Convenient synthesis of *C*-aza-2,3-dideoxynucleosides

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1-Aryl-1,2,3,4-tetradeoxy-1,4-imino-D-pentitols **5** and **9f** are easily synthesized from *N*-Boc-L-pyroglutamate **1** *via* a successive procedure involving regioselective ring-opening, recyclization with dehydration, stereoselective reduction, and reduction of the ester group. Their structures are determined mainly by X-ray crystallography and NMR measurements. Their bioassay is also described.

Introduction

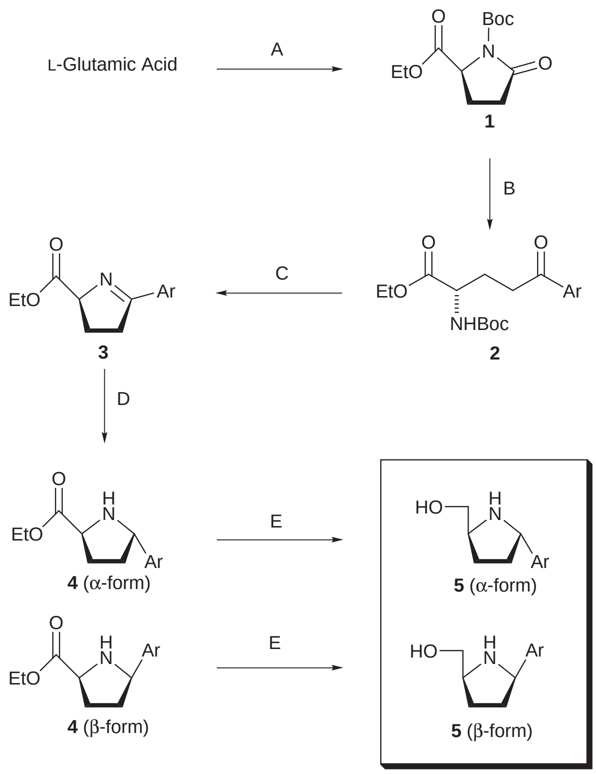
The importance of modification of the sugar moiety in nucleosides has long been recognized to improve their antiviral or anticancer activities. The 2,3-dideoxynucleosides[1] are typical sugar-modified nucleosides, which have been used as both anticancer and antiviral drugs, because DNA synthesis is terminated when they are incorporated into the end of a growing DNA chain. Recently, they have received increased attention due to their activity against the human immunodeficiency virus (HIV).[2] Thus, compounds which would substantially mimic the 2,3-dideoxynucleoside structures have been synthesized and employed as enzyme inhibitors in chemotherapy. In order to provide a new type of potentially active analogue the further modification of nucleoside subunits to a variety of derivatives with potentially different activities is considered to be desirable. In this respect, we chose the azafuranopentose analogues, in which the ring oxygen of furanoses is replaced with nitrogen. Azasugars such as nojirimycin are well known as glycosidase inhibitors. Their activity is ascribed to both the charge–charge interaction and the hydrogen bonding between an enzyme and a protonated azasugar at physiological pH.[3] In the case of the azafuranopentose system, the 1,4-imino group on the sugar ring is protonated to give the corresponding immonium compound like the oxocarbenium ion. Azasugar-containing nucleosides such as *C*-azanucleosides and *N*-azanucleosides have been reported in the literature.[4] However, their synthesis requires multi-step or tedious methods.

From the above standpoint, we intended to synthesize the *C*-aza-2,3-dideoxynucleosides on a large scale by a convenient method. Recently, we have developed a short-step synthesis of some *C*-azanucleosides having 1,4-dideoxy-1,4-imino-L-lyxitol and 1,2,4-trideoxy-1,4-imino-L-lyxitol as the sugar moiety,[5] and it was possible to modify the amino group in the azasugar moiety of these *C*-azanucleosides with an alkyl or acyl group. Therefore, it is expected that functionalization of this amino group would render it a potential linker for attachment to other molecules.

In this report, we describe the synthesis of other analogues, *C*-aza-2,3-dideoxynucleosides, their structure determination mainly with X-ray crystallography and NMR measurements, and, furthermore, their biological activities.

Results and discussion

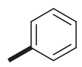
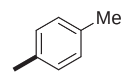
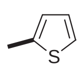
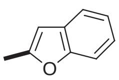
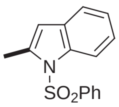
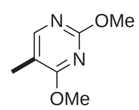
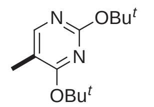
For the synthesis of 1-aryl-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol (*C*-aza-2,3-dideoxynucleoside), we chose *N*-Boc-L-pyroglutamate[6] **1** as the starting material (Scheme 1). Pyroglutamate **1** was prepared from L-glutamic acid by the usual procedure, and the carbonyl group of its amide was attacked regioselectively by aryl metal reagents because of the electron-withdrawing Boc group. Thus, the ring-opening reaction of **1** was achieved with a variety of nucleophiles.[7] Before the reaction of **1** with aromatic metal reagents, we examined the enantiomeric excess[7b] of the starting material **1** by using chiral column chromatography. It was revealed that some racemization occurred to an extent of 4% (92% ee) when L-glutamic acid was treated with $SOCl_2$ and refluxed in ethanol solution.



Scheme 1 *Reagents and conditions*: A, Ref. 6; B, Ar-Metal, THF, −78 to −40 °C, 1 h; C, CF_3CO_2H, $CHCl_3$, rt, 2 h; D, $NaBH_3CN$, HCl, Pr^iOH, rt, 2 h; E, LiAlH, Et_2O, 0 °C, 3 h.

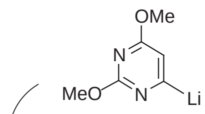
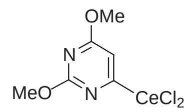
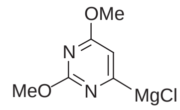
Compound **1** was treated with Grignard reagents (ArMgX) to give 5-aryl-substituted derivatives **2** in a regioselective manner (Table 1, **a** and **b**). In this reaction, we used the easily available lithium reagents of heterocyclic substituents to introduce various kinds of heteroaromatics. The thienyllithium reagent reacted in the same way as the corresponding Grignard reagent (Table 1, **c**). The lithium reagents of other heteroaromatics such as benzofuran, *N*-(phenylsulfonyl)indole, and

Table 1 Preparation of compounds **2**, **3**, **4** and **5**

Ar		Yields (%)[a] **2**	**3**	**4**α/**4**β (total)	**5**α	**5**β
a:		92[b]	89	19/44 (63)	81	83
b:		64[b]	94	18/48 (66)	98	67
c:		84[b] 84[c]	94	33/46 (79)	65	70
d:		51[c]	78	29/47 (76)	89	66
e:		63[c]	90	36/36 (72)	49	75
f:		17[c] 54[b]	63	27/59 (86)	71	73
g:		78[c]	84[d]	[e]		

[a] Isolated yield. [b] Aryl Grignard reagent was used. [c] Aryllithium reagent was used. [d] Ar 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl. [e] see Table 4.

Table 2 Introduction of pyrimidinyl group by using some metal reagents

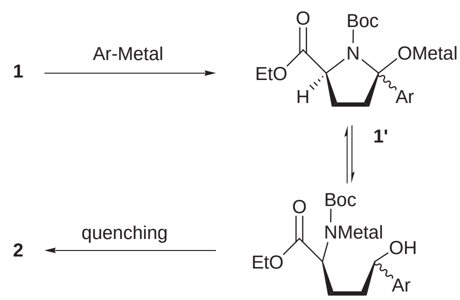
Ar-Metal	Conditions	Yield (%)	ee (%) **1**	**3**
	rt, 10 min, THF	49	92	65
	rt, 30 min, THF	29	92	72
	rt, 8 h, THF	40	92	60
	rt, 1 h, THF	40	92	92

[a] $CeCl_3$, THF, −78 °C, 30 min.

2,4-di(*tert*-butoxy)pyrimidine were also employed for the ring-opening reaction.

Here, the yield of 2,4-dimethoxypyrimidine derivative **2f** was poor with the corresponding lithium reagent because of the decomposition of its lithium salt at above −78 °C. To improve the yield of **2f**, the Grignard reagent of 2,4-dimethoxypyrimidine was prepared from the reaction of 5-bromo-2,4-dimethoxypyrimidine with EtMgBr *via* halogen–metal exchange.[8] Unlike its lithium reagent, the pyrimidine Grignard reagent did not decompose even at room temperature and the ring-opening reaction proceeded cleanly in a regioselective manner. However, no improvement in the yield of **2f** was observed, perhaps because of the small equilibrium constant of the halogen–metal exchange between 5-bromo-2,4-dimethoxypyrimidine and EtMgCl. When this Grignard reagent was prepared in Et_2O, it did not work at all due to its insolubility. Therefore, it should be prepared in THF solution. Next, **2a**–**f** were treated with trifluoroacetic acid to remove the Boc group followed by intramolecular cyclization resulting in the formation of 2-aryl-Δ^1-pyrroline-5-carboxylates **3** in good yields. Since it was possible to separate the enantiomers of **3** (only at analytical level) by chiral column chromatography, the ee-values were rechecked. Compared with the ee-value of **1**, that of **3** was diminished as shown in Table 2, perhaps because 5-H of **1** or **1′** was somewhat removed by alkyl or aromatic lithium reagents in the ring-opening reaction with aromatic lithium reagents in the preparation of **2** (Scheme 2). To prevent this racemization, the reaction was carried out again by using less basic reagents such as pyrimidine cerium or magnesium reagents. Compared with the lithium reagent, the racemization decreased when the cerium reagent[9] was used. Further, no racemization was observed with the use of the magnesium reagent for 1 h (chiral transfer 100%). In the case of other heterocycles, the reaction proceeded in the same manner as for **2f**. It was confirmed that the ee-value did not change during the process **1** ⟶ **4**, by using chiral column chromatography.

The imino group of **3** was reduced with $NaBH_3CN$ under



Scheme 2 Plausible mechanism for racemization.

acidic conditions to give α- and β-forms of 2-arylpyrrolidine-5-carboxylates **4**. As shown in entries 1–5 in Table 3, the reaction showed some β-selectivity probably due to the steric hindrance of the 2-ethoxycarbonyl group. When amine–borane complexes[10] were used as reducing agents (entries 6 and 7), the stereoselectivity was reversed to give the α-form of **4** preferentially. Further, the use of trifluoroacetic acid in place of HCl gave the same result. When this reduction was performed in AcOH, an unexpected (5*S*)-2-aryl-5-ethoxycarbonyl-*N*-ethylpyrrolidine was obtained as the main product, which might be produced by the reaction of **4** with acetaldehyde generated under these reaction conditions. In the case of **2g**, the elimination of two *tert*-butoxy groups took place under acidic conditions to give **3g**, which was then reduced in a 1,4-reductive manner to give an undesired product **7** (Table 4). The reduction with Pd/C[11] or with $NaBH_4$–$CeCl_3$[12] also gave only **7** in place of isomer **8**.

The reduction of **4** with $LiAlH_4$ in Et_2O gave α- and β-forms of 1-aryl-1,2,3,4-tetradeoxy-1,4-imino-D-pentitols **5**. Although we could obtain an α/β-mixture of **5** directly from **3** or *via* 2-aryl-5-hydroxymethyl-Δ^1-pyrrolines such as **6** (Scheme 3), their yields were low. In addition, it was difficult to separate the α- and β-isomers of **5**. On the other hand, the α- and β-isomers of **3** were found to be separated easily on preparative TLC (PLC).

Finally, the α- and β-isomers of **5f** were deprotected by treatment with HCl in MeOH at 60 °C for 3 h to afford the desired α- and β-form of **9f** (*C*-aza-2,3-dideoxyribonucleosides) as HCl salts, respectively (Scheme 4).

In the ^{1}H NMR data of *C*-aza-2,3-dideoxyribonucleosides **5a**–**e** and **9f**, differential nuclear Overhauser effects (NOEs) were observed and the spectral data of the α- and β-forms were compared. Fig. 1 shows the NOEs observed in **9f** as a typical example. A difference between the α- and β-forms is pointed out as follows: In the α-form, an NOE is observed between 1-H and CH_2OH, while in the β-form NOEs are observed between 1-H

Table 3 Reductive conditions of imino group under acidic conditions (**3c** ⟶ **4c**)

Entry	Conditions	HCl (M)	Yield (%) (α/β)
1	$NaBH_3CN$, EtOH, HCl	0.5	22 (4/18)
2	$NaBH_3CN$, EtOH, HCl	1	69 (26/43)
3	$NaBH_3CN$, EtOH, HCl	2	35 (13/22)
4	$NaBH_3CN$, Pr^iOH, HCl	1	79 (33/46)
5	$NaBH_3CN$, Bu^tOH, HCl	1	63 (28/35)
6	$Me_2NH·BH_3$, AcOH		51 (38/13)
7	$Bu^tNH_2·BH_3$, AcOH		60 (40/20)

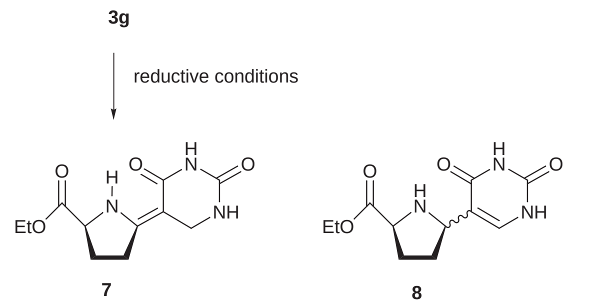
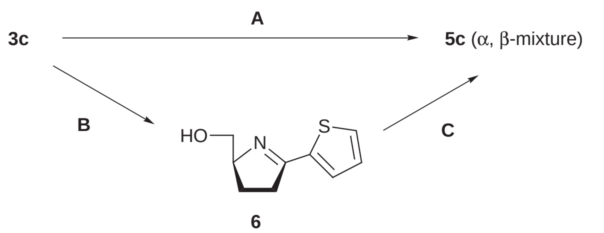
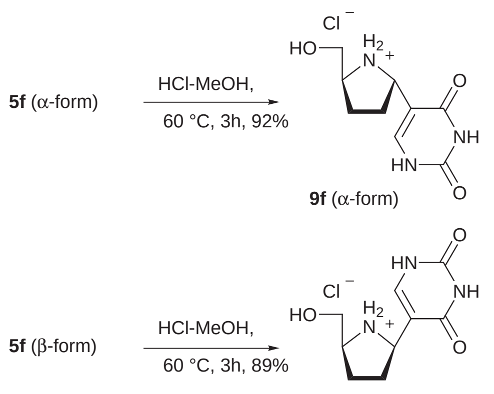


Table 4 Reduction of compound **3g**

	Yields (%)	
Reductive conditions	**7**	**8**
H^+, $NaBH_3CN$, EtOH	55	0
H_2, Pd/C, MeOH	100	0
$CeCl_3$, $NaBH_4$, MeOH	30	0



Scheme 3 *Reagents and conditions*: A, 15% $LiAlH_4$, THF, 0 °C, 2 h; B, 22% excess $NaBH_4$, EtOH, rt, 8 h; C, 70% $NaBH_3CN$, HCl, EtOH, rt, 2 h.



Scheme 4 Deprotection of pyrimidine moiety.

and 4-H, and between uracil 6-H and CH_2OH. In all other *C*-aza-2,3-dideoxyribonucleosides **5a**–**e**, NOEs were observed in the same manner as those of **9f**.

The crystal of **9f**, which was obtained from ethanol–H_2O for X-ray analysis, was found to be a racemic mixture (Fig. 2, Table 5). Judging from the easy crystallization of the racemic compound, reprecipitation seemed appropriate to obtain enantio-

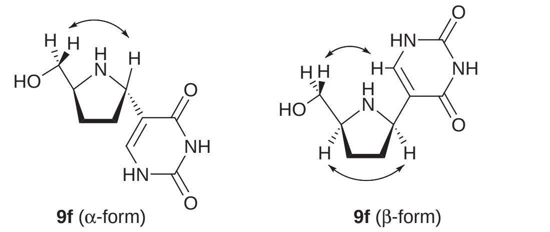


Fig. 1 Observed NOEs in **9f**.

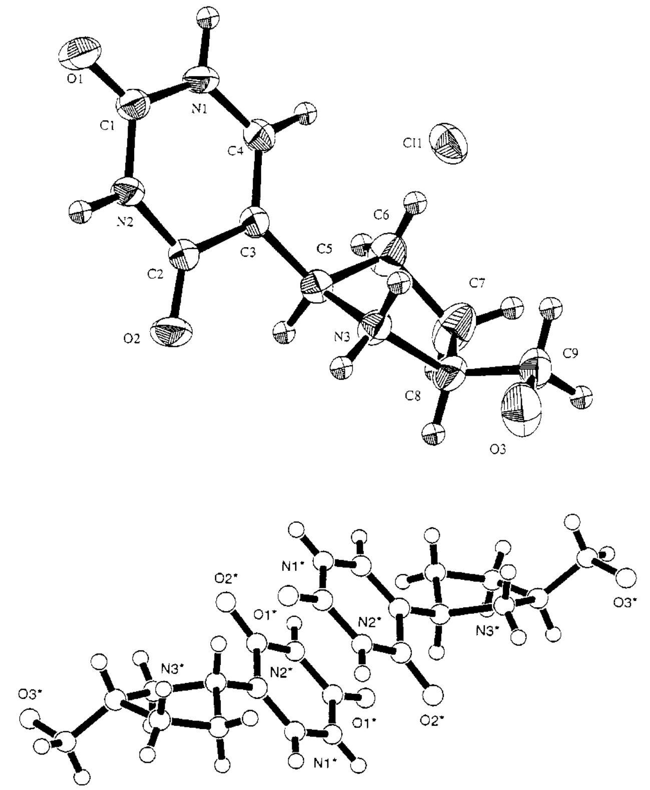


Fig. 2 Top structure: X-ray molecular structure of β-form of **9f**. Bottom structure: **9f** and its enantiomer in the same crystal.

Table 5 Crystallographic data for **9f**†

Empirical formula	$C_9H_{14}ClN_3O_3$
Formula relative molecular mass	247.68
Crystal dimensions/mm	0.20 × 0.25 × 0.02
Crystal system	monoclinic
Space group	*C*2/*c* (#15)
Lattice parameters	a = 13.741(1) Å
	b = 7.2000(7) Å
	c = 24.483(2) Å
	β = 109.322(5)°
Z	8
D_c (g cm^{-3})	1.439
μ(Mo-Kα) (cm^{-1})	29.73
Temp. (T/°C)	23.0
Scan width (°)	1.42 + 0.30 tanθ
2θ/max (°)	135.1
No. of reflections measured	
Total	4199
With $I > 2\sigma(I)$	2006
No. of refinement variables	150
Final R; R_w	0.066; 0.094

pure **9f**. Compound **9f** obtained by the first reprecipitation ($[\alpha]_D^{25}$ −30.5°) was purified by the second reprecipitation (see Experimental section) to give **9f** showing the specific rotation of $[\alpha]_D^{25}$ −33.1°, and was considered to be fully resolved. Attempted

† CCDC reference number 207/309. See http://www.rsc.org/suppdata/p1/1999/1193 for crystallographic files in .cif format.

diastereomeric resolution with salts of **9f** and L-(+)-tartaric acid or **9f** and (*S*)-(+)-camphor-10-sulfonic acid was unsuccessful. Furthermore, the transfer from **4** to **5** turned out to proceed without racemization by the isolation of enantiopure **9f**.

The anti-HIV activities of **3g** and **9f** (β-form) were examined. Very little activity was found (**3g**: EC_{50} > 25 mM; EC_{90} > 25 mM; CC_{50} = 7.9 mM; **9f**: EC_{50} > 30 mM; EC_{90} > 30 mM; CC_{50} = 14.9 mM) like that of a typical anti-HIV drug, 3′-azido-2′,3′-dideoxythymidine (AZT: EC_{50} = 0.056 μM; EC_{90} = 0.153 μM; CC_{50} = 48.0 μM).

In summary, both the α- and β-forms of *C*-aza-2,3-dideoxynucleosides **5** and **9f** were synthesized from L-glutamic acid in 5 or 6 steps. The use of Grignard reagents of heteroaromatics totally prevented the racemization in the reaction of **1** ⟶ **2**. Under the acidic conditions used, compounds **3** were reduced with $NaBH_3CN$ in a β-selective manner and the selectivity was reversed with amine–borane complexes. Enantiopure **9f** could be also obtained by the reprecipitation method.

Experimental

All reactions requiring anhydrous conditions were conducted in oven-dried (120 °C) apparatus under dry argon. Ether and THF were distilled from sodium in the presence of benzophenone ketyl. Microanalyses were performed at the Chemical Analysis Center of Chiba University. ^1H NMR spectra were recorded on a JNM-LA-500 (500 MHz) spectrometer. *J*-Values are in Hz. ^{13}C NMR spectra were recorded on a 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 a JASCO FT/IR-200. 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. Specific rotations were measured with a JASCO DIP-370. Mps were measured using a Yamano Melting Points Apparatus Model MP-21 and uncorrected. Wakogel C-200, C-300 and Silicagel 60 (Kanto Chemical Co., Inc.) were used for column chromatography, Kieselgel 60 F_{254} (Merck) for TLC, and Wakogel B-5F for PLC.

Preparation of Grignard reagents [bromobenzene and *p*-bromotoluene]

A solution of an aryl bromide (5 mmol) in THF (5 ml) was added dropwise to activated magnesium (5.5 mmol) at 0 °C and the solution was allowed to attain rt and stirred for 2 h.

Preparation of lithium reagents (i) [thiophene, benzofuran and *N*-(phenylsulfonyl)indole]

To a solution of an aromatic heterocycle (5 mmol) in THF (20 ml) was added *n*-butyllithium (1.0 mol equiv.) dropwise at 0 °C. The solution was allowed to attain rt and stirred for 1 h.

Preparation of lithium reagents (ii) [2,4-di(*tert*-butoxy)pyrimidine and 2,4-dimethoxypyrimidine]

To a solution of 5-bromo-2,4-di(*tert*-butoxy)pyrimidine or 5-bromo-2,4-dimethoxypyrimidine (5 mmol) in THF at −78 °C (20 ml) was added dropwise a hexane 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.

The nucleophilic ring opening of ethyl *N*-Boc-pyroglutamate 1 to give ethyl (*S*)-5-aryl-2-(*tert*-butoxycarbonylamino)-5-oxopentanoates 2

Typical procedure. To a solution of **1** (1 mmol) in THF (2 ml) was added dropwise a THF solution of an organomagnesium or organolithium reagent (1.1 mol equiv.) at −78 °C. The mixture was allowed to warm slowly to −40 °C. After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and the product was extracted with AcOEt. The extract was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography [eluent: hexane–AcOEt (3 : 1)] to give **2**.

Ethyl (*S*)-2-(*tert*-butoxycarbonylamino)-5-phenyl-5-oxopentanoate 2a. Solid; mp 82–83 °C (Found: C, 64.56; H, 7.61; N, 4.17. Calc. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18%); ν_{max}(KBr)/cm^{-1} 740, 1180, 1220, 1280, 1420, 1590, 1650, 2980, 3370; δ_H($CDCl_3$) 1.28 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.42 (9H, s, Boc), 2.09 (1H, m, 3-H^a), 2.31 (1H, m, 3-H^b), 3.02–3.17 (2H, m, 4-H$_2$), 4.20 (2H, q, *J* 7.0, CH$_3$C*H*$_2$), 4.37 (1H, m, 2-H), 5.16 (1H, d, *J* 7.0, NH), 7.16 (2H, m, Ph), 7.57 (1H, m, Ph), 7.95 (2H, m, Ph).

Ethyl (*S*)-2-(*tert*-butoxycarbonylamino)-5-oxo-5-(*p*-tolyl)-pentanoate 2b. Solid; mp 74–75 °C (Found: C, 65.36; H, 7.75; N, 3.91. Calc. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01%); ν_{max}(KBr)/cm^{-1} 780, 1060, 1160, 1350, 1520, 1680, 1710, 1740, 2980, 3350; δ_H($CDCl_3$) 1.25 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.42 (9H, s, Boc), 2.09 (1H, m, 3-H^a), 2.29 (1H, m, 3-H^b), 2.38 (3H, s, PhC*H*$_3$), 2.98–3.16 (2H, m, 4-H$_2$), 4.18 (2H, q, *J* 7.0, CH$_3$C*H*$_2$), 4.35 (1H, m, 2-H), 5.51 (1H, d, *J* 8.1, NH), 7.23 (2H, d, *J* 7.7, 3′- and 5′-H), 7.84 (2H, d, *J* 7.7, 2′- and 6′-H).

Ethyl (*S*)-2-(*tert*-butoxycarbonylamino)-5-oxo-5-(2-thienyl)-pentanoate 2c. Solid; mp 101–102 °C (Found: C, 56.42; H, 6.87; N, 4.02. Calc. for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10%); ν_{max}(KBr)/cm^{-1} 720, 1060, 1160, 1340, 1520, 1660, 1710, 1740, 3000, 3350; δ_H($CDCl_3$) 1.28 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.42 (9H, s, Boc), 2.09 (1H, m, 3-H^a), 2.30 (1H, m, 3-H^b), 2.95–3.11 (2H, m, 4-H$_2$), 4.20 (2H, q, *J* 7.0, CH$_3$C*H*$_2$), 4.35 (1H, m, 2-H), 5.16 (1H, d, *J* 5.8, NH), 7.13 (1H, dd, *J* 5.0, 3.9, 4′-H), 7.64 (1H, dd, *J* 5.0, 1.0, 3′-H), 7.72 (1H, dd, *J* 3.9, 1.0, 5′-H); δ_C($CDCl_3$) 14.02 (p), 27.03 (s), 28.14 (C(*C*H$_3$)$_3$), 35.14 (s), 53.03 (t), 61.38 (p), 79.76 (*C*(CH$_3$)$_3$), 128.01 (t), 131.84 (t), 133.57 (t), 143.76 (q, Ar), 155.35 (q, CO), 172.16 (q, CO), 191.70 (q, CO).

Ethyl (*S*)-5-(2-benzofuryl)-2-(*tert*-butoxycarbonylamino)-5-oxopentanoate 2d. Oil; ν_{max}/cm^{-1} (neat) 750, 1030, 1160, 1370, 1520, 1680, 1710, 1750, 2980, 3370; HRMS (FAB, NBA) Calc. for $C_{20}H_{26}O_6N$: *m/z* (M + H) 376.1760. Found: *m/z*, 376.1788; δ_H($CDCl_3$) 1.28 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.42 (9H, s, Boc), 2.13 (1H, m, 3-H^a), 2.34 (1H, m, 3-H^b), 3.00–3.18 (2H, m, 4-H$_2$), 4.22 (2H, q, *J* 7.1, CH$_3$C*H*$_2$), 4.39 (1H, m, 2-H), 5.23 (1H, d, *J* 8.0, NH), 7.30 (1H, m, benzofuran), 7.45–7.59 (3H, m, benzofuran), 7.70 (1H, m, benzofuran); δ_C($CDCl_3$) 14.13 (p), 26.75 (s), 28.23 (C(*C*H$_3$)$_3$), 34.83 (s), 53.06 (t), 61.57 (s), 79.98 (*C*(CH$_3$)$_3$), 112.42 (t), 112.81 (t), 123.29 (t), 123.92 (t), 126.96 (q, Ar), 128.29 (t), 152.25 (q), 155.45 (q), 155.57 (q, CO), 172.24 (q, CO), 190.03 (q, CO).

Ethyl (*S*)-2-(*tert*-butoxycarbonylamino)-5-oxo-5-[*N*-(phenylsulfonyl)indol-2-yl]pentanoate 2e. Oil; ν_{max}/cm^{-1} (neat) 690, 730, 1180, 1370, 1450, 1520, 1700, 2980, 3380; HRMS (FAB, NBA) Calc. for $C_{26}H_{31}O_7N_2S$: *m/z* (M + H) 515.1852. Found: *m/z*, 515.1837; δ_H($CDCl_3$) 1.28 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.43 (9H, s, Boc), 2.12 (1H, m, 3-H^a), 2.33 (1H, m, 3-H^b), 3.02–3.15 (2H, m, 4-H$_2$), 4.20 (2H, q, *J* 7.1, CH$_3$C*H*$_2$), 4.35 (1H, m, 2-H), 5.19 (1H, d, *J* 7.9, NH), 7.09 (1H, s, 3′-H), 7.28–8.14 (9H, m, indole and Ph); δ_C($CDCl_3$) 14.18 (p), 27.25 (s), 28.31 (C(*C*H$_3$)$_3$), 38.40 (s), 53.06 (t), 61.57 (s), 79.98 (*C*(CH$_3$)$_3$), 115.65 (t), 116.85 (t), 122.83 (t), 124.48 (t), 127.35 (t), 127.59 (t), 128.52 (q), 128.90 (t), 129.12 (t), 129.63 (t), 133.86 (t), 138.06 (q), 138.60 (q), 139.42 (q), 155.52 (q), 172.33 (q, CO), 193.66 (q, CO).

Ethyl (*S*)-2-(*tert*-butoxycarbonylamino)-5-(2,4-dimethoxypyrimidin-5-yl)-5-oxopentanoate 2f. Oil; ν_{max}/cm^{-1} (neat) 1010, 1170, 1390, 1580, 1720, 2980, 3370; HRMS (FAB, NBA) Calc. for $C_{18}H_{28}O_7N_3$: *m/z* (M + H) 398.1927. Found: *m/z*, 398.1924; δ_H($CDCl_3$) 1.28 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.43 (9H, s, Boc), 2.00 (1H, m, 3-H^a), 2.24 (1H, m, 3-H^b), 2.96–3.12 (2H, m, 4-H$_2$), 4.06 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 4.21 (2H, q, *J* 7.0, CH_3CH_2), 4.33 (1H, m, 2-H), 5.15 (1H, d, *J* 8.0, NH), 8.84 (1H, s, pyrimidine 6′-H); δ_C($CDCl_3$) 14.24 (p), 27.10 (s), 28.35 (p), 39.32 (s), 53.20 (OCH_3), 54.59 (t), 55.56 (OCH_3), 61.53 (s), 79.94 ($C(CH_3)_3$), 113.45 (q), 155.54 (q), 162.91 (t), 166.69 (q), 169.41 (q), 172.57 (q, CO), 196.27 (q, CO).

Ethyl (*S*)-2-(*tert*-butoxycarbonylamino-5-[2,4-di(*tert*-butoxy)-pyrimidin-5-yl]-5-oxopentanoate 2g. Solid; mp 71–72 °C; (Found: C, 59.89; H, 8.32; N, 8.82. Calc. for $C_{24}H_{39}N_3O_7$: C, 59.86; H, 8.16; N, 8.73%); ν_{max}(KBr)/cm^{-1} 1050, 1070, 1370, 1420, 1580, 1700, 2980, 3400; δ_H($CDCl_3$) 1.28 (3H, t, *J* 7.0, CH_3CH_2), 1.42 (9H, s, Boc), 1.63 (9H, s, OBu^t), 1.70 (9H, s, OBu^t), 2.00 (1H, m, 3-H^a), 2.23 (1H, m, 3-H^b), 2.95–3.15 (2H, m, 4-H_2), 4.20 (2H, q, *J* 7.0, CH_3CH_2), 4.32 (1H, m, 2-H), 5.11 (1H, d, *J* 8.3, NH), 8.74 (1H, s, pyrimidine 6′-H); δ_C($CDCl_3$) 14.10 (p), 26.87 (s), 28.23 ($C(CH_3)_3$), 28.28 ($C(CH_3)_3$), 28.55 ($C(CH_3)_3$), 39.53 (s), 53.15 (t), 61.33 (s), 79.72 ($C(CH_3)_3$), 81.76 ($C(CH_3)_3$), 83.94 ($C(CH_3)_3$), 114.18 (q), 155.32 (q), 162.15 (t), 165.39 (q), 168.30 (q), 172.49 (q, CO), 197.20 (q, CO).

Deprotection of *N*-Boc group of 2 to give (*S*)-ethoxycarbonyl-2-aryl-Δ¹-pyrrolines ‡ 3

Typical procedure. To a solution of **2** (2 mmol) in CH_2Cl_2 (30 ml) was added trifluoroacetic acid (30 mmol equiv.) at 0 °C and the resulting solution was allowed to warm to rt. After being stirred for 2 h, the mixture was neutralized with triethylamine (35 mmol), water was added to the mixture, and the organic phase was separated. The aqueous phase was extracted with $CHCl_3$, and the combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by PLC [developer: hexane–AcOEt (3 : 1)] to give the corresponding ethyl 2-aryl-Δ¹-pyrroline-5-carboxylate **3**.

(*S*)-5-Ethoxycarbonyl-2-phenyl-Δ¹-pyrroline 3a. Oil; ν_{max}/cm^{-1} (neat) 700, 760, 1040, 1190, 1270, 1350, 1450, 1620, 1740, 2980; HRMS (FAB, NBA) Calc. for $C_{13}H_{16}O_2N$: *m*/*z* (M + H) 218.1181. Found: *m*/*z*, 218.1201; δ_H($CDCl_3$) 1.31 (3H, t, *J* 7.1, CH_3CH_2), 2.24 (1H, m, 4-H^a), 2.35 (1H, m, 4-H^b), 2.99 (1H, m, 3-H^a), 3.16 (1H, m, 3-H^b), 4.24 (2H, q, *J* 7.1, CH_3CH_2), 4.91 (1H, m, 5-H), 7.39–7.47 (3H, m, 3′-, 4′- and 5′-H), 7.89 (2H, m, 2′- and 6′-H).

(*S*)-5-Ethoxycarbonyl-2-(*p*-tolyl)-Δ¹-pyrroline 3b. Oil; ν_{max}/cm^{-1} (neat) 820, 1040, 1180, 1260, 1340, 1460, 1610, 1740, 2980; HRMS (FAB, NBA) Calc. for $C_{14}H_{17}O_2N$: *m*/*z* (M + H) 232.1338. Found: *m*/*z*, 232.1328; δ_H($CDCl_3$) 1.27 (3H, t, *J* 7.1, CH_3CH_2), 2.16–2.37 (2H, m, 4-H_2), 2.36 (3H, s, $PhCH_3$), 2.95 (1H, m, 3-H^a), 3.12 (1H, m, 3-H^b), 4.20 (2H, q, *J* 7.1, CH_3CH_2), 4.86 (1H, m, 5-H), 7.19 (2H, d, *J* 8.1, 3′- and 5′-H), 7.76 (2H, d, *J* 8.1, 2′- and 6′-H).

(*S*)-5-Ethoxycarbonyl-2-(2-thienyl)-Δ¹-pyrroline 3c. Oil; ν_{max}/cm^{-1} (neat) 720, 1040, 1190, 1260, 1430, 1610, 1740, 2980; HRMS (FAB, NBA) Calc. for $C_{11}H_{14}O_2NS$: *m*/*z* (M + H) 224.0745. Found: *m*/*z*, 224.0742; δ_H($CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_3CH_2), 2.19–2.39 (2H, m, 4-H_2), 2.98 (1H, m, 3-H^a), 3.14 (1H, m, 3-H^b), 4.23 (2H, q, *J* 7.1, CH_3CH_2), 4.86 (1H, m, 5-H), 7.07 (1H, m, 4′-H), 7.39 (1H, m, 3′-H), 7.46 (1H, m, 5′-H); δ_C($CDCl_3$) 14.10 (p), 26.78 (s), 35.96 (s), 61.02 (s), 74.30 (t), 127.38 (t), 129.84 (t), 130.07 (t), 138.46 (q), 170.30 (q), 172.70 (q).

(*S*)-2-(2-Benzofuryl)-5-ethoxycarbonyl-Δ¹-pyrroline 3d. Oil; ν_{max}/cm^{-1} (neat) 760, 810, 1030, 1060, 1190, 1260, 1380, 1630, 1740, 2960; HRMS (FAB, NBA) Calc. for $C_{15}H_{16}O_3N$: *m*/*z* (M + H) 258.1130. Found: *m*/*z*, 258.1132; δ_H($CDCl_3$) 1.32 (3H, t, *J* 7.0, CH_3CH_2), 2.28 (1H, m, 4-H^a), 2.37 (1H, m, 4-H^b), 3.02 (1H, m, 3-H^a), 3.19 (1H, m, 3-H^b), 4.25 (2H, q, *J* 7.0, CH_3CH_2), 4.96 (1H, m, 5-H), 7.24 (1H, s, 3′-H), 7.26 (1H, m, benzofuran), 7.38 (1H, m, benzofuran), 7.53 (1H, m, benzofuran), 7.67 (1H, m, benzofuran); δ_C($CDCl_3$) 14.14 (p), 26.23 (s), 35.43 (s), 61.21 (s), 75.02 (t), 110.66 (t), 111.98 (t), 122.03 (t), 123.32 (t), 126.60 (t), 127.62 (q), 150.36 (q), 155.55 (q), 167.10 (q), 172.41 (q).

(*S*)-5-Ethoxycarbonyl-2-[*N*-(phenylsulfonyl)indol-2-yl]-Δ¹-pyrroline 3e. Oil; ν_{max}/cm^{-1} (neat) 730, 760, 1090, 1180, 1370, 1450, 1630, 1740, 2980, 3070, 3450; HRMS (FAB, NBA) Calc. for $C_{21}H_{21}O_4N_2S$: *m*/*z* (M + H) 397.1222. Found: *m*/*z*, 397.1227; δ_H($CDCl_3$) 1.34 (3H, t, *J* 7.2, CH_3CH_2), 2.23 (1H, m, 4-H^a), 2.48 (1H, m, 4-H^b), 3.13 (1H, m, 3-H^a), 3.27 (1H, m, 3-H^b), 4.29 (2H, q, *J* 7.2, CH_3CH_2), 4.95 (1H, m, 5-H), 6.87 (1H, s, 3′-H), 7.20–8.12 (9H, m, indole and Ph); δ_C($CDCl_3$) 14.23 (p), 27.44 (s), 40.61 (s), 61.13 (s), 74.36 (t), 114.98 (t), 115.65 (t), 121.74 (t), 124.56 (t), 125.94 (t), 127.20 (t), 128.80 (t), 130.14 (q), 133.78 (t), 136.08 (q), 136.29 (q), 137.82 (q), 172.47 (q), 172.70 (q).

(*S*)-5-Ethoxycarbonyl-2-(2,4-dimethoxypyrimidin-5-yl)-Δ¹-pyrroline 3f. Oil; ν_{max}/cm^{-1} (neat) 800, 1010, 1190, 1350, 1390, 1470, 1600, 1740, 2960, 3450; HRMS (FAB, NBA) Calc. for $C_{13}H_{18}O_4N_3$: *m*/*z* (M + H) 280.1297. Found: *m*/*z*, 280.1298; δ_H($CDCl_3$) 1.32 (3H, t, *J* 7.1, CH_3CH_2), 2.18 (1H, m, 4-H^a), 2.30 (1H, m, 4-H^b), 2.99 (1H, m, 3-H^a), 3.17 (1H, m, 3-H^b), 4.04 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.24 (2H, q, *J* 7.1, CH_3CH_2), 4.82 (1H, m, 5-H), 8.86 (1H, s, uracil 6′-H); δ_C($CDCl_3$) 16.07 (p), 28.40 (s), 40.05 (s), 56.07 (p), 57.05 (p), 63.03 (s), 75.45 (t), 111.78 (q), 162.23 (t), 168.02 (q), 170.86 (q), 174.04 (q), 174.75 (q).

(*S*)-5-Ethoxycarbonyl-2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-Δ¹-pyrroline 3g. Powder; mp 210 °C (decomp.); ν_{max}/cm^{-1} (neat) 830, 1300, 1400, 1460, 1520, 1600, 1690, 1740, 2790, 2850, 2970, 3060, 3240, 3450; HRMS (FAB, NBA) Calc. for $C_{11}H_{14}O_4N_3$: *m*/*z* (M + H) 252.0984. Found: *m*/*z*, 252.0957; δ_H(D_2O) 1.30 (3H, t, *J* 7.1, CH_3CH_2), 2.40 (1H, m, 4-H^a), 2.69 (1H, m, 4-H^b), 3.45 (2H, m, 3-H_2), 4.30 (2H, q, *J* 7.1, CH_3CH_2), 5.05 (1H, dd, *J* 9.8 and 5.4, 5-H), 8.61 (1H, s, uracil 6′-H); δ_C(D_2O) 13.95 (p), 24.20 (s), 33.60 (s), 64.40 (s), 66.71 (t), 101.33 (q), 151.19 (q), 157.13 (t), 163.70 (q), 171.36 (q), 181.26 (q).

Reduction of imino group of 3 to give (5*S*)-2-aryl-5-(ethoxycarbonyl)pyrrolidines 4

Typical procedure. To a solution of **3** (1 mmol) in conc. HCl–Pr^iOH (1 ml : 11 ml) was added $NaBH_3CN$ (5.0 mol equiv.) at rt. After being stirred for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was dried (Na_2SO_4) and concentrated. The residue was purified and α- and β-isomers of **4** were separated by PLC [developer: hexane–AcOEt (2 : 1)].

(*S*)-5-Ethoxycarbonyl-2-phenylpyrrolidine § 4a. (**α-Form**) oil; ν_{max}/cm^{-1} (neat) 700, 1030, 1120, 1210, 1370, 1450, 1730, 2980, 3350; MS (EI) Calc. for $C_{13}H_{18}O_2N$: *m*/*z* (M + H) 220. Found: *m*/*z*, 220; δ_H($CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_3CH_2), 1.74 (1H, m, 3-H^a), 1.98 (1H, m, 4-H^a), 2.20 (2H, m and br s, 3-H^b and NH), 2.35 (1H, m, 4-H^b), 4.03 (1H, dd, *J* 8.4 and 5.8, 5-H), 4.21 (2H, q, *J* 7.1, CH_3CH_2), 4.37 (1H, dd, *J* 8.3 and 6.8, 2-H), 7.20–7.40 (5H, m, Ph); δ_C($CDCl_3$) 14.23 (p), 29.78 (s), 34.60 (s), 59.58 (t), 60.95 (s), 61.72 (t), 126.44 (t), 126.84 (t), 128.29 (t), 144.47 (q), 175.92 (q, CO); (**β-form**) oil; ν_{max}/cm^{-1} (neat) 700, 1030, 1170, 1210, 1370, 1450, 1730, 2980, 3370; HRMS (FAB) Calc. for $C_{13}H_{18}O_2N$: *m*/*z* (M + H) 220.1338. Found: *m*/*z*, 220.1327; δ_H($CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_3CH_2), 1.70 (1H, m, 3-H^a), 2.05–2.26 (3H, m, 3-H^b, 4-H_2), 2.52 (1H, br s, NH), 3.87 (1H, dd, *J* 8.7 and 4.4, 5-H), 4.16 (1H, dd, *J* 9.2 and 5.8, 2-H), 4.21

‡ IUPAC-preferred nomenclature: 5-aryl-2-ethoxycarbonyl-3,4-dihydro-2*H*-pyrroles.

§ Non-systematic numbering scheme.

(2H, q, *J* 7.1, CH_3CH_2), 7.22–7.45 (5H, m, Ph); δ_C($CDCl_3$) 14.13 (p), 30.63 (s), 34.09 (s), 60.01 (t), 60.96 (s), 63.51 (t), 126.66 (t), 127.12 (t), 128.38 (t), 143.11 (q), 175.09 (q, CO).

(*S*)-5-Ethoxycarbonyl-2-(*p*-tolyl)pyrrolidine§ 4b. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 810, 1040, 1120, 1210, 1730, 2980, 3350; MS (FAB, NBA) Calc. for $C_{14}H_{20}O_2N$: *m*/*z* (M + H) 234. Found: *m*/*z*, 234; δ_H($CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_3CH_2), 1.72 (1H, m, 3-H^a), 1.97 (1H, m, 4-H^a), 2.17 (1H, m, 3-H^b), 2.33 (3H, s, PhCH_3), 2.34 (1H, m, 4-H^b), 4.02 (1H, dd, *J* 8.7 and 6.1, 5-H), 4.21 (2H, q, *J* 7.1, CH_3CH_2), 4.32 (1H, dd, *J* 8.4 and 6.8, 2-H), 7.13 (2H, d, *J* 8.0, 3′- and 5′-H), 7.26 (2H, d, *J* 8.0, 2′- and 6′-H); δ_C($CDCl_3$) 14.24 (p), 21.02 (p), 29.76 (s), 34.61 (s), 59.53 (t), 60.94 (s), 61.54 (t), 126.37 (t), 128.99 (t), 136.45 (q), 141.37 (q), 175.96 (q); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 820, 1030, 1110, 1210, 1730, 2980, 3350; HRMS (FAB, NBA) Calc. for $C_{14}H_{20}O_2N$: *m*/*z* (M + H) 234.1494. Found: *m*/*z*, 234.1499; δ_H($CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_3CH_2), 1.70 (1H, m, 3-H^a), 2.02–2.23 (3H, m, 3-H^b, 4-H_2), 2.33 (3H, s, PhCH_3), 3.90 (1H, dd, *J* 8.7 and 4.8, 5-H), 4.16 (1H, dd, *J* 9.4 and 5.8, 2-H), 4.21 (2H, q, *J* 7.1, CH_3CH_2), 7.15 (2H, d, *J* 8.1, 3′- and 5′-H), 7.33 (2H, d, *J* 8.1, 2′- and 6′-H); δ_C($CDCl_3$) 14.21 (p), 21.03 (p), 30.76 (s), 34.16 (s), 60.16 (t), 61.02 (s), 63.44 (t), 126.67 (t), 129.14 (t), 136.83 (q), 140.15 (q), 175.21 (q).

(*S*)-5-Ethoxycarbonyl-2-(2-thienyl)pyrrolidine§ 4c. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 700, 1030, 1120, 1310, 1730, 2980, 3350; MS (EI) Calc. for $C_{11}H_{16}O_2NS$: *m*/*z* (M + H) 226. Found: *m*/*z*, 226; δ_H($CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_3CH_2), 1.85 (1H, m, 3-H^a), 1.98 (1H, m, 4-H^a), 2.20 (1H, m, 3-H^b), 2.35 (1H, m, 4-H^b), 2.69 (1H, br s, NH), 4.00 (1H, dd, *J* 8.5 and 5.4, 5-H), 4.21 (2H, q, *J* 7.1, CH_3CH_2), 4.66 (1H, t, *J* 5.0 , 2-H), 6.92 (2H, m, 3′- and 4′-H), 7.16 (1H, dd, *J* 4.9 and 1.2, 5′-H); δ_C($CDCl_3$) 14.20 (p), 29.60 (s), 35.04 (s), 57.62 (t), 59.27 (t), 60.99 (s), 122.83 (t), 123.58 (t), 126.65 (t), 149.84 (q), 175.57 (q, CO); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 700, 1030, 1100, 1210, 1380, 1440, 1740, 2980, 3360; HRMS (FAB) Calc. for $C_{11}H_{16}O_2NS$: *m*/*z* (M + H) 226.0902. Found: *m*/*z*, 226.0903; δ_H($CDCl_3$) 1.29 (3H, t, *J* 7.0, CH_3CH_2), 1.83 (1H, m, 3-H^a), 2.07–2.28 (3H, m, 3-H^b, 4-H_2), 2.38 (1H, br s, NH), 3.88 (1H, dd, *J* 8.5 and 5.9, 5-H), 4.21 (2H, q, *J* 7.0, CH_3CH_2), 4.46 (1H, dd, *J* 8.8 and 5.9, 2-H), 6.95 (1H, dd, *J* 5.1 and 3.4, 4′-H), 7.01 (1H, d, *J* 3.4, 3′-H), 7.20 (1H, dd, *J* 5.1 and 1.0, 5′-H); δ_C($CDCl_3$) 14.33 (p), 30.49 (s), 34.83 (s), 59.02 (t), 60.28 (t), 61.16 (s), 122.87 (t), 124.10 (t), 126.73 (t), 147.70 (q), 174.76 (q, CO).

(*S*)-5-Ethoxycarbonyl-2-(2-benzofuryl)pyrrolidine 4d. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 760, 1030, 1160, 1210, 1370, 1460, 1730, 2980, 3350; MS (FAB) Calc. for $C_{15}H_{18}O_3N$: *m*/*z* (M + H) 260. Found: *m*/*z*, 260; δ_H($CDCl_3$) 1.30 (3H, t, *J* 7.0, CH_3CH_2), 1.97–2.13 (2H, m, 3- and 4-H^a), 2.20 (1H, m, 3-H^b), 2.37 (1H, m, 4-H^b), 4.02 (1H, dd, *J* 8.2 and 5.2, 5-H), 4.22 (2H, q, *J* 7.0, CH_3CH_2), 4.59 (1H, t, *J* 6.9, 2-H), 6.56 (1H, s, 3′-H), 7.16–7.24 (2H, m, 5′- and 6′-H), 7.43 (1H, m, 7′-H), 7.49 (1H, m, 4′-H); δ_C($CDCl_3$) 14.21 (p), 29.55 (s), 30.60 (s), 55.72 (t), 59.55 (t), 61.08 (s), 102.10 (t), 111.08 (t), 120.65 (t), 122.55 (t), 123.64 (t), 128.41 (q), 154.97 (q), 160.11 (q), 175.34 (q, CO); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 760, 1030, 1170, 1210, 1370, 1460, 1730, 2980, 3360; HRMS (FAB) Calc. for $C_{15}H_{18}O_3N$: *m*/*z* (M + H) 260.1287. Found: *m*/*z*, 260.1292; δ_H($CDCl_3$) 1.26 (3H, t, *J* 7.1, CH_3CH_2), 2.01–2.28 (5H, m, 3-, 4-H_2, and NH), 3.91 (1H, dd, *J* 8.2 and 6.7, 5-H), 4.19 (2H, q, *J* 7.1, CH_3CH_2), 4.43 (1H, t, *J* 6.5, 2-H), 6.65 (1H, s, 3′-H), 7.16–7.25 (2H, m, 5′- and 6′-H), 7.42 (1H, m, 7′-H), 7.50 (1H, m, 4′-H); δ_C($CDCl_3$) 14.15 (p), 29.70 (s), 31.26 (s), 56.81 (t), 60.17 (t), 61.08 (s), 102.34 (t), 111.03 (t), 120.74 (t), 122.59 (t), 123.74 (t), 128.39 (q), 154.86 (q), 159.59 (q), 174.58 (q, CO).

(*S*)-5-Ethoxycarbonyl-2-[*N*-(phenylsulfonyl)indol-2-yl]pyrrolidine§ 4e. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 730, 750, 1020, 1170, 1210, 1370, 1450, 1730, 2980, 3360; MS (FAB) Calc. for $C_{21}H_{23}O_4N_2S$: *m*/*z* (M + H) 399. Found: *m*/*z*, 399; δ_H($CDCl_3$) 1.31 (3H, t, *J* 7.1, CH_3CH_2), 2.00 (2H, m, 3- and 4-H^a), 2.20–2.42 (2H, m, 3- and 4-H^b), 3.98 (1H, dd, *J* 8.4 and 4.8, 5-H), 4.23 (2H, q, *J* 7.1, CH_3CH_2), 5.05 (1H, m, 2-H), 6.74 (1H, s, indole 3′-H), 7.17–7.52 (6H, m, indole and Ph), 7.75 (2H, m, Ph), 8.12 (1H, m, indole 4′-H); δ_C($CDCl_3$) 14.22 (p), 29.25 (s), 32.80 (s), 55.82 (t), 59.60 (t), 61.10 (s), 108.80 (t), 114.85 (t), 120.62 (t), 123.71 (t), 124.22 (t), 126.27 (t), 129.15 (t), 129.56 (q), 133.61 (t), 137.61 (q), 137.76 (q), 145.48 (q), 175.52 (q, CO); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 730, 750, 1020, 1170, 1370, 1450, 1730, 2980, 3390; HRMS (FAB) Calc. for $C_{21}H_{23}O_4N_2S$: *m*/*z* (M + H) 399.1379. Found: *m*/*z*, 399.1361; δ_H($CDCl_3$) 1.26 (3H, t, *J* 7.1, CH_3CH_2), 2.00–2.09 (2H, m, 3- and 4-H^a), 2.20 (1H, m, 3-H^b), 2.35 (1H, m, 4-H^b), 3.96 (1H, dd, *J* 5.3 and 4.1, 5-H), 4.17 (2H, q, *J* 7.1, CH_3CH_2), 4.96 (1H, m, 2-H), 6.89 (1H, s, 3′-H), 7.18–7.52 (6H, m, indole and Ph), 7.76 (2H, m, Ph), 8.11 (1H, m, indole 4′-H); δ_C($CDCl_3$) 16.07 (p), 30.85 (s), 35.16 (s), 58.07 (t), 61.81 (t), 62.84 (s), 111.05 (t), 116.71 (t), 122.69 (t), 125.63 (t), 126.25 (q), 128.15 (t), 131.08 (t), 131.38 (t), 135.54 (t), 139.42 (q), 140.76 (q), 146.82 (q), 176.71 (q, CO).

(*S*)-5-Ethoxycarbonyl-2-(2,4-dimethoxypyrimidin-5-yl)pyrrolidine 4f. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 800, 1020, 1080, 1200, 1380, 1470, 1570, 1600, 1730, 2980, 3350; MS (FAB) Calc. for $C_{13}H_{20}O_4N_3$: *m*/*z* (M + H) 282. Found: *m*/*z*, 282; δ_H($CDCl_3$) 1.30 (3H, t, *J* 7.2, CH_3CH_2), 1.67 (1H, m, 3-H^a), 1.96 (1H, m, 4-H^a), 2.14–2.33 (2H, m, 3- and 4-H^b), 3.97 (1H, m, 5-H), 3.98 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.22 (2H, q, *J* 7.1, CH_3CH_2), 4.43 (1H, m, 2-H), 8.33 (1H, s, uracil 6′-H); δ_C($CDCl_3$) 14.18 (p), 29.55 (s), 31.58 (s), 53.79 (p), 54.23 (t), 54.57 (p), 59.28 (t), 61.00 (s), 117.37 (q), 155.34 (t), 164.33 (q), 168.91 (q), 175.68 (q, CO); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 800, 1020, 1080, 1200, 1380, 1470, 1570, 1600, 1730, 2980, 3360; HRMS (FAB) Calc. for $C_{13}H_{20}O_4N_3$: *m*/*z* (M + H) 282.1454. Found: *m*/*z*, 282.1454; δ_H($CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_3CH_2), 1.77 (1H, m, 3-H^a), 2.05 (1H, m, 4-H^a), 2.10–2.24 (2H, m, 3- and 4-H^b), 3.89 (1H, dd, *J* 8.3 and 6.0, 5-H), 3.98 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.21 (2H, q, *J* 7.1, CH_3CH_2), 4.27 (1H, m, 2-H), 8.37 (1H, s, uracil 6′-H); δ_C($CDCl_3$) 14.15 (p), 29.66 (s), 31.27 (s), 53.82 (p), 54.61 (p), 55.61 (t), 59.76 (t), 60.88 (s), 116.25 (q), 155.91 (t), 164.44 (q), 168.81 (q), 174.52 (q, CO).

Reduction of the ester group of 4 to give 1-aryl-1,2,3,4-tetradeoxy-1,4-imino-D-pentitols 5

Typical procedure. To a solution of **4** (0.5 mmol) in Et_2O (5 ml) was added $LiAlH_4$ (1 mol equiv.) at 0 °C and the mixture was stirred at the same temperature for 3 h. After the mixture was quenched with water, the organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified PLC [developer : $CHCl_3$–MeOH (9 : 1)] to give the corresponding (5*S*)-2-aryl-5-(hydroxymethyl)pyrrolidine **5**.

1-Phenyl-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol 5a. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 700, 760, 1040, 1450, 1490, 2870, 2930, 3320; MS (FAB) Calc. for $C_{11}H_{16}ON$: *m*/*z* (M + H) 178. Found: *m*/*z*, 178; δ_H($CDCl_3$) 1.57 (1H, m, 3-H^a), 1.75 (1H, m, 2-H^a), 2.03 (1H, m, 3-H^b), 2.23 (1H, m, 2-H^b), 3.39 (1H, dd, *J* 10.5 and 7.5, 5-H^a), 3.53–3.62 (2H, m, 4-H and 5-H^b), 4.17 (1H, dd, *J* 8.6 and 6.6, 1-H), 7.23–7.35 (5H, m, Ph); δ_C($CDCl_3$) 27.97 (s), 34.68 (s), 29.67 (t), 61.72 (t), 64.98 (s), 126.39 (t), 127.13 (t), 128.53 (t), 143.73 (q); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 700, 760, 1050, 1460, 1490, 2870, 2950, 3330; HRMS (FAB) Calc. for $C_{11}H_{16}ON$: *m*/*z* (M + H) 178.1232. Found: *m*/*z*, 178.1233; δ_H($CDCl_3$) 1.63–1.77 (2H, m, 2- and 3-H^a), 1.94 (1H, m, 3-H^b), 2.14 (1H, m, 2-H^b), 3.43–3.50 (2H, m, 4-H and 5-H^a), 3.63 (1H, dd, *J* 9.9 and 3.2, 5-H^b), 4.24 (1H, dd, *J* 8.9 and 6.7, 1-H), 7.22–7.39 (5H, m, Ph); δ_C($CDCl_3$) 27.72 (s), 34.50 (s), 58.65 (t), 62.69 (t), 65.22 (s), 126.46 (t), 126.93 (t), 128.30 (t), 144.26 (q).

1-(*p*-Tolyl)-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol 5b. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 810, 1050, 1460, 1520, 2870, 2920, 3300; HRMS (FAB) Calc. for $C_{12}H_{18}ON$: *m*/*z* (M + H) 192. Found: *m*/*z*, 192; δ_H($CDCl_3$) 1.55 (1H, m, 3-H^a), 1.73 (1H, m, 2-H^a), 2.02 (1H, m, 3-H^b), 2.20 (1H, m, 2-H^b), 2.33 (3H, s, PhC*H*$_3$), 3.38 (1H, dd, *J* 10.5 and 7.4, 5-H^a), 3.53 (1H, dd, *J* 10.5 and 3.1, 5-H^b), 3.57 (1H, m, 4-H), 4.13 (1H, dd, *J* 8.7 and 6.3, 1-H), 7.13 (2H, d, *J* 8.1, 3′- and 5′-H), 7.20 (2H, d, *J* 8.1, 2′- and 6′-H); δ_C($CDCl_3$) 21.23 (p), 28.25 (s), 34.99 (s), 59.92 (t), 61.73 (t), 65.25 (s), 126.54 (t), 129.43 (t), 136.99 (q), 140.90 (q); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 810, 1050, 1460, 1520, 2870, 2950, 3330; HRMS (FAB) Calc. for $C_{12}H_{18}ON$: *m*/*z* (M + H) 192.1388. Found: *m*/*z*, 192.1380; δ_H($CDCl_3$) 1.60–1.77 (2H, m, 2- and 3-H^a), 1.94 (1H, m, 3-H^b), 2.11 (1H, m, 2-H^b), 2.33 (3H, s, PhC*H*$_3$), 3.40–3.48 (2H, m, 4-H and 5-H^a), 3.63 (1H, dd, *J* 9.8 and 3.2, 5-H^b), 4.20 (1H, dd, *J* 8.9 and 6.6, 1-H), 7.12 (2H, d, *J* 8.1, 3′- and 5′-H), 7.26 (2H, d, *J* 8.1, 2′- and 6′-H); δ_C($CDCl_3$) 20.99 (p), 27.74 (s), 34.45 (s), 58.55 (t), 62.49 (t), 65.17 (s), 126.40 (t), 128.98 (t), 136.54 (q), 141.15 (q).

1-(2-Thienyl)-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol 5c. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 700, 1040, 1400, 1550, 2870, 2940, 3310; MS (FAB) Calc. for $C_9H_{14}ONS$: *m*/*z* (M + H) 184. Found: *m*/*z*, 184; δ_H($CDCl_3$) 1.60 (1H, m, 3-H^a), 1.86 (1H, m, 2-H^a), 2.09 (1H, m, 3-H^b), 2.30 (1H, m, 2-H^b), 3.39 (1H, dd, *J* 10.5 and 7.0, 5-H^a), 3.55 (1H, dd, *J* 10.5 and 5.1, 5-H^b), 3.58 (1H, m, 4-H), 4.46 (1H, t, *J* 6.9, 1-H), 6.92–6.96 (2H, m, 3′- and 4′-H), 7.19 (1H, dd, *J* 4.8 and 4.9, 5′-H); δ_C($CDCl_3$) 27.78 (s), 35.34 (s), 57.51 (t), 59.00 (t), 65.12 (s), 123.50 (t), 123.83 (t), 126.75 (t), 148.62 (q); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 700, 1050, 1440, 1610, 2870, 2940, 3330; HRMS (FAB) Calc. for $C_9H_{14}ONS$: *m*/*z* (M + H) 184.0796. Found: *m*/*z*, 184.0798; δ_H($CDCl_3$) 1.73–1.87 (2H, m, 2- and 3-H^a), 1.94 (1H, m, 3-H^b), 2.20 (1H, m, 2-H^b), 3.42 (1H, dd, *J* 10.3 and 5.5, 5-H^a), 3.48 (1H, m, 4-H), 3.61 (1H, dd, *J* 10.3 and 3.6, 5-H^b), 4.59 (1H, t, *J* 6.8, 1-H), 6.90–6.96 (2H, m, 3′- and 4′-H), 7.16 (1H, dd, *J* 4.9 and 1.3, 5′-H); δ_C($CDCl_3$) 27.74 (s), 35.56 (s), 58.22 (t), 58.65 (t), 65.21 (s), 122.60 (t), 123.45 (t), 126.75 (t), 150.07 (q).

1-(2-Benzofuryl)-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol 5d. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 750, 1050, 1260, 1460, 1580, 1740, 2870, 2940, 3320; MS (FAB) Calc. for $C_{13}H_{16}O_2N$: *m*/*z* (M + H) 218. Found: *m*/*z*, 218; δ_H($CDCl_3$) 1.63 (1H, m, 3-H^a), 1.99–2.11 (2H, m, 2-H^a and 3-H^b), 2.22 (1H, m, 2-H^b), 3.42 (1H, dd, *J* 11.7 and 7.8, 5-H^a), 3.55–3.63 (2H, m, 4-H and 5-H^b), 4.40 (1H, t, *J* 6.2, 1-H), 6.52 (1H, s, 3′-H), 7.17–7.26 (2H, m, 5′- and 6′-H), 7.42 (1H, m, 7′-H), 7.50 (1H, m, 4′-H); δ_C($CDCl_3$) 27.37 (s), 31.32 (s), 55.76 (t), 58.92 (t), 64.97 (s), 101.95 (t), 111.03 (t), 120.70 (t), 122.68 (t), 123.83 (t), 128.32 (q), 154.81 (q), 159.86 (q); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 750, 1050, 1260, 1460, 1600, 1740, 2870, 2940, 3330; HRMS (FAB) Calc. for $C_{13}H_{16}O_2N$: *m*/*z* (M + H) 218.1181. Found: *m*/*z*, 218.1176; δ_H($CDCl_3$) 1.73 (1H, m, 3-H^a), 1.93 (1H, m, 3-H^b), 2.02 (1H, m, 2-H^a), 2.17 (1H, m, 2-H^b), 3.41–3.49 (2H, m, 4-H and 5-H^a), 3.61 (1H, m, 5-H^b), 4.42 (1H, t, *J* 7.3, 1-H), 6.56 (1H, s, 3′-H), 7.15–7.26 (2H, m, 5′- and 6′-H), 7.42 (1H, m, 7′-H), 7.49 (1H, m, 4′-H); δ_C($CDCl_3$) 27.48 (s), 31.08 (s), 56.07 (t), 59.40 (t), 65.21 (s), 101.66 (t), 110.97 (t), 120.65 (t), 122.55 (t), 123.60 (t), 128.40 (q), 154.83 (q), 160.62 (q).

1-[*N*-(Phenylsulfonyl)indol-2-yl]-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol 5e. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 730, 750, 1020, 1090, 1170, 1370, 1450, 2940, 3400; MS (FAB) Calc. for $C_{19}H_{21}O_3N_2S$: *m*/*z* (M + H) 357. Found: *m*/*z*, 357; δ_H($CDCl_3$) 1.63 (1H, m, 3-H^a), 1.95–2.04 (2H, m, 2-H^a and 3-H^b), 2.33 (1H, m, 2-H^b), 3.46 (1H, dd, *J* 10.4 and 6.4, 5-H^a), 3.50 (1H, m, 4-H), 3.60 (1H, dd, *J* 10.4 and 3.6, 5-H^b), 4.94 (1H, dd, *J* 6.8 and 4.6, 1-H), 6.59 (1H, s, indole 3′-H), 7.20–7.54 (6H, m, indole and Ph), 7.75 (2H, m, Ph), 8.15 (1H, m, indole 4′-H); δ_C($CDCl_3$) 26.72 (s), 32.41 (s), 55.37 (t), 58.28 (t), 65.23 (s), 108.23 (t), 114.96 (t), 120.64 (t), 123.80 (t), 124.51 (t), 126.23 (t), 129.19 (t), 129.30 (q), 133.69 (t), 137.57 (q), 138.89 (q), 144.82 (q); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 730, 750, 1020, 1090, 1170, 1370, 1450, 2940, 3390; HRMS (FAB) Calc. for $C_{19}H_{21}O_3N_2S$: *m*/*z* (M + H) 357.1273. Found: *m*/*z*, 357.1275; δ_H($CDCl_3$) 1.75 (1H, m, 3-H^a), 1.91–2.02 (2H, m, 2-H^a and 3-H^b), 2.30 (1H, m, 2-H^b), 3.38 (1H, dd, *J* 10.3 and 5.5, 5-H^a), 3.51 (1H, m, 4-H), 3.57 (1H, dd, *J* 10.3 and 4.1, 5-H^b), 4.85 (1H, t, *J* 7.0, 1-H), 6.73 (1H, s, indole 3′-H), 7.18–7.52 (6H, m, indole and Ph), 7.72 (2H, m, Ph), 8.09 (1H, m, indole 4′-H); δ_C($CDCl_3$) 27.41 (s), 32.29 (s), 55.65 (t), 58.61 (t), 65.39 (s), 108.24 (t), 114.83 (t), 120.76 (t), 123.76 (t), 124.36 (t), 126.12 (t), 129.16 (t), 129.48 (q), 133.61 (t), 137.49 (q), 139.00 (q), 145.36 (q).

1-(2,4-Dimethoxypyrimidin-5-yl)-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol 5f. (α-**Form**) oil; ν_{max}/cm^{-1} (neat) 800, 1040, 1220, 1450, 1670, 2970, 3280; MS (FAB) Calc. for $C_{11}H_{18}O_3N_3$: *m*/*z* (M + H) 240. Found: *m*/*z*, 240; δ_H($CDCl_3$) 1.56 (1H, m, 3-H^a), 1.79 (1H, m, 2-H^a), 2.00 (1H, m, 3-H^b), 2.14 (1H, m, 2-H^b), 3.42 (1H, dd, *J* 10.1 and 6.7, 5-H^a), 3.53 (1H, m, 4-H), 3.56 (1H, dd, *J* 10.1 and 6.0, 5-H^b), 3.97 (3H, s, OMe), 4.00 (3H, s, OMe), 4.22 (1H, t, *J* 7.2, 1-H), 8.18 (1H, s, uracil 6′-H); δ_C($CDCl_3$) 29.51 (s), 33.82 (s), 55.74 (p), 56.50 (p), 56.77 (t), 61.11 (t), 66.83 (s), 118.28 (q), 157.45 (t), 166.39 (q), 170.72 (q); (β-**form**) oil; ν_{max}/cm^{-1} (neat) 800, 1020, 1200, 1380, 1470, 1570, 1600, 2960, 3450; HRMS (FAB) Calc. for $C_{11}H_{18}O_3N_3$: *m*/*z* (M + H) 240.1348. Found: *m*/*z*, 240.1350; δ_H($CDCl_3$) 1.63–1.76 (2H, m, 2- and 3-H^a), 1.94 (1H, m, 3-H^b), 2.16 (1H, m, 2-H^b), 3.43 (1H, dd, *J* 10.1 and 5.5, 5-H^a), 3.47 (1H, m, 4-H), 3.62 (1H, dd, *J* 10.1 and 3.6, 5-H^b), 3.97 (3H, s, OMe), 4.00 (3H, s, OMe), 4.32 (1H, dd, *J* 7.0 and 6.4, 1-H), 8.33 (1H, s, uracil 6′-H); δ_C($CDCl_3$) 27.56 (s), 31.49 (s), 53.89 (p), 54.72 (p), 55.19 (t), 58.42 (t), 65.67 (s), 117.45 (q), 155.44 (t), 164.52 (q), 169.02 (q).

(*S*)-5-Hydroxymethyl-2-(2-thienyl)-Δ^1-pyrroline¶ 6. Solid; mp 95–96 °C; ν_{max}/cm^{-1} (neat) 740, 1090, 1340, 1430, 1610, 2950, 3060, 3230 (Found: C, 59.35; H, 6.08; N, 7.63. Calc. for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73%); MS (FAB) Calc. for $C_9H_{11}NOS$: *m*/*z* (M + H) 181. Found: *m*/*z*, 181; δ_H($CDCl_3$) 1.89 (1H, m, 3-H^a), 2.12 (1H, m, 3-H^b), 2.88 (1H, m, 4-H^a), 3.03 (1H, m, 4-H^b), 3.66 (1H, dd, *J* 11.4 and 5.6, C*H*HOH), 4.00 (1H, dt, *J* 11.4 and 4.1, CH*H*OH), 4.32 (1H, m, 5-H), 7.04 (1H, m, 4′-H), 7.29 (1H, m, 3′-H), 7.40 (1H, m, 5′-H); δ_C($CDCl_3$) 26.42 (s), 38.02 (s), 67.20 (s), 76.34 (t), 129.09 (t), 130.98 (t), 131.29 (t), 140.54 (q), 170.41(q).

(*S*)-5-Ethoxycarbonyl-2-(2,4-dioxo-1,2,3,4,5,6-hexahydropyrimidin-5-ylidene)pyrrolidine§ 7. Powder; ν_{max}/cm^{-1} (neat) 1220, 1460, 1560, 1700, 2980, 3230 (Found: C, 52.25; H, 5.99; N, 16.73. Calc. for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59%); MS (FAB) Calc. for $C_{11}H_{15}N_3O_4$: *m*/*z* (M + H) 254. Found: *m*/*z*, 254; δ_H(DMSO) 1.19 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.91 (1H, m, 4-H^a), 2.24 (1H, m, 4-H^b), 2.55 (2H, m, 3-H$_2$), 3.77 (2H, d, *J* 1.9, CC*H*$_2$NH), 4.11 (2H, q, *J* 7.1, CH$_3$C*H*$_2$), 4.40 (1H, dd, *J* 8.9 and 4.8, 5-H), 7.10 (1H, br s, pyrimidine 1′-NH), 8.79 (1H, br s, NH), 9.20 (1H, br s, NH); δ_C(DMSO) 14.02 (p), 25.27 (s), 29.13 (s), 39.23 (s), 60.29 (t), 60.67 (s), 81.30 (q), 154.35 (q), 161.27 (q), 166.49 (q), 172.41(q).

1-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,2,3,4-tetradeoxy-1,4-imino-D-pentitol 9f

To a MeOH solution (3.0 ml) of **5f** (50 mg) was added conc. HCl (3.0 ml). After being refluxed for 3 h, the reaction solution was evaporated to give a residue, which was then dissolved in a

¶ IUPAC-preferred nomenclature: (*S*)-2-hydroxymethyl-5-(2-thienyl)-3,4-dihydro-2*H*-pyrrole.

small amount of MeOH. The resulting solution was dropped into ether to afford **9f** as the HCl salt (the first reprecipitation). This compound was resolved by the following procedure: (1) dissolve in MeOH and reprecipitate with the minimum quantity of ether; (2) separate the supernatant from the precipitate; (3) evaporate the supernatant, and reprecipitate to give the fully resolved **9f** as its HCl salt.

(α-**Form**) powder; mp 212 °C (decomp.); ν_{max}(KBr)/cm^{-1} 1040, 1220, 1450, 1670, 1690, 2970, 3280; MS (FAB) Calc. for $C_9H_{14}O_3N_3$: *m*/*z* (M + H) 212. Found: *m*/*z*, 212; δ_H(D_2O) 1.90 (1H, m, 3-H^a), 2.26–2.35 (3H, m, 2-H_2 and 3-H^b), 3.77 (1H, dd, *J* 12.3 and 7.0, 5-H^a), 3.91 (1H, dd, *J* 12.3 and 3.8, 5-H^b), 3.97 (1H, m, 4-H), 4.58 (1H, dd, *J* 9.3 and 7.8, 1-H), 7.72 (1H, s, uracil 6′-H); δ_C(D_2O) 29.20 (s), 30.81 (s), 59.96 (t), 62.97 (s), 64.35 (t), 109.90 (q), 145.41 (t), 155.47 (q), 167.98 (q); (β-**form**) powder; mp 212 °C (decomp.); $[\alpha]_D^{25}$ −33.1 (*c* 0.42 in 1 M HCl); ν_{max}(KBr)/cm^{-1} 1010, 1030, 1680, 1710, 2960, 3420; MS (FAB) Calc. for $C_9H_{14}O_3N_3$: *m*/*z* (M + H) 212. Found: *m*/*z*, 212; δ_H(D_2O) 2.04 (1H, m, 3-H^a), 2.20–2.40 (3H, m, 2-H_2 and 3-H^b), 3.79 (1H, dd, *J* 12.4 and 6.6, 5-H^a), 3.86–4.02 (2H, m, 4-H and 5-H^b), 4.56 (1H, t, *J* 8.3, 1-H), 7.72 (1H, s, uracil 6′-H); δ_C(D_2O) 28.01 (s), 29.97 (s), 60.52 (t), 63.14 (s), 64.08 (t), 109.51 (q), 145.27 (t), 155.37 (q), 168.24 (q).

Enantiomeric excess (ee) determinations. Chiral column HPLC

Column: Daicel OD-H (0.46 cm diam. × 25 cm) and OC (0.46 cm diam. × 25 cm). UV Detector: Hitachi L-4000. Pump: Hitachi L-6000.

Ethyl *N*-Boc-pyroglutamate 1. Column: OD-H, detection: 210 nm, EtOH–hexane (1 : 1), flow = 0.15 ml min^{-1}. t_1 = 28.14 min, t_2 = 30.91 min.

(*S*)-5-Ethoxycarbonyl-2-(2,4-dimethoxypyrimidin-5-yl)-Δ^1-pyrroline‖ 3f. Column: OD-H, detection: 254 nm, EtOH–hexane (1 : 1), flow = 0.15 ml min^{-1}. t_1 = 29.20 min, t_2 = 32.62 min.

(*S*)-5-Ethoxycarbonyl-2-(2,4-dimethoxypyrimidin-5-yl)-pyrrolidine 4f. (β-**Form**) column: OC, detection: 254 nm, EtOH–hexane (1 : 1), flow = 0.15 ml min^{-1}. t_1 = 47.12 min, t_2 = 49.42 min.

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 ml^{-1} in RPMI-1640 medium supplemented with 10% heat-inactivated fetal calf serum (FCS), 100 IU ml^{-1} penicillin, and 100 mg ml^{-1} 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 microtiter 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-diphenyl tetrazolium bromide (MTT) to a blue formazan product. The absorbances were read in a microcomputer-controlled photometer (Titertek MultiskanR; 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.[13]

‖ IUPAC-preferred name: (*S*)-5-(2,4-dimethoxypyrimidin-5-yl)-2-ethoxycarbonyl-3,4-dihydro-2*H*-pyrrole.

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References

1 (*a*) H. Mitsuya and S. Broder, *Proc. Natl. Acad. Sci. USA*, 1986, **83**, 1911; (*b*) J. Balzarini, B. Masanori, R. Pauwels, P. Herdewijn, S. G. Wood, M. J. Robins and E. De Clercq, *Mol. Pharmacol*, 1988, **33**, 243; (*c*) E. De Clercq, A. van Aerschot, P. Herdewijn, M. Baba, R. Panwels and J. Balzarini, *Nucleosides*, *Nucleotides*, 1989, **8**, 659.
2 H. Mitsuya, R. Yarochan and S. Broder, *Science*, 1990, **249**, 1533.
3 (*a*) C. H. Wong, L. Provencher, J. A. Porco Jr., S. H. Jung, Y. F. Wang, L. Chen, R. Wang and D. H. Steensma, *J. Org. Chem.*, 1995, **60**, 1492; (*b*) G. C. Look, C. H. Fotsch and C. H. Wong, *Acc. Chem. Res.*, 1993, **26**, 182.
4 ***C*-Azanucleosides:** (*a*) G. D. Kini and W. J. Hennen, *J. Org. Chem.*, 1986, **51**, 4336; (*b*) G. Just and P. Donnini, *Can. J. Chem.*, 1977, **55**, 2998; (*c*) B. A. Horenstein, R. F. Zabinski and V. L. Schramm, *Tetrahedron Lett.*, 1993, **34**, 7213; (*d*) R. H. Furneaux, G. Limberg, P. C. Tyler and V. L. Schramm, *Tetrahedron*, 1997, **53**, 2915; (*e*) L. Deng, O. D. Scharer and G. L. Verdine, *J. Am. Chem. Soc.*, 1997, **119**, 7865; ***N*-Azanucleosides:** (*f*) E. J. Reist, D. E. Gueffroy, R. W. Blackford and L. Googman, *J. Org. Chem.*, 1966, **31**, 4025; (*g*) B. Huang, B. Chen and Y. Yui, *Synthesis*, 1993, 769; (*h*) K. H. Altman, S. M. Freier, U. Piels and T. Winkler, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 1654; (*i*) G. Rassu, L. Pinna, P. Spanu, F. Ulgheri and G. Cashiragi, *Tetrahedron Lett.*, 1994, **35**, 4019.
5 (*a*) A. Momotake, J. Mito, K. Yamaguchi, H. Togo and M. Yokoyama, *J. Org. Chem.*, 1998, **63**, 7207; (*b*) M. Yokoyama, T. Ikeue, Y. Ochiai, A. Momotake, K. Yamaguchi and H. Togo, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2185.
6 (*a*) R. B. Silverman and M. A. Levy, *J. Org. Chem.*, 1980, **45**, 815; (*b*) D. L. Fiynn, R. E. Zelleand and P. A. Grieco, *J. Org. Chem.*, 1983, **48**, 2424.
7 (*a*) T. Ohta, A. Hosoi, T. Kimura and S. Nozoe, *Chem. Lett.*, 1987, 2091; (*b*) J. Ezquerra, J. de Mendoza, C. Pedregal and C. Ramirez, *Tetrahedron Lett.*, 1992, **33**, 5589; (*c*) A. Schoenfelder and A. Mann, *Synth. Commun.*, 1989, **19**, 3485; (*d*) M. T. Molina, C. del Valle, A. M. Escribano, J. Ezquerra and C. Pedregal, *Tetrahedron*, 1993, **49**, 3801.
8 M. Yokoyama, A. Shimura, A. Momotake and H. Togo, *Synthesis*, 1999, 495.
9 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
10 R. O. Hutchins, W.-Y. Su, R. Sivakumar, F. Cistone and Y. P. Stercho, *J. Org. Chem.*, 1983, **48**, 3412.
11 M. B. Eleveld, H. Hogeveen and E. P. Schudde, *J. Org. Chem.*, 1986, **51**, 3635.
12 A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
13 R. Pauwels, J. Balzarini, M. Baba, R. Snoeck, D. Schols, P. Herdewijn, J. Desmyter and E. De Clercq, *J. Virol. Methods*, 1988, **20**, 309.

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