DOI: 10.1002/ejoc.201000997

One-Pot Conversion of Proline Derivatives into Iodinated Iminosugar-Based Nucleosides, Useful Precursors of Highly Functionalized Nucleoside Analogues

Alicia Boto,*[a] Dácil Hernández,[a] and Rosendo Hernández*[a]

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

Readily available proline derivatives can be transformed in one step into β-iodinated iminosugar-based nucleosides, under very mild conditions. The method couples a tandem radical decarboxylation–oxidation–β-iodination to the addition of nitrogen bases. The iodo group is introduced into the previously unfunctionalized 3-position. The resultant β-iodo derivatives are useful precursors of highly functionalized nucleoside analogues.

Introduction

The structural modification of nucleosides and nucleotides has allowed the discovery of new antiviral, antibiotic, antitumoral, and antifungal agents.[1] In the iminosugar-based nucleosides, the furanose ring is replaced by nitrogen heterocycles; some examples are *N*-acetylazathymidine (**1**),[2] which was incorporated to oligonucleotides to reduce their degradation by 3′-exonucleases, and immucilin-H (**2**),[3] which prevents the uncontrolled proliferation of T-cells. Furthermore, some alkaloids resemble iminosugar-based C-nucleosides, such as codonopsin (**3**),[4] isolated from roots of *Codonopsis* sp, which has hypotensive activity without any effect on the central nervous system (Figure 1).

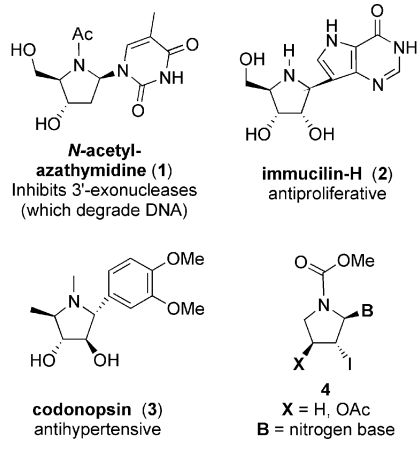
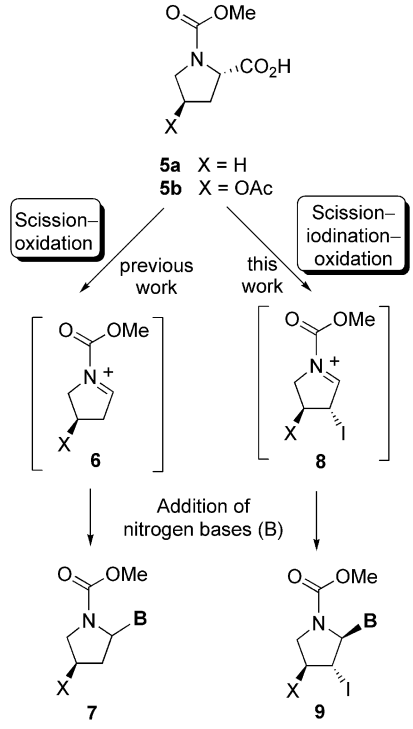


Figure 1. Bioactive iminosugar-based nucleosides.

Due to their interesting biological properties, the synthesis of these nucleoside analogues and related alkaloids has received the attention of many research groups.[5] We reasoned that in order to prepare a diversity of highly functionalized derivatives, the β-iodo compounds **4** could be used as precursors, because the iodo group can be eliminated or replaced by many other functional groups.

In a previous work, we reported the tandem radical decarboxylation–oxidation of proline derivatives **5a** and **5b** (Scheme 1) to give the acyliminium ion **6**, which was



Scheme 1. One-pot conversion of proline derivatives into iminosugar-based nucleosides.

[a] Instituto de Productos Naturales y Agrobiología del CSIC, Avda. Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain
Fax: +34-922260135
E-mail: alicia@ipna.csic.es
rhernandez@ipna.csic.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000997.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

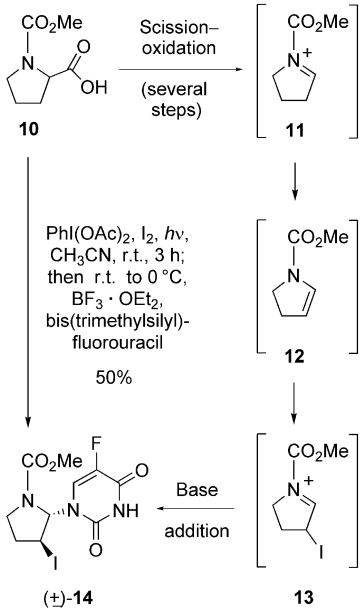
trapped by nitrogen bases to afford the nucleoside analogues **7**.[6] The one-pot process took place in high yields under very mild conditions.

In this article, we report a variation of the process that allows iodination of the previously unfunctionalized 3-position,[7] giving the acyliminium intermediate **8**,[8,9] which reacts with nitrogen bases to give the iodinated iminosugar-based nucleosides **9**. We also report the conversion of these products into other 2,3,4-substituted nucleoside derivatives and into tricyclic systems.

Results and Discussion

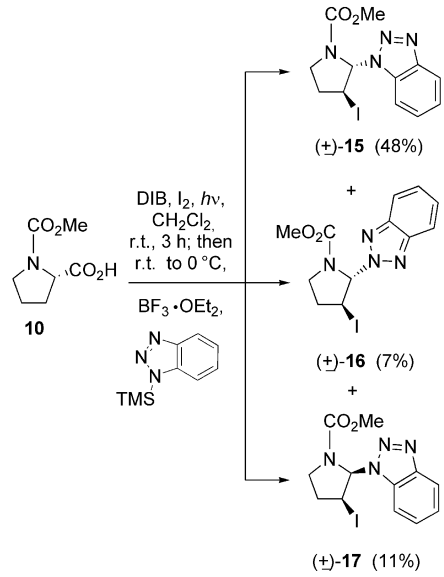
Development of the Radical Scission–Oxidation–β-Iodination–Addition of Nitrogen Base Process

The process was initially studied with proline methyl carbamate **10**[10] (Scheme 2), which was treated with (diacetoxyiodo)benzene (DIB, also called BAIB) and iodine under irradiation with visible light.[11] A radical decarboxylation ensued, generating a 2-pyrrolidinyl radical, which was readily oxidized to the iminium ion **11**.[8] This intermediate isomerized to the encarbamate **12**,[7] which, in the presence of excess iodine, was halogenated to generate a second acyliminium ion **13**.[12] This ion was trapped by the nucleophile bis(trimethylsilyl)fluorouracil,[13] yielding the iodinated 2,3-*trans*-nucleoside analogue **14**; the 2,3-*cis*-isomer was not detected. Product **14** was isolated in 50% yield and, therefore, each of the steps involved in the sequence took place in excellent yield.



Scheme 2. One-pot conversion of proline derivative **10** into the iodinated iminosugar-based nucleoside **14**.

The process was also studied with trimethylsilyl-benzotriazole, because several triazolyl nucleosides are potent cytotoxic, antiviral, and fungicide agents.[14] Several reaction conditions were assessed, and the best results were obtained with dichloromethane as solvent, and 1 equiv. of iodine (excess halogen gave complex product mixtures). Thus, the one-pot process afforded three isomeric nucleoside analogues **15**–**17** (Scheme 3) in good global yield (66%). The major product was the 2,3-*trans*-diastereoisomer (±)-**15** (48%), which was obtained along with the 2-benzotriazole isomer (±)-**16** (7%). In this reaction, the 2,3-*cis* product (±)-**17** (11%) was also isolated.



Scheme 3. One-pot conversion of proline derivative **10** into the iodinated nucleoside analogues **15**–**17**.

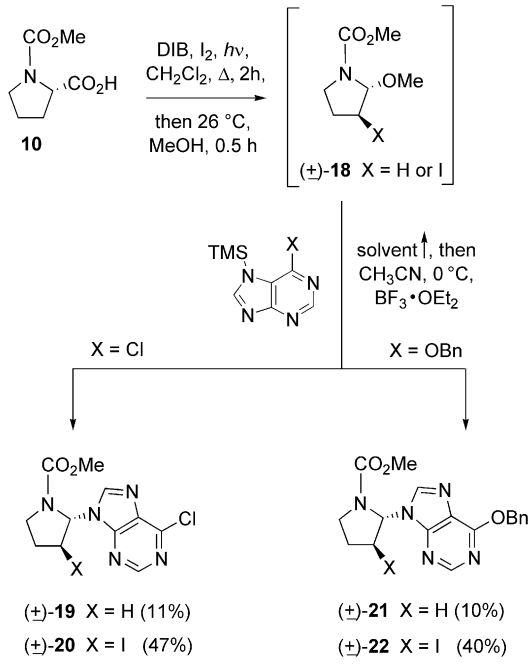
The process also worked with the purine bases trimethylsilyl-chloropurine and trimethylsilyl-benzyloxypurine (Scheme 4). In these cases, the best results were obtained when the intermediate acyliminium ion was trapped with methanol to give (±)-**18**,[7b] followed by solvent removal and replacement with acetonitrile. After addition of the silylated base and the Lewis acid at 0 °C, separable mixtures of non-halogenated and iodinated products were obtained.

In the case of the chloropurine derivatives, the non-halogenated product (±)-**19** (11%)[6] and the desired 2,3-*trans*-3-iodo-nucleoside analogue (±)-**20** (47%) were readily separated. The chloro group in 6-chloropurine can be replaced by other groups (amino, aryl, or alkyl, etc) using sp^n–sp^n couplings, radical reactions, etc.,[15] which allows the formation of libraries of nucleoside derivatives. Moreover, the introduction of a halogen often results in interesting biological activities.[1g]

In a similar manner, the reaction with trimethylsilyl-benzyloxypurine gave the non-iodinated derivative (±)-**21** (10%)[6] and the desired β-iodo-nucleoside analogue (±)-**22** (40%).

The manipulation of the iodo group introduced on C-3 is particularly interesting because it allows the preparation of a range of nucleoside derivatives. Thus, dehalogenation could afford analogues of unsaturated antiviral drugs such as abacavir or stavudine.[1,16] These unsaturated analogues could be further functionalized by dihydroxylation, amino-

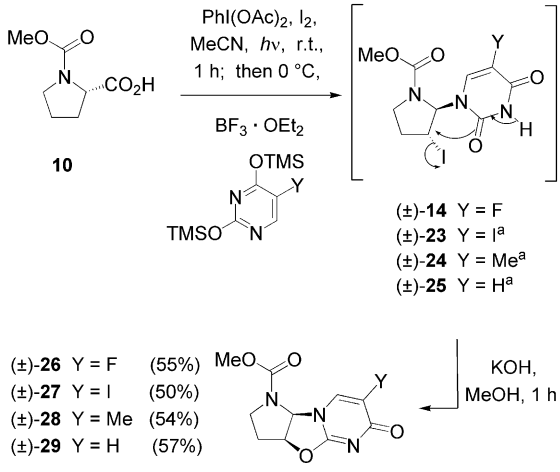
 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 4. One-pot conversion of proline derivative **10** into the iminosugar-based nucleosides **19**–**22**.

hydroxylation, or epoxidation followed by addition of nucleophiles, etc.[17]

The iodo group can also be replaced by other functions, as shown in Scheme 5 (conversions **14**, **23**–**25** → **26**–**29**). Thus, by treatment of pure β-iodo derivative **14** with methanolic KOH, an intramolecular S_N2 reaction took place, yielding the tricyclic compound **26**[18] in 73% yield (37% from proline substrate **10**).

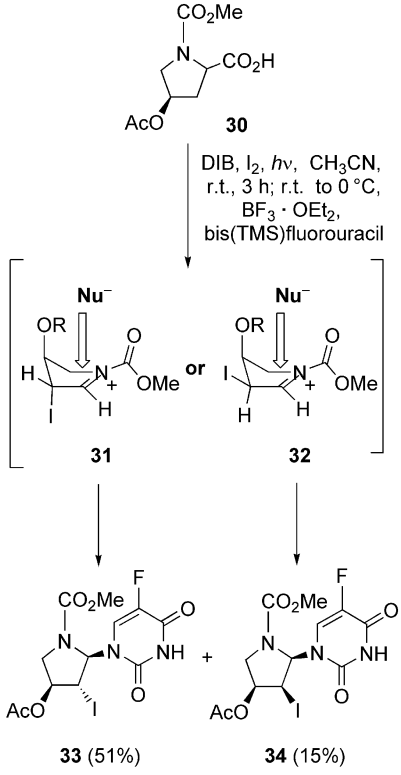


Scheme 5. One-pot conversion of proline derivative **10** into tricyclic compounds. [a] Intermediates **14**, **23**–**25** were not isolated, but transformed directly into products **26**–**29**, respectively.

A simplified scission–β-iodination–base addition–cyclization process was then developed in which the β-iodo-nucleoside analogue **14** was not purified. Thus, the proline derivative **10** underwent the usual scission and addition of the nitrogen base, followed by aqueous work-up and solvent evaporation, yielding a residue, which was treated with methanolic KOH, affording product **26**. The yield obtained in the simplified process (55%) was superior to the global yield of the two-step method (37%).

The simplified methodology also allowed preparation of the crude β-iodo-iminosugar-based nucleosides **23**–**25**, derived from iodouracil, thymine, and uracil, respectively. These crude products were cyclized to give compounds **27** (50%), **28** (54%), and **29** (57%), respectively. To the best of our knowledge, only one example of a related tricyclic azacompound has been reported.[18a] In this manner, a simple amino acid derivative (substrate **10**) was readily converted into complex tricyclic systems in good global yields, in a short period of time, while avoiding the purification of reaction intermediates.

When the 4*R*-acetoxy proline derivative **30** (Scheme 6) was used as the substrate, and bis(trimethylsilyl)fluorouracil as the base, the reaction afforded the all-*trans* compound **33** as the major product (51%). Interestingly, the all-*cis* product **34** was obtained as the minor product (15%),[19] a result which can be explained by using Woerpel's model for the addition of nucleophiles to cyclic iminium (or oxycarbenium) ions.[20]



Scheme 6. One-pot conversion of hydroxyproline derivative **30** into β-iodo-nucleoside analogues **33** and **34**, and an explanation of the stereoselectivity of the process.

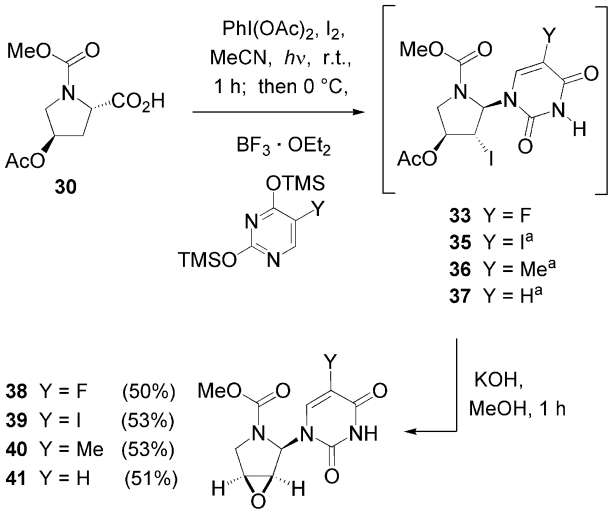
Thus, the possible acyliminium intermediates **31** or **32** adopt envelope conformations in which the benzyloxy group is in a pseudoaxial position, allowing stabilizing electrostatic interactions between the oxygen lone electron pairs and the iminium ion.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

The silylated base adds preferentially from the inner face because, in the resultant staggered structure, the substituents at C-2 and C-3 are not eclipsed. Moreover, in the case of intermediate **31**, addition from the inner face also avoids repulsive interactions with the iodo group. In the case of intermediate **32**, the halogen is in a pseudoequatorial position, and the interactions with the entering base are small.

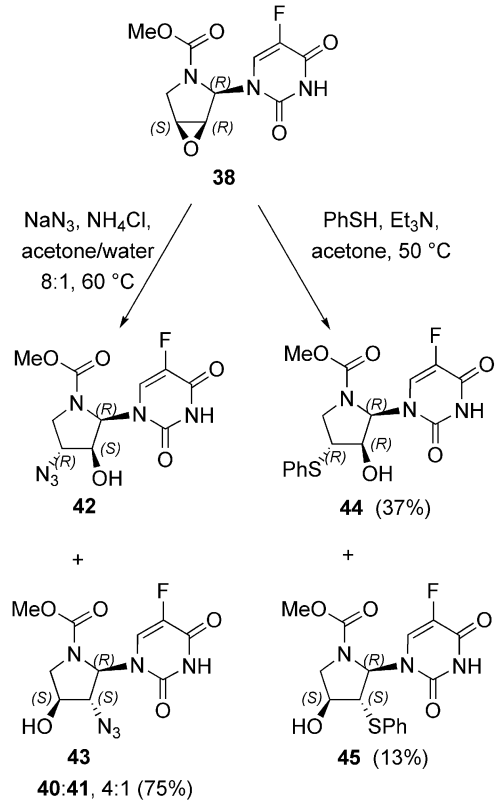
In contrast, addition of the nucleophile from the outer face of intermediates **31** and **32** is disfavored: in this case the initially-formed *trans* product presents strong eclipsing interactions between the substituents at C-2 and C-3.[6,20] Due to this effect, the all-*cis* pyrrolidine **34** is formed in spite of the steric hindrance posed by the iodo group once the initially-formed *trans* product equilibrates to its other conformations.

When the pure 4-acetoxy derivative **33** was treated under basic conditions (methanolic KOH) the acetate was hydrolyzed (Scheme 7), and then an intramolecular S_N2 took place to give the epoxide **38** in 75% yield (38% from proline substrate **30**). When the simplified decarboxylation–base addition–cyclization process was applied to the proline derivative **30**, the yield of epoxide **38** was notably increased (50%). In a similar manner, proline **30** was transformed into the epoxides **39** (53%), **40** (53%), and **41** (51%). In preliminary screenings, the epoxy derivatives **38**–**40** displayed promising antifungal activity, which is currently under study.



Scheme 7. One-pot conversion of hydroxyproline derivative **30** into tricyclic iminosugar-based nucleosides **38**–**41**. [a] Intermediates **35**–**37** were not isolated, but transformed directly into products **39**–**41**, respectively.

The epoxides can be valuable precursors of a variety of nucleoside analogues (Scheme 8).[21] For instance, by cleavage of epoxide **38** with sodium azide, the regioisomers **42** and **43** were isolated in good yield (75%), albeit as an inseparable mixture (**42**/**43**, 4:1). When thiophenol was used as the nucleophile, epoxide **38** underwent ring opening to give the nucleoside analogues **44** (37%) and **45** (13%). Therefore, from readily available amino acids, a library of highly functionalized iminosugar-based nucleosides can be prepared in a few steps, which can enable structure–biological activity relationships to be studied.[22]



Scheme 8. Transformation of epoxy derivative **38** into a range of 2,3,4-substituted nucleoside analogues **42**–**45**.

Conclusions

Readily available proline derivatives can be directly transformed into β-iodinated iminosugar-based nucleosides by using a radical scission–oxidation–β-iodination–addition of nitrogen base process. The introduction of an iodo group in a previously unfunctionalized position is remarkable, and allows further derivatization of the products. Thus, by using an intramolecular S_N2 reaction, epoxy and other tricyclic nucleoside analogues were obtained in good global yields. The epoxy derivatives, which display interesting antifungal activities, were useful precursors of highly functionalized compounds bearing oxygen, nitrogen, and sulfur functionalities. In this manner, by using simple proline precursors, a library of nucleoside analogues can be prepared efficiently in very few steps.

Experimental Section

Preparation of Trimethylsilyl Derivatives of the Nitrogen Bases: Some trimethylsilyl derivatives from the nitrogen bases are commercially available, but use of these products 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,

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

244 mg, 1.2 mmol) under nitrogen. The mixture was heated to 130 °C and stirred for 1 h, then was cooled to 26 °C and anhydrous 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 Procedures for the One-Pot β-Scission–β-Iodination–Base Addition Process

Method A (for Pyrimidine Bases): To a solution of L-proline methyl carbamate **10** (35 mg, 0.2 mmol) or 4-acetoxyproline methyl carbamate **30** (46 mg, 0.2 mmol) in anhydrous CH_3CN, were added DIB (129 mg, 0.4 mmol) and iodine (102 mg, 0.4 mmol). The mixture was stirred at 26 °C under irradiation with visible light (80-W tungsten-filament lamp) for 3 h, then cooled to 0 °C and the freshly prepared silylated base (0.4 mmol) was added dropwise, followed by $BF_3{\cdot}OEt_2$ (57 mg, 50 μL, 0.4 mmol). The mixture was allowed to reach room temp. and stirring was continued for 1 h. The solution was poured into into 10% aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$ (1:1) and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), filtered and the solvents evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc), affording the β-iodo-nucleoside analogues.

Method B (for Benzotriazole): Similar to Method A, but using anhydrous CH_2Cl_2 (4 mL) as solvent and only 1 equiv. of iodine (51 mg, 0.2 mmol).

Method C (for Purine Bases): Similar to Method A, but the scission was carried out in anhydrous CH_2Cl_2 heated to reflux. After 2 h, the reaction mixture was cooled to r.t. (25 °C) and anhydrous methanol was added (0.25 mL). Stirring was continued for 0.5 h and then the solvent was removed under vacuum and the residue was redissolved in anhydrous CH_3CN, cooled to 0 °C, and treated with the silylated base (0.4 mmol) and $BF_3{\cdot}OEt_2$ (0.4 mmol) as described in Method A. Usual work-up and purification by chromatography on silica gel (hexanes/EtOAc), afforded the β-iodo-nucleoside analogues.

5-Fluoro-1-[(2*R,3*S**)-3-iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-uracil (14):** Obtained from proline methyl carbamate **10** and bis(trimethylsilyl)-5-fluorouracil according to Method A (38.5 mg, 50%). Two rotamers at 26 °C (2:1), one rotamer at 70 °C; crystalline solid; m.p. 246–249 °C (from MeOH, decomposition). IR (film): $\tilde{\nu}$ = 3547, 3378, 1713, 1664, 1259, 1177 cm^{-1}. ^1H NMR (500 MHz, CD_3OD, 70 °C): δ = 2.22 (m, 1 H), 2.27 (m, 1 H), 3.72–3.87 (m, 5 H), 4.55 (br. band; d, J = 4.5 Hz at 26 °C, 1 H), 6.09 (br. s, 1 H), 7.71 (d, $J_{F,H}$ = 6.4 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, CD_3OD, 26 °C): major rotamer δ = 24.5 (CH), 34.9 (CH_2), 47.5 (CH_2), 54.1 (CH_3), 81.7 (CH), 125.5 (CH, d, $J_{C,F}$ = 34.7 Hz), 141.4 (C, d, $J_{C,F}$ = 234.3 Hz), 150.7 (C), 156.8 (C), 159.4 (C, d, $J_{C,F}$ = 26.0 Hz); minor rotamer δ = 25.1 (CH), 33.1 (CH_2), 47.6 (CH_2), 54.1 (CH_3), 81.0 (CH), 125.5 (CH, d, $J_{C,F}$ = 34.7 Hz), 141.4 (C, d, $J_{C,F}$ = 234.3 Hz), 150.7 (C), 156.8 (C), 159.4 (C, d, $J_{C,F}$ = 26.0 Hz) ppm. MS (EI): *m*/*z* (%) = 352 (1) [M^+ – OMe], 254 (89) [M^+ + H – 5-fluorouracil], 127 (100) [M^+ + H – (5-fluorouracil + I)]. HRMS: calcd. for $C_9H_8FIN_3O_3$ 351.9594; found 351.9581; calcd. for $C_6H_9NO_2$ 127.0633; found 127.0629. $C_{10}H_{11}FIN_3O_4$ (383.12): calcd. C 31.35, H 2.89, N 10.97; found C 31.54, H 2.96, N 10.77.

1-[(2*R,3*S**)-3-Iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl]benzotriazole (15), 2-[(2*R**,3*S**)-3-Iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl-]benzotriazole (16), and 1-[(2*R**,3*R**)-3-Iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl]benzotriazole (17):** Obtained from proline methyl carbamate **10** and (trimethylsilyl)benzotriazole according to Method B. The reaction mixture was purified by chromatography (hexanes/EtOAc, 8:2 then 6:4), yielding the 2,3-*trans* product (±)-**15** (36 mg, 48%), its regioisomer (±)-**16** (5 mg, 7%), and the 2,3-*cis* product (±)-**17** (8.3 mg, 11%).

Compound (±)-15: Colorless oil; two rotamers at 26 °C (5:2), one rotamer at 70 °C. IR ($CDCl_3$): $\tilde{\nu}$ = 3095, 1707, 1614, 1591, 1132, 1075 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz): major rotamer δ = 1.71 (dd, J = 6.7, 14.8 Hz, 1 H), 2.81 (m, 1 H), 3.19 (s, 3 H), 3.37 (dd, J = 9.0, 9.6 Hz, 1 H), 3.58 (m, 1 H), 4.02 (d, J = 5.2 Hz, 1 H), 6.73 (s, 1 H), 6.92 (dd, J = 7.6, 7.7 Hz, 1 H), 7.05 (dd, J = 7.6, 7.6 Hz, 1 H), 7.59 (d, J = 8.1 Hz, 1 H), 7.89 (d, J = 8.6 Hz, 1 H); minor rotamer δ = 1.54 (dd, J = 6.2, 14.3 Hz, 1 H), 2.30 (m, 1 H), 3.01 (s, 3 H), 3.64 (m, 1 H), 3.75–3.82 (m, 2 H), 6.54 (s, 1 H), 6.92 (dd, J = 7.6, 7.7 Hz, 1 H), 6.97 (d, J = 8.6 Hz, 1 H), 7.01 (dd, J = 6.7, 7.7 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (C_6D_6, 125.7 MHz): major rotamer δ = 24.5 (CH), 36.4 (CH_2), 45.7 (CH_2), 52.6 (CH_3), 79.6 (CH), 110.9 (CH), 119.9 (CH), 124.1 (CH), 127.7 (CH), 133.3 (C), 146.1 (C), 155.4 (C); minor rotamer δ = 25.5 (CH), 34.8 (CH_2), 46.5 (CH_2), 52.6 (CH_3), 79.6 (CH), 109.7 (CH), 120.8 (CH), 124.1 (CH), 127.7 (CH), 136.3 (C), 146.3 (C), 155.4 (C) ppm. MS: *m*/*z* (%) = 372 (7) [M^+], 254 (84) [M^+ + H – benzotriazole], 253 (24) [M^+ – benzotriazole], 127 (100) [M^+ + H – (benzotriazole + I)]. HRMS: calcd. for $C_{12}H_{13}IN_4O_2$ 372.0083; found 372.0118; calcd. for $C_6H_9NO_2$ 127.0633; found 127.0599. $C_{12}H_{13}IN_4O_2$ (372.17): calcd. C 38.73, H 3.52, N 15.05; found C 38.53, H 3.26, N 14.78.

Compound (±)-16: Syrup, two rotamers at 26 °C (6:5), one rotamer at 70 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3096, 3074, 3062, 1716, 1564, 1243, 843 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz): major rotamer δ = 1.48 (dd, J = 5.9, 14.6 Hz, 1 H), 2.24 (m, 1 H), 3.10 (s, 3 H), 3.71 (m, 1 H), 3.81–3.91 (m, 2 H), 6.96–6.99 (m, 3 H), 7.69–7.73 (m, 2 H); minor rotamer δ = 1.55 (dd, J = 6.3, 14.6 Hz, 1 H), 2.34 (m, 1 H), 3.26 (s, 3 H), 3.65 (m, 1 H), 3.81–3.91 (m, 2 H), 6.93–6.99 (m, 2 H), 7.30 (s, 1 H), 7.68–7.74 (m, 2 H) ppm. ^{13}C NMR (C_6D_6, 125.7 MHz): major rotamer δ = 24.9 (CH), 33.9 (CH_2), 46.6 (CH_2), 52.8 (CH_3), 86.1 (CH), 118.8 (2 × CH), 127.0 (2 × CH), 144.9 (2 × C), 155.4 (C); minor rotamer δ = 23.8 (CH), 34.9 (CH_2), 46.0 (CH_2), 52.8 (CH_3), 86.7 (CH), 118.8 (2 × CH), 126.8 (2 × CH), 145.0 (2 × C), 154.4 (C) ppm. MS: *m*/*z* (%) = 372 (7) [M^+], 254 (100) [M^+ + H – benzotriazole], 127 (68) [M^+ + H – (benzotriazole + I)]. HRMS: calcd. for $C_{12}H_{13}IN_4O_2$ 372.0083; found 372.0083; calcd. for $C_6H_9INO_2$ 253.9678; found 253.9745. $C_{12}H_{13}IN_4O_2$ (372.17): calcd. C 38.73, H 3.52, N 15.05; found C 38.84, H 3.26, N 14.76.

Compound (±)-17: Colorless oil, two rotamers at 26 °C (3:2), one rotamer at 70 °C. IR ($CDCl_3$): $\tilde{\nu}$ = 3071, 1706, 1614, 1592, 1216, 1081, 972 cm^{-1}. ^1H NMR (C_6D_6, 500 MHz): major rotamer δ = 1.82 (m, 1 H), 2.92 (m, 1 H), 3.06 (m, 1 H), 3.18 (s, 3 H), 3.42 (dd, J = 9.4, 9.5 Hz, 1 H), 3.57 (m, 1 H), 6.17 (d, J = 6.0 Hz, 1 H), 6.93 (dd, J = 7.5, 7.7 Hz, 1 H), 7.13 (dd, J = 8.0, 8.0 Hz, 1 H), 7.48 (d, J = 8.3 Hz, 1 H), 7.93 (d, J = 8.4 Hz, 1 H); minor rotamer δ = 1.76 (m, 1 H), 2.83 (m, 1 H), 3.00 (s, 3 H), 3.14 (m, 1 H), 3.59 (m, 1 H), 3.63 (m, 1 H), 5.82 (d, J = 5.9 Hz, 1 H), 6.93 (m, 1 H), 7.10–7.20 (m, 2 H), 7.96 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz): major rotamer δ = 19.2 (CH), 34.9 (CH_2), 46.6 (CH_2), 52.6 (CH_3), 72.7 (CH), 110.1 (CH), 120.4 (CH), 124.2 (CH), 127.6 (CH), 134.6 (C); minor rotamer δ = 20.3 (CH), 33.9 (CH_2), 47.1 (CH_2), 56.3 (CH_3), 72.0 (CH), 109.4 (CH), 120.8 (CH), 124.2 (CH), 127.6 (CH), 134.6 (C) ppm; two (C) signals corresponding to an aromatic carbon and the carbamate CO group were not clearly observed. MS: *m*/*z* (%) = 372 (11) [M^+], 254 (100) [M^+ + H – benzotriazole], 127 (79) [M^+ + H – (benzotriazole + I)]. HRMS: calcd. for $C_{12}H_{13}IN_4O_2$ 372.0083; found 372.0077; calcd. for

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

$C_6H_9INO_2$ 253.9678; found 253.9659. $C_{12}H_{13}IN_4O_2$ (372.17): calcd. C 38.73, H 3.52, N 15.05; found C 39.01, H 3.28, N 14.96.

6-Chloro-9-[*N*-(methoxycarbonyl)-2-pyrrolidinyl]purine (±-19) and 6-Chloro-9-[(2*R,3*S**)-3-iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-purine (±)-20:** Obtained from proline methyl carbamate **10** and (trimethylsilyl)chloropurine according to Method C. The reaction mixture was purified by chromatography (hexanes/EtOAc, 7:3), yielding the non-halogenated product (±)-**19** (6 mg, 11%)[6] and the iodinated compound (±)-**20** (38 mg, 47%).

Compound (±)-20: Syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 1693, 1592, 1561, 1454, 1207, 1127, 985 cm^{-1}. ^{1}NMR (500 MHz, CD_3OD, 70 °C): δ = 2.36 (dddd, J = 3.6, 3.6, 6.8, 14.2 Hz, 1 H), 2.71 (dddd, J = 5.8, 5.8, 8.2, 14.3 Hz, 1 H), 3.66 (br. s, 3 H), 3.87–3.97 (m, 2 H), 4.85 (ddd, J = 2.3, 3.4, 5.7 Hz, 1 H), 6.57 (d, J = 2.2 Hz, 1 H), 8.50 (s, 1 H), 8.71 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 70 °C, 125.7 MHz): δ = 23.1 (CH), 36.2 (CH_2), 48.5 (CH_2), 53.8 (CH_3), 80.5 (CH), 133.1 (C), 146.5 (CH), 152.3 (C), 153.1 (CH), 156.0 (C), 156.8 (C) ppm. MS (EI): *m*/*z* (%) = 378/376 (0.58/1.52) [M^+ – OMe], 254 (100) [iodo-*N*-methylcarbamate-pyrrolidine – H]$^+$, 127 (85) [2,3-dehydropyrrolidine-*N*-methylcarbamate]$^+$. HRMS: calcd. for $C_{10}H_8{}^{37}ClIN_5O$ 377.9433/$C_{10}H_8{}^{35}ClIN_5O$ 375.9671; found 377.9439/375.9450; calcd. for $C_6H_9INO_2$ 253.9678; found 253.9671. $C_{11}H_{11}ClIN_5O_2$ (407.60): calcd. C 32.41, H 2.72, N 17.18; found C 32.40, H 2.85, N 17.30.

6-(Benzyloxy)-9-[*N*-(methoxycarbonyl)-2-pyrrolidinyl]purine (±)-21 and 6-(Benzyloxy)-9-[(2*R,3*S**)-3-iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl]purine (±)-22:** Obtained from proline methyl carbamate (**10**) and (trimethylsilyl)(benzyloxy)purine according to Method C. The reaction mixture was purified by chromatography (hexanes/EtOAc, 7:3 then 1:1), giving the non-halogenated product (±)-**21** (7 mg, 10%)[6] and the iodinated compound (±)-**22** (38 mg, 40%).

Compound (±)-22: Syrup. IR ($CHCl_3$): $\tilde{\nu}$ = 3089, 3066, 1705, 1601, 1575, 1452, 1120, 1046 cm^{-1}. ^{1}NMR (500 MHz, CD_3OD, 70 °C): δ = 2.32 (dddd, J = 3.1, 3.2, 6.6, 13.9 Hz, 1 H), 2.66 (dddd, J = 8.0, 8.1, 8.2, 13.9 Hz, 1 H), 3.67 (s, 3 H), 3.87–3.97 (m, 2 H), 4.87 (m, 1 H), 5.68 (s, 2 H), 6.54 (d, J = 2.1 Hz, 1 H), 7.29 (dd, J = 7.3, 7.4 Hz, 1 H), 7.34 (J = 7.1, 7.7.2 Hz, 2 H), 7.50 (d, J = 7.2 Hz, 2 H), 8.22 (s, 1 H), 8.51 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 70 °C, 125.7 MHz): δ = 23.7 (CH), 36.1 (CH), 47.6 (CH_2), 53.8 (CH_3), 69.9 (CH_2-Ph), 80.1 (CH), 122.8 (C), 129.2 (2× CH), 129.3 (CH), 129.5 (2× CH), 137.7 (C), 143.0 (CH), 152.8 (C), 153.4 (CH), 156.9 (C), 161.9 (C) ppm. MS (EI): *m*/*z* (%) = 479 (<1) [M^+], 226 (17) [benzyloxypurine]$^+$, 128 (100) [2,3-dehydropyrrolidine methylcarbamate + H]$^+$, 91 (45) [C_7H_7]$^+$. HRMS: calcd. for $C_{18}H_{18}IN_5O_3$ 479.0454; found 479.0470; calcd. for $C_6H_{10}NO_2$ 128.0712; found 128.0709. $C_{18}H_{18}IN_5O_3$ (479.28): calcd. C 45.11, H 3.79, N 14.61; found C 45.30, H 3.99, N 14.68.

Conversion of β-Iodo-Nucleoside Analogues 14 or 33 into Polycyclic Products 26 or 38: To a 5% methanolic solution of KOH (2 mL) was added β-iodo-nucleoside analogue **14** (77 mg, 0.2 mmol) or **33** (88 mg, 0.2 mmol). The resulting suspension was stirred at 26 °C for 2 h, then the solvent was partially removed under vacuum and the mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried, filtered and concentrated as usual, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH), affording the fused tricyclic compound **26** (37 mg, 73% from substrate **14**) or the epoxy derivative **38** (41 mg, 75% from **33**).

Simplified Procedure for the Synthesis of Fused Tricyclic Compounds 26–29 and Epoxy Compounds 38–41: A solution of proline methyl carbamate **10** (35 mg, 0.2 mmol) or 4-acetoxyproline methyl carbamate **30** (46 mg, 0.2 mmol) in anhydrous MeCN underwent the tandem fragmentation–β-iodination–base addition process, as reported for compounds **14** and **33**. After usual work-up and solvent evaporation, the residue was treated with 5% methanolic KOH (2 mL) and the mixture was stirred at 26 °C for 2 h. The solvent was partially removed under vacuum, followed by work-up and purification as described in the previous procedure.

(3a*R,9a*S**)-7-Fluoro-*N*-(methoxycarbonyl)-6-oxo-2,3,3a,9a-tetrahydropyrrolo[2′,3′:4,5][1,3]oxazolo[3,2-*a*]pyrimidine (26):** Obtained from substrate **10** and bis(trimethylsilyl)-5-fluorouracil, following the simplified procedure for the synthesis of fused tricyclic compounds (28 mg, 55%). Two rotamers at 26 °C (2:1), one rotamer at 70 °C; crystalline solid; m.p. 175–177 °C (from MeOH). IR ($CDCl_3$): $\tilde{\nu}$ = 1703, 1660, 1573, 1247, 1116 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C): δ = 2.30 (m, 1 H), 2.46 (dd, J = 6.1, 14.7 Hz, 1 H), 3.46 (ddd, J = 6.3, 11.1, 11.1 Hz, 1 H), 3.82 (s, 3 H), 3.93 (m, 1 H), 5.57 (dd, J = 5.9, 6.0 Hz, 1 H), 6.28 (d, J = 6.2 Hz, 1 H), 7.71 (br. band, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, 70 °C): δ = 30.8 (CH_2), 44.0 (CH_2), 53.4 (CH_3), 75.0 (CH), 83.8 (CH), 120.6 (CH, $J_{C,F}$ = 32 Hz), 146.2 (C, $J_{C,F}$ = 256 Hz), 152.8 (C), 157.9 (C), 163.9 (C, $J_{C,F}$ = 25.1 Hz) ppm. MS (EI): *m*/*z* (%) = 255 (100) [M]$^+$, 240 (5) [M^+ – Me], 224 (6) [M^+ – MeO], 125 (24) [methyl 1*H*-pyrrole-1-carboxylate]$^+$. HRMS: calcd. for $C_{10}H_{10}FN_3O_4$ 255.0655; found 255.0651. $C_{10}H_{10}FN_3O_4$ (255.21): calcd. C 47.06, H 3.95, N 16.47; found C 46.79, H 4.36, N 16.21.

(3a*R,9a*S**)-7-Iodo-*N*-(methoxycarbonyl)-6-oxo-2,3,3a,9a-tetrahydropyrrolo[2′,3′:4,5][1,3]oxazolo[3,2-*a*]pyrimidine (27):** Obtained from substrate **10** and bis(trimethylsilyl)-5-iodouracil, following the simplified procedure for the synthesis of fused tricyclic compounds (36 mg, 50%).

Compound 27: Crystalline solid; m.p. 168–170 °C (from MeOH); two rotamers at 26 °C (2:1), one rotamer at 70 °C. IR (film): $\tilde{\nu}$ = 1702, 1690, 1264 cm^{-1}. ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ = 1.94 (m, 1 H), 2.19 (m, 1 H), 3.63 (ddd, J = 5.8, 7.9, 10.7 Hz, 1 H), 3.71 (s, 3 H), 3.72 (m, 1 H), 4.48 (dd, J = 5.7, 5.7, 5.7 Hz, 1 H), 6.09 (d, J = 5.5 Hz, 1 H), 7.67 (br. s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ = 32.3 (CH_2), 45.8 (CH_2), 53.7 (CH_3), 67.0 (C), 71.7 (CH), 73.3 (CH), 147.9 (CH), 152.5 (C), 157.2 (C), 162.7 (C) ppm. MS: *m*/*z* (%) = 363 (6) [M]$^+$, 238 (36) [5-iodouracil]$^+$, 144 (100) [3-hydroxy-1-(methoxycarbonyl)pyrrolidine – H]$^+$. HRMS: calcd. for $C_{10}H_{10}IN_3O_4$ 362.9716; found 362.9701; calcd. for $C_6H_{10}NO_3$ 144.0661; found 144.0662. $C_{10}H_{10}IN_3O_4$ (363.11): calcd. C 33.08, H 2.78, N 11.57; found C 32.80, H 2.43, N 11.30.

(3a*R,9a*S**)-*N*-(Methoxycarbonyl)-7-methyl-6-oxo-2,3,3a,9a-tetrahydropyrrolo[2′,3′:4,5][1,3]oxazolo[3,2-*a*]pyrimidine (28):** Obtained from substrate **10** and bis(trimethylsilyl)thymine, following the simplified procedure for the synthesis of fused tricyclic compounds (27 mg, 54%). Two rotamers at 26 °C (2:1), one rotamer at 70 °C; crystalline solid; m.p. 175–177 °C (MeOH). IR ($CHCl_3$): $\tilde{\nu}$ = 1693, 1378, 1214, 1124 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD, 70 °C): δ = 1.87 (s, 3 H), 1.93 (m, 1 H), 2.18 (m, 1 H), 3.59 (ddd, J = 6.7, 7.6, 10.6 Hz, 1 H), 3.69 (s, 3 H), 3.72 (ddd, J = 6.5, 7.4, 10.7 Hz, 1 H), 4.49 (ddd, J = 5.7, 6.0, 6.5 Hz, 1 H), 6.11 (d, J = 5.3 Hz, 1 H), 7.18 (s, 1 H) ppm. ^{13}C NMR (125.7 MHz, CD_3OD, 70 °C): δ = 12.2 (CH_3), 32.2 (CH_2), 45.6 (CH_2), 53.5 (CH_3), 71.8 (CH), 72.4 (CH), 110.6 (C), 139.1 (CH), 152.9 (C), 157.2 (C), 166.5 (C) ppm. MS (EI): *m*/*z* (%) = 251 (24) [M]$^+$, 144 (100) [3-hydroxy-1-(methoxycarbonyl)pyrrolidine – H]$^+$, 126 (21) [thymine]$^+$. HRMS: calcd. for $C_{11}H_{13}N_3O_4$ 251.0906; found 251.0916; calcd. for $C_6H_{10}NO_3$

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

144.0661; found 144.0656. $C_{11}H_{13}N_3O_4$ (251.24): calcd. C 52.59, H 5.22, N 16.72; found C 52.21, H 5.53, N 16.40.

(3a*R,9a*S**)-*N*-(Methoxycarbonyl)-6-oxo-2,3,3a,9a-tetrahydropyrrolo[2′,3′:4,5][1,3]oxazolo[3,2-*a*]pyrimidine (29):** Obtained from substrate **10** and bis(trimethylsilyl)uracil, following the simplified procedure for the synthesis of fused tricyclic compounds (27 mg, 57%). Two rotamers at 26 °C (8:1); one rotamer at 70 °C; crystalline solid; m.p. 155–157 °C (MeOH). IR ($CDCl_3$): $\tilde{\nu}$ = 1702, 1648, 1385, 1214, 1186, 1037 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.28 (m, 1 H), 2.49 (dd, J = 6.1, 14.8 Hz, 1 H), 3.46 (ddd, J = 6.1, 11.4, 11.4 Hz, 1 H), 3.78 (s, 3 H), 3.88 (m, 1 H), 5.49 (dd, J = 5.7, 5.8 Hz, 1 H), 5.99 (d, J = 7.5 Hz, 1 H), 6.26 (d, J = 6.2 Hz, 1 H), 7.74 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 70 °C): δ = 30.6 (CH_2), 43.8 (CH_2), 53.3 (CH_3), 74.1 (CH), 82.7 (CH), 109.9 (CH), 136.3 (CH), 160.2 (C), 171.8 (C) ppm; the (C) signal corresponding to the carbamate is missing. MS (EI): m/z (%) = 237 (100) $[M]^+$, 125 (37) [methyl 1*H*-pyrrole-1-carboxylate]$^+$. HRMS: calcd. for $C_{10}H_{11}N_3O_4$ 237.0750; found 237.0754. $C_{10}H_{11}N_3O_4$ (237.22): calcd. C 50.63, H 4.67, N 17.71; found C 51.03, H 4.53, N 17.40.

1-[(2*S*,3*R*,4*S*)-4-Acetoxy-3-iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-fluorouracil (33) and 1-[(2*R*,3S,4*S*)-4-Acetoxy-3-iodo-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-fluorouracil (34): Obtained from 4-acetoxyproline **30** and bis(trimethylsilyl)-5-fluorouracil as a separable diastereomer mixture (chromatography on silica gel; hexanes/EtOAc, 7:3).

Compound 33: Yield 45 mg (51%); two rotamers at 26 °C (1:1), one rotamer at 70 °C; colorless oil. $[a]_D$ = –20 (c = 0.25, CH_3OH). IR (film): $\tilde{\nu}$ = 3375, 1721, 1751, 1723, 1666, 1376, 1262, 1228, 1198 cm^{-1}. ^1H NMR (500 MHz, CD_3OD, 70 °C): δ = 1.99 (s, 3 H), 3.79 (s, 3 H), 3.91 (br. d, J = 12.5 Hz, 1 H), 4.26 (dd, J = 4.9, 12.5 Hz, 1 H), 4.48 (br. s, 1 H), 5.39 (br. d, J = 4.9 Hz, 1 H), 6.20 (s, 1 H), 7.74 (d, $J_{F,H}$ = 6.7 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, CD_3OD, 70 °C): δ = 20.5 (CH_3), 23.8 (CH), 52.6 (CH_2), 54.3 (CH_3), 79.7 (CH), 81.3 (CH), 126.0 (CH, d, $J_{C,F}$ = 35.2 Hz), 142.0 (C, d, $J_{C,F}$ = 233 Hz), 150.9 (C), 152.7 (C), 170.7 (C) ppm. The (C) signal corresponding to the uracil amide (C-4′) was not clearly observed. MS (EI): m/z (%) = 410 (1) [M^+ – MeO], 312 (29) [M^+ + H – fluorouracil], 252 (74) [M^+ – (5-fluorouracil + $MeCO_2$)], 125 (100) [M^+ – (5-fluorouracil + $MeCO_2$ + I)]. HRMS: calcd. for $C_{11}H_{10}FIN_3O_5$ 409.9649; found 409.9643; calcd. for $C_6H_7NO_2$ 125.0477; found 125.0475. $C_{12}H_{13}FIN_3O_6$ (441.15): calcd. C 32.67, H 2.97, N 9.53; found C 33.06, H 3.18, N 9.26.

Compound 34: Yield 13.5 mg (15%); colorless oil; two rotamers at 26 °C (1:1), one rotamer at 70 °C. $[a]_D$ = +25 (c = 0.10, MeOH). IR ($CHCl_3$): $\tilde{\nu}$ = 3377, 3192, 1747, 1725, 1673, 1266, 1237 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 70 °C): δ = 2.11 (s, 3 H), 3.72 (s, 3 H), 3.75 (dd, J = 3.5, 11.9 Hz, 1 H), 4.00 (dd, J = 4.7, 11.7 Hz, 1 H), 4.92 (dd, J = 4.7, 5.9 Hz, 1 H), 5.10 (ddd, J = 3.6, 4.6, 4.7 Hz, 1 H), 6.05 (d, J = 6.1 Hz, 1 H), 7.73 (d, $J_{F,H}$ = 6.3 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ = 20.8 (CH_3), 24.4 (CH), 51.8 (CH_2), 54.2 (CH_3), 73.1 (CH), 81.1 (CH), 126.1 (CH, br. d, $J_{C,F}$ = 35.0 Hz), 141.8 (C, d, $J_{C,F}$ = 235 Hz), 150.7 (C), 159.2 (C, d, $J_{C,F}$ = 25.0 Hz), 171.2 (C) ppm. The (C) signal corresponding to the methyl carbamate was not clearly observed. MS: m/z (%) = 410 (1) [M^+ – OMe], 312 (100) [M^+ + H – 5-fluorouracil], 126 (84) [M^+ + H – (5-fluorouracil + $MeCO_2$ + I)]. HRMS: calcd. for $C_{11}H_{10}FIN_3O_5$ 409.9649; found 409.9650; calcd. for $C_8H_{11}INO_4$ 311.9733; found 311.9735. $C_{12}H_{13}FIN_3O_6$ (441.15): calcd. C 32.67, H 2.97, N 9.53; found C 32.97, H 3.19, N 9.33.

1-[(2*R*,3*S*,4*R*)-3,4-Epoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-fluorouracil (38): Obtained from substrate **30** and bis(trimethylsilyl)-5-fluorouracil, following the simplified procedure for the synthesis of epoxy compounds (27 mg, 50%). Two rotamers at 26 °C (2:1), one rotamer at 70 °C; syrup. $[a]_D$ = +10 (c = 0.41, CH_3OH). IR ($CHCl_3$): $\tilde{\nu}$ = 3383, 1705, 1669, 1383, 1130, 1077 cm^{-1}. ^1H NMR (500 MHz, DMSO, 70 °C): δ = 3.57 (dd, J = 2.0, 12.3 Hz, 1 H), 3.58 (s, 3 H), 3.85 (d, J = 12.3 Hz, 1 H), 3.96 (dd, J = 2.3, 2.8 Hz, 1 H), 4.04 (dd, J = 2.4, 2.7 Hz, 1 H), 6.19 (dd, J = 1.7, 1.7 Hz, 1 H), 7.63 (d, J = 7.0 Hz, 1 H), 11.63 (br. band, 1 H) ppm. ^{13}C NMR (125.7 MHz, DMSO, 26 °C): major rotamer δ = 48.0 (CH_2), 52.6 (CH_3), 54.9 (CH), 57.2 (CH), 67.9 (CH), 126.1 (CH, d, $J_{C,F}$ = 34.1 Hz), 140.0 (C, d, $J_{C,F}$ = 229.6 Hz), 149.0 (C), 155.0 (C), 156.8 (C, d, $J_{C,F}$ = 26.0 Hz); minor rotamer δ = 48.6 (CH_2), 52.7 (CH_3), 54.9 (CH), 57.8 (CH), 67.6 (CH), 126.0 (CH, d, $J_{C,F}$ = 34.1 Hz), 140.0 (C, d, $J_{C,F}$ = 229.6 Hz), 149.0 (C), 155.0 (C), 157.0 (C, d, $J_{C,F}$ = 26.0 Hz) ppm. MS (EI): m/z (%) = 271 (98) $[M]^+$, 141 (100) [M^+ – 5-fluorouracil], 59 (85) [MeOCO]. HRMS: calcd. for $C_{10}H_{10}FN_3O_5$ 271.0604; found 271.0602; calcd. for $C_6H_7NO_3$ 141.0426; found 141.0424. $C_{10}H_{10}FN_3O_5$ (271.20): calcd. C 44.29, H 3.72, N 15.49; found C 44.59, H 3.45, N 15.21.

1-[(2*R*,3*S*,4*R*)-3,4-Epoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-iodouracil (39): Obtained from substrate **30** and bis(trimethylsilyl)-5-iodouracil, following the simplified procedure for the synthesis of epoxy compounds (40 mg, 53%). Crystalline solid, m.p. 118–120 °C (MeOH); colorless crystals; two rotamers at 26 °C (3:1), one rotamer at 70 °C. $[a]_D$ = +77 (c = 0.41, MeOH). IR ($CHCl_3$): $\tilde{\nu}$ = 3379, 1716, 1690, 1255, 1129, 1052 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 70 °C): δ = 3.47 (dd, J = 2.0, 12.6 Hz, 1 H), 3.57 (s, 3 H), 3.71 (dd, J = 2.1, 3.1 Hz, 1 H), 3.76 (d, J = 12.6 Hz, 1 H), 3.85 (dd, J = 2.1, 3.0 Hz, 1 H), 6.19 (d, J = 2.0 Hz, 1 H), 7.28 (s, 1 H), 7.79 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 26 °C): major rotamer δ = 49.2 (CH_2), 53.6 (CH_3), 55.8 (CH), 58.2 (CH), 68.3 (C), 69.5 (CH), 147.0 (CH), 152.0 (C), 156.9 (C), 162.3 (C); minor rotamer δ = 49.5 (CH_2), 54.1 (CH_3), 55.7 (CH), 58.8 (CH), 68.3 (C), 71.0 (CH), 147.0 (CH), 152.0 (C), 156.9 (C), 162.3 (C) ppm. MS: m/z (%) = 379 (14) $[M]^+$, 142 (100) [M^+ + H – 5-iodouracil]. HRMS: calcd. for $C_{10}H_{10}IN_3O_5$ 378.9665; found 378.9671; calcd. for $C_6H_8NO_3$ 142.0504; found 142.0502. $C_{10}H_{10}IN_3O_5$ (379.11): calcd. C 31.68, H 2.66, N 11.08; found C 31.48, H 2.63, N 10.68.

1-[(2*R*,3*S*,4*R*)-3,4-Epoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]thymine (40): Obtained from substrate **30** and bis(trimethylsilyl)thymine, following the simplified procedure for the synthesis of epoxy compounds (28 mg, 53%). Two rotamers at 26 °C (4:1); one rotamer at 70 °C; syrup. $[a]_D$ = +44 (c = 0.24, MeOH). IR ($CHCl_3$): $\tilde{\nu}$ = 3395, 1703, 1689, 1376, 1257, 1132 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 70 °C): δ = 1.84 (s, 3 H), 3.64 (dd, J = 2.1, 12.6 Hz, 1 H), 3.65 (s, 3 H), 3.88 (dd, J = 2.1, 2.5 Hz, 1 H), 3.90 (d, J = 12.5 Hz, 1 H), 3.99 (dd, J = 2.6, 2.6 Hz, 1 H), 6.26 (d, J = 2.0 Hz, 1 H), 7.29 (s, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ = 12.3 (CH_3), 49.9 (CH_2), 53.7 (CH_3), 55.8 (CH), 58.9 (CH), 69.1 (CH), 111.2 (C), 138.6 (CH), 166.1 (C) ppm. Two (C) signals corresponding to the carbamate and the urea were not clearly observed at 70 °C; at 26 °C they appeared at δ = 152.6 and 157.2 ppm. MS (EI): m/z (%) = 267 (63) $[M]^+$, 142 (100) [M^+ + H – thymine], 126 (78) [thymine]. HRMS: calcd. for $C_{11}H_{13}N_3O_5$ 267.0855; found 267.0845; calcd. for $C_6H_8NO_3$ 142.0504; found 142.0506. $C_{11}H_{13}N_3O_5$ (267.24): calcd. C 49.44, H 4.90, N 15.72; found C 49.70, H 5.23, N 15.40.

1-[(2*R*,3*S*,4*R*)-3,4-Epoxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]uracil (41): Obtained from substrate **30** and bis(trimethylsilyl)uracil, following the simplified procedure for the synthesis of epoxy nucleoside analogues (26 mg, 51%). Two rotamers at 26 °C (1:1); one rotamer at 70 °C; syrup. $[a]_D$ = +40 (c = 0.11, MeOH). IR ($CHCl_3$): $\tilde{\nu}$ = 3389, 1715, 1693, 1374, 1258, 1131, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C): δ = 3.66 (dd, J = 2.1, 12.9 Hz, 1 H),

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

3.70 (s, 3 H), 3.83 (dd, J = 2.5, 2.5 Hz, 1 H), 3.94 (d, J = 12.8 Hz, 1 H), 3.99 (dd, J = 2.2, 2.5 Hz, 1 H), 5.66 (d, J = 8.2 Hz, 1 H), 6.34 (d, J = 1.9 Hz, 1 H), 7.31 (d, J = 8.2 Hz, 1 H), 8.07 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125.7 MHz, 26 °C): δ = 48.8/48.9 (CH_2), 53.3/53.5 (CH_3), 54.5 (CH), 58.1/58.2 (CH), 67.2/67.3 (CH), 102.3/102.3 (CH), 140.8/140.8 (CH), 150.5/150.5 (C), 155.2/155.2 (C), 162.7/126.7 (C) ppm. MS (EI): m/z (%) = 253 (41) $[M]^+$, 142 (100) [M^+ + H – uracil]. HRMS: calcd. for $C_{10}H_{11}N_3O_5$ 253.0699; found 253.0698; calcd. for $C_6H_8NO_3$ 142.0504; found 142.0503. $C_{10}H_{11}N_3O_5$ (253.21): calcd. C 47.43, H 4.38, N 16.59; found C 47.10, H 4.50, N 16.22.

Preparation of 1-[(2*R*,3*S*,4*R*)-4-Azido-3-hydroxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-fluorouracil (42) and 1-[(2*R*,3*S*,4*S*)-3-Azido-4-hydroxy-*N*-(methoxycarbonyl)-2-pyrrolidinyl]-5-fluorouracil (43): To a solution of epoxide **38** (35 mg, 0.13 mmol) in acetone/water (4 mL, 8:1) were added NH_4Cl (16.0 mg, 0.3 mmol) and NaN_3 (42.0 mg, 0.65 mmol). The mixture was stirred at 60 °C for 14 h, then poured into water and extracted with EtOAc. The organic layers were dried and evaporated, and the residue was purified by chromatography (hexanes/EtOAc, 3:7), yielding hydroxy azides **42** and **43** as an inseparable mixture of regioisomers (30 mg, 75%; **42**/**43**, 4:1). Colorless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3383, 2114, 1706, 1257, 1130, 1088 cm^{-1}. ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): two rotamers/regioisomers at 26 °C (1:1), one rotamer/regioisomer at 70 °C; major regioisomer δ = 3.50 (dd, J = 4.7, 11.4 Hz, 1 H), 3.71 (s, 3 H), 3.93 (dd, J = 5.7, 11.4 Hz, 1 H), 4.13 (ddd, J = 4.7, 5.1, 5.7 Hz, 1 H), 4.34 (dd, J = 5.4, 5.4 Hz, 1 H), 6.05 (d, J = 5.6 Hz, 1 H), 7.54 (d, $J_{F,H}$ = 6.6 Hz, 1 H); minor regioisomer δ = 3.65 (dd, J = 2.5, 11.4 Hz, 1 H), 3.74 (s, 3 H), 3.76 (dd, J = 4.7, 11.4 Hz, 1 H), 4.20–4.30 (m, 2 H), 5.81 (br. s, 1 H), 7.70 (d, $J_{F,H}$ = 7.0 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): major regioisomer δ = 50.0 (CH_2), 53.9 (CH_3), 65.6 (CH), 72.7 (CH), 75.4 (CH), 127.8 (CH, d, $J_{C,F}$ = 35.4 Hz), 141.5 (C, d, $J_{C,F}$ = 233.3 Hz), 151.2 (C), 157.0 (C), 159.3 (C, d, $J_{C,F}$ = 25.4 Hz); minor regioisomer δ = 55.1 (CH_3), 71.7 (CH), 73.3 (CH), 76.2 (CH), 126.8 (CH, d, $J_{C,F}$ = 33.6 Hz), 141.5 (C, d, $J_{C,F}$ = 233.3 Hz), 151.0 (C), 157.0 (C), 159.3 (C, d, $J_{C,F}$ = 25.4 Hz). One (CH_2) signal is overlapped by the solvent signal. MS: m/z (%) = 314 (3) $[M]^+$, 254 (12) [M^+ – (N_3 + H_2O)], 185 (100) [M^+ + H – 5-fluorouracil], 130 (46) [5-fluorouracil$^+$], 59 (91) [$MeOCO^+$]. HRMS: calcd. for $C_{10}H_{11}FN_6O_5$ 314.0775; found 314.0770; calcd. for $C_6H_9N_4O_3$ 185.0675; found 185.0666. $C_{10}H_{11}FN_6O_5$ (314.23): calcd. C 38.22, H 3.53, N 26.74; found C 38.42, H 3.23, N 26.84.

Preparation of 5-Fluoro-1-[(2*R*,3*R*,4*R*)-3-hydroxy-*N*-(methoxycarbonyl)-4-phenylthio-2-pyrrolidinyl]uracil (44) and 5-Fluoro-1-[(2*R*,3*S*,4*S*)-4-hydroxy-*N*-(methoxycarbonyl)-3-phenylthio-2-pyrrolidinyl]uracil (45): To a solution of epoxide **38** (27.1 mg, 0.1 mmol) in anhydrous acetone (4 mL) were added Et_3N (41 μL, 0.3 mmol) and PhSH (30 μL, 0.3 mmol). The mixture was stirred under nitrogen at 50 °C for 14 h, then poured into water and extracted with EtOAc. The organic layers were dried, concentrated under vacuum and the residue was purified by chromatography (CH_2Cl_2/MeOH, 9.8:0.2), giving compounds **44** (14 mg, 37%) and **45** (4.9 mg, 13%).

Compound 44: Colorless oil, two rotamers at 26 °C (1:1), one rotamer at 70 °C. $[\alpha]_D$ = +35 (c = 0.26, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3384, 1705, 1550, 1203, 1126 cm^{-1}. ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ = 3.61 (dd, J = 4.4, 11.7 Hz, 1 H), 3.69 (s, 3 H), 3.70 (m, 1 H), 4.05 (dd, J = 6.0, 11.4 Hz, 1 H), 4.31 (dd, J = 4.7, 5.4 Hz, 1 H), 6.19 (d, J = 5.7 Hz, 1 H), 7.27–7.35 (m, 3 H), 7.47–7.50 (m, 2 H), 7.52 (d, $J_{F,H}$ = 6.6 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ = 51.5 (CH_2), 51.8 (CH_3), 53.8 (CH), 73.0 (CH), 75.6 (CH_2), 127.6 (CH, d, $J_{C,F}$ = 31.8 Hz), 129.0 (CH), 130.3 (2 × CH), 133.7 (2 × CH), 134.2 (C), 143.5 (C, d, $J_{C,F}$ = 237.0 Hz), 152.0 (C), 157.2 (C), 160.3 (C, d, $J_{C,F}$ = 29.0 Hz) ppm. MS: m/z (%) = 381 (25) $[M]^+$, 252 (87) [M^+ + H – 5-fluorouracil], 234 (78) [M^+ + H – (5-fluorouracil + H_2O)], 142 (100) [M^+ + H – (5-fluorouracil + PhSH)]. HRMS: calcd. for $C_{16}H_{16}FN_3O_5S$ 381.0795; found 381.0789; calcd. for $C_6H_8NO_3$ 142.0504; found 142.0501. $C_{16}H_{16}FN_3O_5S$ (381.38): calcd. C 50.39, H 4.23, N 11.02; found C 50.34, H 4.57, N 11.40.

Compound 45: Isolated as a mixture with the major regioisomer (**44**/**45**, 2:1). Two rotamers at 26 °C (1:1), one rotamer at 70 °C. ^{1}H NMR (CD_3OD, 500 MHz, 70 °C): δ = 3.60 (m, 1 H), 3.70 (s, 3 H), 3.77 (br. s, 1 H), 3.83 (dd, J = 5.1, 11.4 Hz, 1 H), 4.23 (m, 1 H), 5.95 (d, J = 1.6 Hz, 1 H), 7.27–7.36 (m, 3 H), 7.51–7.54 (m, 2 H), 7.72 (d, $J_{F,H}$ = 6.6 Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ = 51.8 (CH_3), 55.3 (CH_2), 59.0 (CH), 73.9 (CH), 77.6 (CH), 127.2 (CH, d, $J_{C,F}$ = 36.3 Hz), 129.4 (CH), 130.3 (2 × CH), 133.7 (2 × CH), 134.1 (C), 160.2 (C). Several signals of product **45** were not clearly observed, even with the aid of 2D-NMR experiments, and are not described.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of the the new compounds **14**–**17**, **20**, **22**, **26**–**29**, **33**, **34**, and **38**–**45**.

Acknowledgments

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

[1] a) *Modified Nucleosides in Biochemistry Biotechnology and Medicine* (Ed.: P. Herdewijn), Wiley-VCH, Weinheim, **2008**; b) L. A. Agrofoglio, S. R. Challand, *Acyclic, Carbocyclic and* L-*Nucleosides*, Chapman and Hall, **1998**; c) See also: A. Mieczkowski, V. Roy, L. A. Agrofoglio, *Chem. Rev.* **2010**, *110*, 1828–1856; d) E. de Clercq, *J. Med. Chem.* **2010**, *53*, 1438–1450; e) V. B. Kurteva, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 6809–6857; f) J. Stambasky, M. Hocek, P. Kocovský, *Chem. Rev.* **2009**, *109*, 6729–6764; g) W. B. Parker, *Chem. Rev.* **2009**, *109*, 2880–2893, and references cited therein.

[2] For *N*-Acetylazathymidine (**1**), see: K. H. Altmann, S. M. Freier, U. Pieles, T. Winkler, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1654–1657.

[3] For Immucilin-H and analogues, see: a) G. B. Evans, R. H. Furneaux, H. Hausler, J. S. Larsen, P. C. Tyler, *J. Org. Chem.* **2004**, *69*, 2217–2220; b) V. P. Kamath, S. Ananth, S. Bantia, P. E. Morris Jr., *J. Med. Chem.* **2004**, *47*, 1322–1324; c) See also: K. Clinch, G. B. Evans, R. F. G. Fröhlich, R. H. Furneaux, P. M. Kelly, L. Legentil, A. S. Murkin, L. Li, V. L. Schramm, P. C. Tyler, A. D. Woolhouse, *J. Med. Chem.* **2009**, *52*, 1126–1143; d) A. S. Murkin, K. Clinch, J. M. Mason, P. C. Tyler, V. L. Schramm, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5900–5903; e) E. A. Taylor, K. Clinch, P. M. Kelly, L. Li, G. B. Evans, P. C. Tyler, V. L. Schramm, *J. Am. Chem. Soc.* **2007**, *129*, 6984–6985; f) For an orally active immunosuppressant, see: S. Bantia, P. J. Miller, C. D. Parker, S. L. Ananth, L. L. Horn, J. M. Kilpatrick, P. E. Morris, T. L. Hutchison, J. A. Montgomery, J. S. Sandhu, *Int. Immunopharmacol.* **2001**, *1*, 1199–1210.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[4] For Codonopsin, see: D. F. Oliveira, E. A. Severino, C. R. D. Correia, *Tetrahedron Lett.* **1999**, *40*, 2083–2086.

[5] a) For reviews on iminosugar-based nucleosides, see: M. Yokoyama, A. Momotake, *Synthesis* **1999**, 1541–1554; b) V. L. Schramm, P. C. Tyler, *Curr. Top. Med. Chem.* **2003**, *5*, 525–540; c) For recent work on the subject, see: M. Rueping, B. J. Nachtsheim, *Synlett* **2010**, 119–122; d) U. Chiacchio, L. Borrello, L. Crispino, A. Rescifina, P. Merino, B. Macchi, E. Balestrieri, A. Mastino, A. Piperno, G. Romeo, *J. Med. Chem.* **2009**, *52*, 4054–4057; e) G. Enderlin, C. Taillefumier, C. Didierjean, Y. Chapleur, *J. Org. Chem.* **2009**, *74*, 8388–8391; f) R. Flores, R. Alibés, M. Figueredo, J. Font, *Tetrahedron* **2009**, *65*, 6912–6917; g) M. Koszytkowska-Stawinska, E. De Clercq, J. Balzarini, *Bioorg. Med. Chem.* **2009**, *17*, 3756–3762; h) V. Vanek, M. Budešinský, M. Rinnová, I. Rosenberg, *Tetrahedron* **2009**, *65*, 862–876; i) M. Nakano, M. Terada, *Synlett* **2009**, 1670–1674; j) B. Hélal, F. Ferreira, C. Botuha, F. Chemla, A. Pérez-Luna, *Synlett* **2009**, 3115–3118; k) A. Goeminne, M. Berg, M. McNaughton, G. Bal, G. Surpateanu, P. Van der Veken, S. De Prol, W. Versées, J. Steyaert, A. Haemers, K. Augustyns, *Bioorg. Med. Chem.* **2008**, *16*, 6752–6763; l) X. Yue, X. L. Qiu, F. L. Qing, *J. Fluorine Chem.* **2008**, *129*, 866–874; m) E. L. Tsou, S. Y. Chen, M. H. Yang, S. C. Wang, T. R. R. Cheng, W. C. Cheng, *Bioorg. Med. Chem.* **2008**, *16*, 10198–10204; n) D. Rejman, P. Kočalka, M. Budešinský, R. Pohl, I. Rosenberg, *Tetrahedron* **2007**, *63*, 1243–1253; o) S. Castellano, H. D. G. Fiji, S. S. Kinderman, M. Watanabe, P. de Leon, F. Tamanoi, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 5843–5845; p) G. Burton, T. W. Ku, T. J. Carr, T. Kiesow, R. T. Sarisky, J. Lin-Goerke, G. A. Hofmann, M. J. Slater, D. Haigh, D. Dhanak, V. K. Johnson, N. R. Parry, P. Thommes, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1930–1933; q) P. Kočalka, R. Pohl, D. Rejman, I. Rosenberg, *Tetrahedron* **2006**, *62*, 5763–5774, and references cited therein.

[6] A. Boto, D. Hernández, R. Hernández, *Eur. J. Org. Chem.* **2010**, 3847–3857.

[7] a) For a preliminary communication of this work, see: A. Boto, D. Hernández, R. Hernández, *Tetrahedron Lett.* **2008**, *49*, 455–458; b) See also: A. Boto, R. Hernández, Y. León, E. Suárez, *J. Org. Chem.* **2001**, *65*, 7796–7803.

[8] a) For other related work from our group, see: C. Saavedra, R. Hernandez, A. Boto, E. Alvarez, *J. Org. Chem.* **2009**, *74*, 4655–4665; b) A. Boto, D. Hernández, R. Hernández, *Tetrahedron Lett.* **2009**, *50*, 3974–3977; c) A. Boto, D. Hernández, R. Hernández, A. Montoya, E. Suárez, *Eur. J. Org. Chem.* **2007**, 325–334; d) A. Boto, D. Hernández, R. Hernández, *Org. Lett.* **2007**, *9*, 1721–1724; e) A. Boto, D. Hernández, R. Hernández, E. Álvarez, *J. Org. Chem.* **2007**, *72*, 9523–9532; f) C. J. Saavedra, R. Hernández, A. Boto, E. Álvarez, *Tetrahedron Lett.* **2006**, *47*, 8757–8760; g) A. Boto, J. A. Gallardo, R. Hernández, C. J. Saavedra, *Tetrahedron Lett.* **2005**, *46*, 7807–7811; h) A. Boto, R. Hernández, Y. León, J. R. Murguía, A. Rodríguez-Afonso, *Eur. J. Org. Chem.* **2005**, 673–682; i) For related work, see: B. R. Díaz-Sánchez, M. A. Iglesias-Arteaga, R. Melgar-Fernández, E. Juaristi, *J. Org. Chem.* **2007**, *72*, 4822–4825; j) T. Maruyama, Y. Mizuno, I. Shimizu, S. Suga, J. I. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 1902–1903; k) For a review on the modification of amino acids and carbohydrates through radical chemistry, see: S. G. Hansen, T. Skrydstrup, *Top. Curr. Chem.* **2006**, *264*, 135–162; l) For a review covering radical chemistry with hypervalent iodine reagents, see: V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358.

[9] a) For the addition of nucleophiles to iminium ions, see: A. Yazici, S. G. Pyne, *Synthesis* **2009**, 339–368 (part I); A. Yazici, S. G. Pyne, *Synthesis* **2009**, 513–541 (part 2); b) D. Ferraris, *Tetrahedron* **2007**, *63*, 9581–9597; c) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569; d) S. E. Schaus, A. Ting, *Eur. J. Org. Chem.* **2007**, 5797–5815; e) M. Petrini, E. Torregiani, *Synthesis* **2007**, 159–186; f) M. Petrini, *Chem. Rev.* **2005**, *105*, 3949–3977; g) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311–2352; h) B. E. Maryanoff, H. C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628.

[10] A. Boto, R. Hernández, E. Suárez, *J. Org. Chem.* **2000**, *65*, 4930–4937.

[11] Any source of visible light can be used. However, to obtain reproducible results, we carried out the scission reaction with commonly available 80-W tungsten-filament lamps.

[12] The formation of the acyliminium intermediate **13** from the enecarbamate **12** probably proceeds via an iodonium ion.

[13] a) The nucleophiles were prepared from commercial bases 5-fluorouracil, benzotriazole, 6-(benzyloxy)purin, and 6-chloropurin according to a protocol described by Vorbrüggen, see: H. Vorbrüggen, *Acta Biochim. Pol.* **1996**, *43*, 25–36; b) M. G. B. Drew, S. Gorsuch, J. H. M. Gould, J. Mann, *J. Chem. Soc. Perkin Trans. 1* **1999**, 969–978.

[14] a) C. Nájera, J. M. Sansano, *Org. Biomol. Chem.* **2009**, *7*, 4567–4581; b) F. Amblard, J. H. Cho, R. F. Schinazi, *Chem. Rev.* **2009**, *109*, 4207–4220; c) J. Wan, Y. Xia, Y. Liu, M. Wang, P. Rocchi, J. Yao, F. Qu, J. Neyts, J. L. Iovanna, L. Peng, *J. Med. Chem.* **2009**, *52*, 1144–1155; d) S. Bae, M. K. Lakshman, *J. Am. Chem. Soc.* **2007**, *129*, 782–789; e) D. S. Im, C. S. Cheong, S. H. Lee, B. H. Youn, S. C. Kim, *Tetrahedron* **2000**, *56*, 1309–1314.

[15] a) M. Stefko, L. Slavetínska, B. Klepetarova, M. Hocek, *J. Org. Chem.* **2010**, *75*, 442–449; b) R. Pratap, D. Parrish, P. Gunda, D. Venkataraman, M. K. Lakshman, *J. Am. Chem. Soc.* **2009**, *131*, 12240–12249; c) J. Pschierer, H. Plenio, *Org. Lett.* **2009**, *11*, 2551–2554.

[16] For Abacavir and stavudine (D4T), see: a) H. Kumamoto, H. Tanaka, *J. Org. Chem.* **2002**, *67*, 3541–3547; b) M. Ferrero, V. Gotor, *Chem. Rev.* **2000**, *100*, 4319–4347, and references cited therein.

[17] a) For the formation of olefinic nucleoside analogues and their transformation into dihydroxy or amino-hydroxy derivatives, see: D. F. Oliveira, E. A. Severino, C. R. D. Correia, *Tetrahedron Lett.* **1999**, *40*, 2083–2086; b) G. Rassu, L. Pinna, P. Spanu, F. Ulgheri, G. Casiraghi, *Tetrahedron Lett.* **1994**, *35*, 4019–4022.

[18] a) To the best of our knowledge, only one example of related tricyclic aza compounds has been reported, see: E. R. Costenaro, L. A. M. Fontoura, D. F. Oliveira, C. R. D. Correia, *Tetrahedron Lett.* **2001**, *42*, 1599–1602; b) For tricyclic systems from conventional nucleosides, see: Y. Oeda, Y. Ijima, H. Taguchi, A. Ohkubo, K. Seio, M. Sekine, *Org. Lett.* **2009**, *11*, 5582–5585, and references cited therein.

[19] a) Theoretical calculations performed with Macromodel 7.0 support the assigned stereochemistries. Thus, the experimental coupling constants for compound **33** are $J_{2,3}$ = 0 Hz, $J_{3,4}$ = 1 Hz, and $J_{4,5}$ = 0, 4.9 Hz and for its isomer **34** the constants are $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 4.7 Hz, and $J_{4,5}$ = 3.5, 4.7 Hz. The theoretical constants for the (2*R*,3*S*,4*S*) diastereoisomer are $J_{2,3}$ = 0 Hz, $J_{3,4}$ = 0 Hz, and $J_{4,5}$ = 1.2, 4.9 Hz; for the (2*S*,3*S*,4*S*) diastereoisomer are $J_{2,3}$ = 7 Hz, $J_{3,4}$ = 9 Hz, and $J_{4,5}$ = 8.5, 8.5 Hz; for the (2*S*,3*R*,4*S*) diastereoisomer are $J_{2,3}$ = 1 Hz, $J_{3,4}$ = 5.5 Hz, and $J_{4,5}$ = 8.0, 9.0 Hz; and for the (2*R*,3*R*,4*S*) diastereoisomer are $J_{2,3}$ = 7 Hz, $J_{3,4}$ = 4 Hz, and $J_{4,5}$ = 2.0, 4.7 Hz. Therefore, the experimental constants of products **33** and **34** match the theoretical constants of the (2*R*,3*S*,4*S*) and the (2*R*,3*R*,4*S*) isomers, respectively; b) Calculations were made using an AMBER force-field model implanted in the Macromodel 7.0 program. The calculations were also performed with an MMFF force field, by using high quality parameters. Similar results were obtained in both cases. The theoretical coupling constants were calculated over the minimized structures for all possible isomers, by using the Karplus–Altone equation implemented in Macromodel.

[20] a) C. H. Larsen, B. H. Ridgway, J. T. Shaw, K. A. Woerpel, *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209; b) D. M. Smith, M. B. Tran, K. A. Woerpel, *J. Am. Chem. Soc.* **2003**, *125*,

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

14149–14152; c) C. H. Larsen, B. H. Ridgway, J. T. Shaw, D. M. Smith, K. A. Woerpel, *J. Am. Chem. Soc.* **2005**, *127*, 10879–10884; d) D. Smith, K. A. Woerpel, *Org. Biomol. Chem.* **2006**, *4*, 1195–1201; e) K. M. Bonger, T. Wennekes, D. V. Filippov, G. Lodder, G. A. van der Marel, H. S. Overkleeft, *Eur. J. Org. Chem.* **2008**, 3678–3688; f) For similar studies in six-membered-ring oxocarbenium ions, see: J. A. C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2000**, *122*, 168–169; g) L. Ayala, C. G. Lucero, J. A. C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528; h) S. R. Shenoy, K. A. Woerpel, *Org. Lett.* **2005**, *7*, 1157–1160.

[21] a) For the synthesis of other epoxy-pyrrolidines and their conversion into 3,4-disubstituted pyrrolidines, see: A. Kamal, A. A. Shaik, M. Sandbhor, M. Shaheer-Malik, H. Kaga, *Tetrahedron Lett.* **2004**, *45*, 8057–8059; b) B. G. Davis, M. A. T. Maughan, T. M. Chapman, R. Villard, S. Courtney, *Org. Lett.* **2002**, *4*, 103–106; c) J. K. Robinson, V. Lee, T. D. W. Claridge, J. E. Baldwin, C. J. Schofield, *Tetrahedron* **1998**, *54*, 981–996; d) D. P. Schumacher, S. S. Hall, *J. Am. Chem. Soc.* **1982**, *104*, 6076–6080.

[22] a) Because commercially available 4*R*-hydroxyproline can be easily transformed into 4-(*S*)-hydroxy, alkoxy, or acyloxy derivatives, this methodology would also afford the opposite series of enantiomers, see: A. Kamal, D. R. Reddy, P. S. M. M. Reddy, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 803–806; b) A. K. Mandal, J. Hines, K. Kuramochi, C. M. Crews, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4043–4047; c) M. Doi, Y. Nishi, N. Kiritoshi, T. Iwata, M. Nago, H. Nakano, S. Uchiyama, T. Nakazawa, T. Wakamiya, Y. Kobayashi, *Tetrahedron* **2002**, *58*, 8453–8459; d) J. A. Gómez-Vidal, R. B. Silverman, *Org. Lett.* **2001**, *3*, 2481–2484; e) B. Bellier, I. McCort-Tranchepain, B. Ducos, S. Danascimento, H. Meudal, F. Noble, C. Garbay, B. P. Roques, *J. Med. Chem.* **1997**, *40*, 3947–3956.

Received: July 15, 2010
Published Online: October 20, 2010

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim