOH and EtOH and its structure was determined as the β-type of '*C*-aza-2-deoxy-L-lyxonucleoside' (Fig. 1a). In the other isomer of compound **6d**, a single crystal for X-ray analysis could be also obtained by the addition of MeOH and water, and its structure was determined as the α-type of the '*C*-aza-2-deoxy-L-lyxonucleoside' (Fig. 1b). The crystallographic data of compounds **5d** (β-form) and **6d** (α- and β-form) are summarized in Table 4.‡

In ^{1}H NMR data of compounds **4d**, **5d** and **6d**, differential nuclear Overhauser effects (NOEs) were observed between the following protons: (1) **4d**: (α-form) 1-H↔2-Hb, 3-H↔4-H, 3-H↔pyrimidine 6-H, 4-H↔pyrimidine 6-H; (β-form) 1-H↔2-Hb, 1-H↔4-H, 3-H↔4-H. (2) **5d**: (α-form) 1-H↔2-Hb,

‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/222.

Table 4 Crystallographic data for compounds **5d** and **6d**

	β-Form of **5d**	β-Form of **6d**	α-Form of **6d**
Empirical formula	$C_{31}H_{57}N_3O_6Si_2$	$C_9H_{14}ClN_3O_4$	$C_9H_{14}ClN_3O_4$
Formula relative molecular mass	623.98	263.68	263.68
Crystal dimensions/mm	0.10 × 0.03 × 0.4	0.12 × 0.10 × 0.40	0.45 × 0.10 × 0.48
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Lattice parameters	a = 11.198(3) Å	a = 6.596(3) Å	a = 5.508(7) Å
	b = 35.771(2) Å	b = 31.067(2) Å	b = 12.113(5) Å
	c = 9.512(2) Å	c = 5.425(2) Å	c = 8.551(7) Å
			β = 104.85(8)°
Z	4	4	2
D_c (g cm^{-3})	1.088	1.575	1.588
μ(Mo-Kα) (cm^{-1})	11.67	31.66	31.92
Temp. (T/°C)	23.0	23.0	23.0
Scan width (°)	0.79 ± 0.30 tan θ	1.37 ± 0.30 tan θ	1.89 ± 0.30 tan θ
$2\theta_{max}$ (°)	135.2	135.2	134.6
No. of reflections measured			
Total	3891	1225	1154
With $I > 2\sigma(I)$	1515	848	892
No. of refinement variables	380	155	155
Final R; R_w	0.060; 0.063	0.050; 0.061	0.051; 0.062

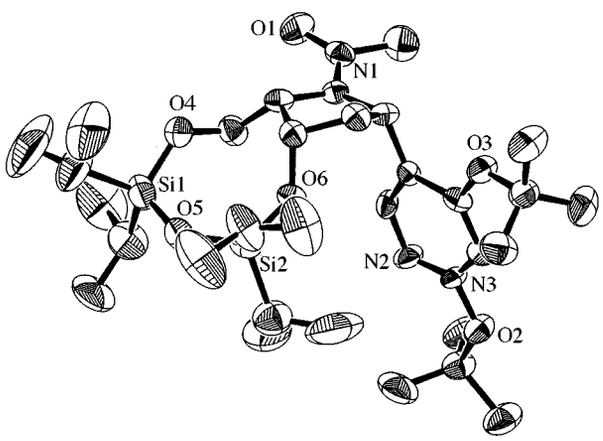


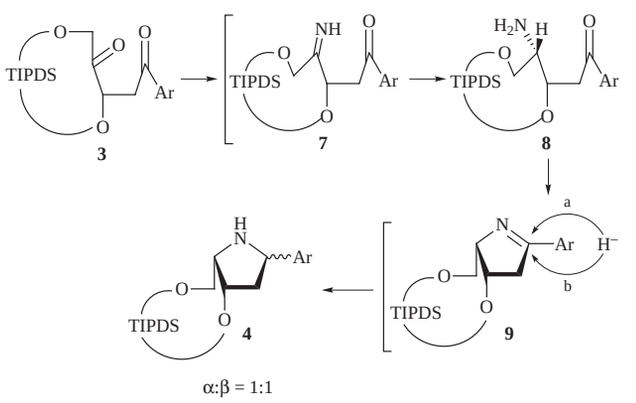
Fig. 1c X-Ray molecular structure of β-form of compound **5d** with crystallographic numbering scheme (hydrogen atoms omitted)

3-H↔4-H; (β-form) 1-H↔2-H, 1-H↔Ac-CH_3, 3-H↔4-H. (3) **6d**: (α-form), 1-H↔2-Ha, 1-H↔uracil 6-H, 2-Hb↔uracil 6-H, 3-H↔4-H; (β-form) 1-H↔2-Hb, 1-H↔uracil 6-H, 3-H↔4-H, 2-Ha↔uracil 6-H.

The following results are summarized based on the above NMR data and X-ray crystallographic data: (1) The differential NOE was not observed between 1-H and 4-H in the β-form of compounds **5d** and **6d**, while it was observed in the β-form of **4d** perhaps because the sugar skeletons of compounds **5d** and **6d** are close to a plane and the distances between 1-H and 4-H are above 3 Å (3.15 and 3.54 Å, respectively). (2) In the β-form of compound **5d**, the rotational isomer in which the CH_3 of the acetyl group faces the base side exists as the major isomer, which shows a differential NOE between 1-H and Ac-CH_3. X-Ray crystallographical data support this (Fig. 1c).

Reaction mechanism

The stereoselectivity of the present reaction can be explained by the following process (Scheme 2). At first, a regio- and stereoselective amination occurs at the 4-carbonyl group to produce an intermediate **8**, which has a 4*S* amino group, *via* an imine intermediate **7** due to the bulky TIPDS group. Next, nucleophilic addition of the 4-amino group to the 1-carbonyl group followed by dehydration gives an iminosugar **9**. Finally, the C-1 of intermediate **9** is attacked by a hydride ion equally through both sides (α and β). Therefore, compound **4** is formed as a 1 : 1 mixture of two stereoisomers. In the case of the thienyl derivative, an intermediate **8a** could be isolated in the first stage of this reaction.



Scheme 2 Plausible reaction mechanism of reductive aminocyclization

Bioassay of 6

The anti-HIV activity of α- and β-stereoisomers of compound **6d** was examined. The result did not show effective activity like that of a typical anti-HIV drug, 3′-azido-2′,3′-dideoxythymidine (AZT: $EC_{50} = 1.5 \times 10^{-3}$ μM; CC_{50} = 68.5 μM; SI = 4.44×10^4). Fig. 2 shows the result of HIV-1 inhibition compared with AZT.

Experimental

All reactions were conducted in oven-dried (120 °C) glassware under dry argon. THF was distilled from sodium benzophenone ketyl. Pyridine was distilled from CaH_2. ^{1}H NMR spectra were recorded on a JEOL JNM-FX-270 (270 MHz), JEOL JNM-LA-400 (400 MHz) or JEOL JNM-LA-500 (500 MHz) spectrometer. *J* Values are given in Hz. ^{13}C NMR spectra were recorded on a JEOL JNM-LA-400 (100 MHz) or JEOL JNM-LA-500 (125 MHz) spectrometer. X-Ray crystallographic data were collected on a Rigaku AFC7S diffractometer with graphite-monochromated Mo-Kα radiation. IR spectra were measured with an Hitachi-IR 215 spectrometer or a JASCO FT/IR-200 spectrometer. Mass spectra were recorded on a JEOL JMS-HX 110 mass spectrometer. For fast-atom bombardment (FAB) mass spectra, NBA refers to *m*-nitrobenzyl alcohol matrix. Mps were measured using a Yamano Melting Point Apparatus Model MP-21 and are uncorrected. Wakogel C-200, C-300 and Silica gel 60 (Kanto Chemical Co., Inc.) were used for column chromatography, Kieselgel 60 F_{254} (Merck) for TLC, and Wakogel B-5F for preparative TLC (pTLC). Columns JAIGEL-1HF (CH_3Cl) and JAIGEL-345-15 (MeOH)

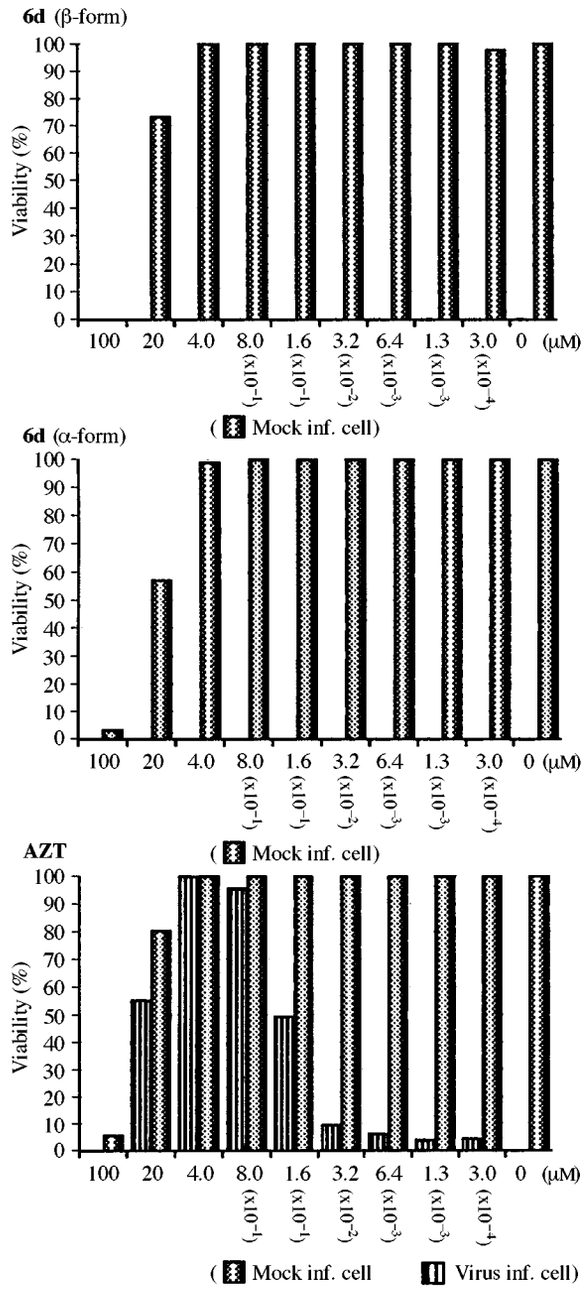


Fig. 2 HIV activity of compound **6d** and AZT

were used for recycling preparative HPLC (Japan Analytical Industry Co., HPLC-908).

2-Deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentofuranose 1

Typical procedure. To a solution of 2-deoxy-D-ribose (5.4 g, 40 mmol) in pyridine (50 ml) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (14 ml, 41 mmol). The reaction mixture was stirred at 40 °C for 2 h, treated with 1 M HCl, and extracted with Et_2O. The extract was washed with saturated aq. $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated off and the residue was purified by column chromatography [eluent: hexane–ethyl acetate (3 : 1)] to give title compound **1**.

Lithiation of aromatic heterocycles [thiophene, benzofuran and *N*-(phenylsulfonyl)indole]. To a solution of aromatic heterocycles (3.0 mmol) in THF (5 ml) was added *n*-butyllithium (1.0 mol equiv.) dropwise at 0 °C. The solution was allowed to attain rt and was stirred for 1 h.

Lithiation of 2,4-di(*tert*-butoxy)pyrimidine. To a solution of 5-bromo-2,4-di(*tert*-butoxy)pyrimidine (3.0 mmol) in THF (5 ml) was added dropwise to a THF solution of *n*-butyllithium (1.0 mol equiv.), which was kept at −78 °C, using a cannula. The solution was stirred at the same temperature for 5 min.

Preparation of 2-deoxyribosyl aromatic heterocycles 2

Typical procedure. To a stirred solution of compound **1** (376 mg, 1 mmol) in THF (5 ml) was added dropwise a solution of an organolithium in THF (5.0 mol equiv.) at 0 or −78 °C. After being stirred at rt for 1.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography [eluent: hexane–ethyl acetate (3 : 1)] to give compounds **2**.

(1*R*)- and (1*S*)-2-Deoxy-1-[*N*-(phenylsulfonyl)indol-2-yl]-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentitol 2c. Oil; ν_{max}(Neat)/cm^{-1} 1150, 1340, 1450, 1580, 2960 and 3500; HRMS (FAB, NBA + KI) [Found: M + K, 672.2250. Calc. for $C_{31}H_{47}KNO_7SSi_2$: (*M* + K) *m*/*z*, 672.2249]; δ_H(400 MHz; $CDCl_3$) (***R*-form**) 0.94–1.27 (28 H, m, TIPDS), 2.10–2.27 (2 H, m, 2-H_2), 2.92 (1 H, br s, 1- or 4-OH), 3.76 (1 H, m, 4-H), 3.95 (1 H, m, 5-H^a), 4.19–4.24 (2 H, m, 3-H and 5-H^b), 4.48 (1 H, br s, 4- or 1-OH), 5.69 (1 H, m, 1-H), 6.85 (1 H, s, indole 3-H), 7.19–8.11 (9 H, m, indole 4-, 5-, 6- and 7-H, and Ph); (***S*-form**) 0.92–1.07 (28 H, m, TIPDS), 2.39–2.60 (3 H, m, 2-H_2 and 1- or 4-OH), 3.69–3.86 (2 H, m, 5-H_2), 4.03 (1 H, m, 4-H), 4.20–4.23 (2 H, m, 3-H and 4- or 1-OH), 5.65 (1 H, m, 1-H), 6.71 (1 H, s, indole 3-H), 7.19–8.13 (9 H, m, indole 4-, 5-, 6- and 7-H, and Ph).

(1*R*)- and (1*S*)-2-Deoxy-1-[2,4-di(*tert*-butoxy)pyrimidin-5-yl]-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentitol 2d. Oil; ν_{max}(Neat)/cm^{-1} 1060, 1160, 1360, 1420, 1460, 1560, 1600, 2940 and 3400; HRMS (FAB, NBA + KI) [Found: (M + H), 601.3671. Calc. for $C_{29}H_{57}N_2O_7Si_2$: (*M* + H) *m*/*z*, 601.3704]; δ_H(400 MHz; $CDCl_3$) (***R*-form**) 0.99–1.12 (28 H, m, TIPDS), 1.56–1.62 (18 H, m, Bu^t), 2.00 (1 H, m, 2-H^a), 2.15 (1 H, m, 2-H^b), 2.41 (1 H, br s, 1- or 4-OH), 3.65 (1 H, m, 4-H), 3.86 (1 H, dd, J_{gem} = 11.6, $J_{4,5a}$ 1.7, 5-H^a), 3.93 (1 H, br s, 4- or 1-OH), 4.03 (1 H, m, 3-H), 4.21 (1 H, dd, J_{gem} 11.6, $J_{4,5b}$ 1.0, 5-H^b), 5.07 (1 H, m, 1-H) and 8.30 (1 H, s, pyrimidine 6-H); (***S*-form**) 0.97–1.11 (28 H, m, TIPDS), 1.60–1.63 (18 H, m, Bu^t), 2.15–2.22 (2 H, m, 2-H_2), 3.63 (1 H, m, 4-H), 3.81 (1 H, dd, J_{gem} 11.8, $J_{4,5a}$ 2.2, 5-H^a), 3.94 (1 H, m, 3-H), 4.18 (1 H, dd, J_{gem} 11.8, $J_{4,5b}$ 1.0, 5-H^b), 5.05 (1 H, dd, $J_{1,2b}$ 7.8, $J_{1,2a}$ 3.6, 1-H) and 8.30 (1 H, s, pyrimidine 6-H).

Oxidation of diols 2 to give aryl diones 3

Typical procedure. A solution of TFAA (5 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a solution of DMSO (6 mmol) in CH_2Cl_2 (5 ml) at −78 °C and the mixture was stirred for 1 h at the same temperature. To the stirring mixture was then added dropwise a solution of a diol **2** (1 mmol) in CH_2Cl_2 (3 ml) at −78 °C, and then the reaction mixture was stirred for an additional 2 h at the same temperature. A solution of Et_3N (8 mmol) in CH_2Cl_2 (3 ml) was added dropwise to the solution and stirring was continued for 0.5 h at −78 °C. The reaction mixture was then removed from the cooling bath and allowed to warm to 0 °C while being stirred. After a quench with water, the reaction mixture was extracted with CH_2Cl_2. The extract was washed successively with 1 M HCl and saturated aq. $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography [eluent: hexane–ethyl acetate (3 : 1)] to give **3**.

3,5-(Tetraisopropyldisiloxane-1,3-diyldioxy)-1-(2-thienyl)-pentane-1,4-dione 3a. Oil; ν_{max}(Neat)/cm^{-1} 1020, 1060, 1410, 1460, 1660, 1720 and 2900; HRMS (FAB, NBA) [Found: (M + H), 457.1895. Calc. for $C_{21}H_{37}O_5SSi_2$: (*M* + H) *m*/*z*, 457.1900]; δ_H(400 MHz; $CDCl_3$) 0.94–1.11 (28 H, m, TIPDS), 3.20 (1 H, dd, J_{gem} 16.9, $J_{2a,3}$ 4.8, 2-H^a), 3.60 (1 H, dd, J_{gem} 16.9, $J_{2b,3}$ 7.7, 2-H^b), 4.20 (1 H, d, J_{gem} 15.4, 5-H^a), 4.66 (1 H, d, J_{gem} 15.4, 5-H^b), 5.41 (1 H, dd, $J_{2b,3}$ 7.7, $J_{2a,3}$ 4.8, 3-H), 7.14 (1 H,

m, thiophene 4-H), 7.65 (1 H, m, thiophene 3-H) and 7.77 (1 H, m, thiophene 5-H).

1-(2-Benzofuryl)-3,5-(tetraisopropyldisiloxane-1,3-diyldioxy)-pentane-1,4-dione 3b. Oil; ν_{max}(Neat)/cm^{-1} 1040, 1120, 1460, 1560, 1680, 1740 and 2940; HRMS (FAB, NBA) [Found: (M + H), 491.2263. Calc. for $C_{25}H_{39}O_6Si_2$ (*M* + H) *m*/*z*, 491.2285]; δ_H(400 MHz; $CDCl_3$) 0.93–1.17 (28 H, m, TIPDS), 3.25 (1 H, dd, J_{gem} 17.0, $J_{2a,3}$ 4.9, 2-H^a), 3.66 (1 H, dd, J_{gem} 17.0, $J_{2b,3}$ 7.7, 2-H^b), 4.20 (1 H, d, J_{gem} 15.4, 5-H^a), 4.68 (1 H, d, J_{gem} 15.4, 5-H^b), 5.45 (1 H, dd, $J_{2b,3}$ 7.7, $J_{2a,3}$ 4.9, 3-H) and 7.29–7.71 (5 H, m, benzofuran 3-, 4-, 5-, 6- and 7-H).

1-[*N*-(Phenylsulfonyl)indol-2-yl]-3,5-(tetraisopropyldisiloxane-1,3-diyldioxy)pentane-1,4-dione 3c. Oil; ν_{max}(Neat)/cm^{-1} 1020, 1180, 1240, 1360, 1460, 1680, 1710 and 2900; HRMS (FAB, NBA) [Found: (M + H), 630.2354. Calc. for $C_{31}H_{44}NO_7SSi_2$: (*M* + H) *m*/*z*, 630.2377]; δ_H(400 MHz; $CDCl_3$) 0.92–1.18 (28 H, m, TIPDS), 3.33 (1 H, dd, J_{gem} 17.2, $J_{2a,3}$ 4.4, 2-H^a), 3.61 (1 H, dd, J_{gem} 17.2, $J_{2b,3}$ 8.4, 2-H^b), 4.17 (1 H, d, J_{gem} 15.4, 5-H^a), 4.64 (1 H, d, J_{gem} 15.4, 5-H^b), 5.38 (1 H, dd, $J_{2b,3}$ 8.4, $J_{2a,3}$ 4.4, 3-H), 7.21 (1 H, s, indole 3-H) and 7.28–8.11 (9 H, m, indole 4-, 5-, 6-, 7-H and Ph).

1-[2,4-Di(*tert*-butoxy)pyrimidin-5-yl]-3,5-(tetraisopropyldisiloxane-1,3-diyldioxy)pentane-1,4-dione 3d. Oil; ν_{max}(Neat)/cm^{-1} 1160, 1420, 1540, 1580, 1680, 1740 and 2940; HRMS (FAB, NBA) [Found: (M + H), 597.3374. Calc. for $C_{29}H_{53}N_2O_7Si_2$: (*M* + H) *m*/*z*, 597.3391]; δ_H(400 MHz; $CDCl_3$) 0.97–1.12 (28 H, m, TIPDS), 1.63–1.71 (18 H, m, Bu^t), 3.26 (1 H, dd, J_{gem} 18.6, $J_{2a,3}$ 4.2, 2-H^a), 3.60 (1 H, dd, J_{gem} 18.6, $J_{2b,3}$ 8.4, 2-H^b), 4.22 (1 H, d, J_{gem} 15.7, 5-H^a), 4.64 (1 H, d, J_{gem} 15.7, 5-H^b), 5.33 (1 H, dd, $J_{2b,3}$ 8.4, $J_{2a,3}$ 4.2, 3-H) and 8.71 (1 H, s, pyrimidine 6-H); δ_C(125 MHz; $CDCl_3$) 12.4–13.0 (TIPDS-3°), 16.9–17.3 (TIPDS-CH_3), 28.3 (^{t}Bu-CH_3), 28.5 (^{t}Bu-CH_3), 46.8 (2-C), 66.3 (5-C), 66.9 (3-C), 81.8 (^{t}Bu-4°), 84.0 (^{t}Bu-4°), 113.8 (pyrimidine 5-C), 162.2 (pyrimidine 6-C), 165.5 (pyrimidine 4-C), 168.5 (pyrimidine 2-C), 195.3 (1-C) and 208.0 (4-C).

Reductive aminocyclization of diones 3 to give azasugars 4

Typical procedure. Ammonium formate (5 mmol), $NaBH_3CN$ (5 mmol), 3 Å molecular sieves (500 mg) and a dione **3** (1 mmol) were dissolved in MeOH (20 ml). After stirring of the mixture for 18 h at rt, $NaBH_4$ was added and the stirring was continued for 2 h at the same temperature. The reaction mixture was filtrated through Celite (Wako hyflo super-cell), extracted with $CHCl_3$, and the extract was dried over Na_2SO_4. The solvent was removed, and the residue was purified by pTLC [developer: hexane–ethyl acetate (3 : 1)] to give the corresponding azasugar **4**.

1,2,4-Trideoxy-1,4-imino-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-1-(2-thienyl)-L-*threo*-pentitol 4a. Oil; ν_{max}(Neat)/cm^{-1} 1250, 1380, 1460, 1660, 2960 and 3340; HRMS (FAB, NBA) [Found: (M + H), 442.2225. Calc. for $C_{21}H_{40}NO_3Si_2$: (*M* + H) *m*/*z*, 442.2267]; δ_H(400 MHz; $CDCl_3$) (**α-form**) 0.91–1.09 (28 H, m, TIPDS), 2.03–2.11 (2 H, m, 2-H_2), 3.45 (1 H, ddd, $J_{4,5a}$ 10.1, $J_{4,5b}$ 4.6, $J_{3,4}$ 3.3, 4-H), 3.79 (1 H, dd, J_{gem} 10.2, $J_{4,5a}$ 10.1, 5-H^a), 3.84 (1 H, dd, J_{gem} 10.2, $J_{4,5b}$ 4.6, 5-H^b), 3.96 (1 H, m, 3-H), 4.57 (1 H, t, $J_{1,2}$ 3.3, 1-H), 6.91–6.93 (2 H, m, thiophene 3- and 4-H) and 7.16 (1 H, m, thiophene 5-H); (**β-form**) 0.91–1.10 (28 H, m, TIPDS), 2.35 (1 H, m, 2-H^a), 2.60 (1 H, m, 2-H^b), 3.18 (1 H, m, 4-H), 4.42 (1 H, dd, J_{gem} 12.9, $J_{4,5a}$ 3.8, 5-H^a), 4.51 (1 H, dd, J_{gem} 12.9, $J_{4,5b}$ 6.6, 5-H^b), 4.67 (1 H, m, 3-H), 4.81 (1 H, dd, $J_{1,2a}$ 6.6, $J_{1,2b}$ 9.6, 1-H), 6.92–6.94 (2 H, m, thiophene 3- and 4-H) and 7.18 (1 H, m, thiophene 5-H).

1-(Benzofuran-2-yl)-1,2,4-trideoxy-1,4-imino-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-L-*threo*-pentitol 4b. Oil; ν_{max}(Neat)/cm^{-1} 1040, 1260, 1460, 1660, 2960 and 3360; HRMS (FAB, NBA) [Found: (M + H), 476.2654. Calc. for $C_{25}H_{42}O_4Si_2$: (*M* + H) *m*/*z*, 476.2652]; δ_H(400 MHz; $CDCl_3$) (**α-form**) 1.00–1.14 (28 H, m, TIPDS), 2.20–2.33 (2 H, m, 2-H_2), 3.14 (1 H, m, 4-H), 3.85 (1 H, dd, J_{gem} 11.7, $J_{4,5a}$ 6.2, 5-H^a), 4.00 (1 H, dd, J_{gem} 11.7, $J_{4,5b}$ 3.4, 5-H^b), 4.47 (1 H, m, 3-H), 4.56 (1 H, dd, $J_{1,2b}$ 7.4, $J_{1,2a}$ 6.3, 1-H), 6.56 (1 H, s, benzofuran 3-H) and 7.16–7.50 (4 H, m, benzofuran 4-, 5-, 6- and 7-H); (**β-form**) 1.02–1.09 (28 H, m, TIPDS), 1.75 (1 H, br s, NH), 2.13 (1 H, dd, $J_{1,2a}$ 5.5, J_{gem} 13.8, 2-H^a), 2.52 (1 H, m, 2-H^b), 3.17 (1 H, ddd, $J_{3,4}$ 3.4, $J_{4,5a}$ 10.0, $J_{4,5b}$ 4.4, 4-H), 3.86 (1 H, dd, J_{gem} 10.2, $J_{4,5a}$ 10.0, 5-H^a), 3.96 (1 H, dd, J_{gem} 10.2, $J_{4,5b}$ 4.4, 5-H^b), 4.41 (1 H, dd, $J_{1,2b}$ 9.2, $J_{1,2a}$ 5.5, 1-H), 4.54 (1 H, d, $J_{3,4}$ 3.4, 3-H), 6.59 (1 H, s, benzofuran 3-H) and 7.18–7.51 (4 H, m, benzofuran 4-, 5-, 6- and 7-H).

1,2,4-Trideoxy-1,4-imino-1-[*N*-(phenylsulfonyl)indol-2-yl]-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-L-*threo*-pentitol 4c. Oil; ν_{max}(Neat)/cm^{-1} 1250, 1380, 1460, 1540, 1600, 1680, 2960 and 3450; HRMS (FAB, NBA) [Found: (M + H), 615.2626. Calc. for $C_{31}H_{47}N_2O_5SSi_2$: (*M* + H) *m*/*z*, 615.2690]; δ_H(400 MHz; $CDCl_3$) (**α-form**) 0.93–1.26 (28 H, m, TIPDS), 2.42 (1 H, ddd, J_{gem} 14.7, $J_{2a,3}$ 6.6, $J_{1,2a}$ 3.0, 2-H^a), 2.56 (1 H, ddd, J_{gem} 14.7, $J_{1,2b}$ 8.1, $J_{2b,3}$ 3.3, 2-H^b), 3.70 (1 H, ddd, $J_{3,4}$ 9.2, $J_{4,5a}$ 2.2, $J_{4,5b}$ 1.5, 4-H), 3.84 (1 H, dd, J_{gem} 11.8, $J_{4,5a}$ 2.2, 5-H^a), 4.00 (1 H, ddd, $J_{3,4}$ 9.2, $J_{2a,3}$ 6.6, $J_{2b,3}$ 3.3, 3-H), 4.20 (1 H, dd, J_{gem} 11.8, $J_{4,5b}$ 1.5, 5-H^b), 5.66 (1 H, dd, $J_{1,2b}$ 8.1, $J_{1,2a}$ 3.0, 1-H), 6.71 (1 H, s, indole 3-H), 7.20–8.13 (9 H, m, indole 4-, 5-, 6- and 7-H, and Ph); (**β-form**) 0.98–1.10 (28 H, m, TIPDS), 2.30 (1 H, ddd, J_{gem} 13.9, $J_{2a,3}$ 4.0, $J_{1,2a}$ 2.6, 2-H^a), 2.53 (1 H, ddd, J_{gem} 13.9, $J_{1,2b}$ 10.3, $J_{2b,3}$ 9.2, 2-H^b), 3.66 (1 H, dd, J_{gem} 10.2, $J_{4,5a}$ 9.6, 5-H), 3.85 (1 H, ddd, $J_{4,5a}$ 9.6, $J_{4,5b}$ 5.3, $J_{3,4}$ 0.8, 4-H), 3.89 (1 H, dd, J_{gem} 10.2, $J_{4,5b}$ 5.3, 5-H^b), 4.52 (1 H, ddd, $J_{2b,3}$ 9.2, $J_{2a,3}$ 4.0, $J_{3,4}$ 0.8, 3-H), 5.41 (1 H, dd, $J_{1,2b}$ 10.3, $J_{1,2a}$ 2.6, 1-H), 6.74 (1 H, s, indole 3-H), 7.20–8.09 (9 H, m, indole 4-, 5-, 6- and 7-H, and Ph).

1,2,4-Trideoxy-1-[2,4-di(*tert*-butoxy)pyrimidin-5-yl]-1,4-imino-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-L-*threo*-pentitol 4d. Oil; ν_{max}(Neat)/cm^{-1} 1020, 1180, 1400, 1460, 1560, 1600, 2940 and 3320; δ_H(400 MHz; $CDCl_3$) (**α-form**) 1.02–1.23 (28 H, m, TIPDS), 1.59 (9 H, m, ^{t}Bu), 1.62 (9 H, s, ^{t}Bu), 1.95 (1 H, ddd, J_{gem} 12.8, $J_{1,2a}$ 9.6, $J_{2a,3}$ 3.5, 2-H^a), 2.19 (1 H, dd, J_{gem} 12.8, $J_{1,2b}$ 6.4, 2-H^b), 3.36 (1 H, ddd, $J_{4,5a}$ 10.2, $J_{4,5b}$ 4.5, $J_{3,4}$ 3.1, 4-H), 3.79 (1 H, dd, $J_{4,5a}$ 10.2, J_{gem} 10.1, 5-H^a), 3.86 (1 H, dd, J_{gem} 10.1, $J_{4,5b}$ 4.5, 5-H^b), 4.48 (1 H, dd, $J_{1,2a}$ 9.6, $J_{1,2b}$ 6.4, 1-H), 4.51 (1 H, m, 3-H) and 8.21 (1 H, s, pyrimidine 6-H); (**β-form**) 0.98–1.14 (28 H, m, TIPDS), 1.59–1.61 (18 H, m, ^{t}Bu), 1.80 (1 H, m, 2-H^a), 2.49 (1 H, ddd, J_{gem} 13.9, $J_{1,2b}$ 9.4, $J_{2b,3}$ 5.6, 2-H^b), 3.18 (1 H, ddd, $J_{4,5a}$ 8.9, $J_{4,5b}$ 8.9, $J_{3,4}$ 3.6, 4-H), 3.90 (2 H, m, 5-H_2), 4.31 (1 H, dd, $J_{1,2b}$ 9.4, $J_{1,2a}$ 5.8, 1-H), 4.48 (1 H, m, 3-H) and 8.35 (1 H, s, pyrimidine 6-H); δ_C(125 MHz; $CDCl_3$) (**α-form**) 12.4–13.4 (TIPDS-3°), 17.0–17.5 (TIPDS-CH_3), 28.3 (^{t}Bu-CH_3), 28.5 (^{t}Bu-CH_3), 42.1 (2-C), 54.6 (1-C), 60.8 (5-C), 64.6 (4-C), 72.3 (3-C), 79.7 (^{t}Bu-4°), 81.3 (^{t}Bu-4°), 117.7 (pyrimidine), 156.0 (pyrimidine 6-C), 163.2 (pyrimidine) and 167.6 (pyrimidine); (**β-form**) 12.4–13.3 (TIPDS-3°), 17.0–17.5 (TIPDS-CH_3), 28.4 (^{t}Bu-CH_3), 28.5 (^{t}Bu-CH_3), 42.3 (2-C), 53.2 (1-C), 60.7 (5-C), 65.8 (4-C), 71.3 (3-C), 79.6 (^{t}Bu-4°), 81.1 (^{t}Bu-4°), 118.4 (pyrimidine), 156.6 (pyrimidine 6′-C), 162.9 (pyrimidine) and 167.2 (pyrimidine).

Acetylation of azasugars 4

Typical procedure. To a stirred mixture of a compound **4** (0.1 mmol), Et_3N (0.2 mmol), and dry THF (2 ml) was added dropwise acetyl chloride (0.15 mmol) at rt. After further stirring at the same temperature, the reaction mixture was quenched with saturated aq. $NaHCO_3$ and was then extracted with diethyl ether. The extract was dried over Na_2SO_4 and condensed to give an oil, which was purified by pTLC [developer: hexane–ethyl acetate (3 : 1)] to give the corresponding acetamide.

***N*-Acetyl-1,2,4-trideoxy-1-[2,4-di(*tert*-butoxy)pyrimidin-5-yl]-1,4-imino-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-L-*threo*-pentitol 5d.** Powder, mp 158–161 °C; ν_{max}(KBr)/cm^{-1} 1020, 1160, 1420, 1560, 1600, 1660 and 2960; HRMS (FAB, NBA) [Found: (M + H), 624.3837. Calc. for $C_{31}H_{58}N_3O_6Si_2$: (M + H) *m*/*z*, 624.3864]; δ_H(400 MHz; $CDCl_3$) (**α-form**) 1.03–1.10 (28 H, m, TIPDS), 1.61 (9 H, s, ^{t}Bu), 1.62 (9 H, s, ^{t}Bu), 2.06 (1 H, m, 2-H^a), 2.20 (3 H, s, Ac), 2.27 (1 H, ddd, J_{gem} 12.0, $J_{1,2b}$ 7.6, $J_{2b,3}$

3.7, 2-H^b), 3.85 (1 H, dd, J_{gem} 10.1, $J_{4,5a}$ 10.0, 5-H^a), 4.14 (1 H, m, 4-H), 4.60 (1 H, m, 3-H), 4.72 (1 H, dd, J_{gem} 10.1, $J_{4,5b}$ 4.0, 5-H^b), 4.95 (1 H, t, $J_{1,2}$ 7.6, 1-H) and 7.99 (1 H, s, pyrimidine 6-H); (**β-form**) 0.97–1.04 (28 H, m, TIPDS), 1.59 (9 H, s, ^{t}Bu), 1.63 (9 H, s, ^{t}Bu), 1.95 (3 H, s, Ac), 2.28 (2 H, m, 2-H$_2$), 3.87 (1 H, dd, $J_{4,5a}$ 9.6, J_{gem} 9.2, 5-H^a), 4.14 (1 H, ddd, $J_{4,5a}$ 9.6, $J_{3,4}$ 4.5, $J_{4,5b}$ 4.0, 4-H), 4.59 (1 H, m, 3-H), 4.62 (1 H, dd, J_{gem} 9.2, $J_{4,5b}$ 4.0, 5-H^b), 4.91 (1 H, t, $J_{1,2}$ 4.8, 1-H) and 7.98 (1 H, s, pyrimidine 6-H); δ_C(125 MHz; $CDCl_3$) (**α-form**) 12.5–13.0 (TIPDS-3°), 17.2–17.5 (TIPDS-CH_3), 23.9 (Ac), 28.3 (^{t}Bu-CH_3), 28.5 (^{t}Bu-CH_3), 41.1 (2-C), 57.1 (1-C), 58.7 (5-C), 65.0 (4-C), 70.1 (3-C), 80.4 (^{t}Bu-4°), 82.4 (^{t}Bu-4°), 116.1 (pyrimidine), 156.1 (pyrimidine 6-C), 163.6 (pyrimidine), 166.8 (pyrimidine) and 170.5 (pyrimidine or Ac-4°); (**β-form**) 12.3–13.2 (TIPDS-3°), 16.8–17.5 (TIPDS-CH_3), 22.8 (Ac), 28.4 (^{t}Bu-CH_3), 28.6 (^{t}Bu-CH_3), 40.4 (2-C), 57.7 (1-C), 58.5 (5-C), 65.0 (4-C), 71.3 (3-C), 79.8 (^{t}Bu-4°), 81.7 (^{t}Bu-4°), 115.9 (pyrimidine), 155.3 (pyrimidine 6-C), 163.3 (pyrimidine), 166.5 (pyrimidine) and 171.9 (pyrimidine or Ac-4°) (Found: C, 59.5; H, 9.2; N, 6.7. Calc. for $C_{31}H_{57}N_3O_6Si_2$: C, 59.67; H, 9.21; N, 6.73%).

Deprotection of azasugars 4 to give '*C*-azadeoxynucleosides' 6

Typical procedure. To a MeOH solution (1 ml) containing compound **4d** (50 mg) was added 6 M HCl (3 ml). After being stirred for 30 min under reflux, the reaction solution was evaporated to give a residue, which was then dissolved in a small amount of MeOH. The resulting MeOH solution was dropped into a sufficient volume of diethyl ether to afford the HCl salt **6d** quantitatively.

1,2,4-Trideoxy-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,4-imino-L-*threo*-pentitol hydrochloride 6d. Powder, ν_{max}(KBr)/cm^{-1} 1080, 1260, 1440, 1540, 1680, 1720, 2940, 3200 and 3360; HRMS (FAB, NBA) [Found: (M + H), 228.0990. Calc. for $C_9H_{14}N_3O_4$: (M + H), *m*/*z*, 228.0984]; δ_H(400 MHz; D_2O) (**α-form**) 2.29 (1 H, m, 2-H^a), 2.54 (1 H, ddd, J_{gem} 14.2, $J_{1,2b}$ 11.4, $J_{2b,3}$ 2.4, 2-H^b), 3.91 (1 H, dd, J_{gem} 10.8, $J_{4,5b}$ 8.2, 5-H^b), 3.95 (1 H, m, 4-H), 4.00 (1 H, dd, J_{gem} 10.8, $J_{4,5a}$ 3.7, 5-H^a), 4.68 (1 H, m, 3-H), 4.84 (1 H, dd, $J_{1,2b}$ 11.4, $J_{1,2a}$ 7.0, 1-H) and 7.72 (1 H, s, pyrimidine 6-H); (**β-form**) 2.24 (1 H, m, 2-H^a), 2.73 (1 H, m, 2-H^b), 3.74 (1 H, ddd, $J_{4,5a}$ 7.5, $J_{4,5b}$ 5.1, $J_{3,4}$ 4.5, 4-H), 3.93 (1 H, dd, J_{gem} 12.2, $J_{4,5a}$ 7.5, 5-H^a), 4.00 (1 H, dd, J_{gem} 12.2, $J_{4,5b}$ 5.1, 5-H^b), 4.65–4.70 (2 H, m, 1- and 3-H) and 7.77 (1 H, s, pyrimidine 6-H); δ_C(100 MHz; D_2O) (**α-form**) 39.6 (2-C), 58.4 (1-C), 60.5 (5-C), 68.3 (4-C), 73.0 (3-C), 110.0 (pyrimidine), 145.5 (pyrimidine 6-C), 155.5 (pyrimidine) and 167.8 (pyrimidine); (**β-form**) 38.8 (2-C), 56.9 (1-C), 60.2 (5-C), 67.7 (4-C), 72.0 (3-C), 110.3 (pyrimidine), 145.8 (pyrimidine 6-C) and 168.2 (pyrimidine).

4-Amino-3,5-(tetraisopropyldisiloxane-1,3-diyldioxy)-1-(2-thienyl)pentan-1-one 8a. Oil; ν_{max}(Neat)/cm^{-1} 1030, 1060, 1420, 1460, 1660, 2960 and 3450; HRMS (FAB, NBA) [Found: (M + H), 457.1992. Calc. for $C_9H_{14}N_3O_4$ (M + H) *m*/*z*, 457.2138]; δ_H(400 MHz; $CDCl_3$) 0.91–1.08 (28 H, m, TIPDS), 3.25 (1 H, dd, J_{gem} 15.9, $J_{2a,3}$ 6.2, 2-H^a), 3.34 (1 H, dd, J_{gem} 15.9, $J_{2b,3}$ 6.2, 2-H^b), 3.58–3.67 (2 H, m, 4-H and 5-H^a), 3.85 (1 H, dd, J_{gem} 9.9, $J_{4,5b}$ 4.7, 5-H^b), 4.81 (1 H, m, 3-H), 7.14 (1 H, m, thiophene 4-H), 7.65 (1 H, m, thiophene 3-H) and 7.78 (1 H, m, thiophene 5-H).

Bio-assay test

Cell lines. The human T lymphotropic virus type I (HTLV-I)-positive human T-cell line, MT-4, was subcultured twice weekly at a density of 3 × 105 cells μl^{-1} in RPMI-1640 medium supplemented with 10% heat-inactivated foetal calf serum (FCS), 100 IU (international units) μl^{-1} penicillin, and 100 mg ml^{-1} of streptomycin.

Virus. The HTLV-IIIB strain was used in the anti-HIV assay. The virus was prepared from the culture supernatants of MOLT-4/HTLV-IIIB cells, which were persistently infected with HTLV-IIIB. HIV stocks were titrated in MT-4 cells as determined by 50% tissue culture infectious doses ($TCID_{50}$) and plaque-forming units, and stored at −80 °C until use.

Anti-HIV assay. The anti-HIV activity of test compounds in a fresh, cell-free HIV infection was determined as protection against HIV-induced cytopathic effects (CPE). Briefly, MT-4 cells were infected with HTLV-IIIB at a multiplicity of infection (MOI) of 0.01. HIV-infected or mock-infected MT-4 cells (1.5 × 105 ml, 200 ml) were placed into 96-well microtitre plates and incubated in the presence of various concentrations of test compounds. The dilution ranged from one- to five-fold and nine concentrations of each compound were examined. All experiments were performed in triplicate. After a 5-day incubation at 37 °C in a CO_2 incubator, the cell viability was quantified by a calorimetric assay that monitored the ability of the viable cells to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to a blue formazan product. The absorbances were read in a microcomputer-controlled photometer (Titertek Multiskan®; Labsystem Oy, Helsinki, Finland) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from that at 540 nm, to eliminate the effects of non-specific absorption. All data represent the mean values of triplicate wells. These values were then translated into percentage cytotoxicity and percentage antiviral protection, from which the 50% cytotoxic concentration (CC_{50}), the 50% effective concentration (EC_{50}), and the selectivity indexes (SI) were calculated.[12]

Acknowledgements

We thank Professor Hiroshi Takaku (Chiba Institute of Technology) for the assay test of HIV and Dr Hiroko Seki and Miss Rituko Hara (Chemical Analysis Center of Chiba University) for measurements of NMR and mass spectra. This work was supported by Grant-in-Aid No. 07554085 for Scientific Research from the Ministry of Education, Science and Culture, Japan and the Fund for Researching Assistant of Chiba University (T. I. and A. M.).

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Paper 8/02247J
Received 23*rd March* 1998
Accepted 13*th May* 1998