DOI: 10.1002/ejoc.201000360

One-Pot Synthesis of Azanucleosides from Proline Derivatives – Stereoselectivity in Sequential Processes

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Keywords: Radical reactions / Sequential processes / Amino acids / Nucleosides / Nitrogen heterocycles

Common amino acid derivatives can be transformed in one-step fashion into *N*-azanucleosides. The method is a *sequential* process initiated by a *domino* radical decarboxylation/oxidation reaction; an acyliminium ion is formed as an intermediate and can be trapped by nitrogen bases (purines, pyrimidines, and benzotriazole). The mildness of the reaction conditions and the good yields obtained make this procedure an interesting alternative to the conventional processes. Good stereoselectivities were obtained with 4-(silyloxy)proline derivatives as substrates.

Introduction

In the search[1] for new antiviral, antitumor, and antifungal agents, azanucleosides (Figure 1) have recently received considerable attention. In these nucleoside analogues, the furanose sugar is replaced by a nitrogen heterocycle; occasionally, additional heteroatoms have been introduced. The base has also been modified, and its position on the ring has been shifted.[2]

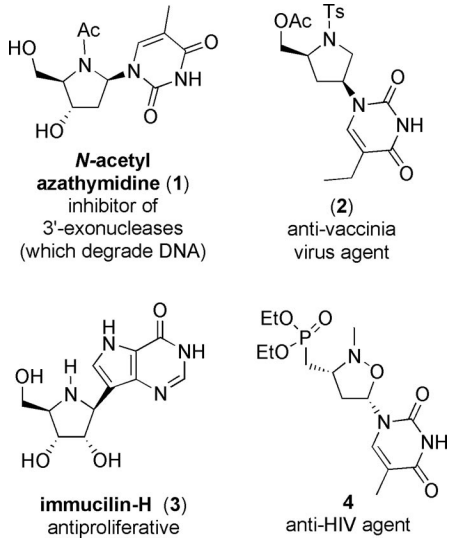

Figure 1. Nucleoside analogues.

The work in this area has provided compounds with potent biological activities. The incorporation of *N*-acetyl azathymidine **1** (Figure 1) into oligonucleotides, for instance, resulted in strong inhibition of their degradation by 3′-exonucleases.[3] Compound **2**, on the other hand, was found to inhibit the vaccinia virus,[4] whereas the *C*-azanucleoside immucilin-H (**3**) prevented the uncontrolled proliferation of T-cells.[5] The isoxazolidine **4** was an efficient anti-HIV agent, comparable to AZT in potency, but with low levels of cytotoxicity.[6]

Recently we have started to study *N*-azanucleosides of structures **5** and **6** (Figure 2) in order to find new pharmacological leads. In the case of compounds **5**, the nitrogen protecting group (such as certain acyl or amino acyl units) could be removed in vivo, giving unstable derivatives which could release a cytotoxic base (such as fluorouracil). In the case of compounds **6**, the hydroxy group on C-4 could be phosphorylated and incorporated into oligonucleotides. Chain extension of the nucleic acids would then be blocked, because these compounds do not possess a second anchoring unit.[1]

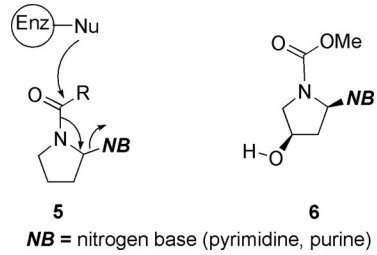

Figure 2. Target nucleoside analogues.

In previous works we have reported one-pot transformations of the proline derivatives **7** (Scheme 1) into the 2-substituted pyrrolidines **8**,[7] via the acyliminium ions **9**, through domino radical fragmentation/oxidation reactions coupled with the addition of nucleophiles. The process took place in good yields and under very mild conditions. These

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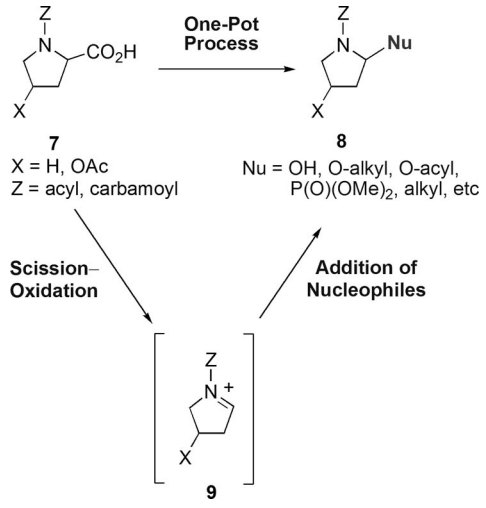
one-pot conversions[8] avoided the need for purification of reaction intermediates, saving time and materials with respect to other reported methods and reducing waste.



Scheme 1. One-pot conversions of proline derivatives into 2-substituted pyrrolidines.

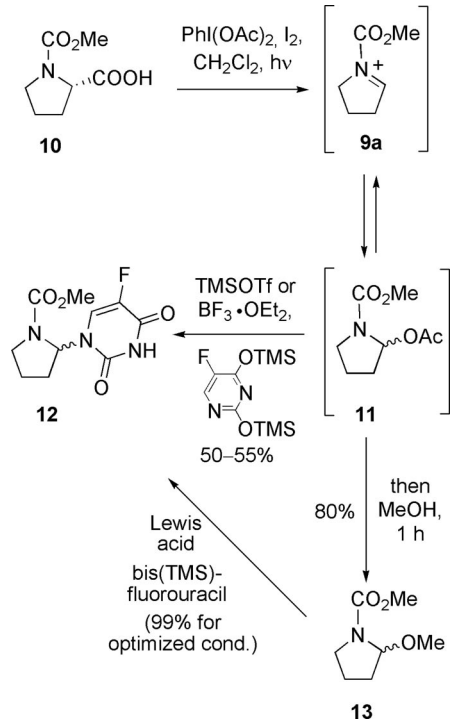
We reasoned that the addition of silylated nitrogen bases to the acyliminium intermediates **9** should afford the desired azanucleosides. The feasibility of this approach, with use of model systems, is reported here.

Results and Discussion

Development of the Radical Scission/Oxidation/Addition of Nitrogen Bases Reactions

The one-pot scission/oxidation/addition of nitrogen bases processes were explored with a proline-derived carbamate, *N*-(methoxycarbonyl)proline (**10**)[9] (Scheme 2), which was treated with (diacetoxyiodo)benzene (DIB)[10] and iodine at room temperature in the presence of visible light (sunlight or tungsten-filament lamps).[11] Under these conditions, radical decarboxylation took place,[7] followed by oxidation to the acyliminium intermediate **9a**. This acyliminium ion exists in equilibrium with the *N*,*O*-acetal **11**,[12] as a result of the addition of acetate ions from DIB. On addition of Lewis acids (BF_3·OEt_2 or TMSOTf), the acyliminium ion was regenerated, and reacted with bis(trimethylsilyl)fluorouracil[13,14] to afford the product **12**.

Several sets of reaction conditions were tried, with CH_2Cl_2 or MeCN as solvents, and with variation of the reaction times and temperatures, but only moderate yields were obtained (50–55%). In order to improve these results, the scission/oxidation reaction and the addition of nitrogen bases were studied separately (Scheme 2). In this approach, the substrate **10** underwent the scission/oxidation reaction, and the *N*,*O*-acetal **11** was converted into the more stable α-methoxy pyrrolidine **13**[15] by treatment with methanol (80%). Unlike the acetoxy derivative **11**, the methoxy derivative **13** could be purified by chromatography and completely characterized. Once the *N*,*O*-acetal **13** was available, it was used to optimize the addition of the nitrogen bases. The best conditions were found for MeCN as the solvent, BF_3·OEt_2 as the Lewis acid, and 0 °C as the addition temperature, affording **12** in 99% yield.

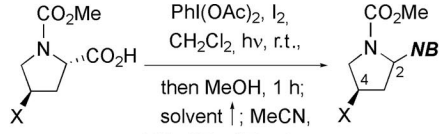


Scheme 2. Conversion of the proline carbamate **10** into the azanucleoside **12**.

We then returned to the development of the one-pot process. After considerable experimentation, it was found that the best solvent for the scission step was CH_2Cl_2, whereas the best solvent for the addition step was MeCN. The addition of methanol after the scission was also necessary to obtain good yields; the alcohol probably deactivated excess reagents (DIB/I_2) from the scission step, and at the same time generated the stable acetal **13**. Finally, BF_3·OEt_2 again proved superior to TMSOTf as the Lewis acid.

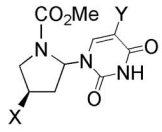
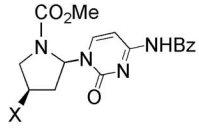
In the optimized one-pot procedure (Table 1), the scission of the substrate **10** was carried out at room temperature in CH_2Cl_2 as solvent. Methanol was added after 3 h, generating the *N*,*O*-acetal **13**, which was not isolated. The solvent was removed under vacuum and replaced with MeCN. The reaction mixture was then cooled to 0 °C, and BF_3·OEt_2 and the nucleophile were added, affording the *N*-azanucleoside **12** in good yield (80%). The optimized conditions were later applied with other silylated pyrimidine bases (Table 1). Some were derived from common pyrimidines (uracil, thymine, cytosine); 5-iodouracil was also selected, because the introduction of a halogen often results in interesting biological activities[1g] and the iodo group can also be replaced by other functionalities (through sp^n–sp^n couplings, radical reactions, etc.).[16]

Table 1. One-pot conversion of proline derivatives into azanucleosides with pyrimidine bases.



10 X = H
14 X = OAc

12, 15–27

substrate	base[a]	products	(%)[b]
			
		Y = F	
10 X = H	**A**	**(±)-12** X = H	(80)
14 X = OAc		**15** X = OAc, 2,4-*cis*	(48)
		16 X = OAc, 2,4-*trans*	(29)
		Y = I	
10 X = H	**B**	**(±)-17** X = H	(81)
14 X = OAc		**18** X = OAc, 2,4-*cis*	(47)
		19 X = OAc, 2,4-*trans*	(36)
		Y = Me	
10 X = H	**C**	**(±)-20** X = H	(83)
14 X = OAc		**21** X = OAc, 2,4-*cis*	(48)
		22 X = OAc, 2,4-*trans*	(39)
		Y = H	
10 X = H	**D**	**(±)-23** X = H	(81)
14 X = OAc		**24** (89, *cis*:*trans* 2:1)	
			
10 X = H	**E**	**(±)-25** X = H	(80)
14 X = OAc		**26** X = OAc, 2,4-*cis*	(54)
		27 X = OAc, 2,4-*trans*	(27)

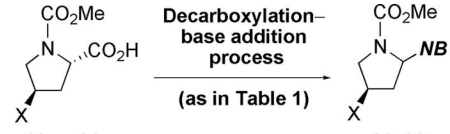
[a] Base **A**: bis(trimethylsilyl)-5-fluorouracil; base **B**: bis(trimethylsilyl)-5-iodouracil; base **C**: bis(trimethylsilyl)thymine; base **D**: bis(trimethylsilyl)uracil; base **E**: bis(trimethylsilyl)-*N*-(benzoyl)cytosine. [b] Yields of products purified by column chromatography.

The sequential process was also studied with the hydroxyproline derivative **14** (Table 1).[9] Interestingly, the reaction afforded the 2,4-*cis* diastereomers[17] as the major products, as discussed later.

The scission/addition products **12** and **15**–**27** were obtained in good to excellent yields, and in the case of the 4-hydroxyazanucleosides the *cis* and *trans* diastereomers were usually readily separated by column chromatography.

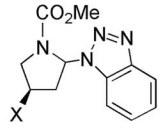
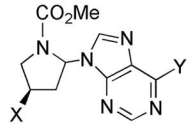
The process was also studied with silylated derivatives of benzotriazole and purine bases as nucleophiles (Table 2).[13,18] Benzotriazole was selected because several triazolyl nucleosides are potent cytotoxic, antiviral, and fungicide agents.[19] The chosen purine bases were 6-chloropurine, 6-benzyloxypurine, and *N*-benzyladenine. As has been commented on before, the chloro group in 6-chloropurine is replaceable by other groups (amino, aryl, alkyl, etc.)[16] affording collections of compounds.

Table 2. One-pot conversions of proline derivatives into azanucleosides with purine bases.



10 or 14

28–38

substrate	base[a]	products	(%)[b]
			
10 X = H	**F**	**(±)-28** X = H	(51)
14 X = OAc		**29** X = OAc, 2,4-*cis*	(43)
		30 X = OAc, 2,4-*trans*	(33)
			
		Y = Cl	
10 X = H	**G**	**(±)-31** X = H	(67)
14 X = OAc		**32** (61, *cis*:*trans* 1:1)	
		Y = OBn	
10 X = H	**H**	**(±)-33** X = H	(72)
14 X = OAc		**34** X = OAc, 2,4-*cis*	(34)
		35 X = OAc, 2,4-*trans*	(31)
		Y = NHBn	
10 X = H	**I**	**(±)-36** X = H	(66)
14 X = OAc		**37** X = OAc, 2,4-*cis*	(32)
		38 X = OAc, 2,4-*trans*	(29)

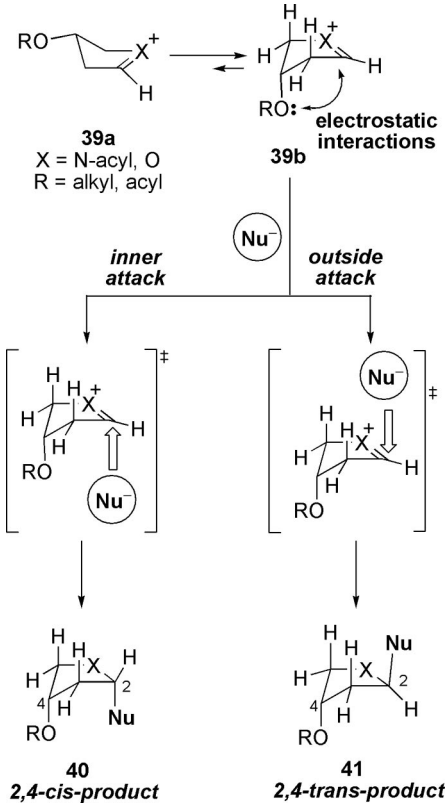
[a] Base **F**: (trimethylsilyl)benzotriazole; base **G**: (trimethylsilyl)-6-chloropurine; base **H**: (trimethylsilyl)-6-benzyloxypurine; base **I**: bis(trimethylsilyl)-*N*-benzyladenine. [b] Yields of products purified by column chromatography.

The one-pot method provided good overall yields of the desired azanucleosides **28**–**38**, even with the adenine derivatives. When the hydroxyproline derivative **14** was used as substrate, the reactions gave mixtures of the 2,4-*cis* and 2,4-*trans* azanucleosides, which in most cases were readily separated. Whereas the smaller pyrimidine bases gave a certain diastereoselectivity, benzotriazole and the purine bases afforded 1:1 mixtures of diastereomers. The stereoselectivity of the reaction is discussed below.

Stereoselectivity of the Scission/Oxidation/Addition of Nitrogen Bases Processes

Interestingly, in those cases in which stereoselectivity is observed (pyrimidine derivatives), the major products are not the 2,4-*trans* compounds, but the more hindered 2,4-*cis* isomers (*cis*/*trans* ratios from 1.5:1 to 2:1). A plausible explanation can be found in Woerpel's model for the addition of nucleophiles to cyclic oxycarbenium and acyliminium ions.[20]

According to this model, the addition of nucleophiles to C4-substituted, five-membered-ring iminium or oxycarbenium ions (intermediates **39**, Scheme 3) is stereoselective and the preferred face for the addition depends on the nature of the substituent. In the case of 4-alkoxyl groups, the preferred envelope conformation is **39b**, with a pseudoaxial substituent, allowing stabilizing electrostatic interactions between the oxygen lone electron pairs and the iminium ion.



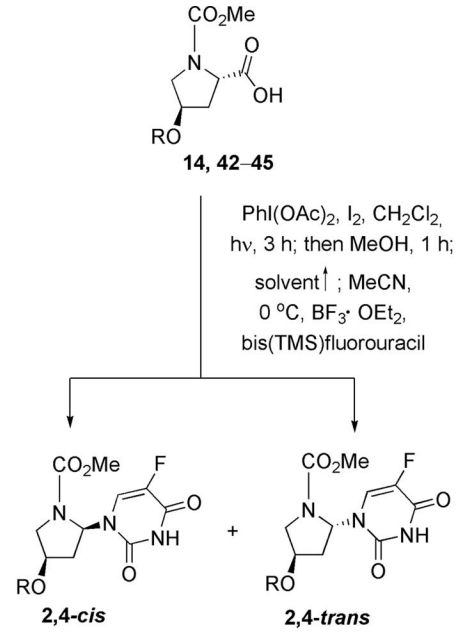
Scheme 3. Stereoselectivity in the addition of nucleophiles to 4-substituted cyclic acyliminium or oxycarbenium ions.

The nucleophile adds preferentially from the inner face, to avoid eclipsing interactions on the formation of the product. The addition generates a staggered structure **40** (2,4-*cis* product) in which the substituents at C-2 and C-3 are not eclipsed. The addition of the nucleophile from the outer face of intermediate **39b** is disfavored, due to the eclipsing interactions developed between the substituents at C-2 and C-3 in the transition structure leading to the initially formed *trans* product **41**.[20,21]

When bulkier bases are used, the repulsive interactions between the nucleophile entering from the inner face and the 4-alkoxy group increase, and as a result, the stereoselectivity decreases.[22]

The scission/oxidation/addition procedure was also carried out with the substrates **42**–**45**[23] (Table 3), in order to determine the influence of the protecting group R on the stereoselectivity. The results obtained with bis(trimethylsilyl)fluorouracil as the nucleophile were compared with the conversion **14**→**15**+**16**.

Table 3. Influence of the R group on the stereoselectivity of the scission/oxidation/addition procedures.



substrate	R	products (yield)
14	Ac	**15** (*cis*, 48%); **16** (*trans*, 29%)
42	Bz	**46** (*cis*, 40%); **47** (*trans*, 27%)
43	Piv	**48** (*cis*, 29%); **49** (*trans*, 28%)
44	TBS	**50** (*cis*, 65%); **51** (*trans*, 13%)
45	TBDPS	**52** (*cis*, 39%); **53** (*trans*, 13%)

As shown in Table 3, the processes took place with good overall yields, affording the azanucleosides **46**–**53**. A remarkable increase in stereocontrol was achieved with R = TBS (78%, *cis*/*trans* 5:1), whereas increasing the volume of the protecting group decreased both the yield and the stereoselectivity (52%, 3:1 ratio for R = TBDPS). With the acyl protecting groups, the best results corresponded to R = Ac (77%, *cis*/*trans* 1.7:1); a lower yield and stereoselectivity were observed for R = Bz (67%, *cis*/*trans* 1.5:1), and no stereoselectivity was achieved when R = Piv (57%, *cis*/*trans* 1:1).

It should be noted that the stereoselectivity achieved when R = Ac is lower than that seen with the bulkier silyl protecting groups TBS and TBDPS. One possible explanation is that the electron-donating silyl group favors the electrostatic stabilization of the pseudoaxial conformer **39b**, increasing its population. In fact, it is known that when substituted benzoates are used as protecting groups, the stereoselectivity is related to the electron-withdrawing or electron-donating natures of the substituents. A decrease in the electron density at the oxygen atom (EWG-BzO) leads to a decrease in the stereoselectivity.[20c,20g] On the other hand, the longer length of the Si–O bond with respect to the C–O bond would reduce the steric stress in the inner attack transition state.

Partial blockage of the inside face by neighboring ester group participation is less likely but cannot be ruled out completely.[24] Further studies will be carried out to address this point. In any case, both steric and electronic effects seem to influence the stereoselectivity of the process.

Finally, the development of this procedure for the direct conversion of proline derivatives into azanucleosides has opened the way to the creation of libraries of azanucleosides **5** with different *N*-protecting groups (acyl, aminoacyl), as well as the 4-hydroxyazanucleoside derivatives **6** with a variety of *O*-protecting groups [such as phosphate, $(CH_2)_nP(O)(OMe)_2$, etc.]. These derivatives are currently being prepared, in order to study structure/activity relationships, as will be reported in due course.

Conclusions

In conclusion, readily available proline derivatives can be directly transformed into *N*-azanucleosides by processes involving radical scission/oxidation/addition of nitrogen bases. The reactions proceed in good yields and under mild conditions, and allow the introduction of a variety of purine and pyrimidine bases, as well as benzotriazole.

When 4-hydroxyproline derivatives and pyrimidine bases are used as substrates and bases, respectively, the processes afford mainly the 2,4-*cis* azanucleosides, due to stereoelectronic effects. With use of appropriate *O*-protecting groups, satisfactory stereoselectivities were achieved. In this way, relatively inexpensive substrates can afford a variety of azanucleosides for study of structure/activity relationships.

Experimental Section

Preparation of Trimethylsilyl Derivatives of the Nitrogen Bases: Some trimethylsilyl derivatives of the nitrogen bases are commercial products, but they gave variable yields. However, the reagents can be readily prepared by treatment of the bases (0.4 mmol) with *N*,*O*-bis(trimethylsilyl)acetamide (297 μL, 244 mg, 1.2 mmol) under nitrogen. The mixtures were heated to 130 °C and stirred for 1 h; they were then cooled to 26 °C and dry toluene (1 mL) was added. The volatiles were removed under vacuum, and the operation was repeated twice. The silylated bases were used in the next step without further purification.

General Procedure for the One-Pot Scission/Oxidation/Base Addition Sequence: Iodine (25 mg, 0.1 mmol) and (diacetoxyiodo)benzene (DIB, 129 mg, 0.4 mmol) were added to a solution of the proline substrate **10** or the acetoxyproline substrate **14** (0.2 mmol) in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred at 25 °C for 3 h under irradiation with visible light (80 W tungsten-filament lamp). MeOH was then added (0.25 mL) and the stirring was continued for 30 min. The solvent was removed under vacuum and the residue was redissolved in dry CH_3CN (2 mL). The solution was cooled to 0 °C and freshly prepared silylated base (0.4 mmol) was injected, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (51 μL, 0.4 mmol). After having been stirred for 1 h, the mixture was poured into aqueous sodium thiosulfate (10%) and saturated aqueous $NaHCO_3$ (1:1) and extracted with dichloromethane. The organic layer was dried with Na_2SO_4 and filtered, and the solvents were evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc), to afford the azanucleosides.

5-Fluoro-1-[*N*-(methoxycarbonyl)-2-pyrrolidinyl]uracil (12): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and bis(trimethylsilyl)-5-fluorouracil (80%); crystalline solid; two rotamers at 26 °C (9:1), one rotamer at 70 °C; m.p. 248–250 °C (from MeOH, decomposition). ^{1}H NMR (500 MHz, DMSO, 70 °C): δ_H = 1.80–2.00 (m, 3 H), 2.26 (dddd, *J* = 7.5, 7.9, 8.5, 13.2 Hz, 1 H), 3.42 (ddd, *J* = 7.4, 7.8, 10.1 Hz, 1 H), 3.61 (s, 3 H), 3.63–3.76 (m, 1 H), 5.90 (dd, *J* = 2.0, 6.5 Hz, 1 H), 7.76 (d, $J_{F,H}$ = 7.0 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, DMSO, 70 °C): δ_C = 21.5 (CH_2), 31.3 (CH_2), 46.5 (CH_2), 52.0 (CH_3), 70.4 (CH), 124.8 (d, $J_{C,F}$ = 33.6 Hz, CH), 139.3 (d, $J_{C,F}$ = 230.4 Hz, C), 148.3 (C), 153.9 (C), 156.5 (d, $J_{C,F}$ = 26.0 Hz, C) ppm. IR (film): $\tilde{\nu}$ = 3441, 1692, 1674, 1197, 1102 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 226 (1) [M – OMe]$^+$, 128 (100) [M + H – 5-fluorouracil]$^+$. HRMS (EI, 70 eV): calcd. for $C_9H_9FN_3O_3$ 226.0628; found 226.0620; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0651. $C_{10}H_{12}FN_3O_4$ (257.22): calcd. C 46.70, H 4.70, N 16.34; found C 46.98, H 4.85, N 15.93.

1-[(2*R*,4*R*)- and 1-[(2*S*,4*R*)-4-Acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-fluorouracil (15 and 16): These compounds were obtained from (4*R*)-4-acetoxy-*N*-(methoxycarbonyl)-L-proline (**14**) and bis(trimethylsilyl)-5-fluorouracil as a separable diastereomer mixture (chromatography on silica gel, hexanes/EtOAc, 7:3).

Product 15: Colorless oil (48%); two rotamers at 26 °C (9:1), one rotamer at 70 °C. $[\alpha]_D$ = +80.5 (*c* = 0.48, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C): δ_H = 2.01 (s, 3 H), 2.25 (d, *J* = 15.6 Hz, 1 H), 2.61 (ddd, *J* = 5.4, 7.6, 15.5 Hz, 1 H), 3.75 (s, 3 H), 3.77 (d, *J* = 12.7 Hz, 1 H), 3.80 (dd, *J* = 4.0, 12.3 Hz, 1 H), 5.34–5.38 (m, 1 H), 6.16 (d, *J* = 7.7 Hz, 1 H), 7.43 (d, $J_{F,H}$ = 6.5 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C = 20.7 (CH_3), 38.7 (CH_2), 53.5 (CH_3), 54.0 (CH_2), 70.3 (CH), 71.3 (CH), 124.0 (d, $J_{C,F}$ = 35.1 Hz, CH), 140.3 (d, $J_{C,F}$ = 237.6 Hz, C), 149.1 (C), 154.8 (C), 156.8 (d, $J_{C,F}$ = 26.5 Hz, C), 169.4 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3377, 3192, 1703, 1668, 1266, 1237 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 315 (<1) [M]$^+$, 186 (38) [M + H – 5-fluorouracil]$^+$, 126 (100) [M – (5-fluorouracil + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{12}H_{14}FN_3O_6$ 315.0867; found 315.0879; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0554. $C_{12}H_{14}FN_3O_6$ (315.26): calcd. C 45.72, H 4.48, N 13.33; found C 45.59, H 4.78, N 13.20.

Product 16: Colorless oil (29%); two rotamers at 26 °C (2:1), one rotamer at 70 °C. $[\alpha]_D$ = –5.1 (*c* = 0.39, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C): δ_H = 2.04 (s, 3 H), 2.54–2.60 (m, 2 H), 3.74 (s, 3 H), 3.75 (d, *J* = 12.2 Hz, 1 H), 3.92 (dd, *J* = 5.0, 12.3 Hz, 1 H), 5.40 (dddd, *J* = 2.2, 4.5, 4.8, 5.0 Hz, 1 H), 5.83–5.89 (m, 1

H), 7.28 (d, $J_{F,H}$ = 5.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ_C = 20.8 (CH_3), 37.6 (CH_2), 53.3 (CH_3), 53.4 (CH_2), 72.3 (CH), 73.3 (CH), 126.5 (d, $J_{C,F}$ = 33.7 Hz, CH), 140.4 (d, $J_{C,F}$ = 237.3 Hz, C), 148.7 (C), 155.1 (C), 156.9 (d, $J_{C,F}$ = 24.7 Hz, C), 170.0 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3381, 3188, 1725, 1707, 1673, 1201 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 284 (<1) [M – MeO]$^+$, 186 (10) [M + H – 5-fluorouracil]$^+$, 126 (100) [M – (5-fluorouracil + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{11}H_{11}FN_3O_5$ 284.0683; found 284.0693; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0560. $C_{12}H_{14}FN_3O_6$ (315.26): calcd. C 45.72, H 4.48, N 13.33; found C 45.67, H 4.49, N 13.41.

5-Iodo-1-[*N*-(methoxycarbonyl)-2-pyrrolidinyl]uracil (17): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**[2]) and bis(trimethylsilyl)-5-iodouracil (80%) as described in the General One-Pot Procedure; crystalline solid; m.p. 179–181 °C (from MeOH); two rotamers at 26 °C (1.5:1), one rotamer at 70 °C. ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 1.90–2.05 (m, 2 H), 2.07–2.14 (m, 1 H), 2.36 (dddd, *J* = 7.9, 7.9, 8.1, 15.9 Hz, 1 H), 3.58 (ddd, *J* = 7.9, 8.1, 15.8 Hz, 1 H), 3.72 (s, 3 H), 4.30–4.50 (m, 1 H), 5.96 (dd, *J* = 2.9, 7.2 Hz, 1 H), 7.79 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz): major rotamer δ_C = 31.9 (CH_2), 39.0 (CH_3), 40.7 (CH_2), 56.4 (CH_2), 62.1 (CH), 81.2 (C), 156.4 (CH), 159.5 (C), 164.0 (C), 170.0 (C) ppm; minor rotamer δ_C = 31.1 (CH_2), 39.0 (CH_3), 41.9 (CH_2), 56.8 (CH_2), 61.5 (CH), 80.1 (C), 154.9 (CH), 160.7 (C), 163.7 (C), 170.9 (C) ppm. IR (film): $\tilde{\nu}$ = 3381, 1707, 1694, 1222 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 365 (2) [M]$^+$, 238 (30) [iodouracil]$^+$, 128 (100) [M + H – iodouracil]$^+$. HRMS (EI, 70 eV): calcd. for $C_{10}H_{12}IN_3O_4$ 364.9873; found 364.9882; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0716. $C_{10}H_{12}IN_3O_4$ (365.13): calcd. C 32.90, H 3.31, N 11.51; found C 32.80, H 3.33, N 11.27.

1-[(2*S*,4*R*)- and 1-[(2*R*,4*R*)-4-Acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-iodouracil (18 and 19): These compounds were obtained from 4-acetoxy-*N*-(methoxycarbonyl)proline (**14**[2]) and bis(trimethylsilyl)-5-iodouracil as described in the General One-Pot Procedure. The products were purified by column chromatography (hexanes/EtOAc, 7:3).

Product 18: Colorless oil (47%); two rotamers at 26 °C (1:1), one rotamer at 70 °C. $[\alpha]_D$ = +34.8 (*c* = 0.64, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 2.06 (s, 3 H), 2.19 (d, *J* = 15.4 Hz, 1 H), 2.61–2.69 (m, 1 H), 3.75 (s, 3 H), 3.80–3.82 (m, 2 H), 5.32–5.36 (m, 1 H), 6.15 (dd, *J* = 0.8, 7.8 Hz, 1 H), 7.93 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ_C = 21.3 (CH_3), 39.4 (CH_2), 54.0 (CH_3), 55.0 (CH_2), 67.1 (C), 72.0 (CH), 73.4 (CH), 146.8 (CH), 152.2 (C), 156.8 (C), 162.6 (C), 171.5 (C) ppm. IR (film): $\tilde{\nu}$ = 3381, 1710, 1688, 1212 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 424 (1) [M + H]$^+$, 238 (5) [5-iodouracil]$^+$, 186 (16) [M + H – 5-iodouracil]$^+$, 126 (100) [M – (5-iodouracil + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{12}H_{15}IN_3O_6$ 424.0006; found 424.0010; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0553. $C_{12}H_{14}IN_3O_6$ (423.16): calcd. C 34.06, H 3.33, N 9.93; found C 34.36, H 3.51, N 9.88.

Product 19: Colorless oil (36%); two rotamers at 26 °C (5:1), one rotamer at 70 °C. $[\alpha]_D$ = +9.1 (*c* = 0.55, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 2.02 (s, 3 H), 2.55 (dd, *J* = 8.1, 13.8 Hz, 1 H), 2.64 (ddd, *J* = 6.0, 6.0, 14.5 Hz, 1 H), 3.70 (d, *J* = 13.2 Hz, 1 H), 3.71 (s, 3 H), 3.97 (dd, *J* = 4.9, 12.1 Hz, 1 H), 5.36–5.41 (m, 1 H), 5.95 (dd, *J* = 6.8, 7.2 Hz, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 100.6 MHz): major rotamer δ_C = 20.9 (CH_3), 37.5 (CH_2), 53.6 (CH_3), 54.2 (CH_2), 67.8 (C), 73.8 (CH), 74.4 (CH), 150.2 (CH), 151.7 (C), 156.8 (C), 163.0 (C), 172.1 (C) ppm; minor rotamer δ_C = 20.9 (CH_3), 38.6 (CH_2), 53.7 (CH_3), 54.3 (CH_2), 67.8 (C), 73.9 (CH), 75.0 (CH), 149.8 (CH), 151.9 (C), 156.7 (C), 163.1 (C), 172.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3381, 1718, 1696, 1228 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 423 (<1) [M]$^+$, 186 (29) [M + H – 5-iodouracil]$^+$, 126 (100) [M – (5-iodouracil + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{12}H_{14}IN_3O_6$ 422.9927; found 422.9936; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0551. $C_{12}H_{14}IN_3O_6$ (423.16): calcd. C 34.06, H 3.33, N 9.93; found C 34.01, H 3.31, N 10.06.

1-(*N*-Methoxycarbonyl-2-pyrrolidinyl)thymine (20): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and bis(trimethylsilyl)thymine as described in the General One-Pot Procedure; crystalline solid (83%); two rotamers at 26 °C (1.5:1); one rotamer at 70 °C; m.p. 219–221 °C (from MeOH). ^{1}H NMR ([D$_6$]DMSO, 500 MHz, 70 °C): δ_H = 1.78 (s, 3 H), 1.85–1.95 (m, 3 H), 2.20–2.30 (m, 1 H), 3.45 (ddd, *J* = 7.2, 7.4, 10.8 Hz, 1 H), 3.60 (s, 3 H), 3.67 (ddd, *J* = 4.9, 7.2, 10.4 Hz, 1 H), 5.94 (dd, *J* = 2.5, 7.1 Hz, 1 H), 7.24 (s, 1 H), 10.90 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 125.7 MHz, 70 °C): δ_C = 11.5 (CH_3), 21.7 (CH_2), 31.6 (CH_2), 46.7 (CH_2), 52.0 (CH_3), 69.8 (CH), 108.4 (C), 135.9 (CH), 149.8 (C), 154.0 (C), 163.6 (C) ppm. IR (film): $\tilde{\nu}$ = 3394, 1703, 1684, 1379, 1224 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 253 (1) [M]$^+$, 128 (100) [M + H – thymine]$^+$, 126 (9) [thymine]$^+$. HRMS (EI, 70 eV): calcd. for $C_{11}H_{15}N_3O_4$ 253.1063; found 253.1069; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0712. $C_{11}H_{15}N_3O_4$ (253.26): calcd. C 52.17, H 5.97, N 16.59; found C 52.49, H 6.19, N 16.28.

1-[(2*S*,4*R*)- and 1-[(2*R*,4*R*)-4-Acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]thymine (21 and 22): These compounds were obtained from 4-acetoxy-*N*-(methoxycarbonyl)proline (**14**) and bis(trimethylsilyl)thymine as described in the General One-Pot Procedure. The products were purified by column chromatography (hexanes/EtOAc, 1:1).

Product 21: Colorless oil (48%); two rotamers at 26 °C (5:1), one rotamer at 70 °C. $[\alpha]_D$ = +61.4 (*c* = 0.49, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 1.90 (s, 3 H), 1.98 (s, 3 H), 2.18 (ddd, *J* = 1.5, 1.5, 1.5, 14.7 Hz, 1 H), 2.66 (ddd, *J* = 5.7, 7.7, 15.3 Hz, 1 H), 3.73 (s, 3 H), 3.80 (ddd, *J* = 1.6, 1.6, 12.3 Hz, 1 H), 3.84 (dd, *J* = 4.7, 12.4 Hz, 1 H), 5.31 (dddd, *J* = 1.7, 2.4, 4.9, 5.2 Hz, 1 H), 6.13 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.40 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz): major rotamer δ_C = 12.4 (CH_3), 21.0 (CH_3), 38.9 (CH_2), 53.8 (CH_3), 54.6 (CH_2), 71.6 (CH), 73.7 (CH), 110.2 (C), 138.1 (CH), 152.4 (C), 156.7 (C), 166.5 (C), 171.5 (C) ppm; minor rotamer δ_C = 12.4 (CH_3), 21.0 (CH_3), 39.7 (CH_2), 53.8 (CH_3), 54.6 (CH_2), 70.9 (CH), 72.9 (CH), 110.2 (C), 138.1 (CH), 152.1 (C), 156.7 (C), 166.5 (C), 172.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3393, 1743, 1716, 1686, 1379, 1237 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 311 (<1) [M]$^+$, 219 (8) [M – ($MeCO_2H$ + MeOH)]$^+$, 186 (9) [M + H – thymine]$^+$, 126 (100) [M – (thymine + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{13}H_{17}N_3O_6$ 311.1117; found 311.1129; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0554. $C_{13}H_{17}N_3O_6$ (311.29): calcd. C 50.16, H 5.50, N 13.50; found C 50.33, H 5.58, N 13.33.

Product 22: Two rotamers at 26 °C (5:1), one rotamer at 70 °C; colorless oil. $[\alpha]_D$ = +4.7 (*c* = 0.32, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 1.88 (s, 3 H), 2.04 (s, 3 H), 2.55 (br. dd, *J* = 4.9, 6.5 Hz, 2 H), 3.70 (s, 3 H), 3.72 (d, *J* = 13.3 Hz, 1 H), 3.97 (dd, *J* = 4.8, 12.2 Hz, 1 H), 5.38 (dddd, *J* = 1.7, 4.2, 4.5, 4.6 Hz, 1 H), 5.99 (dd, *J* = 6.5, 6.8 Hz, 1 H), 7.33 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz): major rotamer δ_C = 12.3 (CH_3), 20.9 (CH_3), 37.7 (CH_2), 53.5 (CH_3), 54.0 (CH_2), 72.1 (CH), 73.6 (CH), 111.0 (C), 140.7 (CH), 152.1 (C), 156.7 (C), 166.5 (C), 172.1 (C) ppm; minor rotamer δ_C = 12.4 (CH_3), 21.0 (CH_3), 38.8 (CH_2), 53.6 (CH_3), 54.1 (CH_2), 72.1 (CH), 74.2 (CH), 111.0 (C), 139.7 (CH),

152.1 (C), 156.7 (C), 166.5 (C), 172.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3391, 1738, 1714, 1687, 1387, 1244 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 311 (<1) $[M]^+$, 126 (100) [M – (thymine + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{13}H_{17}N_3O_6$ 311.1117; found 311.1107; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0559. $C_{13}H_{17}N_3O_6$ (311.29): calcd. C 50.16, H 5.50, N 13.50; found C 50.22, H 5.64, N 13.37.

1-(*N*-Methoxycarbonyl-2-pyrrolidinyl)uracil (23): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and bis(trimethylsilyl)uracil as described in the General One-Pot Procedure; colorless oil (81%); two rotamers at 26 °C (1:1), one rotamer at 70 °C. ^{1}H NMR (500 MHz, CD_3OD, 70 °C): δ_H = 1.95–2.01 (m, 2 H), 2.05 (dddd, *J* = 3.0, 6.0, 8.7, 10.7 Hz, 1 H), 2.29–2.39 (m, 1 H), 3.56 (ddd, *J* = 5.1, 7.6, 10.4 Hz, 1 H), 3.69 (s, 3 H), 3.70 (ddd, *J* = 3.8, 9.1, 10.7 Hz, 1 H), 5.63 (d, *J* = 8.0 Hz, 1 H), 6.01 (dd, *J* = 2.8, 7.1 Hz, 1 H), 7.43 (d, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, CD_3OD, 70 °C): δ_C = 23.4 (CH_2), 33.4 (CH_2), 49.5 (CH_2), 53.5 (CH_3), 72.8 (CH), 102.3 (CH), 142.4 (CH), 152.2 (C), 156.8 (C), 166.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3392, 1698, 1636, 1265, 1185 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 239 (1) $[M]^+$, 128 (100) [M + H – uracil]$^+$. HRMS (EI, 70 eV): calcd. for $C_{10}H_{13}N_3O_4$ 239.0906; found 239.0896; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0708. $C_{10}H_{13}N_3O_4$ (239.23): calcd. C 50.21, H 5.48, N 17.56; found C 49.95, H 5.77, N 17.40.

1-[(2*R*/*S*,4*R*)-4-Acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]uracil (24): This compound was obtained from 4-acetoxy-*N*-(methoxycarbonyl)proline (**14**) and bis(trimethylsilyl)uracil as described in the General One-Pot Procedure, as an inseparable diastereomer mixture (*cis*/*trans* 2:1, 89%); colorless oil; two rotamers at 26 °C (and one at 70 °C) for each diastereomer. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): major diastereomer δ_H = 2.01 (s, 3 H), 2.41–2.51 (m, 1 H), 2.56–2.60 (m, 1 H), 3.34 (s, 3 H), 3.41–3.78 (m, 2 H), 5.12–5.22 (m, 1 H), 5.52 (d, *J* = 7.9 Hz, 1 H), 5.93 (br. b, 1 H), 7.60 (d, *J* = 8.1 Hz, 1 H), 11.29 (s, 1 H) ppm; minor diastereomer δ_H = 1.91 (s, 3 H), 2.41–2.51 (m, 1 H), 2.56–2.60 (m, 1 H), 3.31 (s, 3 H), 3.51–3.68 (m, 2 H), 5.20–5.25 (m, 1 H), 5.55 (d, *J* = 7.0 Hz, 1 H), 5.95 (br. b, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 11.26 (s, 1 H) ppm. Some minor bands corresponding to the minor rotamers are observed. ^{13}C NMR ([D$_6$]DMSO, 125.7 MHz, 70 °C): major diastereomer δ_C = 20.2 (CH_3), 37.3 (CH_2), 52.2 (CH_3), 52.6 (CH_2), 69.2 (CH), 71.2 (CH), 99.8 (CH), 140.2 (CH), 150.0 (C), 153.5 (C), 162.7 (C), 169.0 (C) ppm; minor diastereomer δ_C = 20.2 (CH_3), 36.6 (CH_2), 52.2 (CH_3), 52.6 (CH_2), 69.2 (CH), 71.6 (CH), 100.7 (CH), 142.2 (CH), 149.6 (C), 153.5 (C), 162.7 (C), 169.4 (C) ppm. IR (film): $\tilde{\nu}$ = 3450, 3392, 1738, 1691, 1376, 1237 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 297 (<1) $[M]^+$, 186 (20) [M + H – uracil]$^+$, 126 (100) [M – (uracil + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{12}H_{15}N_3O_6$ 297.0961; found 297.0953; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0560. $C_{12}H_{15}N_3O_6$ (297.27): calcd. C 48.49, H 5.09, N 14.14; found C 48.82, H 5.19, N 13.87.

4-*N*-Benzoyl-1-[*N*-(methoxycarbonyl)-2-pyrrolidinyl]cytosine (25): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and bis(trimethylsilyl)-*N*-(benzoyl)-cytosine (80%) as described in the General One-Pot Procedure; crystalline solid; two rotamers at 26 °C (3:2), one rotamer at 70 °C; m.p. 223–225 °C (from MeOH). ^{1}H NMR ([D$_6$]DMSO, 500 MHz, 70 °C): δ_H = 1.80–1.92 (m, 3 H), 2.22–2.32 (m, 1 H), 3.44 (ddd, *J* = 8.2, 8.9, 8.9 Hz, 1 H), 3.57 (s, 3 H), 3.69 (ddd, *J* = 3.4, 7.5, 10.5 Hz, 1 H), 5.97 (dd, *J* = 1.1, 7.0 Hz, 1 H), 7.22 (br. s, 1 H), 7.46 (dd, *J* = 7.7, 7.7 Hz, 2 H), 7.57 (dd, *J* = 7.3, 7.4 Hz, 1 H), 7.90 (d, *J* = 7.3 Hz, 1 H), 7.95 (d, *J* = 7.6 Hz, 2 H), 10.86 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100.6 MHz): major rotamer δ_C = 22.7 (CH_2), 32.6 (CH_2), 47.8 (CH_2), 53.5 (CH_3), 73.1 (CH), 96.6 (C), 129.1 (2 × CH), 129.3 (2 × CH), 133.5 (CH), 134.1 (C), 146.2 (CH), 155.0 (C), 155.4 (C), 163.8 (C), 168.1 (C) ppm; minor rotamer δ_C = 21.8 (CH_2), 33.6 (CH_2), 48.2 (CH_2), 53.5 (CH_3), 72.3 (CH), 96.6 (C), 129.3 (4 × CH), 133.5 (CH), 134.1 (C), 146.2 (CH), 155.0 (C), 155.4 (C), 163.7 (C), 168.0 (C) ppm. IR (film): $\tilde{\nu}$ = 3532, 3414, 1703, 1675, 1241 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 342 (1) $[M]^+$, 215 (15) [*N*-benzoylcytosine]$^+$, 128 (42) [M + H – *N*-benzoylcytosine]$^+$, 105 (100) $[PhCO]^+$, 77 (90) $[Ph]^+$. HRMS (EI, 70 eV): calcd. for $C_{17}H_{18}N_4O_4$ 342.1328; found 342.1342; calcd. for C_7H_5O 105.0340; found 105.0341. $C_{17}H_{18}N_4O_4$ (342.35): calcd. C 59.64, H 5.30, N 16.37; found C 59.68, H 5.30, N 16.48.

1-[(2*R*,4*R*)- and 1-[(2*S*,4*R*)-4-Acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-4-*N*-benzoylcytosine (26 and 27): These compounds were obtained from 4-acetoxy-*N*-(methoxycarbonyl)proline (**14**) and bis-(trimethylsilyl)-*N*-(benzoyl)cytosine as described in the General One-Pot Procedure. The products were purified by column chromatography (hexanes/EtOAc, 70:30).

Product 26: Crystalline solid (54%); two rotamers at 26 °C (3:1), one rotamer at 70 °C; m.p. 226–228 °C (from MeOH). $[\alpha]_D$ = +135.5 (*c* = 0.20, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C): δ_H = 1.93 (s, 3 H), 2.42 (d, *J* = 15.5 Hz, 1 H), 2.64 (ddd, *J* = 5.2, 7.4, 15.5 Hz, 1 H), 3.73 (s, 3 H), 3.84 (d, *J* = 12.7 Hz, 1 H), 3.89 (dd, *J* = 4.6, 12.7 Hz, 1 H), 5.37 (dd, *J* = 4.8, 4.8 Hz, 1 H), 6.24 (d, *J* = 7.3 Hz, 1 H), 7.50 (dd, *J* = 7.5, 7.8 Hz, 3 H), 7.58 (dd, *J* = 7.4, 7.5 Hz, 1 H), 7.75 (d, *J* = 7.5 Hz, 1 H), 7.95 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ_C = 20.8 (CH_3), 38.7 (CH_2), 53.4 (CH_3), 54.3 (CH_2), 71.8 (2 × CH), 95.8 (CH), 127.8 (2 × CH), 129.0 (2 × CH), 133.1 (CH), 133.3 (C), 143.9 (CH), 154.8 (C), 155.0 (C), 162.6 (C), 167.0 (C), 169.4 (C) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 1738, 1705, 1664, 1377, 1239 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 400 (1) $[M]^+$, 214 (16) [*N*-benzoylcytosine – H]$^+$, 186 (28) [M + H – *N*-benzoylcytosine]$^+$, 105 (100) $[PhCO]^+$. HRMS (EI, 70 eV): calcd. for $C_{19}H_{20}N_4O_6$ 400.1383; found 400.1390; calcd. for C_7H_5O 105.0340; found 105.0342. $C_{19}H_{20}N_4O_6$ (400.39): calcd. C 57.00, H 5.03, N 13.99; found C 56.61, H 5.39, N 13.84.

Product 27: Colorless oil (27%); two rotamers at 26 °C (2:1), one rotamer at 70 °C. $[\alpha]_D$ = –36.1 (*c* = 0.18, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 2.05 (s, 3 H), 2.60–2.70 (m, 2 H), 3.69 (s, 3 H), 3.77 (dd, *J* = 3.1, 11.6 Hz, 1 H), 4.05 (dd, *J* = 5.1, 12.1 Hz, 1 H), 5.42 (dddd, *J* = 2.4, 2.5, 3.3, 5.2 Hz, 1 H), 6.10 (dd, *J* = 6.4, 6.7 Hz, 1 H), 7.49 (br. b, 1 H), 7.51 (dd, *J* = 7.5, 7.9 Hz, 2 H), 7.59 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.95 (d, *J* = 7.2 Hz, 2 H), 7.99 (d, *J* = 7.4 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ_C = 20.8 (CH_3), 38.6 (CH_2), 53.7 (CH_3), 54.4 (CH_2), 74.0 (CH), 75.4 (CH), 98.3 (CH), 129.1 (2 × CH), 129.7 (2 × CH), 134.0 (CH), 134.8 (C), 148.5 (CH), 156.6 (C), 157.4 (C), 164.9 (C), 169.3 (C), 172.2 (C) ppm. IR (film): $\tilde{\nu}$ = 3413, 1739, 1703, 1672, 1325, 1240 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 400 (<1) $[M]^+$, 215 (50) [*N*-benzoylcytosine]$^+$, 105 (100) $[PhCO]^+$, 91 (58) $[PhCH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_{19}H_{20}N_4O_6$ 400.1383; found 400.1382; calcd. for C_7H_5O 105.0340; found 105.0343. $C_{19}H_{20}N_4O_6$ (400.39): calcd. C 57.00, H 5.03, N 13.99; found C 57.31, H 5.40, N 13.84.

1-(*N*-Methoxycarbonyl-2-pyrrolidinyl)benzotriazole (28): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and (trimethylsilyl)benzotriazole as described in the General One-Pot Procedure (51%); syrup; two rotamers at 26 °C (2:1); one rotamer at 70 °C. ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 2.12–2.21 (m, 1 H), 2.32–2.39 (m, 1 H), 2.43–2.53 (m, 1 H), 2.55–2.64 (m, 1 H), 3.58 (br. b, 3 H), 3.65–3.73 (m, 1 H), 3.84 (ddd, *J* = 3.6, 8.5, 10.4 Hz, 1 H), 6.72 (dd, *J* = 2.0, 6.9 Hz, 1 H), 7.42 (dd, *J* = 8.0, 8.1 Hz, 1 H), 7.56 (dd, *J* = 7.8, 7.9 Hz, 1 H),

7.77–7.90 (m, 1 H), 7.94 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz): major rotamer δ_C = 24.8 (CH_2), 33.9 (CH_2), 48.4 (CH_2), 53.4 (CH_3), 72.6 (CH), 112.1 (CH), 119.8 (CH), 125.6 (2 × CH), 128.8 (C), 146.4 (C) ppm; minor rotamer δ_C = 23.8 (CH_2), 35.0 (CH_2), 48.0 (CH_2), 53.4 (CH_3), 72.0 (CH), 111.6 (CH), 120.0 (CH), 125.6 (2 × CH), 129.0 (C), 146.4 (C) ppm. The (C) signal of the carbamate was not observed. IR ($CHCl_3$): $\tilde{\nu}$ = 1702, 1614, 1493, 1116 cm^{-1}. MS (EI, 70 eV): m/z (%) = 246 (4) $[M]^+$, 128 (100) [M + H – benzotriazole]$^+$, 119 (55) [benzotriazole]$^+$. HRMS (EI, 70 eV): calcd. for $C_{12}H_{14}N_4O_2$ 246.1117; found 246.1123; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0719. $C_{12}H_{14}N_4O_2$ (246.27): calcd. C 58.53, H 5.73, N 22.75; found C 58.46, H 5.36, N 22.56.

1-[(2*R*,4*R*)- and 1-[(2*S*,4*R*)-4-Acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]benzotriazole (29 and 30): These compounds were obtained from 4-acetoxy-*N*-(methoxycarbonyl)proline (**14**) and (trimethylsilyl)benzotriazole as described in the General One-Pot Procedure. The products were purified by column chromatography (hexanes/EtOAc, 8:2).

Product 29: Syrup (43%); two rotamers at 26 °C (1:1), one rotamer at 70 °C. $[a]_D$ = +111.1 (c = 0.31, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 1.73 (s, 3 H), 2.61 (d, J = 15.0 Hz, 1 H), 2.99 (ddd, J = 6.3, 7.4, 14.7 Hz, 1 H), 3.73 (s, 3 H), 3.89 (dd, J = 2.5, 12.3 Hz, 1 H), 4.10 (dd, J = 5.9, 12.2 Hz, 1 H), 5.36–5.41 (m, 1 H), 6.83 (dd, J = 2.0, 7.6 Hz, 1 H), 7.35 (dd, J = 7.6, 7.7 Hz, 1 H), 7.58 (dd, J = 7.4, 8.1 Hz, 1 H), 7.75 (d, J = 8.5 Hz, 1 H), 7.98 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 100.6 MHz): δ_C = 21.2 (CH_3/CH_3), 40.1/41.1 (CH_2/CH_2), 54.4 (CH_3/CH_3), 54.5/54.8 (CH_2/CH_2), 73.8 (CH/CH), 74.1 (CH/CH), 113.0 (CH/CH), 120.6 (CH/CH), 126.2 (CH/CH), 129.4 (CH/CH), 133.0 (C/C), 147.5 (C/C), 154.0 (C/C), 172.6 (C/C) ppm. IR (film): $\tilde{\nu}$ = 1739, 1714, 1452, 1382, 1242 cm^{-1}. MS (EI, 70 eV): m/z (%) = 304 (4) $[M]^+$, 126 (100) [M – (benzotriazole + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{14}H_{16}N_4O_4$ 304.1172; found 304.1181; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0551. $C_{14}H_{16}N_4O_4$ (304.31): calcd. C 55.26, H 5.30, N 18.41; found C 55.06, H 5.66, N 18.74.

Product 30: Crystalline solid (33%); two rotamers at 26 °C (1:1), one rotamer at 70 °C; m.p. 204–206 °C (from MeOH). $[a]_D$ = +5.2 (c = 0.20, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 2.09 (s, 3 H), 2.82 (ddd, J = 4.8, 7.5, 14.4 Hz, 1 H), 2.96 (ddd, J = 4.2, 6.1, 14.4 Hz, 1 H), 3.56 (s, 3 H), 3.81 (dd, J = 2.2, 11.9 Hz, 1 H), 4.09 (dd, J = 5.7, 12.0 Hz, 1 H), 5.72 (dddd, J = 3.8, 4.5, 5.6, 5.7 Hz, 1 H), 6.88 (dd, J = 4.3, 7.8 Hz, 1 H), 7.42 (dd, J = 7.7, 7.9 Hz, 1 H), 7.57 (dd, J = 7.4, 7.9 Hz, 1 H), 7.83 (br. b, 1 H), 7.97 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz): δ_C = 20.8 (CH_3/CH_3), 39.2/40.2 (CH_2/CH_2), 52.9 (CH_3/CH_3), 53.3/53.5 (CH_2/CH_2), 70.5/70.9 (CH/CH), 73.2/73.8 (CH/CH), 111.7/112.2 (CH/CH), 119.9/120.1 (CH/CH), 125.7 (CH/CH), 128.9/129.1 (CH/CH), 134.2/134.3 (C/C), 146.4 (C/C), 154.0/156.2 (C/C), 172.2 (C/C) ppm. IR (film): $\tilde{\nu}$ = 1741, 1709, 1452, 1385, 1242 cm^{-1}. MS (EI, 70 eV): m/z (%) = 304 (1) $[M]^+$, 273 (1) [M – MeO]$^+$, 126 (100) [M – (benzotriazole + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{14}H_{16}N_4O_4$ 304.1172; found 304.1186; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0554. $C_{14}H_{16}N_4O_4$ (304.31): calcd. C 55.26, H 5.30, N 18.41; found C 55.12, H 5.45, N 18.24.

6-Chloro-9-[*N*-(methoxycarbonyl)-2-pyrrolidinyl]purine (31): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and (trimethylsilyl)-6-chloropurine as described in the General One-Pot Procedure; crystalline solid (69%); two rotamers at 26 °C (1:1), one rotamer at 70 °C; m.p. 155–157 °C (from MeOH, decomposition). ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C): δ_H = 2.02–2.10 (m, 1 H), 2.25–2.35 (m, 1 H), 2.44–2.48 (m, 2 H), 3.59 (s, 3 H), 3.57–3.65 (m, 1 H), 3.80 (ddd, J = 4.1, 7.9, 10.3 Hz, 1 H), 6.31 (dd, J = 5.4, 5.7 Hz, 1 H), 8.12 (s, 1 H), 8.65 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ_C = 23.1 (CH_2), 32.5 (CH_2), 47.1 (CH_2), 52.8 (CH_3), 69.8 (CH), 132.4 (C), 144.3 (CH), 151.0 (2 × C), 151.6 (CH), 154.9 (C) ppm. IR (film): $\tilde{\nu}$ = 1705, 1592, 1560, 1205, 1120, 945 cm^{-1}. MS (EI, 70 eV): m/z (%) = 283/281 (1/3) $[M]^+$, 252/250 (4/12) [M – OMe]$^+$, 154/156 (15/44) [6-chloropurine]$^+$, 128 (100) [M + H – 6-chloropurine]$^+$. HRMS (EI, 70 eV): calcd. for $C_{11}H_{12}{}^{37}ClN_5O_2$/$C_{11}H_{12}{}^{35}ClN_5O_2$ 283.0650/281.0680; found 283.0659/281.0687; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0712. $C_{11}H_{12}ClN_5O_2$ (281.70): calcd. C 46.90, H 4.29, N 24.86; found C 47.26, H 4.52, N 24.53.

9-[(2*R*/*S*,4*R*)-4-Acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-6-chloropurine (32): This compound was obtained from 4-acetoxy-*N*-(methoxycarbonyl)proline (**14**) and (trimethylsilyl)-6-chloropurine as described in the General One-Pot Procedure as an inseparable diastereomer mixture (61%, *cis*/*trans* 1:1). Each diastereomer exists as two rotamers at 26 °C (1:1), one rotamer at 70 °C; colorless oil. ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): two sets of signals were observed, each corresponding to one diastereomer δ_H = 1.87 (s, 3 H), 2.07 (s, 3 H), 2.54 (d, J = 15.1 Hz, 1 H), 2.73–2.82 (m, 1 H), 2.86 (ddd, J = 5.7, 7.6, 15.2 Hz, 1 H), 3.03 (ddd, J = 5.7, 5.7, 14.8 Hz, 1 H), 3.59 (s, 3 H), 3.66 (s, 3 H), 3.82 (d, J = 12.3 Hz, 1 H), 3.94 (d, J = 12.2 Hz, 1 H), 3.97 (dd, J = 4.9, 12.3 Hz, 1 H), 4.18 (dd, J = 4.9, 12.0 Hz, 1 H), 5.40–5.44 (m, 1 H), 5.62–5.66 (m, 1 H), 6.52 (dd, J = 5.7, 8.2 Hz, 1 H), 6.56 (dd, J = 1.6, 7.6 Hz, 1 H), 8.52 (s, 1 H), 8.55 (s, 1 H), 8.68 (s, 1 H), 8.70 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): Two sets of signals were observed, each corresponding to one diastereomer δ_C = 20.7/20.7 (CH_3), 38.8/39.4 (CH_2), 53.2/53.5 (CH_3), 53.8/54.4 (CH_2), 70.2/70.2 (CH), 73.5/73.9 (CH), 133.0/133.3 (C), 146.2/146.9 (CH), 148.1/148.6 (C), 152.8/152.9 (C), 153.0/153.0 (CH), 157.4/157.4 (C), 171.6/172.1 (C) ppm. IR (film): $\tilde{\nu}$ = 1738, 1708, 1592, 1561, 1234, 1203 cm^{-1}. MS (EI, 70 eV): m/z (%) = 341/339 (0.3/1) $[M]^+$, 282/280 (5/15) [M – $MeCO_2$]$^+$, 186 (69) [M + H – 6-chloropurine]$^+$, 126 (100) [M – (6-chloropurine + $MeCO_2$)]$^+$. HRMS (EI, 70 eV): calcd. for $C_{13}H_{14}{}^{37}ClN_5O_4$/$C_{13}H_{14}{}^{35}ClN_5O_4$ 341.0705/339.0548; found 341.0708/ 339.0533; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0555. $C_{13}H_{14}ClN_5O_4$ (339.74): calcd. C 45.96, H 4.15, N 20.61; found C 45.69, H 4.51, N 20.90.

6-Benzyloxy-9-[*N*-(methoxycarbonyl)-2-pyrrolidinyl]purine (33): This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and (trimethylsilyl)-6-(benzyloxy)-purine as described in the General One-Pot Procedure (72%); two rotamers at 26 °C (1:1), one rotamer at 70 °C; colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C): δ_H = 1.93–2.02 (m, 1 H), 2.17–2.26 (m, 1 H), 2.32–2.45 (m, 2 H), 3.56 (s, 3 H), 3.52–3.61 (m, 1 H), 3.76 (ddd, J = 4.1, 7.9, 10.4 Hz, 1 H), 5.62 (s, 2 H), 6.26 (dd, J = 3.2, 6.7 Hz, 1 H), 7.20 (dd, J = 7.3, 7.3 Hz, 1 H), 7.25 (dd, J = 7.0, 7.9 Hz, 2 H), 7.45 (d, J = 7.3 Hz, 2 H), 7.86 (s, 1 H), 8.44 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ_C = 23.0 (CH_2), 32.8 (CH_2), 47.1 (CH_2), 52.7 (CH_3), 68.4 (CH_2), 69.3 (CH), 122.4 (C), 127.9 (CH), 128.2 (2 × CH), 128.3 (2 × CH), 136.5 (C), 141.0 (CH), 151.6 (C), 151.8 (CH), 154.9 (C), 160.7 (C) ppm. IR (film): $\tilde{\nu}$ = 3196, 3064, 1705, 1601, 1319, 1118 cm^{-1}. MS (EI, 70 eV): m/z (%) = 353 (4) $[M]^+$, 226 (26) [6-benzyloxypurine]$^+$, 128 (100) [M + H – benzyloxypurine]$^+$. HRMS (EI, 70 eV): calcd. for $C_{18}H_{19}N_5O_3$ 353.1488; found 353.1493; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0712. $C_{18}H_{19}N_5O_3$ (353.38): calcd. C 61.18, H 5.42, N 19.82; found C 60.81, H 5.52, N 20.20.

6-Benzyloxy-9-[(2*S*,4*R*)- and 6-Benzyloxy-9-[(2*R*,4*R*)-4-acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]purine (34 and 35): These com-

pounds were obtained from 4-acetoxy-*N*-(methoxycarbonyl)proline (**14**) and (trimethylsilyl)-6-benzyloxypurine as described in the General One-Pot Procedure. The products were purified by column chromatography (hexanes/EtOAc, 7:3).

Product 34: Colorless oil (34%); two rotamers at 26 °C (1:1), one rotamer at 70 °C. $[\alpha]_D$ = –4.5 (*c* = 0.89, $CHCl_3$). ^1H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 1.86 (s, 3 H), 2.51 (dd, *J* = 2.9, 15.1 Hz, 1 H), 2.82 (ddd, *J* = 5.5, 7.4, 15.0 Hz, 1 H), 3.65 (s, 3 H), 3.92 (dd, *J* = 2.0, 12.3 Hz, 1 H), 3.96 (dd, *J* = 4.6, 12.3 Hz, 1 H), 5.40 (dddd, *J* = 1.9, 1.9, 4.5, 4.5 Hz, 1 H), 5.69 (s, 2 H), 6.51 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.28 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.34 (dd, *J* = 7.1, 7.7 Hz, 2 H), 7.50 (d, *J* = 7.3 Hz, 2 H), 8.31 (s, 1 H), 8.52 (s, 1 H) ppm. ^{13}C NMR (125.7 MHz, CD_3OD, 70 °C): δ_C = 21.0 (CH_3), 39.1 (CH_2), 53.4 (CH_3), 53.7 (CH_2), 67.9 (CH), 68.7 (CH_2), 71.9 (CH), 122.2 (C), 128.2 (2 × CH), 128.1 (CH), 128.4 (2 × CH), 136.8 (C), 140.6 (CH), 152.1 (C), 152.4 (CH), 161.0 (C), 162.6 (C), 170.0 (C) ppm. IR (film): $\tilde{\nu}$ = 3095, 3067, 1739, 1706, 1451, 1383, 1235 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 411 (2) $[M]^+$, 352 (4) $[M - MeCO_2]^+$, 226 (36) [6-benzyloxypurine]$^+$, 126 (100) [M – (6-benzyloxypurine + $MeCO_2$)]$^+$, 91 (64) $[PhCH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_{20}H_{21}N_5O_5$ 411.1543; found 411.1556; calcd. for $C_6H_8NO_2$ 126.0555; found 126.0551. $C_{20}H_{21}N_5O_5$ (411.42): calcd. C 58.39, H 5.14, N 17.02; found C 58.59, H 5.41, N 16.71.

Product 35: Colorless oil (31%); two rotamers at 26 °C (2:1), one rotamer at 70 °C. $[\alpha]_D$ = –20.2 (*c* = 0.58, $CHCl_3$). ^1H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 2.07 (s, 3 H), 2.74 (ddd, *J* = 2.5, 7.9, 12.5 Hz, 1 H), 3.00 (ddd, *J* = 5.7, 5.8, 12.5 Hz, 1 H), 3.56 (s, 3 H), 3.82 (dd, *J* = 6.1, 12.7 Hz, 1 H), 4.19 (dd, *J* = 4.9, 12.1 Hz, 1 H), 5.61–5.65 (m, 1 H), 5.65 (br. s, 2 H), 6.46 (dd, *J* = 5.7, 8.0 Hz, 1 H), 7.28 (dd, *J* = 7.2, 7.3 Hz, 1 H), 7.34 (dd, *J* = 7.7, 7.9 Hz, 2 H), 7.49 (d, *J* = 7.3 Hz, 2 H), 8.29 (s, 1 H), 8.49 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ_C = 20.7 (CH_3), 38.7 (CH_2), 53.4 (CH_3), 53.8 (CH_2), 69.5 (CH_2 + CH), 73.9 (CH), 122.7 (C), 129.0 (CH), 129.1 (2 × CH), 129.3 (2 × CH), 137.5 (C), 144.5 (CH), 152.4 (C), 152.9 (CH), 156.5 (C), 161.6 (C), 172.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3095, 3067, 1739, 1706, 1383, 1235 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 411 (19) $[M]^+$, 352 (22) $[M - MeCO_2]^+$, 226 (100) [6-benzyloxypurine]$^+$, 91 (63) $[PhCH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_{20}H_{21}N_5O_5$ 411.1543; found 411.1537; calcd. for $C_{12}H_{10}N_4O$ 226.0855; found 226.0850. $C_{20}H_{21}N_5O_5$ (411.42): calcd. C 58.39, H 5.14, N 17.02; found C 58.33, H 5.35, N 17.18.

***N*-Benzyl-9-[1-(methoxycarbonyl)-2-pyrrolidinyl]adenine (36):** This compound was obtained as a racemic mixture from *N*-(methoxycarbonyl)-L-proline (**10**) and bis(trimethylsilyl)-*N*-benzyladenine (purification by chromatography with CH_2Cl_2/MeOH 98:2); syrup (67%); two rotamers at 26 °C (1:1). ^1H NMR (CD_3OD, 400 MHz, 26 °C): δ_H = 1.98–2.08 (m, 1 H), 2.10–2.30 (m, 2 H), 2.41 (br. s, 1 H), 3.54–3.64 (br. b, 3 H), 3.60–3.73 (m, 1 H), 3.84 (ddd, *J* = 3.7, 7.9, 11.4 Hz, 1 H), 4.79 (br. s, 2 H), 6.30 (dd, *J* = 1.8, 6.6 Hz, 1 H), 7.21 (dd, *J* = 7.1, 7.4 Hz, 1 H), 7.27 (dd, *J* = 7.2, 7.4 Hz, 2 H), 7.34 (d, *J* = 7.2 Hz, 2 H), 8.05 (s, 1 H), 8.24 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 26 °C): δ_C = 23.2/24.1 (CH_2/CH_2), 33.7/34.7 (CH_2/CH_2), 45.1 (CH_2/CH_2), 48.5/48.8 (CH_2/CH_2), 53.5 (CH_3/CH_3), 69.9/70.7 (CH/CH), 120.9 (C/C), 128.2 (2 × CH/CH), 128.5 (2 × CH/CH), 128.6 (CH/CH), 140.3 (CH/CH), 140.6 (C/C), 149.3 (C/C), 153.8 (C/C), 156.0 (CH/CH), 156.5 (C/C) ppm. IR (film): $\tilde{\nu}$ = 3428, 3325, 3030, 3019, 1701, 1618, 1226, 1205 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 352 (10) $[M]^+$, 225 (91) [*N*-benzyladenine]$^+$, 128 (100) [M + H – *N*-benzyladenine]$^+$, 106 (48) $[PhCH_2NH]^+$. HRMS (EI, 70 eV): calcd. for $C_{18}H_{20}N_6O_2$ 352.1648; found 352.1641; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0708. $C_{18}H_{20}N_6O_2$ (352.40): calcd. C 61.35, H 5.72, N 23.85; found C 61.29, H 6.07, N 24.13.

***N*-Benzyl-9-[(2*S*,4*R*)- and *N*-Benzyl-9-[(2*R*,4*R*)-4-acetoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]adenine (37 and 38):** These compounds were obtained from (4*R*)-4-acetoxy-*N*-(methoxycarbonyl)-L-proline (**14**) and bis(trimethylsilyl)-*N*-benzyladenine as a separable diastereomer mixture (column chromatography, CH_2Cl_2/MeOH, 9:1).

Product 37: Colorless oil (32%); two rotamers at 26 °C (1:1), one rotamer at 70 °C. $[\alpha]_D$ = = +7.1 (*c* = 1.26, MeOH). ^1H NMR (CD_3OD, 500 MHz, 26 °C): δ_H = 1.86 (s, 3 H), 2.43 (d, *J* = 15.2 Hz, 1 H), 2.72–2.81 (m, 1 H), 3.60 (rotamer A)/3.70 (rotamer B) (br. s, 3 H), 3.88–3.97 (m, 2 H), 4.70–4.90 (m, 2 H), 5.36–5.40 (m, 1 H), 6.41 (d, *J* = 6.7 Hz, 1 H), 7.22 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.29 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.37 (d, *J* = 7.3 Hz, 2 H), 8.17 (s, 1 H), 8.26 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ_C = 20.3 (CH_3), 42.4 (CH_2), 45.5 (CH_2), 53.4 (CH_3), 57.4 (CH_2), 69.4 (CH), 70.2 (CH), 120.8 (C), 128.2 (CH), 128.6 (2 × CH), 129.5 (2 × CH), 140.4 (CH), 141.8 (C), 149.4 (C), 153.5 (CH), 156.2 (C), 157.1 (C), 173.3 (C) ppm. IR (film): $\tilde{\nu}$ = 3426, 3095, 3067, 1703, 1620, 1205 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 410 (<1), $[M]^+$, 351 (22) $[M - MeCO_2]^+$, 226 (100) [*N*-benzyladenine + H]$^+$, 91 (63) $[PhCH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_{20}H_{22}N_6O_4$ 410.1703; found 410.1707; calcd. for $C_{12}H_{12}N_5$ 226.1093; found 226.1098. $C_{20}H_{22}N_6O_4$ (410.43): calcd. C 58.53, H 5.40, N 20.48; found C 58.19, H 5.08, N 20.21.

Product 38: Syrup (29%); two rotamers at 26 °C (1:1), one rotamer at 70 °C. $[\alpha]_D$ = = –3.3 (*c* = 0.97, MeOH). ^1H NMR (CD_3OD, 500 MHz, 70 °C): δ_H = 2.06 (s, 3 H), 2.67–2.73 (m, 1 H), 2.97 (ddd, *J* = 5.7, 6.0, 14.9 Hz, 1 H), 3.59 (s, 3 H), 3.80 (d, *J* = 11.4 Hz, 1 H), 4.17 (dd, *J* = 4.7, 11.9 Hz, 1 H), 4.83 (d, *J* = 6.4 Hz, 2 H), 5.56–5.61 (m, 1 H), 6.39 (dd, *J* = 6.0, 7.9 Hz, 1 H), 7.21 (dd, *J* = 7.0, 7.3 Hz, 1 H), 7.28 (dd, *J* = 7.0, 7.3 Hz, 2 H), 7.36 (d, *J* = 7.9 Hz, 2 H), 8.05 (s, 1 H), 8.24 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ_C = 20.8 (CH_3), 39.1 (CH_2), 45.5 (CH_2), 53.4 (CH_3), 53.9 (CH_2), 69.4 (CH), 74.0 (CH), 121.2 (C), 128.2 (CH), 128.6 (2 × CH), 129.5 (2 × CH), 140.4 (CH), 141.8 (C), 149.7 (C), 154.2 (CH), 156.2 (C), 156.7 (C), 172.2 (C) ppm. IR (film): $\tilde{\nu}$ = 3428, 3095, 3067, 1737, 1705, 1618, 1230 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 410 (1) $[M]^+$, 225 (100) [*N*-benzyladenine]$^+$, 106 (66) $[PhCH_2NH]^+$, 91 (41) $[PhCH_2]^+$. HRMS (EI, 70 eV): calcd. for $C_{20}H_{22}N_6O_4$ 410.1703; found 410.1706; calcd. for $C_{12}H_{11}N_5$ 225.1014; found 225.1019. $C_{20}H_{22}N_6O_4$ (410.43): calcd. C 58.53, H 5.40, N 20.48; found C 58.57, H 5.53, N 20.27.

Supporting Information (see also the footnote on the first page of this article): Preparation of proline precursor **45**, synthesis and spectroscopic data for products **46**–**53**. ^1H and ^{13}C NMR spectra of the new compounds **12**, **15**–**38**, **46**–**53**.

Acknowledgments

This work was supported by the Investigation Programmes CTQ2006-14260/PPQ and CTQ2009-07109 of the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Ministerio de Educación y Ciencia (MEC) and Ministerio de Ciencia e Innovación (MICINN), Spain. We also acknowledge financial support from FEDER funds. D. H. thanks MEC for an FPU fellowship, and the Gobierno de Canarias (ACIISI)−BIOSIGMA SL for a research contract.

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Received: March 16, 2010
Published Online: May 19, 2010

