Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5231–5240

TETRAHEDRON

Stereoselective synthesis of new bicyclic *N,O-iso*-homonucleoside analogues

Barbara Richichi,[a,†] Stefano Cicchi,[a] Ugo Chiacchio,[c] Giovanni Romeo[b,*] and Alberto Brandi[a,*]

[a]*Dipartimento di Chimica Organica 'Ugo Schiff', Universita' di Firenze, Polo Scientifico, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Firenze, Italy*
[b]*Dipartimento Farmaco-Chimico, Universita' di Messina, Viale Annunziata, Messina I-98100, Italy*
[c]*Dipartimento di Scienze Chimiche, Universita' di Catania, Viale A. Doria 6, Catania I-95125, Italy*

Received 3 March 2003; revised 23 April 2003; accepted 16 May 2003

Abstract—The synthesis of two new bicyclic nucleoside analogues is reported. These compounds are *iso*-homonucleoside and are synthesised through a 1,3-dipolar cycloaddition of an enantiopure cyclic nitrone to protected allyl acohol and subsequent introduction of thymine by a Mitsunobu reaction.

Nucleoside analogues display a wide range of biological activities and have attracted particular attention as anticancer and antiviral agents.[1] Accordingly, the synthesis of new modified nucleosides represents an important and increasing area of interest for organic chemists in the search for compounds with improved biological properties. Since hydrogen bond interactions of heterocyclic bases are fundamental for the biological activity of nucleoside analogues, any variation of the base moiety should preserve such intramolecular forces.[2] As a consequence, only minor variations of bases are found in biologically active nucleoside analogues.[3] The most notable modification is found in *C*-nucleosides, in which the typical C–N glycosidic bond has been replaced by a non-hydrolizable C–C bond.[4] On the contrary extensive modifications have been made to the sugar moiety,[5] which has been substituted by acyclic,[6] heterocyclic[2] and carbocyclic moieties.[7]

The biological activity of nucleoside analogues is often modulated by the nature and the spatial disposition of specific functional groups on the sugar moiety.[8] Such functional groups exert a profound effect on the conformation and puckering of the ribose ring,[9] or any of the several different carbocyclic or heterocyclic rings present in the analogues, and are able to control the outcome of the reactions between these prodrugs and the specific enzymes. The correlation between the conformational preference demanded by the enzyme and a particular sugar conformation proves troublesome due to the flexibility of the furan ring. Such flexibility is responsible for significant differences between the conformation in solid state and in solution.[10] For this reason, conformationally locked nucleoside analogues were synthesised with the double aim to develop more efficient antiviral drugs and to obtain a deeper insight into the interaction between the substrate and the enzyme.

Some authors have proposed examples of bicyclic nucleoside analogues characterised by a restricted conformational freedom: typical examples are the 2′,3′-dideoxy-2′3′-α-methylenecytidine **1**[11] and bicarbocyclic nucleoside **2**.[12]

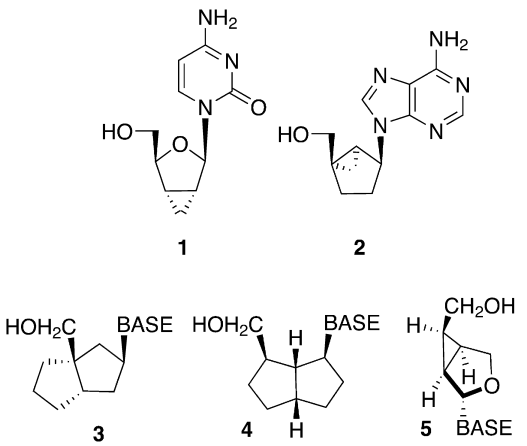


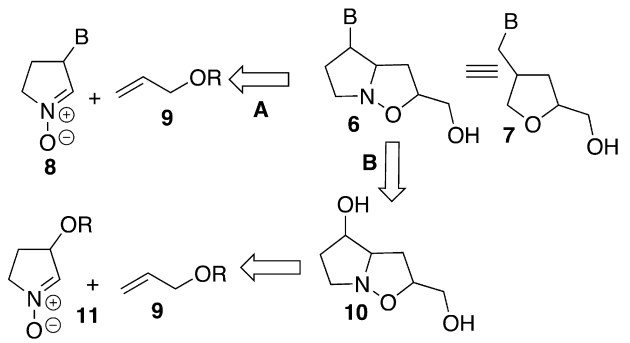
Chart 1.

Keywords: nucleoside analogues; 1,3-dipolar cycloaddition; Mitsunobu reaction.

* Corresponding authors. Tel.: +390554573485; fax: +390554573531; e-mail: alberto.brandi@unifi.it

† On leave from the Università di Messina

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00772-5



Scheme 1. Two possible retrosynthetic pathways for compound **6**.

These nucleosides were recently found to have moderate to significant antiviral activity against HIV through inhibition of HIV reverse transcriptase.

These findings triggered further studies on byciclic nucleoside analogues bearing the CH_2OH group and the base on the same ring or on different rings, as compounds **3**–**5**[13,14] (Chart 1). These considerations prompted us to exploit bicyclic isoxazolidines as useful scaffolds for the synthesis of new conformationally restricted nucleoside analogues, where the sugar unit has been replaced by an isoxazolidine ring. Simple *N*,*O*-nucleosides have already been described as nucleoside analogues which are able to inhibit the reverse transcriptase.[15]

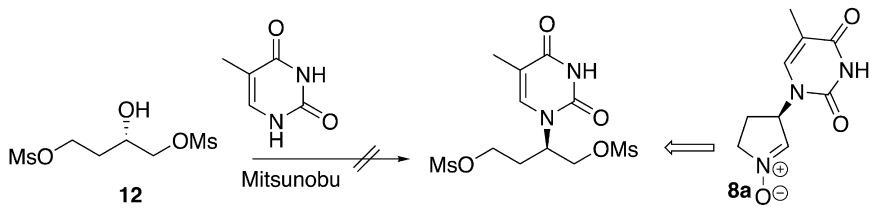
In this paper we have turned our attention to the design of a synthetic approach to bicyclic nucleosides **6** (Scheme 1), which can be regarded as *N*,*O*-*iso*-homonucleosides, strictly correlated to *iso*-homonucleosides with general structure **7**, where the isoxazolidine ring mimics the sugar moiety and the nucleobase is linked to the 3′ position[16] through a carbon bridge.[17] The presence of the second five membered ring fused to the isoxazolidine moiety induces a restricted conformational mobility which might result in a more reliable structure-reactivity relationship.

The 1,3-dipolar cycloaddition reaction of nitrones is a powerful tool for the synthesis of isoxazolidines[18] and, under certain conditions, allows a strict control on the several stereocenters formed in the reaction. These characteristics make this approach particularly useful for the synthesis of a class of substrates where a proper relative disposition of substituents is a primary requisite. Recent results using enantiopure five membered cyclic nitrones demonstrate their versatility in the control of the configuration of the different stereogenic centers produced in the 1,3-dipolar cycloaddition.[19] In this paper we report our first results on the stereoselective synthesis of bicyclic *N*,*O*-*iso*-homonucleosides bearing a thymine group with the aim of demonstrating the feasibility of the approach.

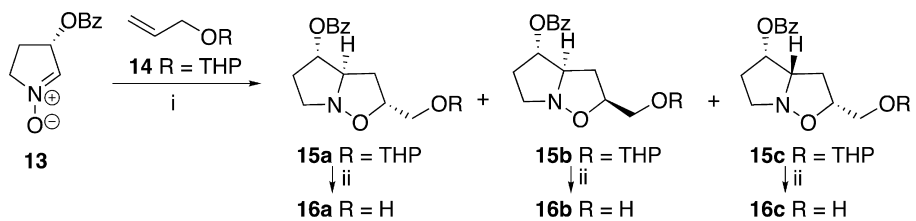
The first and more direct approach was the one depicted by the retrosynthetic arrow A (Scheme 1) in which a properly substituted nitrone, **8**, undergoes a 1,3-dipolar cycloaddition with allylic alcohol **9**. A known procedure[20] was modified in order to insert a pyrimidine base, namely thymine, in the precursor, dimesylate **12**, of the desired nitrone **8a**. However, several unsuccessful experiment according to the Mitsunobu[21] reaction between **12** and the nucleobase, performed under different conditions, showed that this procedure was not practicable (Scheme 2).

Thus, we turned our attention onto the retrosynthetic pathway B (Scheme 1) which proceeds through the insertion of the nucleobase directly onto the cycloadduct **10** derived from the cycloaddition of nitrone **11** to allylic alcohol **9** (R=H).

The cycloaddition reaction of nitrone **13**[22] with allylic alcohol, protected as tetrahydropyranyl ether, **14**[23] proceeded smoothly and quantitatively afforded three different diastereomers **15a**–**c** in the relative ratio 5:1.7:1, respectively (Scheme 3). Structural assignments to all the adducts isolated have been demonstrated, after deprotection (Scheme 3) of the primary hydroxyl function, on the basis of a n.O.e. analysis, as shown in Figure 1, as well as by comparison with previous reported results.[22,24] Compound **16a** was assigned as derived from an *exo*–*anti* approach of the dipolarophile to the nitrone, while **16c** was assigned as deriving from an *endo*–*syn* approach, on the basis of a



Scheme 2.



Scheme 3. (i) Refluxing toluene, 8 h, quantitative; (ii) Amberlyst 15, MeOH, 70% **16a**, 90% **16b**, 84% **16c**.

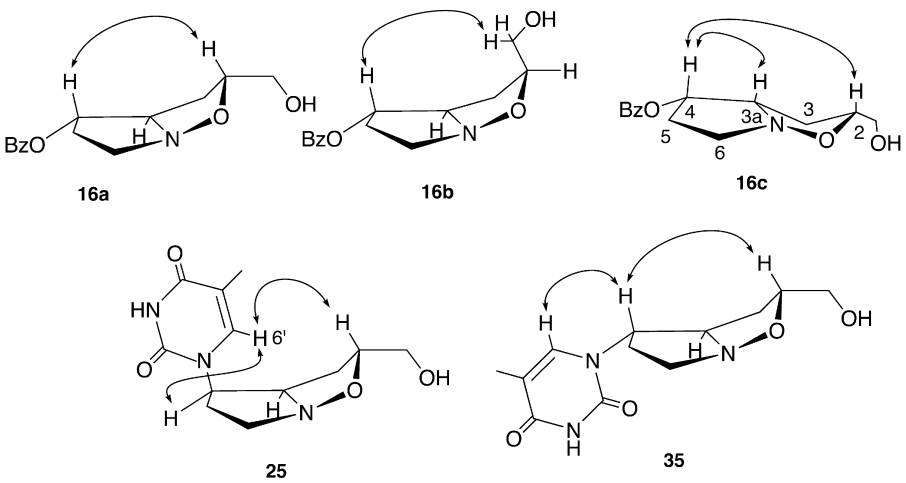
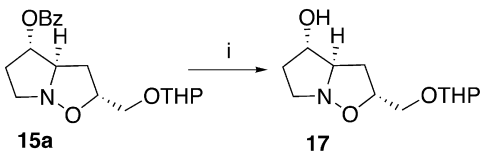


Figure 1. n.O.e. for compounds **16a–c**, **25** and **35**.



Scheme 4. (i) NaOH, MeOH, 1 h, 93% yield.

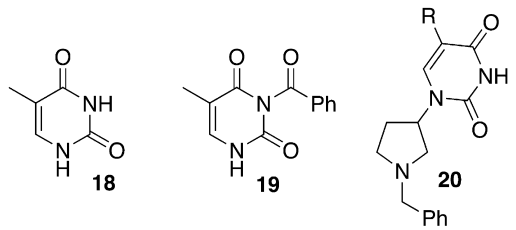
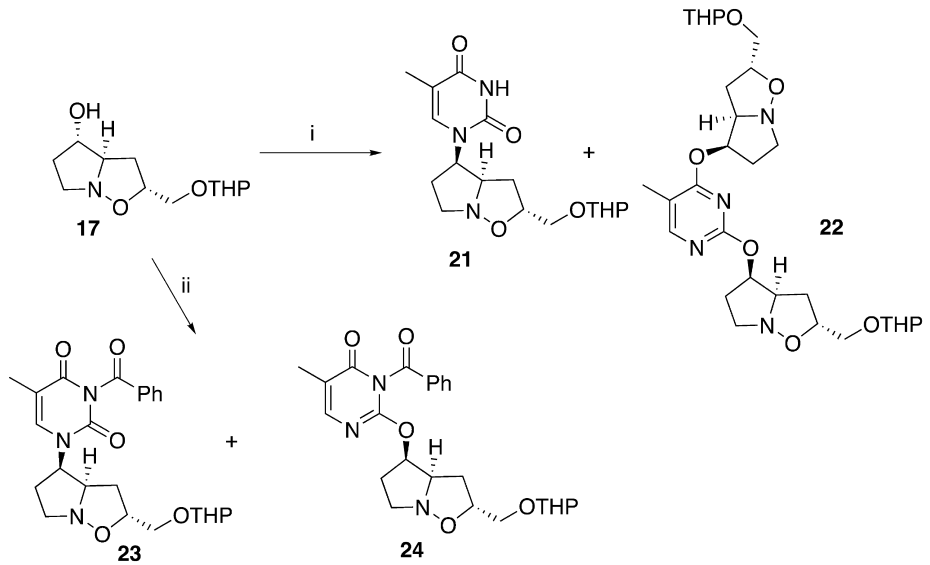


Chart 2.

n.O.e. between H4 and H2 which lacks in **16b** (*endo–anti*) (Fig. 1).

Deprotection of the secondary hydroxyl function in the major product **15a** led to isoxazolidine **17**, which is the synthetic precursor of nucleoside analogues (Scheme 4). On the basis of our previous experience in the synthesis of thymine and uracil substituted pyrrolidine **20**,[25] we decided to carry out the nucleosidation reaction under Mitsunobu condition. A comparison of thymine **18** and its N^3-protected derivative **19** as nucleophile in the reaction was also examined (Chart 2).[26] In the synthesis of compounds **20**, the free base **18** revealed more efficient than **19**, avoiding the formation of *O*-alkylated byproducts, which often are produced in the reactions of **19** (Scheme 5).[27] The use of **19** afforded a mixture of compounds **23** and **24**, with the *O*-alkylated derivative **24** as the major component. The temperature proved to be a crucial parameter, since decrease of the reaction temperature from 110 to 80°C resulted in an increase of the relative ratio of **23/24** from 1:2.3 to 1:1.9 (Table 1, entries 1 and 2). The best results were obtained

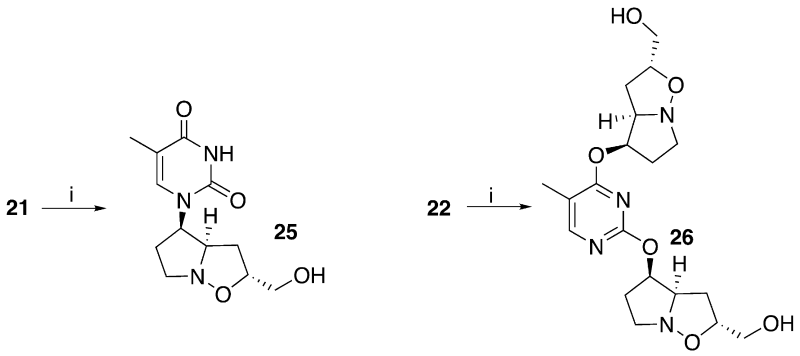


Scheme 5. (i) **18**, PPh_3, DEAD, dioxane; (ii) **19**, PPh_3, DEAD, dioxane.

Table 1.

Entry	Reagents	21/22	23/24	Yield (%)
1	**19**/P(Ph)$_3$/DEAD 4 h, 110°C, 4 h		1:2.3	22 (**23**)
2	**19**/P(Ph)$_3$/DEAD 4 h, 80°C, 4 h		1:1.9	20 (**23**)
3	**18**/P(Ph)$_3$/DEAD 4 h, 110°C, 4 h	1: 1.1		21 (**21**)
4	**18**/P(Ph)$_3$/DEAD 4 h, 50°C, 4 h	2.3:1		42 (**21**)
5	**18**/P(Ph)$_3$/DEAD 4 h, 40°C, 4 h	3.3:1		42 (**21**)

The reactivity of reagents **18** and **19** were strikingly different. Protected thymine **19** afforded mainly *O*-alkylated products while thymine (**18**), even at high temperature, afforded a better ratio of the *N*-alkylated derivative **21**, which became the major product at lower temperature. While in the reaction with simple hydroxypyrrolidine no *O*-alkylated derivatives where detected, in this case *O*-alkylation is a side reaction and, apparently, the first

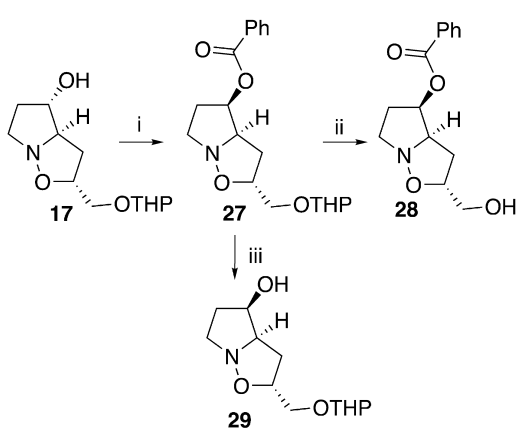


Scheme 6. (i) MeOH, Amberlyst 15, yield 90% (**25**), yield 52% (**26**).

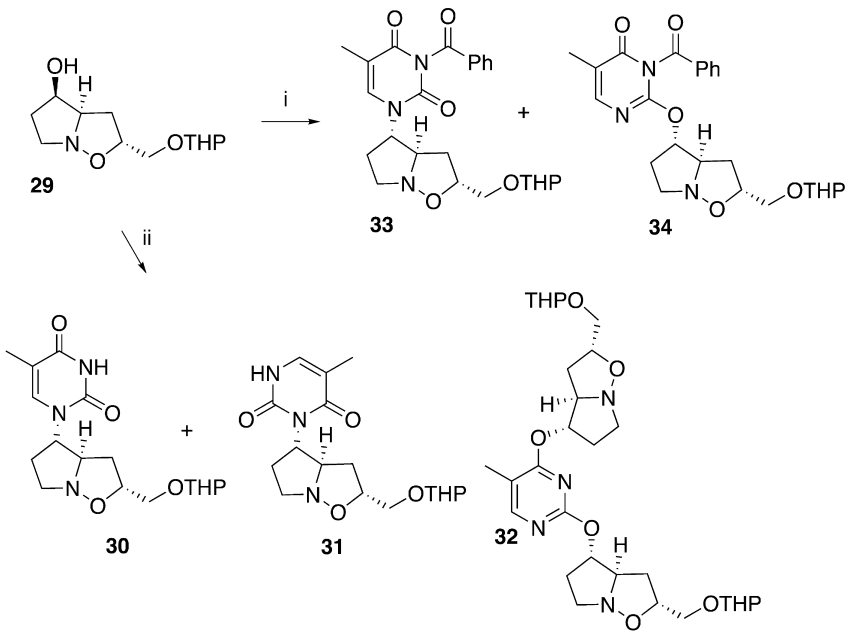
using the free base, **18**, which afforded, at 110°C, a mixture of compounds **21** and **22** in a 1:1 ratio, optimizable at a 3.3:1 ratio by performing the reaction at 40°C (entry 5). Compounds **21**–**24** were separated by chromatography and their structure confirmed by comparison of both ^{1}H and ^{13}C NMR data with literature precedents.[25] The O^2,O^4 dialkylated derivative **22** was identified on the basis of the chemical shift[27a] of the H-4′ and H-4″ signals of **22** (δ 5.60, 5.37, respectively) which were appreciably shifted downfield with respect to H-4 of **21** (δ 5.28 ppm) and H-3 of **20a** and **b** (5.11, 5.18 ppm, respectively).[25] Furthermore, the chemical shifts of C-4′ and C-4″ in **22** (δ 76.1, 2C) were also shifted downfield with respect to C-4 of **21** (δ 57.6 ppm) and C-3 of **20a** and **b** (53.5, 53.1 ppm, respectively).[25] The same analysis was applied to compound **24** (H-4 δ 5.43 ppm, C-4 δ 84.0 ppm). All compounds were mixtures of epimers at the tetrahydropyranyl stereocenter. Compounds **21** and **22** were deprotected to afford the desired final compound **25** and the bis-*O*-alkylated derivative **26** (Scheme 6). Their structures were confirmed on the basis of n.O.e. measurements.

For compound **25** the NOESY spectrum evidenced the presence of a n.O.e. effect between H-6 of thymine ring (resonating at 7.24 ppm) and H-4 of the bicyclic moiety (Fig. 1). The n.O.e. between the H-6-thymine and H-2 confirmed the inversion of configuration at C-4 during the Mitsunobu reaction, supported also by the large coupling constant between H-3a and H-4 (8.1 Hz). The presence of these n.O.e. effects confirms also the assignment of the regiochemistry, as observed in similar systems.[27b] The deprotection of compounds **22** afforded compound **26** whose complex spectrum did not allowed a complete n.O.e. analysis, but showed a correlation between the H-6 of the thymine ring and the H-3 and H-5 of both the isoxazolidinyl rings. The absence of any correlation between H-6 of the thymine and H-4 of the isoxazolidines ring, confirmed, with the lowfield chemical shift in the ^{13}C NMR spectrum, the bis-*O*-alkylation (76.8 and 76.2 ppm). *O*-alkylated derivative is reactive enough to react with another molecule of isoxazolidine to afford compound **22**. No traces of N^3-alkylated product could be detected in the crude reaction mixture.

Compound **17** was also the starting material for the synthesis of another potential antiviral agent epimeric at the carbon atom bearing the thymine ring. A Mitsunobu reaction with benzoic acid afforded, in good yield, benzoate **27** with inversion of configuration at C-4 (Scheme 7). The inversion of configuration was demonstrated by a comparison of **28**, obtained by deprotection of the primary hydroxyl function of **27**, with **16a**. The n.O.e. present in **16a** between H-4 and H-2 is now absent (compare with Figure 1) and in the ^{1}H NMR spectrum the proton H-3a (3.90 ppm) showed two *cis* coupling constant (J=7.6, 7.0 Hz) and one *trans* (J=1.6 Hz) in agreement with the *cis* relationship between H-4 and H-3a. The hydrolysis of the ester group afforded **29** which was the substrate for a new Mitsunobu reaction with thymine Scheme 8). The reaction of thymine, under the



Scheme 7. (i) Benzoic acid, DEAD, P(Ph)$_3$, 87% yield; (ii) MeOH, Amberlyst 15, 89% yield; (iii) MeOH, NaOH, 83%.



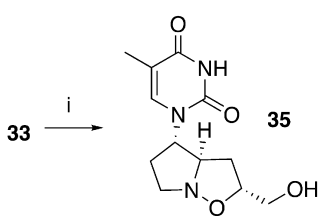
Scheme 8. (i) **19**, PPh_3, DEAD; (ii) **18**, PPh_3, DEAD.

same conditions used for **17**, afforded an inseparable mixture of three compounds in a 1.6:1:1.5 ratio which were tentatively assigned structures **30**–**32**, respectively. The formation of compound **31**, where the pyrimidine proton resonates at lower field respect to N^1-alkylated derivatives (0.2 ppm) and did not show any n.O.e. with H-4, was unprecedented in this kind of reactions and make the use of free thymine synthetically unsuitable.

This time the use of N^3-benzoylated thymine **19** proved feasible even at 40°C affording derivatives **33** and **34** in 1.2:1 ratio, respectively. Derivative **33** was isolated from the reaction mixture in 42% yield.

Finally compound **33**, after purification, was deprotected to afford the desired compound **35**, whose n.O.e. data (Fig. 1) confirmed the expected structure (Scheme 9). Thus, the presence of a correlation between H-4 and H-2 of the bicyclic system and between thymine-H-6 with H-4, together with the absence of a correlation between thymine-H-6-and H-2, demonstrated the inversion of configuration at C4.

Two new different nucleoside analogues, **25** and **35** can be synthesised through this 1,3-dipolar cycloaddition-Mitsunobu reaction approach.



Scheme 9. (i) MeOH, Amberlyst 15, 2 h, 50°C; (ii) $MeOH/NH_3$ 4:1, 2 h, room temperature 56%.

Although it appears necessary to tune the reaction conditions to obtain satisfactory yields of compounds **25** and **35**, the general strategy was feasible and straightforward for the preparation of a new class of bicyclic nucleosides analogues. The use of protected thymine **19** and thymine (**18**) was complementary allowing a synthetically useful yield of the desired product. This result, together with the use of other dipolarophiles, will afford access to other nucleoside analogues with a different spatial arrangement of the pharmacophores, allowing a tailored synthesis for new potential antiviral and anticancer drugs.

1. Experimental

1.1. General

All reaction were carried out under nitrogen. R_f values refer to TLC carried out on 0.25 mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography separation. Microanalyses were carried out with a Perkin–Elmer 240 analyzer. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, with a Varian Gemini, 400 and 100 MHz, respectively, with a Bruker UXNMR; the chemical shifts for ^1H and ^{13}C NMR spectra are given in ppm from TMS. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer. Optical rotation measurements were carried out with a Jasco DIP-370 polarimeter. Nitrone **13** was synthesised according to Ref. 22.

1.2. Cycloaddition of nitrone 13 to 2-allyloxy-tetrahydropyran (14)

A solution of **14** (16.7 mmol, 2.08 g) and nitrone **13** (6.8 mmol, 1.4 g) in toluene (3 mL) was stirred under reflux for 8 h. The solution was then concentrated and the crude mixture purified by flash column chromatography to afford

cycloadducts **15a–c** in a 5:1.7:1 ratio calculated by ^{1}H NMR signals integration in the crude mixture.

1.2.1. (2*R*,3a*R*,4*S*)-Benzoic acid 2-(tetrahydro-pyran-2′-yloxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (15a). Colorless oil, 1.54 g, 65% yield; R_f (pet. ether/AcOEt 2:3)=0.54; ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J*=7.4 Hz), 7.56 (m, 1H), 7.43 (m, 2H), 5.22 (m, 1H, 4-*H*), 4.63 (s, 1H, *THP*), 4.34 (m, 1H, 2-*H*), 3.92–3.84 (m, 1H, 3a-*H*), 3.85–3.38 (m, 2H, CH_2OTHP), 3.73–3.52 (m, 2H, *THP*), 3.40–3.30 (m, 2H, 6-*H*), 2.60–2.30 (m, 3H, 3-5-*H*), 2.00 (dddd, 1H, *J*=9.8, 9.4, 3.2, 2.8 Hz, 5-*H*), 1.86–1.5 (m, 6H, *THP*); ^{13}C NMR ($CDCl_3$): δ 163.1 (s, 1C, C=O), 133.0 (d, 1C), 129.7 (s, 1C), 128.4 (d, 2C), 128.3 (d, 2C), 99.0–98.8 (d, 1C, *THP*), 81.2–80.9 (d, 1C, 4-*C*), 76.7–76.3 (d, 1C, 2-*C*), 71.9 (d, 1C, 3a-*C*), 68.7–68.0 (t, 1C, *C*H_2OTHP), 62.2–62.0 (t, 1C, *THP*), 55.5–55.4 (t, 1C, 6-*C*), 37.4–37.2 (t, 1C, 3-*C*), 30.9 (t, 1C, 5-*C*), 30.4 (t, 1C, *THP*), 25.3 (t, 1C, *THP*), 19.4 (t, 1C, *THP*); IR ($CDCl_3$): ν 2946, 2872, 1713, 1201, 1177 cm^{-1}; MS (*m*/*z*): [M+1] 348, 264, 247, 225, 158, 142. Anal. calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found C, 65.81; H, 7.36; N, 4.25.

1.2.2. (2*S*,3a*R*,4*S*)-Benzoic acid 2-(tetrahydro-pyran-2′-yloxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (15b). Colorless oil, 521 mg, 22% yield; R_f (AcOEt)=0.62; ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 2H, *J*=7.4 Hz), 7.54 (m, 1H), 7.40 (m, 2H), 5.20 (t, 1H, *J*=6.0 Hz, 4-*H*), 4.66 (s, 1H, *THP*), 4.16 (m, 1H, 2-*H*), 3.93–3.75 (m, 3H, 3a-*H*, CH_2OTHP), 3.66–3.36 (m, 3H, 6-*H*+*THP*), 3.25 (ddd, *J*=13.1, 12.0, 5.7 Hz, 1H, 6-*H*), 2.75–2.43 (m, 2H, 3-5-*H*), 2.20 (m, 1H, 5-*H*), 1.93 (dd, 1H, *J*=13.8, 5.6 Hz, 3-*H*), 1.82–1.50 (m, 6H, *THP*); ^{13}C NMR ($CDCl_3$): δ 166.2 (s, 1C, *C*=O), 133.0 (d, 1C), 129.6 (s, 1C), 129.4 (d, 2C), 128.3 (d, 2C), 98.6 (d, 1C, *THP*), 82.4 (d, 1C, 4-*C*), 76.6 (d, 1C, 2-*C*), 73.2 (d, 1C, 3a-*C*), 66.3 (t, 1C, *C*H_2OTHP), 62.0 (t, 1C, *THP*), 55.2 (t, 1C, 6-*C*), 37.1 (t, 1C, 3-*C*), 30.4 (2C, 5-*C*+*THP*), 25.3 (t, 1C, *THP*), 19.2 (t, 1C, *THP*); IR ($CDCl_3$): ν 2944, 2872, 1713 cm^{-1}; MS (*m*/*z*): 347, 263, 247, 225, 140, 111. Anal. calcd for $C_{19}H_{25}NO_5$: C 65.69, H 7.25, N 4.03. Found C 65.67, H 7.57, N 4.21.

1.2.3. (2*S*,3a*S*,4*S*)-Benzoic acid 2-(tetrahydro-pyran-2′-yloxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (15c). Colorless oil, 308 mg, 13% yield; R_f (AcOEt/MeOH 3:1)=0.62; ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J*=7.0 Hz), 7.62 (m, 1H), 7.43 (m, 2H), 5.47 (q, 1H, *J*=5.8 Hz, 4-*H*), 4.60 (s, 1H, *THP*), 4.38 (m, 1H, 2-*H*), 3.97–3.90 (m, 1H, 3a-*H*), 3.85–3.40 (m, 2H, *CH*$_2$OTHP), 3.74–3.50 (m, 2H, *THP*), 3.43–3.33 (m, 1H, 6-*H*), 3.24–3.15 (m, 1H, 6-*H*), 2.42–1.98 (m, 4H, 3-5-*H*), 1.80–1.50 (m, 6H, *THP*); ^{13}C NMR ($CDCl_3$): δ 165.6 (s, 1C, *C*=O), 133.4 (d, 1C), 129.6 (s, 1C), 129.3 (d, 2C), 128.3 (d, 2C), 99.1–98.6 (d, 1C, *THP*), 76.6 (d, 1C, 4-*C*), 74.8–74.7 (d, 1C, 2-*C*), 69.1 (d, 1C, 3a-*C*), 68.1–67.6 (t, 1C, *CH*$_2$OTHP), 62.3–61.9 (t, 1C, *THP*), 53.3 (t, 1C, 6-*C*), 33.1–33.0 (t, 1C, 3-*C*), 31.5–31.4 (t, 1C, 5-*C*), 30.4–30.3 (t, 1C, *THP*), 25.3 (t, 1C, *THP*), 19.5–19.2 (t, 1C, *THP*); IR ($CDCl_3$): ν 2944, 2872, 1715 cm^{-1}; MS (*m*/*z*): 347, 262, 247, 232, 207, 140, 124. Anal. calcd for $C_{19}H_{25}NO_5$C, 65.69; H, 7.25; N, 4.03. Found C, 65.72; H, 7.40; N, 4.29.

1.2.4. (2*R*,3a*R*,4*S*)-2-(Tetrahydro-pyran-2′-yloxymethyl)-hexahydro-pyrrolo[1,2]isoxazol-4-ol (17). To a solution of NaOH (343 mg, 8.58 mmol) in MeOH (10 mL) was added a solution of **15a** (426 mg, 1.22 mmol) in MeOH (3 mL). The mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in water (10 mL) and the solution was extracted with CH_2Cl_2 (2×20 mL). The organic phase was dried with Na_2SO_4 and concentrated to give 279 mg (93% yield) of compound **17** as a colorless oil.

R_f (CH_2Cl_2/MeOH 9:1)=0.61; ^{1}H NMR ($CDCl_3$): δ 4.60 (m, 1H, *THP*), 4.26–4.16 (m, 1H, 2-*H*), 4.1 (m, 1H, 4-*H*), 3.85 (m, 1H, 3a-*H*), 3.75–3.63 (m, 2H, *CH*$_2$OTHP), 3.57–3.30 (m, 4H, 6-*H*, *THP*, O*H*), 3.23–3.12 (m, 1H, 6-*H*), 2.36–2.01 (m, 3H, 3-5*H*), 1.80–1.46 (m, 7H, 5*H*, *THP*); ^{13}C NMR ($CDCl_3$): δ 99.1–98.9 (d, 1C, *THP*), 77.4–77.2 (d, 1C, 2-*C*), 76.4–76.1 (d, 1C, 4-*C*), 73.28–73.21 (d, 1C, 3a-*C*), 68.6–68.0 (t, 1C, *CH*$_2$OTHP), 62.29–62.18 (t, 1C, *THP*), 55.16 (t, 1C, 6-*C*), 37.1–36.9 (t, 1C, 3-*C*), 33.6 (t, 1C, 5-*C*), 30.4 (t, 1C, *THP*), 25.3 (t, 1C, *THP*), 19.4 (t, 1C, *THP*); IR ($CDCl_3$) ν 3607, 2945, 2866, 1118 cm^{-1}; MS (*m*/*z*): 243, 225, 158, 143, 129, 122. Anal. calcd for $C_{12}H_{21}NO_4$ C, 59.24; N, 5.76; H, 8.70. Found C, 58.96; N, 5.59; H 9.02.

1.3. Mitsunobu reaction of 17 with 18

DEAD (537 mg, 3.1 mmol) was added over 2 h to a suspension of PPh_3 (808 mg, 3.1 mmol), **18** (153 mg, 1.21 mmol), and **17** (250 mg, 1.03 mmol) in dry dioxane (4 mL) at 40°C. After stirring for 2 h at 40°C the solvent was removed under reduced pressure. The yellow residue was purified by flash chromatography on silica gel to afford **21** (150 mg, 0.43 mmol) and **22** (120 mg, 0.21 mmol).

1.3.1. 5-Methyl-1-[(2*R*,3a*R*,4*R*) 2-(tetrahydro-pyran-2-yloxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl]-1*H*-pyrimidine-2,4-dione (21). Pale yellow oil, R_f (CH_2Cl_2/MeOH 95:5)=0.51; ^{1}H NMR ($CDCl_3$): δ 7.20 (s, 1H, C*H-Thymine*), 5.28 (m, 1H, 4-*H*), 4.63 (m, 1H, *THP*), 4.20–4.10 (m, 2H, 2-3a-*H*), 3.94–3.44 (m, 4H, *THP*, CH_2OTHP), 3.30 (dd, 1H, *J*=10.3, 5.1 Hz, 6-*H*), 3.10 (m, 1H, 6-*H*), 2.33–2.18 (m, 3H, 3-5*H*), 1.95 (s, 3H, *CH*$_3$-*Thymine*), 1.92–1.53 (m, 7H, 5*H*, *THP*); ^{13}C NMR ($CDCl_3$): δ 163.5 (s, 1C, *C*=O), 151.0 (s, 1C, *C*=O), 137.2 (d, 1C, *C*H-*Thymine*), 111.2 (s, 1C, *C-Thymine*), 99.5–99.1 (t, 1C, *THP*), 76.8–76.4 (d, 1C, 2-*C*), 69.2–69.0 (t, 1C, *C*H_2OTHP), 68.0 (d, 1C, 3a-*C*), 62.6–62.5 (t, 1C, *THP*), 57.6–57.5 (d, 1C, 4-*C*), 52.9 (t, 1C, 6-*C*), 33.6–33.4 (t, 1C, 3-*C*), 30.5 (t, 1C, 5-*C*), 29.5–29.3 (t, 1C, *THP*), 25.4 (t, 1C, *THP*), 19.6–19.5 (t, 1C, *THP*), 12.6 (q, 1C, *C*H$_3$-*Thymine*); IR ($CDCl_3$): ν 3392, 2941, 1268, 2862, 1686, 1467 cm^{-1}; MS (*m*/*z*): 351, 236, 225, 142, 126, 111. Anal. calcd for $C_{17}H_{25}N_3O_5$: C, 58.11; N, 11.96; H, 7.17. Found C, 58.13; N, 11.95; H, 6.89.

1.3.2. 5-Methyl-2,4-bis-[(2*R*,3a*R*,4*R*)-(2″*R*,3a″*R*,4″*R*)-2-2″-(tetrahydro-pyrany-2-yloxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4yl]-pyrimidine (22). Colorless oil, R_f (CH_2Cl_2/MeOH 95:5)=0.47; ^{1}H NMR ($CDCl_3$): δ 8.04 (s, 1H, C*H-Thymine*), 5.60 (q, 1H, *J*=6.4 Hz, 4-*H*), 5.37 (q, 1H, *J*=5.8 Hz, 4″-*H*), 4.65 (s, 2H, *THP*), 4.20 (m, 2H, 2-2″-*H*),

4.10–3.96 (m, 2H, 3a-3a″-*H*), 3.92–3.72 (m, 4H, C*H*$_2$-OTHP), 3.54–3.46 (m, 4H, *THP*), 3.42–3.04 (m, 2H, 6-6″-*H*), 3.27–3.15 (m, 2H, 6-6″-*H*), 2.45–2.24 (m, 6H), 2.10 (s, 3H, C*H*$_3$-*Thymine*), 2.05–1.97 (m, 2H), 1.94–1.50 (m, 12H, *THP*); ^{13}C NMR ($CDCl_3$): δ 168.3 (s, 1C, *C*–O-*Thymine*), 162.9 (s, 1C, *C*–O-*Thymine*), 157.9 (d, 1C, *C*H-*Thymine*), 111.2 (s, 1C, *C-Thymine*), 99.3–98.9 (d, 2C, *THP*), 77.2-76.7 (d, 2C, 2-2″-*C*), 76.1 (d, 2C, 4-4″-*C*), 69.1–68.8 (t, 1C, *C*H$_2$OTHP), 68.1–67.9 (t, 1C, *C*H$_2$OTHP), 67.6- 67.3 (d, 2C, 3a-3a″-*C*), 62.1 (t, 2C, *THP*), 53.2–53.1 (t, 2C, 6-6″-*C*), 33.3–33.1 (t, 1C, 3-*C*), 32.9–32.5 (t, 1C, 3″-*C*), 31.7 (t, 2C, 5-5″-*C*), 30.4 (t, 2C, *THP*), 25.3 (t, 2C, *THP*), 19.3 (t, 2C, *THP*), 11.8 (q, 1C, *C*H$_3$-*Thymine*); IR ($CDCl_3$): ν 2927, 2857, 1661, 1602, 1422 cm^{-1}; FAB-MS (*m*/*z*) calcd 576.3159. Found 577.3230 [M$^+$+1]. Anal. calcd for $C_{29}H_{44}N_4O_8$: C, 60.40; H, 7.69; N, 9.72. Found C, 60.05; H, 7.68; N, 9.94.

1.4. Mitsunobu reaction of 17 and 19

DEAD (323 mg, 1.86 mmol) was added over 2 h to a suspension of PPh_3 (487 mg, 1.86 mmol), **19** (156 mg, 0.68 mmol), and **17** (150 mg, 0.62 mmol) in dry dioxane (4 mL) at 80°C. After stirring for 2 h at 80°C the solvent was removed under reduced pressure. The yellow residue was purified by flash chromatography on silica gel (eluent petroleum ether/ethyl acetate 1:9) to give **23** (54 mg, 0.11 mmol, 20%) and **24** (102 mg, 0.22 mmol, 40%).

1.4.1. *N*^{1}-[(2*R*,3a*R*,4*R*)-2-(Tetrahydro-pyran-2-yloxy-methyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl]-*N*^{3}-(benzoyl)-thymine (23). Yellow oil, ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J*=7.6 Hz), 7.60 (m, 1H), 7.53 (m, 2H), 7.35 (s, 1H, C*H-Thymine*), 5.22 (m, 1H, 4-*H*), 4.64 (m, 1H, *THP*), 4.15 (m, 1H, 2-*H*), 3.94–3.46 (m, 5H, 3a-*H*, *THP*, *CH$_2$O*THP), 3.30 (m, 1H, 6-*H*), 3.00 (m, 1H, 6-*H*), 2.36–3.0 (m, 3H, 3-5-*H*), 1.97 (s, 3H, C*H*$_3$-*Thymine*), 1.86–1.24 (m, 7-H, 5-*H*, *THP*); ^{13}C NMR ($CDCl_3$): δ 168.2 (s, 1C, *C*=O), 158.3 (s, 1C, *C*=O), 137.2 (d, 1C, *C*H-*Thymine*), 135.4 (d, 1C), 131.1 (s, 1C), 130.3 (d, 2C), 128.5 (d, 2C), 110.2 (s, 1C, *C-Thymine*), 100.1 (t, 1C, *THP*), 76.6 (d, 1C, 2-*C*), 69.2 (t, 1C, *C*H$_2$OTHP), 67.9 (d, 1C, 3a-*C*), 62.54–62.44 (t, 1C, *THP*), 57.88–57.64 (d, 1C, 4-*C*), 52.79–52.72 (t, 1C, 6-*C*), 33.67–33.46 (t, 1C, 3-*C*), 30.4 (t, 1C, 5-*C*), 29.4 (t, 1C, *THP*), 25.3 (t, 1C, *THP*), 19.6 (t, 1C, *THP*), 12.6 (q, 1C, *C*H$_3$-*Thymine*).

1.4.2. *O*^{2}-[(2*R*,3a*R*,4*R*)-2-(Tetrahydro-pyran-2-yloxy-methyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl]-*N*^{3}-(benzoyl)-thymine (24). Yellow oil, ^{1}H NMR ($CDCl_3$): δ 8.42 (s, 1H, CH-Thymine), 7.90 (d, 2H, *J*=7.6 Hz), 7.62 (m, 1H), 7.46 (m, 2H), 5.43 (q, 1H, *J*=4.6 Hz, 4-*H*), 4.64 (s, 1H, *THP*), 4.40 (m, 1H, 2-*H*), 4.24–3.20 (m, 7H, 3a-6-*H*, *CH$_2$O*THP, *THP*), 2.39–2.00 (m, 2-H, 3-*H*), 1.99 (s, 3H, C*H*$_3$-*Thymine*), 1.80–1.30 (m, 8H, 5-*H*, *THP*); ^{13}C NMR ($CDCl_3$): δ 162.4 (s, 1C, C=O), 137.7 (d, 1C, *C*H-*Thymine*), 135.2 (d, 1C), 131.2 (s, 1C), 130.2 (d, 2C), 129.4 (d, 2C), 112.0 (s, 1C, *C-Thymine*), 98.9 (t, 1C, *THP*), 84.3 (d, 1C, 4-*C*), 76.3 (d, 1C, 2-*C*), 68.7 (t, 1C, *C*H$_2$OTHP), 67.5 (d, 1C, 3a-*C*), 62.1 (t, 1C, *THP*), 53.4 (t, 1C, 6-*C*), 32.9 (t, 1C, 3-*C*), 30.8 (t, 1C, 5-*C*), 29.5 (t, 1C, *THP*), 25.2 (t, 1C, *THP*), 19.2 (t, 1C, *THP*), 12.3 (q, 1C, *C*H$_3$-*Thymine*).

1.4.3. (2*R*,3a*R*,4*R*)-Benzoic acid 2-(tetrahydro-pyran-2′-yloxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (27). A solution of **17** (279 mg, 1.15 mmol), PPh_3 (902 mg, 3.44 mmol), and benzoic acid (168 mg, 1.37 mmol), in dry THF (6 mL), was stirred for 20 min at 0°C under N_2. DEAD (600 mg, 0.53 mL, 3.44 mmol) was added dropwise and the mixture was stirred, for 1 h at 0°C, and at room temperature for 15 h. The solvent was removed under reduced pressure. The yellow residue was purified by flash chromatography on silica gel to afford **27** (345 mg, 0.9 mmol) as colorless oil in 87% of yield; R_f (CH_2Cl_2/MeOH 95:5)=0.41; ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J*=6.8 Hz), 7.54 (m, 1H), 7.40 (m, 2H), 5.40 (q, 1H, *J*=5.8 Hz, 4-*H*), 4.60 (s, 1H, *THP*), 4.42 (m, 1H, 2-*H*), 3.80–3.10 (m, 2H, *H*CHOTHP, 3a-*H*), 3.70–3.60 (m, 1H, THP), 3.54–3.30 (m, 3H, HC*H*OTHP, *THP*, 6-*H*), 3.23–3.10 (m, 1H, 6-*H*), 2.34 (ddd, 1H, *J*=12.4, 7.0, 1.8 Hz, 5-*H*), 2.26–2.12 (m, 2H, 3-*H*), 2.10–1.90 (m, 1H, 5-*H*), 1.80–1.30 (m, 6H, *THP*); ^{13}C NMR ($CDCl_3$): δ 165.6 (s, 1C, *C*=O), 132.0 (d, 1C), 129.5 (s, 1C), 129.3 (d, 2C), 128.2 (d, 2C), 99.0–98.6 (d, 1C, *THP*), 76.9 (d, 1C, 4-*C*), 74.7 (d, 1C, 2-*C*), 69.3 (t, 1C, *C*H$_2$OTHP), 67.5 (d, 1C, 3a-*C*), 62.2–61.8 (t, 1C, *THP*), 53.0 (t, 1C, 6-*C*), 33.0–32.9 (t, 1C, 3-*C*), 31.4–31.2 (t, 1C, 5-*C*), 30.2–30.1 (t, 1C, *THP*), 25.4 (t, 1C, *THP*), 19.3–19.1 (t, 1C, *THP*); IR ($CDCl_3$): ν 3020, 2946, 2874, 1718, 1216, 1178 cm^{-1}; MS (*m*/*z*): 347, 263, 245, 225, 140. Anal. calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.26; N, 4.03. Found C, 65.67; H, 7.20; N, 3.73.

1.4.4. (2*R*,3a*R*,4*R*)-2-(Tetrahydro-pyran-2-yloxy-methyl)-hexahydro-pyrrolo[1,2]isoxazol-4-ol (29). To a solution of NaOH (230 mg, 5.75 mmol) in MeOH (7 mL) was added a solution of **27** (287 mg, 0.83 mmol) in MeOH (2 mL). The mixture was stirred for 1 h at room temperature and then the solvent was evaporated. The residue was dissolved in water and the solution was extracted by CH_2Cl_2. The organic phase was dried with Na_2SO_4 and concentrated to give 166 mg (0.68 mmol, 83% yield) of the desired compound **29** as a colorless oil.

R_f (CH_2Cl_2/MeOH 95:5)=0.33; ^{1}H NMR ($CDCl_3$): δ 4.60 (m, 1H, *THP*), 4.34–4.21 (m, 2H, 2-4-*H*), 3.88–3.80 (m, 1H, 3a-*H*), 3.82–3.42 (m, 4H, C*H$_2$*OTHP, *THP*), 3.32–3.08 (m, 3H, 6-*H*, O*H*), 2.54 (m, 1H, 5-*H*), 2.05–1.73 (m, 3H, 3-*H*, 5-*H*), 1.68–1.48 (m, 6H, *THP*); ^{13}C NMR ($CDCl_3$): δ 98.9–98.6 (d, 1C, *THP*), 77.1–76.7 (d, 1C, 4-*C*), 72.1–71.8 (d, 1C, 2-*C*), 68.9 (d, 1C, 3a-*C*), 68.7 (t, 1C, *C*H$_2$OTHP), 62.1–62.0 (t, 1C, *THP*), 53.0 (t, 1C, 6-*C*), 34.3–34.2 (t, 1C, 3-*C*), 32.2 (t, 1C, 5-*C*), 30.3 (t, 1C, *THP*), 25.3 (t, 1C, *THP*), 19.3 (t, 1C, *THP*); IR ($CDCl_3$): ν 3619, 2945, 1216 cm^{-1}; MS (*m*/*z*): 243, 158, 140, 129. Anal. calcd for $C_{12}H_{21}NO_4$: C, 59.24; N, 5.76; H, 8.70. Found C, 59.28; N, 5.56; H, 8.77.

1.5. Mitsunobu reaction of 29 and 19

DEAD (324 mg, 0.29 mL, 1.86 mmol) was added over 1 h to a suspension of PPh_3 (488 mg, 1.86 mmol), **19** (171 mg, 0.74 mmol), and **29** (151 mg, 0.62 mmol) in dry dioxane (5 mL) at 40°C. After stirring for 3 h at 40°C the solvent was removed under reduced pressure. ^{1}H NMR spectrum revealed the presence of compounds **33** and **34** in a 1.2:1 ratio. The yellow residue was purified by flash

chromatography on silica gel to give **33** (130 mg, 0.28 mmol) and **34** (55 mg, 0.156 mmol).

1.5.1. 3-Benzoyl-5-methyl-1-[(2*R*,3a*R*,4*S*)-2-(tetrahydropyran-2-yloxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl]-1*H*-pyrimidin-2,4-dione (33). Yellow oil, yield: 46%; R_f (AcOEt)=0.36; ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 2H, *J*=7.4 Hz), 7.65 (m, 1H), 7.5 (m, 2H), 7.36 (d, 1H, *J*=0.2 Hz, C*H-Thymine*), 5.07 (m, 1H, 4-*H*), 4.60 (m, 1H, *THP*), 4.50 (m, 1H, 2-*H*), 3.84–3.70 (m, 2H, CH_2OTHP), 3.6 (m, 1H, 3a-*H*), 3.56–3.47 (m, 3H, *THP*, 6-*H*), 3.15 (m, 1H, 6-*H*), 2.60–2.37 (m, 2H, 3-5-*H*), 2.3 (m, 2H, 3-5-*H*), 1.98 (s, 3H, CH_3-*Thymine*), 1.93–1.54 (m, 6H, *THP*); ^{13}C NMR ($CDCl_3$): δ 168.0 (s, 1C, *C*=O), 155.0 (s, 1C, *C*=O), 136.1 (d, 1C, *C*H-*Thymine*), 135.3 (d, 1C), 131.2 (s, 1C), 130.4 (d, 2C), 129.1 (d, 2C), 112.5 (s, 1C, *C-Thymine*), 99.0 (d, 1C, *THP*), 76.3 (d, 1C, 2-*C*), 69.7–69.6 (d, 1C, 3a-*C*), 68.5–67.8 (t, 1C, *C*H_2OTHP), 62.2 (t, 1C, *THP*), 58.9–58.1 (d, 1C, 4-*C*), 53.8–53.4 (t, 1C, 6-*C*), 36.6 (t, 1C, 3-*C*), 36.2 (t, 1C, 5-*C*), 30.3–30.1 (t, 1C, *THP*), 25 (t, 1C, *THP*), 19 (t, 1C, *THP*), 12.6 (q, 1C, *C*H_3-*Thymine*); IR ($CDCl_3$): ν 3020, 2942, 1729, 1700, 1659, 1250 cm^{-1}; *HRMS*: calcd 455.2056. Found 456.2131 [M^++1]; MS (*m*/*z*): 456 [M^++1], 372, 312, 232.

1.5.2. 3-Benzoyl-5-methyl-2-[(2*R*,3a*R*,4*S*)-2-(tetrahydropyran-2-yloxymethyl)-hexahydro-pyrrolo[1,2]isoxazol-4-yloxy]-3*H*-pyrimidin-4-one (34). Pale yellow oil, yield: 25%; R_f (AcOEt)=0.16; ^{1}H NMR ($CDCl_3$): δ 7.50 (s, 1H, C*H-Thymine*), 5.20 (m, 1H, 4-*H*), 4.60 (s, 1H, *THP*), 4.30 (m, 1H, 2-*H*), 3.80–3.63 (m, 3H, 3a*H*, CH_2OTHP), 3.50–3.20 (m, 4H, 6-*H*, *THP*), 2.50–2.30 (m, 4H, 3-5-*H*), 1.96 (s, 3H, CH_3-*Thymine*), 1.80–1.40 (m, 6H, *THP*); ^{13}C NMR ($CDCl_3$): δ 164.7 (s, 1C, *C*=O), 154.8 (s, 1C, *C*=O), 150.8 (d, 1C, *C*H-*Thymine*), 117.7 (s, 1C, *C-Thymine*), 99.1–98.8 (d, 1C, *THP*), 84.1–83.8 (d, 1C, 4-*C*), 76.6 (d, 1C, 2-*C*), 71.6 (d, 1C, 3a-*C*), 68.8–68.1 (t, 1C, *C*H_2OTHP), 62.3–62.1 (t, 1C, *THP*), 55.3 (t, 1C, 6-*C*), 37.4 (t, 1C, 3-*C*), 30.8–30.39 (t, 1C, 5-*C*), 29.6 (t, 1C, *THP*), 25.3 (t, 1C, *THP*), 19.45–19.36 (t, 1C, *THP*), 12.3 (q, 1C, *C*H_3-*Thymine*); IR ($CDCl_3$): ν 3686, 2942, 1728, 1676, 1272, 1250 cm^{-1}; MS (*m*/*z*): 351, 337, 311, 233, 235.

1.6. General procedure for the deprotection of THP group using Amberlyst 15

A solution of the substrate (0.3 mmol) in MeOH (3 mL), was added with Amberlyst 15 (500 mg). The suspension was stirred at 50°C for 2 h. The solution was filtered off and the resin was washed with methanol. Finally the resin was eluted with a solution of MeOH/NH_3 4:1. The solution was concentrated under reduced pressure and the crude mixture was purified by flash chromatography to afford the corresponding alcohol.

1.6.1. (2*R*,3a*R*,4*S*)-Benzoic acid 2-hydroxymethyl-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (16a). Colorless oil, yield: 70%; R_f (AcOEt)=0.39; $[\alpha]_D^{25}$=−45.9 (*c*=0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J*=7.6 Hz), 7.60 (m, 1H), 7.44 (m, 2H), 5.20 (d, 1H, *J*=7.2 Hz, 4-*H*), 4.26 (m, 1H, 2-*H*), 3.84 (m, 1H, 3a-*H*), 3.72–3.57 (m, 2H, CH_2-OH), 3.50 (ddd, 1H, *J*=14.0, 6.8, 2.0 Hz, 6-*H*), 3.33 (ddd, 1H, *J*=14.0 10.1, 6.4 Hz, 6-*H*), 3.02 (bs, 1H, O*H*), 2.60–2.53 (m, 1H, 3-*H*), 2.50–2.40 (m, 1H, 5-*H*), 2.46 (dd, 1H, *J*=7.2, 2.8 Hz, 3-*H*), 2.00 (ddd, 1H, *J*=12.0, 5.6, 2.0 Hz, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 166.1 (s, 1C, *C*=O), 133.1 (d, 1C), 129.7 (s, 1C), 129.5 (d, 2C), 128.3 (d, 2C), 81.5 (d, 1C, 4-*C*), 77.9 (d, 1C, 2-*C*), 72.7 (d, 1C, 3a-*C*), 64.6 (t, 1C, *C*H_2OH), 55.3 (t, 1C, 6-*C*), 36.3 (t, 1C, 3-*C*), 30.8 (t, 1C, 5-*C*); MS (*m*/*z*): 263, 245, 159, 140. Anal. calcd for $C_{14}H_{17}NO_4$ C, 63.87; H, 6.51; N, 5.32. Found C, 63.72; H, 6.40; N, 5.29.

1.6.2. (2*S*,3a*R*,4*S*)-Benzoic acid 2-hydroxymethyl-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (16b). Colorless oil, yield: 90%; R_f (AcOEt)=0.31; $[\alpha]_D^{25}$=−10.2 (*c*=0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J*=7.3 Hz), 7.6 (m, 1H), 7.44 (m, 2H), 5.20 (d, 1H, *J*=6.0 Hz, 4-*H*), 4.10 (m, 1H, 2-*H*), 3.85–3.60 (m, 2H, CH_2OH), 3.83–3.80 (m, 1H, 3a-*H*), 3.50 (dd, 1H, *J*=13.6, 6.0 Hz, 6-*H*), 3.28 (ddd, 1H, *J*=13.5, 11.8, 7.0 Hz, 6-*H*), 3.00 (bs, 1H, O*H*), 2.67 (ddd, 1H, *J*=12.5, 8.8, 6.2 Hz, 3-*H*), 2.53 (m, 1H, 5-*H*), 2.12 (m, 1H, 3-*H*), 1.99 (dt, 1H, *J*=13.6, 6.0 Hz, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 166.2 (s, 1C, *C*=O), 133.1 (d, 1C), 129.8 (s, 1C), 129.6 (d, 2C), 128.3 (d, 2C), 82.2 (d, 1C, 4-*C*), 78.3 (d, 1C, 2-*C*), 73.25 (d, 1C, 3a-*C*), 62.4 (t, 1C, *C*H_2OH), 55.3 (t, 1C, 6-*C*), 36.5 (t, 1C, 3-*C*), 30.3 (t, 1C, 5-*C*); MS (*m*/*z*): 263, 246, 231, 158, 123. Anal. calcd for $C_{14}H_{17}NO_4$ C, 63.87; H, 6.51; N, 5.32. Found C, 63.94; H, 6.68; N, 5.42.

1.6.3. (2*S*,3a*S*,4*S*)-Benzoic acid 2-hydroxymethyl-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (16c). Colorless oil, yield: 84%; R_f (AcOEt) 0.16; $[\alpha]_D^{25}$=+100.0 (*c*=0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, *J*=7.5 Hz), 7.6 (m, 1H), 7.5 (m, 2H), 5.52 (q, 1H, *J*=6.8 Hz, 4-*H*), 4.33 (dddd, 1H, *J*=7.2, 6.4, 6.0, 2.8 Hz, 2-*H*), 3.93 (ddd, 1H, *J*=7.6, 6.5, 2.0 Hz, 3a-*H*), 3.72–3.60 (m, 2H, *CH*$_2$OH), 3.46 (ddd, 1H, *J*=13.2, 6.8, 6.0 Hz, 1H, 6-*H*), 3.2 (ddd, 1H, *J*=13.2, 7.2, 6.4 Hz, 6-*H*), 2.78 (bs, 1H, O*H*), 2.38 (ddd, 1H, *J*=13.2, 7.2, 2.0 Hz, 3-*H*), 2.33–2.22 (m, 3H, 3*H*, 5*H*); ^{13}C NMR ($CDCl_3$): δ 165.8 (s, 1C, *C*=O), 133.3 (s, 1C), 129.7 (d, 1C), 129.4 (d, 2C), 128.5 (d, 2C), 78.5 (d, 1C, 4-*C*), 74.9 (d, 1C, 2-*C*), 68.4 (d, 1C, 3a-*C*), 64.5 (t, 1C, *CH*$_2$*OH*), 53.3 (t, 1C, 6-*C*), 31.7 (t, 1C, 3-C), 31.6 (t, 1C, 5-*C*); MS (*m*/*z*): 263, 158, 141, 113. Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found C, 63.60; H, 6.35; N, 5.50.

1.6.4. (2*R*,3a*R*,4*R*)-1-(2-Hydroxymethyl-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl)-5-methyl-1*H*-pyrimidine-2,4-dione (25). 45 mg, pale yellow oil, yield: 90%; $[\alpha]_D^{25}$=+65.2 (*c*=0.09, $CHCl_3$); R_f (CH_2Cl_2/MeOH 95:5)=0.47; ^{1}H NMR ($CDCl_3$): δ 9.70 (bs, 1H, N*H*), 7.24 (s, 1H, C*H-Thymine*), 5.28 (q, 1H, *J*=8.1 Hz, 4-*H*), 4.04 (m, 1H, 2-*H*), 3.9 (t, 1H, *J*=8.1 Hz, 3a-*H*), 3.66–3.06 (m, 3H, 6-*H*, CH_2OH), 3.09 (ddd, 1H, *J*=14.5, 12.0, 8.1 Hz, 6-*H*,), 3.00 (bs,1H, *OH*), 2.34–2.23 (m, 3H, 3-*H*, 5-*H*), 1.96–1.9 (m, 1H, 3-*H*), 1.93 (s, 3H, CH_3-*Thymine*); ^{13}C NMR ($CDCl_3$): δ 163.6 (s, 1C, *C*=*O*), 151.7 (s, 1C, *C*=*O*), 137.1 (d, 1C, *C*H-*Thymine*), 111 (s, 1C, *C-Thymine*), 77.9 (d, 1C, 2-*C*), 68.2 (d, 1C, 3a-*C*), 65.3 (t, 1C, *CH*$_2$*OH*), 57.4 (d, 1C, 4-*C*), 52.6 (t, 1C, 6-*C*), 32 (t, 1C, 3-*C*), 29.2 (t, 1C, 5-*C*), 12.6 (q, 1C, *C*H_3-*Thymine*); IR ($CDCl_3$): ν 3691, 3556, 2926, 2857, 1704, 1686, 1600 cm^{-1}; MS-FAB (*m*/*z*): calcd 267.1219. Found 268.1202 [M^++1]. Anal. calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found C, 54.15; H, 6.07; N, 15.62.

1.6.5. 5-Methyl-2,4-bis-[(2*R*,3a*R*,4*R*)-(2*R*′,3a*R*′,4′*R*)-2-2′-(hydroxymethyl)-hexahydro-pyrrolo[1,2-*b*]isoxazol-4yl]-pyrimidine (26). Pale yellow oil, 18 mg, yield: 52%; $[\alpha]_D^{25}=-15.9$ (c=0.36, $CHCl_3$); R_f (AcOEt/MeOH 1:1)=0.20; ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 1H, J=0.7 Hz, C*H*-*Thymine*), 5.57 (q, 1H, J=6.6 Hz, 4-*H*), 5.38 (q, 1H, J=6.5 Hz, 4′-*H*), 4.35 (m, 1H, 2-*H*), 4.30 (m, 1H, 2′-*H*), 4.06–3.97 (m, 2H, 3a-3a′-*H*), 3.76–3.65 (m, 4H, CH_2OH), 3.40 (ddd, 2H, J=13.4, 13.0, 7.1 Hz, 6-6′-*H*), 3.17 (ddd, 2H, J=13.5, 13.2, 7.3 Hz, 6-6′-*H*), 2.76 (bs, 2H, O*H*), 2.39–2.10 (m, 8H, 3-5-3′-5′-*H*), 2.08 (d, 3H, J=0.9 Hz, CH_3-*Thymine*); ^{13}C NMR ($CDCl_3$): δ 168.2 (s, 1C, *C*–O-*Thymine*), 162.7 (s, 1C, *C*–O-*Thymine*), 157.8 (d, 1C, *C*H-*Thymine*), 111.2 (s, 1C, *C-Thymine*), 78.5 (d, 2C, 2-2′-*C*), 76.84 (d, 1C, 4-*C*), 76.2 (d, 1C, 4′-*C*), 68.2 (d, 1C, 3a-*C*), 67.9 (d, 1C, 3a′-*C*), 64.4 (t, 1C, *C*H_2OH), 64.1 (t, 1C, *C*H_2OH), 53.6 (t, 2C, 6-6′-*C*), 31.6 (t, 2C, 3-3′-*C*), 30.9 (t, 2C, 5-5′-*C*), 11.9 (q, 1C, *C*H_3-*Thymine*); IR ($CDCl_3$): ν 3690, 2945, 2871, 1602, 1572, 1421 cm^{-1}; MS (*m*/*z*): 409 [M$^+$+1], 268, 142. Anal. calcd for $C_{19}H_{28}N_4O_6$ C, 55.87; H, 6.91; N, 13.72. Found C, 55.54; H, 7.09; N, 14.04.

1.6.6. (2*R*,3a*R*,4*R*)-Benzoic acid 2-hydroxymethyl-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (28). Pale brown oil, 70 mg, yield: 89%; $[\alpha]_D^{25}=-102.1$ (c=0.29, $CHCl_3$); R_f (AcOEt)=0.41; ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, J=7.6 Hz), 7.68 (m, 1H), 7.4 (m, 2H), 5.5 (q, 1H, J=6.8 Hz, 4-*H*), 4.30 (ddt, 1H, J=6.8, 6.2, 2.8 Hz, 2-*H*), 3.90 (ddd, 1H, J=7.6, 7.1, 1.6 Hz, 3a-*H*), 3.70–3.56 (m, 2H, CH_2OH), 3.40 (ddd, 1H, J=13.2, 6.8, 6.6 Hz, 6-*H*), 3.16 (ddd, 1H, J=13.6 7,.6.2, 6.0 Hz, 6-*H*), 2.9 (bs, 1H, O*H*), 2.33 (ddd, 1H, J=12.9, 7.2, 2.4 Hz, 3-*H*), 2.30–2.18 (m, 3H, 3*H*, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 165.0 (s, 1C, *C*═O), 133.0 (d. 1C), 129.4 (s, 1C), 129.2 (d, 2C), 128.6 (d, 2C), 78 (d, 1C, 4-*C*), 74.7 (d, 1C, 2-*C*), 68 (d, 1C, 3a-*C*), 64 (t, 1C, *C*H_2OH), 53.1 (t, 1C, 6-*C*), 31.5 (t, 2C, 3*C*, 5*C*); MS (*m*/*z*): 263, 245, 159, 140. Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found C, 63.52; H, 6.63; N, 5.46.

1.6.7. (2*R*,3a*R*,4*S*)-1-[(2-Hydroxymethyl-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl]-5-methyl-1*H*-pyrimidin-2,4-dione (35). To a solution of **33** (55 mg, 0.12 mmol) in MeOH (3 mL), Amberlyst 15 was added. The mixture was stirred at 50°C for 2 h. The solution was filtered off and the resin was washed with methanol. The resin was then stirred, at room temperature with a mixture of MeOH/NH_3 4:1 for 2 h. The solution was filtered off and the solvent was removed under reduced pressure. The crude was purified by flash cromatography (eluent AcOEt/MeOH 92:8) to give 18 mg of **35** as a colorless oil. Yield: 56%; $[\alpha]_D^{25}=-9.5$ (c=0.18, $CHCl_3$); R_f (AcOEt/MeOH 92:8) 0.15; ^{1}H NMR ($CDCl_3$): δ 9.39 (bs, 1H, N*H*), 7.22 (s, 1H, C*H*-*Thymine*), 5.00 (dt, 1H, J=9.8, 4.8 Hz, 4-*H*), 4.40 (m, 1H, 2-*H*), 3.77–3.65 (m, 2H, CH_2OH), 3.64 (ddd, 1H, J=8.2, 4.8, 4.6 Hz, 3a-*H*), 3.49 (m, 1H, 6-*H*), 3.21 (m, 1H, 6-*H*), 2.6 (bs, 1H, O*H*), 2.56 (m, 1H, 5-*H*), 2.45 (m, 1H, 3-*H*), 2.3 (m, 1H, 3-*H*), 1.94 (s, 3H, CH_3-*Thymine*), 1.94–1.85 (m, 1H, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 163.5 (s, 1C, *C*═O), 151.0 (s, 1C, *C*═O), 136.8 (d, 1C, *C*H-*Thymine*), 112.19 (s, 1C, *Thymine*), 77.8 (d, 1C, 2-*C*), 70.1 (d, 1C, 3a-*C*), 63.8 (t, 1C, *C*H_2OH), 59.17 (d, 1C, 4-*C*), 54.1 (t, 1C, 6-*C*), 35.6 (t, 1C, 3-*C*), 30.8 (t, 1C, 5-*C*), 12.5 (q, 1C, *C*H_3-*Thymine*); MS (*m*/*z*): 268 [M$^+$+1], 208. Anal. calcd for $C_{12}H_{17}N_3O_6$: C, 53.92; H, 6.41; N, 15.72. Found C, 54.05; H, 6.18; N, 15.95.

Acknowledgements

We thank MIUR (Ministero per l'Istruzione l'Universita'e Ricerca) for financial support (COFIN 2002).

References

1. (a) Pergaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903. (b) Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017. (c) Pan, S.; Amankulor, N. M.; Zhao, K. *Tetrahedron* **1998**, *54*, 6587–6604. (d) Challand, R.; Young, R. J. *Antiviral Chemotherapy*; Oxford University: Oxford, 1998.
2. Merino, P. *Curr. Med. Chem.-Anti-Infective Agents* **2002**, *1*, 389–411.
3. (a) Furneaux, R. H.; Tyler, P. C. *J. Org. Chem.* **1999**, *64*, 8411–8412. (b) De Clerq, E.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl Acad. Sci. USA* **1979**, *76*, 2947–2951. (c) Maudgal, P. C.; De Clerq, E.; Descamps, J.; Missotten, L.; De Somer, P.; Busson, R.; Vanderhaeghe, H.; Verhelst, G.; Walker, R. T.; Jones, A. S. *Antimicrob. Agents Chemother.* **1980**, *17*, 8–12. (d) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Schramm, V. L.; Tyler, P. C. *Tetrahedron* **2000**, *56*, 3053–3062.
4. (a) Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem.* **1997**, *68*, 223–432. (b) Chiadhuri, N. C.; Ren, R. X. F.; Kool, E. T. *Synlett* **1997**, 341–347.
5. (a) Marquez, V. *Adv. Antiviral Drug Des.* **1996**, *2*, 89–146. (b) Freeman, S.; Gardiner, J. M. *Mol. Biotechnol.* **1996**, *5*, 125–137. (c) Mansour, T. S.; Storer, R. *Curr. Pharm. Des.* **1997**, *3*, 227–264.
6. Hu, C. K.; Cutler, S. J. *J. Heterocycl. Chem.* **1986**, *23*, 289–319.
7. (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 517–623. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611–10670. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272.
8. Herdewijn, P.; Balzarini, J.; De Clercq, E. *2′,3′-Dideoxynucleoside Analogues as Anti-HIV Agents in Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI: Greenwich, CT, 1993; Vol. 1, pp 233–318.
9. (a) Taylor, E. W.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. *Antiviral Chem. Chemother.* **1990**, *1*, 163–173. (b) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barhi, J. J., Jr. *J. Med. Chem.* **1994**, *37*, 3389–3399.
10. (a) Jagannadh, B.; Reddy, D. V.; Kunwar, A. C. *J. Biochem. Biophys. Res. Commun.* **1991**, *179*, 386–391. (b) Plavec, J.; Koole, L. H.; Chattopadaya, J. *J. Biochem. Biophys. Methods* **1992**, *25*, 253–272.
11. Obake, M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *30*, 2203–2206.
12. Rodriguez, J. B.; Marquez, V.; Nicklaus, M. C.; Mitsuya, H.; Barchi, J. J. *J. Med. Chem.* **1994**, *37*, 3389–3399.
13. (a) Chao, Q.; Nair, V. *Tetrahedron Lett.* **1995**, *36*, 7375–7378. (b) Chao, Q.; Nair, V. *Tetrahedron* **1997**, *53*, 1957–1970.
14. Lescop, C.; Huet, F. *Tetrahedron* **2000**, *56*, 2995–3003.

15. (a) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321–9327. (b) Chiacchio, U.; Rescifina, A.; Corsaro, A.; Pistarà, V.; Romeo, G.; Romeo, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2045–2048.
16. (a) Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951–7953. (b) Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Rubin, B.; Slusarchyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221–1229. (c) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Todaro, L. J.; Weigele, M.; Sim, I. S.; Frank, K. B.; Richman, D. D.; Mitsuya, H.; Broder, S. *Ann. N.Y. Acad. Sci.* **1990**, *615*, 530.
17. Clemens, L. *Org. Prep. Proced. Int.* **2002**, *34*, 149–167.
18. (a) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 83. (b) Brandi, A.; Cicchi, A.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, 103. article ASAP.
19. (a) Cordero, F. M.; Pisaneschi, F.; Gensini, M.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2002**, 1941–1951. (b) Cordero, F. M.; Gensini, M.; Goti, A.; Brandi, A. *Org. Lett.* **2000**, *2*, 2475–2477. (c) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. In *Current Trends in Organic Synthesis*; Scolastico, C., Nicotra, F., Eds.; Kluwer Academic/Plenum: New York, 1999; pp 213–220.
20. Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748.
21. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.
22. Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119–3125.
23. Takahashi, M.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1982**, *23*, 1079–1082.
24. (a) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748. (b) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633–3645.
25. Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. *Tetrahedron Lett.* **2002**, *43*, 4013–4015.
26. Cruickshank, A. J.; Jiricny, J.; Reese, B. C. *Tetrahedron Lett.* **1984**, *25*, 681–684.
27. (a) Youhoon, C.; Gumina, G.; Chung, K. C. *Tetrahedron: Asymmetry* **2000**, *1*, 4853–4875. (b) Yamada, K.; Sakata, S.; Yoshimura, Y. *J. Org. Chem.* **1998**, *63*, 6891.