Tetrahedron 65 (2009) 6912–6917

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly stereoselective synthesis of novel cyclobutane-fused azanucleosides

Ramon Flores, Ramon Alibés *, Marta Figueredo, Josep Font

Universitat Autònoma de Barcelona, Departament de Química, 08193 Bellaterra, Spain

ARTICLE INFO

Article history:
Received 11 May 2009
Received in revised form 15 June 2009
Accepted 18 June 2009
Available online 23 June 2009

ABSTRACT

Stereoselective syntheses of several 3-azabicyclo[3.2.0]heptane nucleoside analogues have been efficiently completed starting from a homochiral a,b-unsaturated-g-lactam. The target compounds were prepared by condensation of a common bicyclic acetate intermediate with pyrimidine and purine bases under modified Vorbrüggen conditions. The anti-HIV activity of the newly synthesized azanucleosides has been evaluated.

1. Introduction

Over several decades, the search for potential agents against AIDS and viral hepatitis has been focused on structurally modified nucleosides. These efforts have led to the discovery of a number of 2′,3′-dideoxynucleosides, some of which have proven to be effective therapeutic agents against the human immunodeficiency (HIV) and hepatitis B viruses.[1] However, side effects, limited stability, and the emergence of drug-resistant mutants remain a problem of these antiviral agents.[2] Therefore, there is a continuous demand for structurally new nucleoside derivatives with potent antiviral activities and low toxicity, and also for new insights into the structure–activity relationship of these compounds.

The search for new active nucleoside analogues has been primarily focused on modification of the carbohydrate moiety. Nevertheless, in recent years, the design of mimetic furanose rings by introducing different heteroatoms has led to the development of new nucleoside analogues having a modified heterocyclic sugar unit.[3] Among them, the azanucleosides, in which the glycone oxygen atom is replaced by a nitrogen atom seems to be one of the most interesting modifications reported in the literature.[4] In the search for beneficial biological activity, this kind of nucleosides opens a plethora of possibilities for further modification by varying the groups carried by the nitrogen atom. Several examples of pyrimidine *N*-acyl-2′,3′-dideoxyazanucleosides have been described in the literature (Fig. 1), although their antiviral activity proved to be weak or not mentioned.[5] But, to the best of our knowledge, there is no report describing purine 2′,3′-dideoxyazanucleosides.

On the other hand, it is well known that the conformation and puckering of the glycon moiety of nucleosides play a critical role in modulating their biological activity.[2a,6] During the past few years, conformationally restricted nucleosides have drawn considerable attention because the sugar moiety is locked in determined puckering pattern, providing useful information regarding the relationship between sugar ring conformation and biological activity.[7] In a recent paper, we have described the synthesis and conformational analysis of a novel class of nucleoside analogues built on a 3-oxabicyclo[3.2.0]heptane scaffold, **5** and **6**, which substantially mimic the 2′,3′-didehydro-2′,3′-dideoxynucleoside structure of the well-known antiviral agents d4T and d4A.[8]

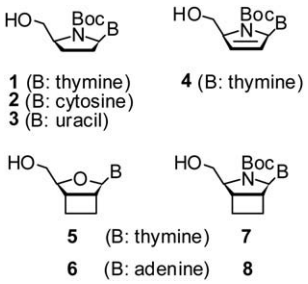


Figure 1. Known 2′,3′-dideoxyazanucleosides **1**–**4** and newly 2′,3′-dideoxy-2′,3′-α-ethano nucleosides **5**–**8**.

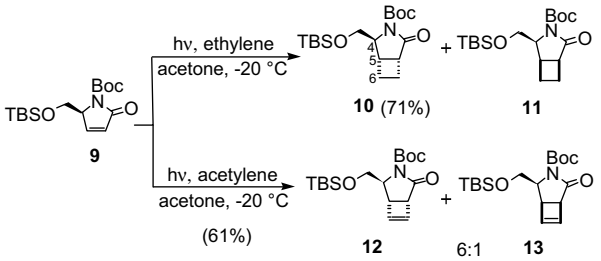
Considering all these aspects, and in continuation of our efforts to explore the feasibility of synthesizing constrained cyclobutane nucleosides, we have turned our attention to the elaboration of the 2′,3′-fused bicylic azanucleosides, where the furanose oxygen was replaced by nitrogen and the pyrrolidine ring was conformationally restricted by a two-carbon chain between positions 2′ and 3′. Herein, we describe the synthesis of the novel [3.2.0]heptane-type azanucleosides **7** and **8** starting from commercially available L-pyroglutamic acid. Our strategy involves the construction of the cyclobutane ring through a photochemical reaction of a chiral α,β-unsaturated-γ-lactam with ethylene and subsequent introduction of the selected bases by a Vorbrüggen-type protocol.

* Corresponding author. Tel.: +34 93 581 2897; fax: +34 93 581 1265.
E-mail address: ramon.alibes@uab.cat (R. Alibés).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.06.067

2. Results

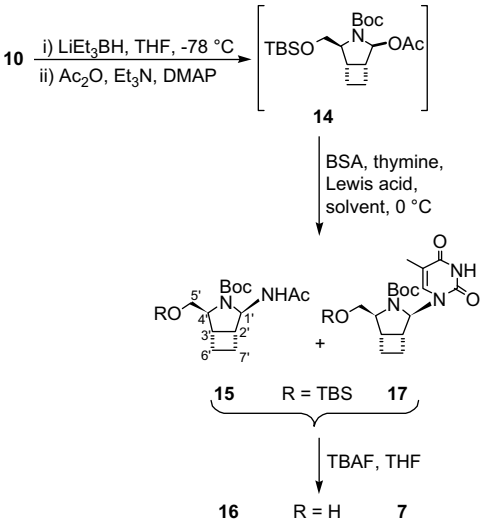
The *N*-Boc protected chiral γ-lactam **9** (Scheme 1) was prepared in 57% overall yield from L-pyroglutamic acid according to a previously reported methodology,[9] $[\alpha]_D$ −173.2 (*c* 0.8, $CHCl_3$) [lit.[10] $[\alpha]_D$ −175.6 (*c* 0.9, $CHCl_3$)]. The protecting group selection on **9** was guided by previous work in this area.[8]



Scheme 1. Photochemical reactions.

The [2+2] photocycloaddition of chiral α,β-unsaturated-γ-lactones to unsaturated substrates has been widely investigated by us and used as a key step in the synthesis of naturally occurring cyclobutane pheromones[11] and nucleosides.[8,12] In contrast, the photocycloaddition of α,β-unsaturated-γ-lactams to unsaturated substrates has been less studied,[13] although the photochemical reaction of **9** with ethylene was reported by the group of Ohfune.[14] These authors described that, upon irradiation through a Pyrex filter of an acetone solution of **9** and ethylene at 0 °C, a 92:8 mixture of the expected cycloadducts **10** and **11** was obtained in 68% combined yield (Scheme 1). In our hands, when the photoreaction was performed under the same conditions but lowering the temperature to −20 °C, the exclusive formation of the *anti* cycloadduct **10** was observed, which was isolated in 71% yield. This result indicates that the diastereofacial selectivity of the process is temperature dependent.[15] In view of the high stereoselectivity achieved in this reaction, we judged interesting to examine the [2+2] photocycloaddition of **9** to acetylene. Under the foregoing conditions, this reaction proceeded smoothly affording a 6:1 mixture of the cyclobutene adducts **12** and **13** in 61% overall yield. In this case, the photoreaction was stopped before complete consumption of the starting lactam to avoid the formation of by-products. Remarkably, the high stereoselectivity found in the photochemical reactions of lactam **9** with ethylene and acetylene is in strong contrast with that shown by the analogous photoreactions of 2(5*H*)-furanones,[16] suggesting that the *N*-Boc moiety may play an important role in favoring the *anti* approach. The relative configuration of the major cycloadducts was assigned considering the low value of the coupling constant between H-4 and H-5 (∼0 Hz for **10** and 1.0 Hz for **12**) and it was further corroborated by a NOESY experiment, which showed cross-peaks between H-4 and the cyclobutane protons H-6. Since both photoreactions proceed with good chemical yield and excellent facial selectivity, the resulting cycloadducts become attractive precursors for the synthesis of enantiomerically pure cyclobutane and cyclobutene derivatives. As an example, we proceeded further with the synthetic sequence to cyclobutane nucleosides.

According to the plan, the lactam function of **10** was partially reduced with superhydride ($LiEtBH_3$) in THF to provide the corresponding aminol, which was converted to the key acetate intermediate **14** by treatment with Ac_2O and DMAP in pyridine (Scheme 2). Due to its low stability, the acetate **14** was subjected to the coupling reactions with the selected nucleobases without further purification.



Scheme 2. Preparation of the thymine azanucleoside analogue, **7**.

At first, the N-glycosylation reaction of thymine with **14** was conducted under modified Vorbrüggen conditions,[17] which had been successfully used by us in the synthesis of **5,** namely the nucleobase was silylated in situ by reaction with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) in the presence of trimethylsilyl triflate (TMSOTf) in CH_3CN at room temperature (Table 1, entry1).[8] However, under these conditions, the condensation reaction of **14** with silylated thymine failed and we exclusively isolated the β-acetamide derivative **15** in 60% yield from **10,** instead of the expected azanucleoside adduct **17**.

Table 1
Thymine N-glycosylation reaction

Entry	Lewis acid	**14**/BSA/thymine[a]	Solvent	Compounds
1	TMSOTf	1:3:1.2	CH_3CN	**15** (60%)[b]
2	TMSOTf	1:3:2	CH_3CN	**15** (42%),[c] **17** (21%)[c]
3	TMSOTf	1:3:2	Toluene	**15** (70%)[b]
4	$SnCl_4$	1:3:2	CH_3CN	**15** (14%),[c] **17** (56%)[c]
5	$SnCl_4$	1:3:2	DCE	**15** (12%),[c] **17** (37%)[c]
6	$SnCl_4$	1:3:2	Toluene	**15** (57%),[c] **17** (25%)[c]

[a] Molar ratio.
[b] Isolated yield after column chromatography.
[c] Estimated yield by ^1H NMR.

The incorporation of acetamide might be rationalized envisaging a nucleophilic attack of *N*-monosilylated or free acetamide, which are formed during silylation of thymine with BSA, to the highly reactive *N*-acyliminium ion derived from **14**. Such a side process had been observed on silylation of 1,2,4,6-thiatriazin-3-one 1,1-dioxides with BSA followed by treatment with peracylated sugars in the presence of TMSOTf in boiling acetonitrile,[18] but, to our knowledge, it has never been reported in the field of azanucleoside synthesis. Therefore, in an attempt to gain some insight into the formation of **15**, the acetate **14** was submited to the above conditions except for the absence of thymine and, in an independent experiment, it was treated with acetamide and TMSOTf. In both cases the acetamido derivative **15** was cleanly formed. Removal of the silyl protecting group of **15** furnished the unprotected derivarive **16** in 76% yield.

In view of the above result, alternative coupling condensation conditions were investigated (Table 1). By decreasing the BSA/thymine ratio[19] from 3:1.2 to 3:2 (entry 2), a 2:1 mixture of **15** and the β-azanucleoside **17** was formed. Further modification of the reagent ratio did not produce better results. The effect of the solvent and Lewis acid on the outcome of this reaction was next

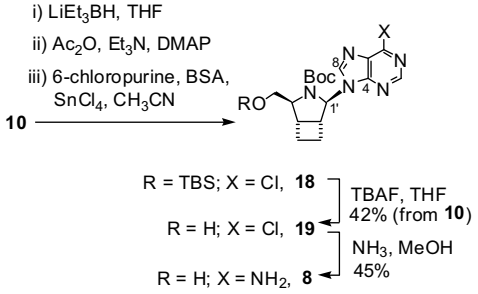
investigated (entries 3–6). Gratifingly, when the reaction was performed in acetonitrile and in the presence of tin(IV) chloride a mixture of **15** and **17** in a 1:4 ratio was obtained (entry 4). Since **15** could not be separated from **17** by column chromatography, this mixture was submitted to silyl deprotection under standard conditions, affording a readily separable mixture wherefrom the target azanucleoside **7** was isolated (40% overall yield from **10**). A 3:1 ratio of **15** and **17** was found (entry 5) when the reaction was carried out in 1,2-dichloroethane (DCE), while in toluene, the acetamide **15** was again the major product (entry 6).

In order to avoid the formation of **15**, an alternative methodology to silylate the nucleobase was investigated. Thus, thymine was per-silylated with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) under reflux in the presence of a catalytic amount of $(NH_4)_2SO_4$ and then added to a solution of the crude acetate **14** and $SnCl_4$ in CH_3CN at 0 °C. This protocol afforded the targeted β-azanucleoside **7** in 48% overall yield from **10.** Interestingly, the reaction conditions employed during the nucleobase incorporation also led to clean cleavage of the silyl protection, thereby eliminating the need of an otherwise necessary additional reaction step. The Boc protecting group was not removed because the *N*-azanucleosides bearing a free NH group have proved to be unstable.[5b]

The β configuration of the anomeric center in **16** and **7** was elucidated by ^{1}H NMR analysis, including NOESY experiments.[20] Both compounds display very small coupling constants $J_{1',2'}$ (~0 Hz) and present cross-peaks between the anomeric proton H-1′ and H-4′ in their NOESY spectra. Moreover, for compound **7**, a correlation between the thymine H-6 proton and the methylene protons H-5′ was observed, while **16** showed a correlation between the NH proton and H-5′. At room temperature, mixtures of rotamers were observed in the NMR spectra of both **7** and **16**.[5h] Variable temperature NMR measurements were conducted and, at 330 K, coalescence of the unfolded signals was observed giving a unique set of resonances.

Remarkably, the highly β-stereoselectivity achieved during the Lewis acid catalyzed coupling of the silylated base with the *N*-Boc-iminium ion derived from **14** is in strong contrast with theanalogous furan-based congeners previously investigated by us, which exhibit unselective nucleobase coupling behavior. It has been suggested that nitrogen pyramidalization with preferential trans disposition of the *N*-Boc moiety may play a role in hindering the α-face of the pyrrolidinone nucleus, favoring the attack of the base by the less demanding β-face.[5g]

Next, the synthesis of the adenine azanucleoside **8** was targeted for attention (Scheme 3). In this case, the condensation of the acetate **14** with 6-chloropurine, using BSA as the silylating agent and $SnCl_4$ as the Lewis acid promoter in CH_3CN at 0 °C, afforded the expected β-nucleoside **18**, which underwent partial silyl cleavage during the chromatographic purification process. Since desilylation was a planned step in the synthesis, we decided to remove the silyl protecting group immediately after purine addition by direct treatment with FTBA without isolation of **18**. This protocol



Scheme 3. Preparation of the adenine azanucleoside analogue, **8**.

delivered **19** in 42% overall yield from **10**. Interestingly, no presence of the acetamide derivative **15** could be detected in the reaction crude.

The β-anomeric configuration of **18** was elucidated as above, by the small coupling constant $J_{1',2'}$ (1.3 Hz) and the correlation between the anomeric proton H-1′ and the cyclobutane moiety (H-6′ and H-7′) observed in the NOESY spectrum. The attachment site (*N*7 or *N*9) of the purine base was established by an HMBC experiment, which showed correlation between H-1′ and the carbon atoms C4 and C8.

Treatment of **18** with ammonia-saturated methanol in a sealed-tube at 90 °C gave a complex crude wherefrom the target adenosine analogue **8** was isolated in 45% yield. The ^{1}H NMR spectra of both purine derivatives **19** and **8** show the presence of rotamers in varying ratios.

As a preliminary test, the azanucleoside analogues **7** and **8** and the acetamide derivative **16** have been evaluated on MT4 cells for anti-HIV-1 activity against wild-type NL4-3 strain. However, no activity or toxicity was found for any of the compounds below a concentration of 25 μg/mL.

3. Conclusions

In summary, it has been found that the photochemical cycloaddition of the chiral lactam **9** with ethylene and acetylene proceeds in an *anti* stereoselective manner giving the [2+2] cycloadducts in good yields. The *anti* cyclobutane adduct **10** has been used as starting material in the synthesis of new nucleosides built on a 3-azabiciclo[3.2.0]heptane scaffold. Remarkably, the coupling reactions of the common intermediate **14** with silylated thymine or 6-chloropurine under modified Vörbruggen conditions are completely stereoselective, providing only the β anomeric nucleosides. Work is in progress to use the azabicycles **10** and **12** for the synthesis of other compounds with potential biological activity.

4. Experimental

4.1. General

Commercially available reagents were used as received. Solutions were concentrated using an evaporator at 15–20 Torr. Flash column chromatography was carried out on silica gel (230–400 mesh). Melting points were determined on hot stage and are uncorrected. The signals in the IR spectra are reported in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded at the *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona* at 250 and 62.5 MHz or 360 and 90 MHz or 400 and 100 MHz. NMR signals were assigned with the help of DEPT, COSY, HMBC and HMQC experiments. High resolution mass spectra (HRMS) and Microanalyses were performed at the *Servei d'Anàlisi Elemental de la Universitat Autònoma de Barcelona*. Optical rotations were measured at 22±2 °C.

4.2. General procedure for photochemical reactions

Irradiations were performed in a small conventional photochemical reactor (two-necked vessel fitted with a Pyrex immersion type cooling jacket) using a high pressure 125 W mercury lamp (Cathodeon HPK-125). Methanol at −15 °C was used for refrigeration of the immersion well jacket. The vessel was externally cooled at −20 °C with a dry ice/CCl_4 bath. The progress of the reaction was monitored by GC or ^{1}H NMR analysis of aliquot samples. Acetylene (acetone free) or ethylene gas was bubbled through the solution for 15 min. Once the lamp was turned on, a slow flow of gas was maintained throughout the irradiation.

*4.2.1. (1R,4S,5S)-N-(tert-Butoxycarbonyl)-4-tert-butyldimethylsilyloxymethyl-3-azabicyclo[3.2.0]heptan-2-one (**10**)*

A solution of lactam **9** (215 mg, 0.66 mmol) in freshly distilled acetone (65 mL) saturated with ethylene was irradiated for 2.5 h at −20 °C. Evaporation of the solvent and column chromatography of the residue (from hexane/diethyl ether 20:1 to hexane/diethyl ether 5:1) afforded **10** (165 mg, 0.46 mmol, 71% yield) as a white solid: mp: 55–57 °C (from diethyl ether); $[\alpha]_D$ −119.2 (*c* 1.3, $CHCl_3$) (lit.[13] $[\alpha]_D$ −118.8 (*c* 1.0 $CHCl_3$)); IR (ATR) 2951, 2930, 1736, 1708, 1249, 1098; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.89 (br dd, $J_{4,8}$=3.5 Hz, $J_{4,8}$=2.1 Hz, 1H, H-4), 3.81 (dd, J_{gem}=10.3 Hz, $J_{8,4}$=3.5 Hz, 1H, H-8), 3.56 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=2.1 Hz, 1H, H-8), 3.00 (m, 1H, H-1), 2.89 (m, 1H, H-5), 2.46 (m, 1H, H-7*exo*), 2.26 (m, 1H, H-6*exo*), 2.08 (m, 1H, H-7*endo*), 2.00 (m, 1H, H-6*endo*), 1.54 (s, 9H, (CH_3)$_3$CO), 0.84 (s, 9H, (CH_3)$_3$CSi), 0.01 (s, 3H, CH_3Si), −0.01 (s, 3H, CH_3Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.2 (C=O, C-2), 150.7 (C=O), 82.9 (C, (CH_3)$_3$CO), 65.2 (CH, C-4), 64.1 (CH_2, C-8), 43.4 (CH, C-1), 33.6 (CH, C-5), 28.1 (CH_3, (CH_3)$_3$CO), 25.9 (CH_3, (CH_3)$_3$CSi), 24.8 (CH_2, C-6), 24.3 (CH_2, C-7), 18.1 (C, (CH_3)$_3$CSi), −5.6 (CH_3, CH_3Si), −5.6 (CH_3, CH_3Si). Anal. Calcd for ($C_{18}H_{33}NO_4Si$): C, 60.81; H, 9.36; N, 3.94. Found: C, 60.81; H, 9.55; N, 3.82.

*4.2.2. (1R,4S,5S)-N-(tert-Butoxycarbonyl)-4-tert-butyldimethylsilyloxymethyl-3-azabicyclo[3.2.0]hept-6-en-2-one (**12**) and (1S,4S,5R)-N-(tert-butoxycarbonyl)-4-tert-butyldimethylsilyloxymethyl-3-azabicyclo[3.2.0]hept-6-en-2-one (**13**)*

A solution of γ-lactam **9** (200 mg, 0.61 mmol) in freshly distilled acetone (65 mL) saturated with acetylene was irradiated for 5 h at −20 °C. Evaporation of the solvent and purification of the residue by column chromatography (hexane/diethyl ether 3:1) afforded the following fractions: (i) a 6:1 mixture of **12** and **13** (132 mg, 0.37 mmol, 61% yield) and (ii) unreacted starting material **9** (40 mg, 0.12 mmol, 20%). Repetitive column chromatography (from hexane/diethyl ether 20:1 to hexane/diethyl ether 5:1) allowed the isolation of pure **12** as a white solid and an enriched fraction of **13** as oil. Compound **12**: mp: 72–75 °C (from EtOAc); $[\alpha]_D$ −91.5 (*c* 2.0, $CHCl_3$); IR (ATR) 2928, 2856, 1736, 1710, 1311, 1150; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.27 (br s, 2H, H-6, H-7), 4.00 (ddd, $J_{4,8}$=3.4 Hz, $J_{4,8}$=2.1 Hz, $J_{4,5}$=1.0 Hz, 1H, H-4), 3.88 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=3.4 Hz, 1H, H-8), 3.64 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=2.1 Hz, 1H, H-8), 3.52 (br dd, $J_{1,5}$=3.3 Hz, J=0.8 Hz, 1H, H-1), 3.24 (br d, $J_{5,1}$=3.3 Hz, 1H, H-5), 1.51 (s, 9H, (CH_3)$_3$CO), 0.86 (s, 9H, (CH_3)$_3$CSi), 0.03 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.9 (C=O, C-2), 151.1 (C=O), 141.0 (CH, C-6), 139.6 (CH, C-7), 82.6 (C, (CH_3)$_3$CO), 64.3 (CH_2, C-8), 58.3 (CH, C-4), 51.5 (CH, C-1), 40.6 (CH, C-5), 28.0 (CH_3, (CH_3)$_3$CO), 25.7 (CH_3, (CH_3)$_3$CSi), 18.0 (C, (CH_3)$_3$CSi), −5.7 (CH_3, CH_3Si), −5.7 (CH_3, CH_3Si). Anal. Calcd for ($C_{18}H_{31}NO_4Si$): C, 61.15; H, 8.84; N, 3.96. Found: C, 60.89; H, 8.85; N, 3.72. Compound **13**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.35 (m, 1H, H-6/H-7), 6.32 (m, 1H, H-7/H-6), 4.10 (m, 1H, H-4), 3.73 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=3.8 Hz, 1H, H-8), 3.57 (m, 2H, H-8 and H-1/H-5), 3.43 (m, 1H, H-5/H-1), 1.51 (s, 9H, (CH_3)$_3$CO), 0.84 (s, 9H, (CH_3)$_3$CSi), 0.00 (s, 3H, CH_3Si), −0.01 (s, 3H, CH_3Si); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.9 (C=O, C-2), 151.1 (C=O), 139.1, 138.0 (2CH, C-6, C-7), 82.9 (C, (CH_3)$_3$CO), 62.6 (CH_2, C-8), 56.7 (CH, C-4), 43.9, 43.7 (2CH, C-1, C-5), 29.6 (CH_3, (CH_3)$_3$CO), 28.0 (CH_3, (CH_3)$_3$CSi), 18.0 (C, (CH_3)$_3$CSi), −5.6 (2CH_3, CH_3Si).

*4.2.3. (1R,2S,4S,5S)-N-(tert-Butoxycarbonyl)-2-acetamido-4-tert-butyldimethylsilyloxymethyl-3-azabicyclo[3.2.0]heptane (**15**)*

To a −78 °C solution of **10** (150 mg, 0.42 mmol) in dry THF (8 mL), was added $LiEt_3BH$ (1.05 mL, a 1.0 M in THF, 1.05 mmol) dropwise. After being stirred for 2 h at −78 °C, the reaction mixture was quenched by the slow addition of H_2O (4 mL) and was allowed to warm to room temperature. Then, H_2O (4 mL) was added and the mixture was extracted with diethyl ether (4×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness affording a crude material that was used in the next reaction without further purification.

To an ice-cooled solution of the above material in CH_2Cl_2 (15 mL), DMAP (44 mg, 0.36 mmol), Et_3N (2.4 mL, 16.0 mmol) and acetic anhydride (850 μL, 9.0 mmol) were added dropwise and successively. The mixture was stirred for 16 h at room temperature and then H_2O (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness using toluene as coevaporant to give **14**, which was immediately used in the next step.

N,*O*-Bis(trimethylsilyl)acetamide (BSA) (271 μL, 1.11 mmol) was added to a suspension of thymine (55 mg, 0.44 mmol) in dry acetonitrile (2.5 mL) under argon atmosphere. Then, a solution of crude acetate **14** (151 mg, 0.38 mmol) in dry acetonitrile (1.9 mL) and TMSOTf (56 μL, 0.55 mmol) were added dropwise and successively, under argon atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for 3.5 h. CH_2Cl_2 (5 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3×4 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane/EtOAc 5:1) to afford **15** (101 mg, 0.25 mmol, 60% yield from **10**) as a colorless oil: $[\alpha]_D$ −51.9 (*c* 0.54, $CHCl_3$); IR (ATR) 3335, 2927, 2855, 1698, 1695, 1376, 1104; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 6.76 (d, $J_{NH,2}$=8.8 Hz)+6.54 (d, $J_{NH,2}$=8.7 Hz) (1H, NH), 5.79 (d, $J_{2,NH}$=8.7 Hz)+5.75 (d, $J_{2,NH}$=8.8 Hz) (1H, H-2), 4.07 (dd, J_{gem}=10.4 Hz, $J_{8,4}$=1.4 Hz, 1H, H-8), 3.97 (br s)+3.85 (br s) (1H, H-4), 3.51 (dd, J_{gem}=10.4 Hz, $J_{8,4}$=1.6 Hz, 1H, H-8), 2.79 (m, 1H, H-5), 2.68 (m, 1H, H-1), 2.22 (m, 2H, H-6*exo*, H-7*exo*), 1.91–1.83 (m, 4H, H-7*endo*, CH_3CO), 1.73 (m, 1H, H-6*endo*), 1.46 (s, 9H, (CH_3)$_3$CO), 0.92 (s, 9H, (CH_3)$_3$CSi), 0.11 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{1}H NMR (400 MHz, $CDCl_3$, 330 K) δ 6.62 (br s, 1H, NH), 5.77 (d, $J_{2,NH}$=8.5 Hz, 1H, H-2), 4.06 (m, 1H, H-8), 3.98 (br s, 1H, H-4), 3.53 (dd, J_{gem}=10.3 Hz, $J_{8,4}$=1.7 Hz, 1H, H-8), 2.80 (m, 1H, H-5), 2.69 (m, 1H, H-1), 2.24 (m, 2H, H-6*exo*, H-7*exo*), 1.89 (m, 4H, H-7*endo*, CH_3CO), 1.74 (m, 1H, H-6*endo*), 1.48 (s, 9H, (CH_3)$_3$CO), 0.94 (s, 9H, (CH_3)$_3$CSi), 0.12 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 167.7 (C=O, CH_3CO), 153.9 (C=O, (CH_3)$_3$OCO), 80.3+80.1 (C, (CH_3)$_3$CO), 69.9+69.4 (CH, C-2), 67.3+66.7 (CH, C-4), 65.3+64.4 (CH_2, C-8), 46.2+45.7 (CH, C-1), 40.0+39.1 (CH, C-5), 28.4 (CH_3, (CH_3)$_3$CO), 26.0 (CH_3, (CH_3)$_3$CSi), 24.6 (CH_2, C-6), 23.6 (CH_2, C-7), 23.4 (CH_3, CH_3CO), 18.6 (C, (CH_3)$_3$CSi), −5.1 (CH_3, CH_3Si), −5.4 (CH_3, CH_3Si). HRMS (ESI) calcd for $[C_{20}H_{38}N_2O_4S+Na]^+$: 421.2493. Found: 421.2489.

*4.2.4. (1R,2R,4S,5S)-N-(tert-Butoxycarbonyl)-2-acetamido-4-hydroxymethyl-3-azabicyclo[3.2.0]heptane (**16**)*

To an ice-cooled solution of **15** (35 mg, 0.09 mmol) in THF (2 mL), a 1.0 M solution of TBAF in THF (130 μL, 0.13 mmol) was added and the resulting solution was stirred for 4 h at room temperature. After removal of the solvent, the residue was purified by column chromatography (EtOAc/hexane 3:1) to afford **16** (19 mg, 0.07 mmol, 76% yield) as colorless oil: $[\alpha]_D$ −90.0 (*c* 0.30, $CHCl_3$); IR (ATR) 3306, 2976, 1699, 1655, 1384, 1162; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.07 (d, $J_{NH,2}$=8.1 Hz)+6.98 (d, $J_{NH,2}$=8.5 Hz) (1H, NH), 5.66 (d, $J_{2,NH}$=8.3 Hz, 1H, H-2), 4.02 (br s)+3.96 (br s) (1H, H-4), 3.93 (m)+3.85 (m) (1H, H-8), 3.57 (m, 1H, H-8), 2.89 (m)+2.82 (m) (1H, H-5), 2.75 (m, 1H, H-1), 2.58 (br s)+2.44 (br s) (1H, OH), 2.25 (m, 2H, H-6*exo*, H-7*exo*), 1.87–1.85 (m, 4H, H-7*endo*, CH_3CO), 1.75 (m, 1H, H-6*endo*), 1.49 (s)+1.46 (s) (9H, (CH_3)$_3$CO); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 168.3+167.7 (C=O, CH_3CO), 154.1+153.4 (C=O, (CH_3)$_3$COCO), 79.9 (C, (CH_3)$_3$CO), 69.5 (CH, C-2), 66.9+66.4 (CH, C-4), 64.0+63.7 (CH_2, C-8), 45.8+45.3 (CH, C-1), 40.0+39.2 (CH, C-5), 28.0 (CH_3, (CH_3)$_3$CO), 24.7+24.5 (CH_2, C-6), 23.3 (CH_3, CH_3CO), 23.3+23.1 (CH_2, C-7). HRMS (ESI) calcd for $[C_{14}H_{24}N_2O_4+Na]^+$: 307.1628. Found: 307.1623.

*4.2.5. (1′R,2′R,4′S,5′S)-1-[N-(tert-Butoxycarbonyl)-4′-hydroxymethyl-3′-azabicyclo[3.2.0]hept-2′-yl]thymine (**7**)*

Procedure A: *N*,*O*-Bis(trimethylsilyl)acetamide (BSA) (271 μL, 1.11 mmol) was added to a suspension of thymine (93 mg, 0.74 mmol) in dry acetonitrile (3.2 mL) under argon atmosphere. The reaction was stirred for 20 min and cooled to 0 °C. Then, a solution of crude acetate **14** (148 mg, 0.37 mmol), prepared from **10** (145 mg, 0.40 mmol) as above, in dry acetonitrile (2.8 mL) and $SnCl_4$ (66 μL, 0.56 mmol) were added dropwise and successively, and the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (2.5 mL) and the resulting mixture was extracted with CH_2Cl_2 (4×5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane/EtAcO 3:1) to afford 129 mg of a 1:4 mixture of **15** and **17**.

To an ice-cooled solution of the above mixture in THF (7 mL), a 1.0 M solution of TBAF in THF (442 μL, 0.44 mmol) was added and the resulting solution was stirred for 2.5 h at room temperature. After removal of the solvent, the residue was purified by column chromatography (EtOAc/hexane 2:1) to afford **7** (57 mg, 0.16 mmol, 40% yield from **10**) as a white solid and **16** (9 mg, 0.03 mmol, 8% yield from **10**).

Procedure B: A suspension of thymine (166 mg, 1.34 mmol) and $(NH_4)_2SO_4$ (55 mg, 0.46 mmol) in hexamethyldisilazane (HMDS) (8 mL) was heated at 140 °C overnight. Then the excess HMDS was removed under reduced pressure and the residue coevaporated with toluene (2×6 mL). The resulting clear oil was dissolved in dry CH_3CN (8 mL) and it was added to a solution of crude acetate **14** (152 mg, 0.38 mmol), prepared from **10** (145 mg, 0.42 mmol) as above, in dry CH_3CN (4.5 mL). The solution was cooled to 0 °C and $SnCl_4$ (67 μL, 0.55 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 3.5 h. Then, saturated aqueous $NaHCO_3$ (6 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (EtOAc-hexane 3:1) to afford **7** (71 mg, 0.20 mmol, 48% yield from **10**) as a white solid.

Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 8.37 (br s, 1H, NH), 7.51 (m, 1H, H-6), 6.03 (br s, 1H, H-2′), 3.98 (m, 2H, H-4′, H-8′), 3.68 (dd, J_{gem}=10.7 Hz, $J_{8',4'}$=3.6 Hz, 1H, H-8′), 2.94 (m, 1H, H-1′), 2.80 (m, 1H, H-5′), 2.37 (m, 1H, H-7′*exo*), 2.23 (m, 1H, H-6′*exo*), 2.05 (m, 1H, H-7′*endo*), 1.94–1.85 (m, 4H, H-6′*endo*, CH_3-C5), 1.41 (br s, 9H, (CH_3)$_3$CO), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.09 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si); ^{13}C NMR (90 MHz, $CDCl_3$, 333 K) δ 163.5 (C=O, C-4), 155.2 (C=O, $(CH_3)_3COCO$), 150.3 (C=O, C-2), 136.8 (CH, C-6), 109.2 (C, C-5), 81.5 (C, $(CH_3)_3CO$), 77.2 (CH, C-2′), 68.2 (CH, C-4′), 64.6 (CH_2, C-8′), 46.4 (CH, C-5′), 40.4 (CH, C-1′), 28.3 (CH_3, (CH_3)$_3$CO), 26.0, 25.8 (CH_3, (CH_3)$_3$CSi), 24.7 ($2CH_2$, C-6′, C-7′), 18.4 (C, (CH_3)$_3$CSi), 12.5 (CH_3, CH_3-C5), −5.2 (CH_3, CH_3Si), −5.3 (CH_3, CH_3Si).

Compound **7**: mp: 56–59 °C (from EtOAc); $[\alpha]_D$ −41.3 (*c* 0.80, $CHCl_3$); IR (ATR) 3418, 3054, 2962, 2924, 1675, 1364, 1259, 1165; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 8.13 (br s, 1H, NH), 7.44 (m, *J*=2.4 Hz, *J*=1.2 Hz, 1H, H-6), 5.87 (br s, 1H, H-2′), 4.14 (m, 1H, H-4′), 3.98 (dt, J_{gem}=11.0 Hz, *J*=3.3 Hz, *J*=3.1 Hz, 1H, H-8′), 3.66 (ddd, J_{gem}=11.0 Hz, *J*=5.8 Hz, *J*=3.6 Hz, 1H, H-8′), 2.92 (m, 3H, H-1′, H-5′, OH), 2.35 (m, 2H, H-6′*exo*, H-7′*exo*), 2.06 (m, 1H, H-7′*endo*), 1.92–1.83 (m, 4H, H-6′*endo*, CH_3-C5), 1.47 (s, 9H, (CH_3)$_3$CO); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 163.5 (C=O, C-4), 155.3 (C=O, $(CH_3)_3COCO$), 150.3 (C=O, C-2), 137.6 (CH, C-6), 109.9 (C, C-5), 82.3 (C, $(CH_3)_3CO$), 77.2 (CH, C-2′), 69.0 (CH, C-4′), 65.2 (CH_2, C-8′), 45.5 (CH, C-1′), 40.6 (CH, C-5′), 28.4 (CH_3, (CH_3)$_3$CO), 25.0, 24.7 ($2CH_2$, C-6′, C-7′), 12.1 (CH_3, CH_3-C5). HRMS (ESI) calcd for $[C_{17}H_{25}N_3O_5+Na]^+$: 374.1686. Found: 374.1680.

*4.2.6. (1′R,2′R,4′S,5′S)-6-Chloro-9-[N-(tert-butoxycarbonyl)-4′-hydroxymethyl-3′-azabicyclo[3.2.0]hept-2′-yl]-9H-purine (**19**)*

N,*O*-Bis(trimethylsilyl)acetamide (BSA) (183 μL, 0.75 mmol) was added to a suspension of 6-chloropurine (77 mg, 0.50 mmol) in dry acetonitrile (2.2 mL) under argon atmosphere. The reaction mixture was stirred for 20 min and cooled to 0 °C. Then, a solution of crude acetate **14** (100 mg, 0.25 mmol) prepared from **10** (93 mg, 0.26 mmol) as above, in dry acetonitrile (1.9 mL) and $SnCl_4$ (44 μL, 0.37 mmol) were added dropwise and successively, and the reaction mixture was stirred at 0 °C for 90 min. The reaction was quenched with aqueous saturated $NaHCO_3$ (3 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×6 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was used in the next reaction without further purification.

To an ice-cooled solution of the previous reaction crude in THF (6 mL), a 1.0 M solution of TBAF in THF (380 μL, 0.38 mmol) was added and the resulting solution was stirred for 2.5 h at room temperature. The solvent was removed and the resulting residue was purified by column chromatography (EtOAc/hexane 1:1) to afford **19** (42 mg, 0.11 mmol, 42% yield from **10**) as a colorless oil: $[\alpha]_D$ −18.6 (*c* 0.70, $CHCl_3$); IR (ATR) 3326, 3103, 2972, 2931, 1701, 1360, 1333, 1163, 1133; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 8.70 (s, 1H, H-2), 8.46 (s, 1H, H-8), 6.29 (d, $J_{2',1'}$=1.3 Hz, 1H, H-2′), 4.22 (br s, 1H, H-4′), 3.98 (m, 1H, H-8′), 3.69 (dd, J_{gem}=10.9 Hz, $J_{8',4'}$=5.3 Hz, 1H, H-8′), 3.38 (br s, 1H, H-1′), 3.22 (br s, 1H, H-5′), 3.15 (br s, 1H, OH), 2.44 (m, 2H, H-6′*exo*, H-7′*exo*), 2.14 (m, 1H, H-7′*endo*), 1.98 (m, 1H, H-6′*endo*), 1.39 (s, 9H, (CH_3)$_3$CO); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 154.8 (C=O, $(CH_3)_3COCO$), 151.5 (CH, C-2), 151.3, 150.9 (2C, C-4/C-6), 145.1 (CH, C-8), 132.4 (CH, C-5), 82.4 (C, (CH_3)$_3$CO), 77.2 (CH, C-2′), 69.2 (CH, C-4′), 64.9 (CH_2, C-8′), 45.5+45.3 (CH, C-1′), 40.9 (CH, C-5′), 28.3 (CH_3, (CH_3)$_3$CO), 24.9, 24.6 ($2CH_2$, C-6′/C-7′). HRMS (ESI) calcd for $[C_{17}H_{22}ClN_5O_3+Na]^+$: 402.1303. Found: 402.1308.

*4.2.7. (1′R,2′R,4′S,5′S)-9-[N-(tert-Butoxycarbonyl)-4′-hydroxymethyl-3′-azabicyclo[3.2.0]hept-2′-yl]adenine (**8**)*

A solution of **19** (25 mg, 0.06 mmol) in saturated NH_3/MeOH (8 mL) was heated at 90 °C in a sealed tube for 65 h. After cooling at room temperature, the solvent was removed under vacuum and the residue was purified by column chromatography (CH_2Cl_2/MeOH 15:1) to afford **8** (11 mg, 0.03 mmol, 45% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO, 333 K) δ 8.20 (s)+8.12 (s)+8.11 (s)+8.0 (s) (2H, H-2+H-8), 6.95 (br s, 2H, NH_2), 6.20 (s)+6.17 (s) (1H, H-2′), 5.05 (br s)+4.93 (t) (1H, OH), 4.00 (m)+3.96 (m) (1H, H-4′), 3.70 (m, 1H, H-8′), 3.54 (m, 1H, H-8′), 3.20–3.10 (m, 2H, H-1′, H-5′), 2.29 (m, 2H, H-6′*exo*, H-7′*exo*), 2.02 (m, 1H, H-7′*endo*), 1.85 (m, 1H, H-6′*endo*), 1.31 (br s, 9H, (CH_3)$_3$CO); ^{13}C NMR (100 MHz, DMSO, 333 K) δ 156.6 (C, C-6), 152.9 (CH, C-2), 152.7 (C=O, $(CH_3)_3COCO$), 149.4 (C, C-4), 140.0 (CH, C-8), 119.7 (C, C-5), 80.8 (C, (CH_3)$_3$CO), 76.0 (CH, C-2′), 71.2 (CH, C-4′), 69.0 (CH_2, C-8′), 45.5 (CH, C-1′), 40.0 (CH, C-5′), 28.5 (CH_3, (CH_3)$_3$CO), 25.0/24.5 ($2CH_2$, C-6′,C-7′). HRMS (ESI) calcd for $[C_{17}H_{24}N_6O_3+Na]^+$: 383.1802. Found: 383.1806.

Acknowledgements

We acknowledge financial support from DGES (project CTQ2007-60613/BQU) and a grant from the Ministerio de Educación y Ciencia (R.F.). We also acknowledge Dr. José A. Esté of the IrsiCaixa Foundation, Hospital Universitari Germans Trias i Pujol, for the biological assays.

References and notes

1. (a) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115–133; (b) Warnke, D.; Barreto, J.; Temesgen, Z. *J. Clin. Pharmacol.* **2007**, *47*, 1570–1579.
2. (a) Herdewijn, P. *Drug Discov. Today* **1997**, *5*, 465–476; (b) Rando, R. F.; Nguyen-Ba, N. *Drug Discov. Today* **2000**, *5*, 465–476.

3. (a) Ichikawa, E.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 385–423; (b) Merino, P. *Curr. Med. Chem. AIA* **2002**, *1*, 389–411.
4. Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541–1554.
5. (a) Huang, B.; Chen, B.; Hui, Y. *Synthesis* **1993**, 769–771; (b) Altmann, K.-A. *Tetrahedron Lett.* **1993**, *34*, 7721–7724; (c) Altmann, K.-H.; Freier, S. M.; Pieles, U.; Winkler, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1654–1657; (d) Pickering, L.; Malhi, B. S.; Coe, P. L.; Walker, R. T. *Tetrahedron* **1995**, *51*, 2719–2728; (e) Pickering, L.; Malhi, B. S.; Coe, P. L.; Walker, R. T. *Nucleosides Nucleotides* **1994**, *13*, 1493–1506; (f) Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G. *Tetrahedron Lett.* **1994**, *35*, 4019–4022; (g) Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168–180; (h) Varaprasad, C. V.; Averett, D.; Ramasamy, K. S.; Wu, J. *Tetrahedron* **1999**, *55*, 13345–13368; (i) Costenaro, E. R.; Fontoura, L. A. M.; Oliveira, D. F.; Correia, C. R. D. *Tetrahedron Lett.* **2001**, *42*, 1599–1602; (j) Varaprasad, C. V. N. S.; Ramasamy, K. S.; Hong, Z. *J. Heterocycl. Chem.* **2006**, *43*, 325–336.
6. Wang, J.; Froeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; de Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 736–745.
7. Mathé, C.; Périgaud, C. *Eur. J. Org. Chem.* **2008**, 1489–1505 and references cited therein.
8. Alibés, R.; Alvarez-Larena, A.; de March, P.; Figueredo, M.; Font, J.; Parella, T.; Rustullet, A. *Org. Lett.* **2006**, *8*, 491–494.
9. (a) Drew, M. G. B.; Harrison, R. J.; Mann, J.; Tench, A. J.; Young, R. J. *Tetrahedron* **1999**, *55*, 1163–1172; (b) Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353–6359.
10. Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167–4176.
11. (a) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Parella, T. *Org. Lett.* **2004**, *6*, 1449–1452; (b) Racamonde, M.; Alibés, R.; Figueredo, M.; Font, J.; de March, P. *J. Org. Chem.* **2008**, *73*, 5944–5952.
12. Rustullet, A.; Alibés, R.; de March, P.; Figueredo, M.; Font, J. *Org. Lett.* **2007**, *9*, 2827–2830.
13. (a) Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306–307; (b) Crimmins, M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 123–150 and references cited therein.
14. Tsujishima, H.; Nakatani, K.; Shimamoto, K.; Shigeri, Y.; Yumoto, N.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 1193–1196.
15. (a) Hoffmann, N.; Buschmann, H.; Raabe, G.; Scharf, H.-D. *Tetrahedron* **1994**, *50*, 11167–11186; (b) Curtius, F. W.; Scharf, H.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 2957–2961.
16. (a) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267–1278; (b) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Fu, X.; Racamonde, M.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 1283–1289.
17. For an extensive review of this reaction, see: Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*; John Wiley & Sons: New York, NY, 2001.
18. Ochoa, C.; Provencio, R.; Jimeno, M. L.; Balzarini, J.; De Clerq, E. *Nucleosides Nucleotides* **1998**, *17*, 901–910.
19. Similar BSA/thymine ratio has been succesfull used in the synthesis of a serie of 3′-deoxy-3′-difluoromethyl azanucleosides, see: Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2005**, *70*, 3826–3837.
20. The nucleoside numbering system is utilized to compare the structure of 3-azabicyclo[3.2.0]heptane with regular nucleosides. The systematic numbering for these compounds is used in the Experimental information.