Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1543–1554

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of L-isoxazolidinyl thymidine from *N*-benzyl-1,2-di-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN)

Pedro Merino,* Eva M. del Alamo, Santiago Franco, Francisco L. Merchan, Ana Simon and Tomas Tejero

Departamento de Química Orgánica, ICMA, Facultad de Ciencias, Universidad de Zaragoza, E-50009 Aragon, Spain

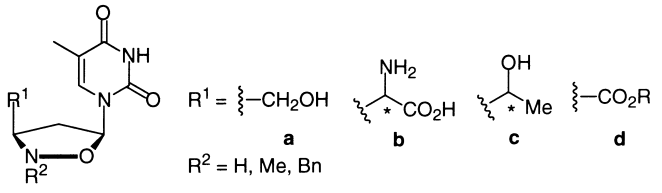
Received 1 February 2000; accepted 9 March 2000

Abstract

A synthetic approach to L-isoxazolidinyl nucleosides is demonstrated by the stereoselective conversion of *N*-benzyl-1,2-di-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN) into *cis* and *trans* L-isoxazolidinyl thymidine. The methodology consists of the 1,3-dipolar cycloaddition of BIGN with either vinyl acetate or a vinyl base to give key intermediates that are easily transformed into the target compound. The experimental results of the cycloaddition reactions can be qualitatively explained by theoretical ab initio calculations.

1. Introduction

Nucleoside analogues in which the furanose ring has been replaced by a different carbo- or heterocyclic ring have attracted special interest by virtue of their biological action mainly as antiviral agents.[1] In particular, isoxazolidinyl nucleosides **1** are emerging as an important class of compounds which are interesting to synthesize in order to investigate their pharmacological activities.[2]



1

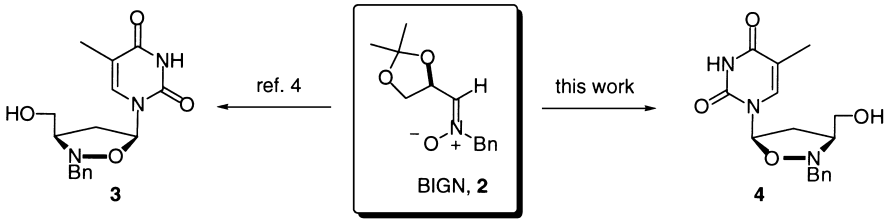
* Corresponding author. Fax: +34 976 762075; e-mail: pmerino@posta.unizar.es

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00094-X

In connection with our synthetic studies on the utility of chiral nitrones for the synthesis of biologically interesting nitrogenated compounds,[3] we have recently devised a new synthetic route to isoxazolidinyl nucleosides of type **1** via nucleophilic addition of enolates to α-alkoxy-[4] and α-aminonitrones.[5] By this route simple analogues **1a** and more complex products such as α-amino acid isoxazolidinyl nucleosides **1b** have become accessible.

Previously reported synthetic approaches to enantiomerically pure isoxazolidinyl nucleosides **1** included Michael addition of *N*-methyl hydroxylamine to unsaturated esters[6] and lactones,[7] and 1,3-dipolar cycloaddition reactions of nitrones with vinyl acetate.[8] By the first route Zhao and co-workers described the synthesis of both D- and L-analogues of type **1a**; by the second one, Chiacchio and co-workers have recently reported the synthesis of compounds **1c** and **1d**.

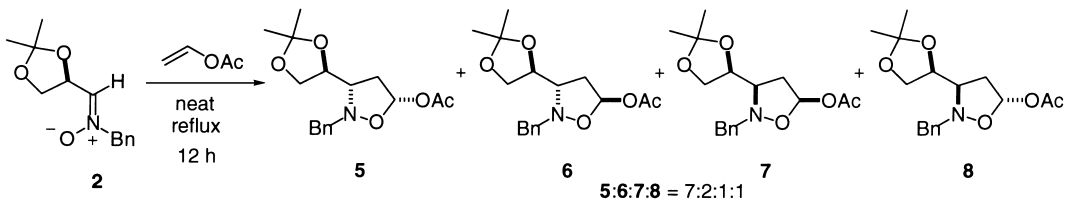
Since we had achieved[4] the synthesis of D-isoxazolidinyl thymidine **3** starting from BIGN **2** (Scheme 1) — via nucleophilic addition of sodium enolate — and it has also been reported[9] that 1,3-dipolar cycloaddition of electron-rich alkenes to chiral α-alkoxy nitrones gave preferentially *anti* adducts,[10] we realized that application of Chiacchio's methodology to nitrone **2** could serve as a strategy for the synthesis of enantiomeric[11] L-isoxazolidinyl nucleosides like **4**. This has prompted us to publish our work on the stereodivergent synthesis of such compounds and this paper describes the synthesis of L-isoxazolidinyl thymidine **4** as well as its *trans*-isomer. We also report the first stereoselective 1,3-dipolar cycloaddition of a vinyl base to form homochiral isoxazolidinyl nucleosides.[12]



Scheme 1.

2. Results and discussion

The nitrone **2** is readily available from 2,3-*O*-isopropylidene-D-glyceraldehyde and it can be prepared in multigram scale as described.[13] The cycloaddition of **2** with vinyl acetate took place without solvent to give a mixture of four stereoisomeric isoxazolidines **5**–**8** in an isomer ratio of ca. **5**:**6**:**7**:**8** = 7:2:1:1 and a combined yield of 94% (Scheme 2).



Scheme 2.

The crude mixture was purified by preparative centrifugally accelerated, radial, TLC[14] and the four cycloadducts **5**–**8** could be obtained in pure form with the only exception being **8**, which was contaminated by 8% of **7** judged by integration of H-5 hydrogens (isoxazolidine ring numbering) in the ^{1}H NMR spectrum. The *cis*/*trans* stereochemistry of the adducts was readily deduced by means of NOE measurements (Fig. 1). Thus, for *cis* compounds **5** and **7** irradiation of H-4a produced strong enhancements of both H-3 (10–12%) and H-5 (8–10.5%) along with a much larger enhancement of H-4b (20–22%, not indicated in Fig. 1). Irradiation of H-5 produced enhancement of H-4a (9–11%) and a much smaller enhancement of H-4b (2–2.5%, not indicated in Fig. 1). Irradiation of H-3 only produced enhancement of H-4a (9–10%). For *trans* compounds **6** and **8**, irradiation of H-3 produced a strong enhancement of only H-4a (8–10%) and irradiation of H-5 produced enhancement of only H-4b (8–9%). In addition, irradiation of H-4a and H-4b in the same experiment produced enhancements of H-3 (9–10%) and H-5 (9–11%).

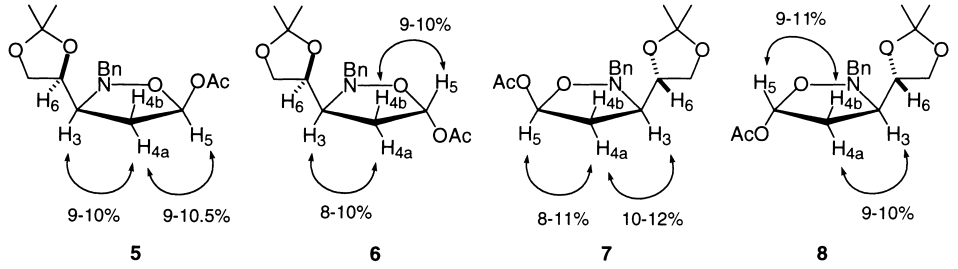
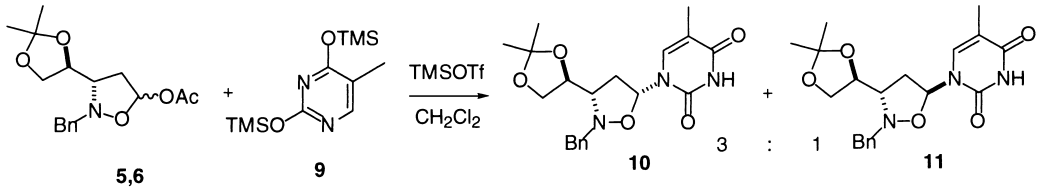


Figure 1. Selected NOEs observed for compounds **5**–**8** (η_{obs} given as percent of η_{max})

The absolute configurations were established by comparison of adducts **7** and **8** with the same compounds previously prepared by us through the nucleophilic addition route.[4] Furthermore, conversion of these compounds into known isoxazolidinyl thymidine **3** and transformation of adducts **5**/**6** into enantiomeric **4** also support the assigned stereochemistry (see below).

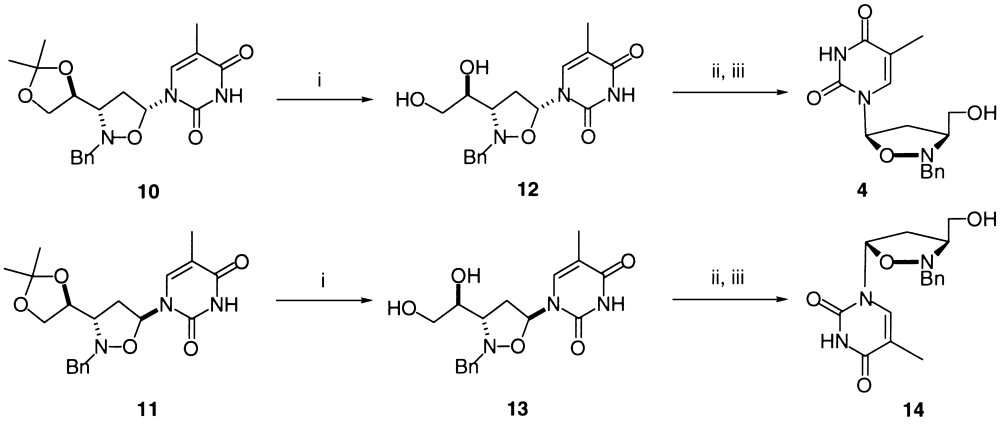
A mixture of *anti* adducts **5**/**6** was transformed into isoxazolidinyl nucleoside analogues as depicted in Scheme 3.[15] The condensation of a mixture of **5** and **6** with silylated thymine,[16] using the glycosylation methodology developed by Vörbruggen,[17] resulted in a nucleoside product consisting of *cis*-**10** and *trans*-**11** isomers (3:1) which were isolated in 80% combined yield. The anomers could be separated by flash chromatography, the *trans*-isomer showing the lower R_f.



Scheme 3.

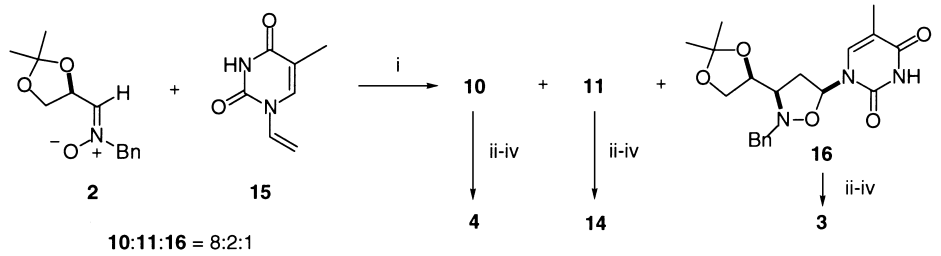
The anomeric configuration of **10** and **11** was assigned by ^{1}H NMR and NOE experiments in which the irradiation of H-4a (δ 2.30) in **10** increased the proton signals of H-5 (δ 6.05) and H-3 by 14% and 5%, respectively, indicating that the relative configuration of **11** must be *cis*. Similarly, upon irradiation of the H-5 proton of **11** the signal for H-4b (δ 2.49) was enhanced by 8%. NOE was also observed as a 6% increase between H-3 and H-4a; however, H-4b was not affected.

Deprotection of the separated anomers was achieved by using catalytic *p*-TosOH in MeOH (Scheme 4). The resulting 1,2-diols were treated sequentially with sodium periodate and sodium borohydride. Purification by column chromatography on silica gel led to the isolation of isoxazolidinyl nucleosides **4** and **14** in high yields (66% and 48% overall yields from **10** and **11**, respectively). The structure of compound **4** was assigned as L-isoxazolidinyl thymidine with a specific rotation of $[\alpha]_D = -6.9$ (c 1.10, MeOH). This assignment was based on the independent synthesis of its antipode **3** with $[\alpha]_D = +6.1$ (c 0.80, MeOH), prepared from the nucleophilic addition of methyl acetate enolates to **2**.[4] Similarly, D-isoxazolidinyl thymidine **3** was produced from a mixture of minor adducts **7** and **8** as we had described previously.[4] The synthesis of **3** provided additional proof for the structure of cycloadducts **7** and **8** and as a consequence for that of major ones **5** and **6**.



Scheme 4. Reaction conditions: (i) *p*-TosOH, MeOH, reflux. (ii) $NaIO_4$, MeOH–H_2O, 0°C. (iii) $NaBH_4$, MeOH, 0°C

The direct 1,3-dipolar cycloaddition between vinyl thymine[12d] **15** and **2** was also examined (Scheme 5). As has been illustrated by earlier reports concerning racemic compounds,[12] this approach should be a highly promising reaction for the straightforward synthesis of a variety of isoxazolidinyl nucleosides. However, to the best of our knowledge, chiral versions of that reaction have not yet been investigated. The reaction between **2** and **15** in refluxing toluene proceeded smoothly to give an 8:2:1 mixture of three adducts **10**, **11** and **16** in 88% combined yield.



Scheme 5. Reaction conditions: (i) toluene, reflux. (ii) *p*-TosOH, MeOH, 60°C. (iii) $NaIO_4$, MeOH–H_2O, 0°C. (iv) $NaBH_4$, MeOH, 0°C

The three stereoisomers could be obtained in a pure state by means of column chromatography and configuration of each isomer was determined by comparison with the same compounds previously prepared from the corresponding isoxazolidines **5**–**8** (see above).

The obtained cycloadducts were transformed into the corresponding isoxazolidinyl nucleosides by using the same conditions described above. Using the results of this transformation, the overall yield of L-isoxazolidinyl thymidine **4** from BIGN **2** was 42.2% (four steps).

2.1. Theoretical calculations

The observed difference in selectivity in the cycloaddition reaction between BIGN **2** and vinyl acetate is well reproduced by calculations of the transition states. We attempted an explanation of the selectivity on the basis of both semiempirical[18] and ab initio[19] theoretical calculations. For the purpose of comparison all fully optimized structures (reactants, transition states and products) were calculated at PM3 and HF/3-21G* levels without any geometry restriction.

The more stable conformation was chosen for nitrone (after exhaustive exploration of the potential energy surface) and alkene (*s-cis* conformation). The optimized geometries of the nitrone **2** and vinyl acetate showed the expected bond lengths and angles. The sum of the calculated heats of formation of nitrone and alkene was considered to be the heat of formation of the reactants. The TSs for the four different approaches of vinyl acetate to **2** were located by the calculation of a reaction path profile starting from optimized geometries of the corresponding final adducts, followed by an optimization of the TS with respect to all structural variables. The TSs were characterized through the calculation of the force constant matrix by ensuring that they had one and only one imaginary harmonic vibrational frequency corresponding to the formation of new

Table 1
Total electronic energies,[a] electronic activation energies[b] and relative Gibbs energies[c] of reactants, transition states and products for cycloadditions of BIGN **2** with vinyl acetate

structure	PM3 (kcal mol^{-1})	HF/3-21G* (Hartrees)	ΔG (kcal mol^{-1})	HF/6-31G* (Hartrees)[e]	ΔG (kcal mol^{-1})	B3LYP/6-31G* (Hartrees)[e]	ΔG (kcal mol^{-1})
nitrone[d] **2**	-79.756	-548.297399		-551.350382		-554.693674	
vinyl acetate	-68.539	-302.880245		-304.578251		-306.373792	
TS exo-Si	-113.74 *(34.56)*	-851.148119 *(18.53)*	31.88	-855.878703 *(31.33)*	44.69	-861.046832 *(12.95)*	26.84
TS endo-Si	-113.64 *(34.66)*	-851.146373 *(19.62)*	33.04	-855.876398 *(32.78)*	46.08	-861.044612 *(14.34)*	29.88
TS exo-Re	-115.14 *(33.16)*	-851.142663 *(21.95)*	34.59	-855.876329 *(32.82)*	46.04	-861.045719 *(13.65)*	29.04
TS endo-Re	-115.01 *(33.29)*	-851.141528 *(22.66)*	35.70	-855.873337 *(34.70)*	47.80	-861.042805 *(15.48)*	30.74
(3S,5R)-**5**[f]	-187.66	-851.261539	-38.87	-855.989973	-24.41	-861.120717	-18.43
(3S,5S)-**6**[g]	-188.10	-851.261775	-38.82	-855.991357	-25.39	-861.121904	-17.69
(3R,5S)-**7**[h]	-187.10	-851.256496	-36.25	-855.991938	-25.99	-861.122036	-18.41
(3R,5R)-**8**[i]	-187.60	-851.254989	-35.45	-855.990495	-25.18	-861.121015	-17.92

[a]Including ZPVE corrections for ab initio calculations. [b]For TSs, potential energy barriers (kcal mol^{-1}) relative to the corresponding reactant, are given in brackets. [c]Calculated at 298.15 K and 1 atm relative to the reactants. [d]For simplicity the N-benzyl group of the nitrone was replaced for a methyl group. [e]Single point calculations using HF/3-21G* geometries. [f]from TS exo-Si. [g]from TS endo-Si. [h]from TS exo-Re. [i]from TS endo-Re

bonds. Both sides of the reaction path were also investigated starting from each transition state by using the internal reaction coordinate (IRC) procedure. In all cases, it could be verified that the TSs proceed from the reactants (nitrone+alkene) and give rise to the products (isoxazolidines). Single point calculations at HF/6-31G*//HF/3-21G and B3LYP/6-31G*//HF/3-21G levels have been carried out in order to check the energetic results. These results are summarized in Table 1 and the TSs illustrated in Fig. 2.† The calculated bond lengths for the TSs and products are also given in Table 2.

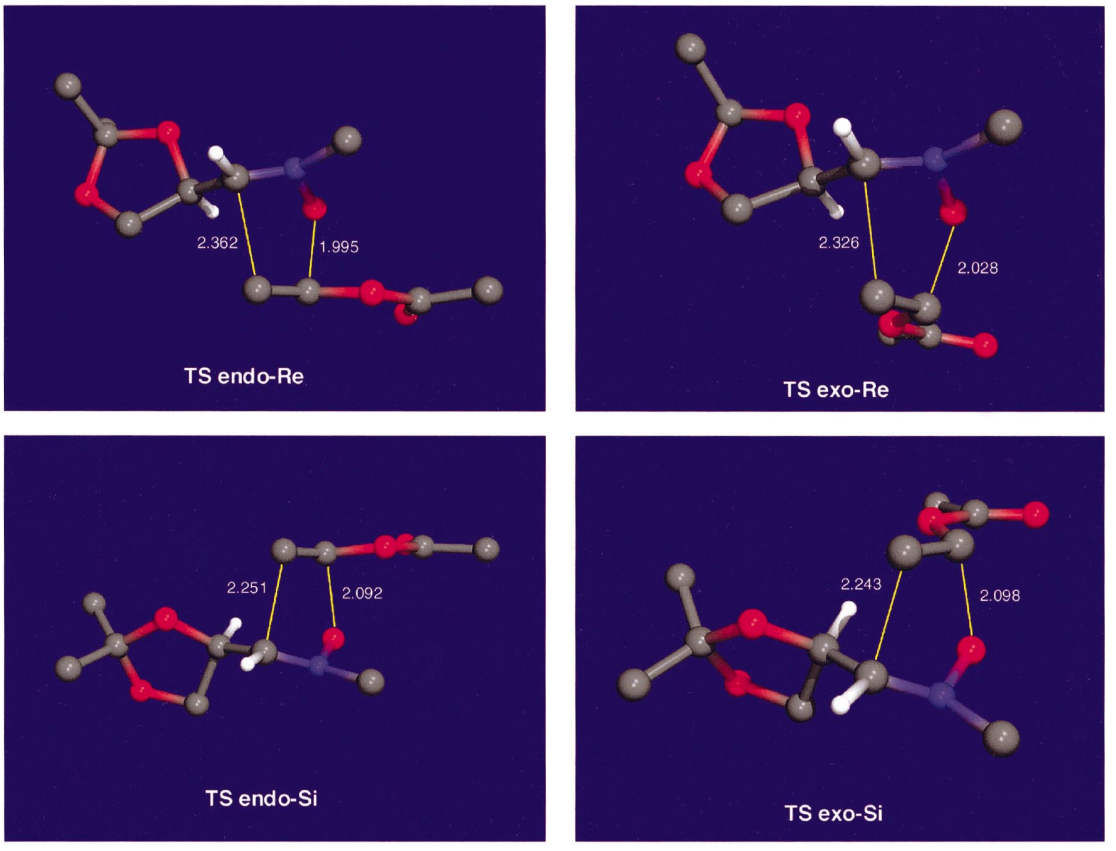
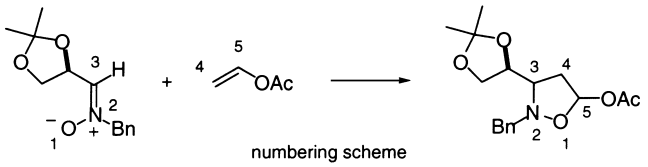


Figure 2. Optimized transition states (HF/3-21G) for the cycloaddition of BIGN with vinyl acetate. Forming bond lengths are given in Å. Selected hydrogens have been omitted for clarity

Whereas the most stable transition state (TS *exo*-Si) is predicted to be the same by ab initio methods, irrespective of the theory level used, semiempirical methods (PM3) do not predict correctly the observed selectivity. For this reason, PM3 values were not considered further. The extent of bond formation in the transition states will be approximately in inverse proportion to the lengths of the incipient bonds. As expected for 1,3-dipolar cycloadditions all TSs were asynchronous, the newly created C–O bond being formed to a greater extent than the C–C bond.

† Full thermodynamic data and optimized geometries of all stationary points are available from the authors.

Table 2
HF/3-21G* Calculated properties of transition structures and products



	TS exo-Si	TS endo-Si	TS exo-Re	TS endo-Re	(3S,5R)-**5**	(3S,5S)-**6**	(3R,5S)-**7**	(3R,5R)-**8**
Bond lengths (Å)								
O1-N2	1.377	1.380	1.367	1.371	1.483	1.468	1.482	1.492
N2-C3	1.300	1.298	1.295	1.292	1.490	1.480	1.486	1.492
C3-C4	2.243	2.251	2.326	2.362	1.533	1.539	1.543	1.532
C4-C5	1.356	1.356	1.359	1.360	1.519	1.533	1.539	1.520
C5-O1	2.098	2.092	2.028	1.995	1.420	1.433	1.413	1.403
neg. freq. (cm^{-1})	-603.1	-621.7	-574.0	-581.6				

In the discussion on the selectivity derived from the relative values of the Gibbs energies of activation (ΔGs), it is clear that only the estimation of the major adduct **5**, coming from TS *exo*-Si, is always correct. Experimental findings on the presence (and absence in the case of cycloaddition of **2** with **15**) of minor products are only reproduced in the HF/3-21G calculations. However, the close values (differences lower than 1 kcal mol^{-1}) calculated for TS *endo*-Si and TS *exo*-Re in both HF/6-31G* and B3LYP/6-31G* single point calculations suggest a satisfying congruence between trends in the computed Gibbs energies and the experimental results. So, it appears that the calculated energy differences by ab initio methods are qualitatively correct and account for the stereoselectivities observed for the reaction.

3. Conclusions

In summary, two stereoselective approaches to L-isoxazolidinyl nucleosides, based on 1,3-dipolar cycloaddition chemistry of nitrone **2**, are described. The major stereoisomers of the key cycloaddition reactions arise from an *exo* transition state, as is well documented for cycloaddition of α-alkoxy nitrones with electron-rich alkenes,[9] and from reaction on the more sterically accessible *Si* face of the nitrone. Theoretical ab initio calculations correctly predicted the preferential formation of the major adducts since the lowest calculated TS energy is for the *exo* approach of the dipolarophile to the *Si* face of the nitrone **2**. The methodology is complementary to the previously reported approach for the synthesis of D-isoxazolidinyl nucleosides and makes nitrone **2** a suitable starting material for the stereodivergent synthesis of isoxazolidinyl nucleosides by two routes that are potentially amenable to the preparation of multi-gram quantities. Investigation of isoxazolidinyl nucleosides with different substitutions on the 4′- and 5′- positions as well as biological evaluations of the synthesized compounds are in progress and will be reported elsewhere.

4. Experimental

4.1. General remarks

The reaction flasks and other glass equipment were heated in an oven at 130°C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the positions of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid and iodine. Preparative column chromatography was performed on columns of silica gel (60–240 mesh) and with solvents that were distilled prior to use. Preparative centrifugally accelerated radial thin-layer chromatography (PCAR-TLC) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA); the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644–6) and the eluting solvents were delivered by the pump at a flow-rate of 0.5–1.5 mL min^{-1}. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity or on a Bruker 300 instrument in $CDCl_3$ at 55°C. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. Optical rotations were taken at 25°C on a Perkin–Elmer 241 polarimeter. Elemental analysis was performed on a Perkin–Elmer 240B microanalyzer. Nitrone **2**[13] and vinyl thymine[12d] were prepared according to the reported procedures. Vinyl acetate **2** was purchased (Aldrich) and distilled prior to use.

4.2. Cycloaddition of BIGN *2* with vinyl acetate *3*

BIGN **2** (0.710 g, 3 mmol) was dissolved in vinyl acetate **3** (12.92 g, 150 mmol) and the resulting mixture was stirred at reflux under an Ar atmosphere until no more nitrone was observed by TLC (12 h). The mixture was evaporated under reduced pressure and the products ratio was established by ^1H NMR analysis of the crude product. The residue was purified by preparative, centrifugally accelerated, radial, thin-layer chromatography (Chromatotron®) using an 80:20 mixture of hexane:EtOAc as an eluent.

4.2.1. (3S,5R)-5-Acetoxy-2-benzyl-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidine *5*

(0.580 g, 60%); Oil; R_f (hexane:EtOAc, 80:20) = 0.30; $[\alpha]_D$ –82.1 (*c* 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.34 (s, 3H), 2.06 (s, 3H), 2.43 (ddd, 1H, J = 1.0, 3.3, 13.8 Hz), 2.53 (ddd, 1H, J = 5.7, 8.6, 13.8 Hz), 3.19 (dt, 1H, J = 3.3, 8.6 Hz), 3.44 (dd, 1H, J = 5.7, 8.5 Hz), 3.95 (d, 1H, J = 13.2 Hz), 3.97 (dd, 1H, J = 6.1, 8.5 Hz), 4.07 (d, 1H, J = 13.2 Hz), 4.23 (dt, 1H, J = 5.9, 8.3 Hz), 6.46 (dd, 1H, J = 1.0, 4.9 Hz), 7.30–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.3, 25.2, 26.8, 37.3, 63.2, 64.3, 67.6, 75.7, 96.5, 109.2, 127.9, 128.5, 129.6, 135.9, 170.1. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.28; H, 7.40; N, 4.19.

4.2.2. (3S,5S)-5-Acetoxy-2-benzyl-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidine *6*

(0.164 g, 17%); Oil; R_f (hexane:EtOAc, 80:20) = 0.35; $[\alpha]_D$ +97.7 (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.34 (s, 3H), 2.10 (s, 3H), 2.63 (ddd, 1H, J = 2.6, 7.4, 14.1 Hz), 2.70 (ddd, 1H, J = 4.7, 5.7, 14.1 Hz), 3.34 (dt, 1H, J = 4.7, 7.4 Hz), 3.40 (m, 1H), 3.94 (m, 2H), 4.00 (d, 1H, J = 12.8 Hz), 4.29 (d, 1H, J = 12.8 Hz), 6.45 (dd, 1H, J = 2.6, 5.7 Hz), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.4, 25.2, 26.8, 38.3, 64.2, 65.5, 67.7, 76.6, 98.8, 109.3, 127.8, 128.5, 129.1, 136.6, 169.9. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.71; H, 7.35; N, 4.47.

4.2.3. (3R,5S)-5-Acetoxy-2-benzyl-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidine **7**

(0.087 g, 9%); Oil; R_f (hexane:EtOAc, 80:20) = 0.23; $[\alpha]_D$ +137.2 (*c* 0.39, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.40 (s, 3H), 2.00 (ddd, 1H, J = 2.0, 7.9, 13.8 Hz), 2.04 (s, 3H), 2.60 (ddd, 1H, J = 6.4, 8.9, 13.8 Hz), 3.10 (dt, 1H, J = 7.9, 8.9 Hz), 3.70 (dd, 1H, J = 7.0, 8.3 Hz), 3.99 (dd, 1H, J = 5.6, 8.3 Hz), 4.00 (d, 1H, J = 14.1 Hz), 4.17 (q, 1H, J = 6.8 Hz), 4.42 (d, 1H, J = 14.1 Hz), 6.24 (dd, 1H, J = 2.0, 6.4 Hz), 7.24–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.3, 25.2, 26.6, 39.1, 61.4, 66.0, 66.8, 76.7, 94.8, 110.0, 127.3, 128.1, 129.4, 136.5, 170.4. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.62; H, 7.08; N, 4.25.

4.2.4. (3R,5R)-5-Acetoxy-2-benzyl-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidine **8**

(0.086 g, 9%); Oil; R_f (hexane:EtOAc, 80:20) = 0.20; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.38 (s, 3H), 2.03 (s, 3H), 2.30–2.40 (m, 2H), 3.42 (dt, 1H, J = 6.8, 8.4 Hz), 3.68 (dd, 1H, J = 6.0, 8.2 Hz), 4.00 (dd, 1H, J = 6.5, 8.2 Hz), 4.06 (q, 1H, J = 6.5 Hz), 4.21 (ABq, 2H, J = 13.4 Hz), 6.30 (dd, 1H, J = 1.2, 4.0 Hz), 7.25–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.1, 26.6, 38.0, 64.5, 64.7, 66.3, 76.9, 97.2, 109.7, 127.5, 128.3, 129.4, 136.9, 169.9. Compound **8** was shown to contaminate 8% of the stereoisomer **7** judged by integration of H-5 hydrogens in the ^1H NMR spectrum of the products. Nevertheless, some diastereomeric enrichment could be accomplished by repeated chromatography.

4.3. 1-{(3S,5R)-2-Benzyl-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidin-5-yl}thymine **10** *and 1-{(3S,5S)-2-benzyl-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidin-5-yl}thymine* **11**

A 7:2 mixture of **5** and **6** (0.6 g, 1.87 mmol) was dissolved in CH_3CN (35 mL) and treated sequentially with bis(trimethylsilyl)thymine (0.810 g, 3 mmol) and TMSOTf (0.58 mL, 3 mmol). The resulting mixture was stirred at ambient temperature for 4 h at which time saturated aqueous $NaHCO_3$ (50 mL) was added. The reaction mixture was diluted with EtOAc (50 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc) on silica gel.

Eluted first was **10** (0.435, 60%): oil; R_f ($CHCl_3$:MeOH, 98:2) = 0.39; $[\alpha]_D$ –21.8 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.40 (s, 3H), 1.81 (d, 3H, J = 1.0 Hz), 2.27 (ddd, 1H, J = 3.3, 7.9, 13.8 Hz), 2.98 (ddd, 1H, J = 7.8, 8.5, 13.8 Hz), 3.20 (dt, 1H, J = 3.5, 8.5 Hz), 3.70 (dd, 1H, J = 6.9, 8.1 Hz), 3.90 (d, 1H, J = 14.0 Hz), 4.04 (dd, 1H, J = 6.7, 8.1 Hz), 4.25 (dt, 1H, J = 3.5, 6.8 Hz), 4.31 (d, 1H, J = 14.0 Hz), 6.05 (dd, 1H, 3.3, 7.8 Hz), 7.30–7.39 (m, 5H), 7.49 (q, 1H, J = 1.0 Hz), 8.40 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 24.8, 26.1, 39.3, 61.7, 65.6, 66.3, 74.6, 82.9, 109.8, 109.9, 127.9, 128.6, 128.9, 136.5, 136.6, 150.4, 163.7. Anal. calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 61.83; H, 6.48; N, 11.00.

Eluted second was **11** (0.145 g, 20%): oil; R_f ($CHCl_3$:MeOH, 98:2) = 0.33; $[\alpha]_D$ –13.6 (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.42 (s, 3H), 1.79 (d, 3H, J = 1.1 Hz), 2.45 (ddd, 1H, J = 5.4, 7.7, 13.4 Hz), 2.97 (ddd, 1H, J = 3.8, 7.2, 13.4 Hz), 3.40 (m, 1H), 3.65 (dd, 1H, J = 6.5, 8.3 Hz), 4.08 (dd, 1H, J = 6.6, 8.3 Hz), 4.13 (ABq, 2H, J = 13.7 Hz), 4.28 (q, 1H, J = 6.3 Hz), 6.02 (dd, 1H, J = 5.4, 7.2 Hz), 7.10 (q, 1H, J = 1.1 Hz), 7.30–7.38 (m, 5H), 8.30 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 25.0, 26.5, 37.5, 62.9, 65.2, 67.3, 74.1, 85.0, 109.8 (2C), 128.0, 128.6, 129.0, 135.5, 136.1, 150.5, 162.0. Anal. calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 61.92; H, 6.63; N, 10.65.

4.4. Cycloaddition of BIGN **2** with vinyl thymine **15**

To a solution of BIGN **2** (0.235 g, 1 mmol) in toluene (50 mL) was added vinyl thymine (0.761 g, 5 mmol) and the resulting mixture was stirred at reflux under an Ar atmosphere until no more nitrone was observed by TLC (15 h). The mixture was evaporated under reduced pressure and the products ratio was established by ^{1}H NMR analysis of the crude product. The residue was purified by preparative, centrifugally accelerated, radial, thin-layer chromatography (Chromatotron®) using a 98:2 mixture of chloroform:methanol as an eluent. Eluted first was compound **10** (0.248 g, 64%); eluted second was compound **11** (62 mg, 16%) and eluted third was compound **16** (31 mg, 8%).

4.4.1. 1-{(3R,5S)-2-Benzyl-3-[(1S)-2,2-dimethyl-1,3-dioxolan-4-yl]isoxazolidin-5-yl}thymine **16**

Oil; R_f ($CHCl_3$:MeOH, 98:2) = 0.29; $[\alpha]_D$ –36.2 (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.45 (s, 3H), 1.78 (d, 3H, J = 1.2 Hz), 2.35 (ddd, 1H, J = 3.8, 7.6, 13.8 Hz), 2.52 (ddd, 1H, J = 6.2, 7.6, 13.8 Hz), 3.40 (q, 1H, J = 7.6 Hz), 3.68 (dd, 1H, J = 6.2, 8.1 Hz), 4.06 (dd, 1H, J = 6.4, 8.1 Hz), 4.21 (d, 1H, J = 14.2 Hz), 4.30 (q, 1H, J = 7.1 Hz), 4.40 (d, 1H, J = 14.2 Hz), 5.98 (dd, 1H, J = 3.8, 7.6 Hz), 7.01 (q, 1H, J = 1.2 Hz), 7.36–7.42 (m, 5H), 8.21 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 25.1, 26.5, 38.9, 60.5, 65.9, 67.8, 75.3, 86.1, 109.8, 109.9, 127.6, 128.3, 129.5, 135.4, 136.6, 151.0, 161.8. Anal. calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 61.73; H, 6.38; N, 10.99.

4.5. 1-[(3S,5R)-2-Benzyl-3-(hydroxymethyl)isoxazolidin-5-yl]thymine **4** (L-isoxazolidinyl thymidine)

To a solution of **10** (0.4 g, 1.03 mmol) in MeOH (60 mL) was added *p*-TosOH (43 mg, 0.25 mmol) and the resulting solution was heated under reflux for 4 h. The reaction mixture was cooled at ambient temperature and neutralized with Amberlite IRA-400. The mixture was filtered and the filtrate evaporated under reduced pressure. The crude diol **12** (^{1}H NMR (acetone-d_6+D_2O) δ 1.80 (bs, 3H), 2.47 (ddd, 1H, J = 5.8, 8.2, 13.6 Hz), 2.65 (ddd, 1H, J = 3.2, 8.4, 13.6 Hz), 2.90 (q, 1H, J = 8.3 Hz), 3.60 (m, 2H), 3.79 (d, 1H, J = 14.4 Hz), 3.90 (m, 1H), 4.10 (d, 1H, J = 14.4 Hz), 6.14 (dd, 1H, J = 5.8, 8.4 Hz), 7.20–7.40 (m, 6H)) was taken up into a 1:1 mixture of MeOH:H_2O (30 mL), cooled at 0°C and treated with $NaIO_4$ (0.214 g, 1 mmol). The resulting suspension was stirred at 0°C for 1 h and then filtered. The filtrate was maintained at 0°C and treated with solid $NaBH_4$ (0.117 g, 3 mmol). The mixture was stirred at 0°C for an additional hour, at which time it was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc) on silica gel to give pure **4** (0.216 g, 66%) as a foam; R_f (EtOAc) = 0.37; $[\alpha]_D$ –6.9 (*c* 1.10, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.74 (d, 3H, J = 0.8 Hz), 2.29 (ddd, 1H, J = 3.4, 8.5, 13.6 Hz), 2.53 (bs, 1H), 2.98 (dt, 1H, J = 7.7, 13.7 Hz), 3.12 (ddt, 1H, J = 3.7, 4.8, 8.5 Hz), 3.68 (m, 1H), 3.78 (bd, 1H, J = 11.8 Hz), 3.84 (d, 1H, J = 13.9 Hz), 4.31 (d, 1H, J = 13.9 Hz), 5.92 (dd, 1H, J = 3.4, 7.4 Hz), 7.23–7.40 (m, 6H), 9.37 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 40.7, 61.5, 61.6, 66.3, 83.3, 109.7, 127.8, 128.5, 128.9, 136.0, 136.7, 150.5, 164.2. Anal. calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.72; H, 6.21; N, 13.05.

4.6. 1-[(3S,5S)-2-Benzyl-3-(hydroxymethyl)isoxazolidin-5-yl]thymine **14**

The method described above to convert **10** to **4** was applied to **11** (0.1 g, 0.258 mmol) to give, after column chromatography (EtOAc), pure **14** (39 mg, 48%) as an oil; R_f (EtOAc) = 0.25; $[\alpha]_D$ –38.8 (c 0.89, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.79 (d, 3H, J = 1.2 Hz), 1.87 (bs, 1H), 2.44 (ddd, 1H,

J = 4.6, 7.9, 13.7 Hz), 2.80 (ddd, 1H, J = 5.3, 7.6, 13.7 Hz), 3.45 (m, 1H), 3.74 (m, 2H), 4.19 (s, 2H), 6.00 (dd, 1H, J = 4.6, 7.6 Hz), 7.08 (q, 1H, J = 1.2 Hz), 7.30–7.40 (m, 5H), 8.15 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.3, 38.6, 59.9, 61.6, 64.7, 84.0, 110.7, 127.9, 128.6, 129.1, 135.7, 136.3, 150.0, 163.3. Anal. calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.37; H, 6.19; N, 13.46.

4.7. 1-[(3R,5S)-2-Benzyl-3-(hydroxymethyl)isoxazolidin-5-yl]thymine 3 (D-isoxazolidinyl thymidine)

The method described above to convert **10** to **4** was applied to **16** (30 mg, 0.077 mmol) to give, after column chromatography (EtOAc), pure **3** (13 mg, 55%) as an oil; R_f (EtOAc) = 0.37; $[\alpha]_D$ +6.1 (*c* 0.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.70 (bs, 1H), 1.77 (d, 3H, J = 1.2 Hz), 2.29 (ddd, 1H, J = 3.6, 8.5, 13.7 Hz), 2.99 (dt, 1H, J = 7.4, 13.7 Hz), 3.15 (ddt, 1H, J = 3.6, 5.2, 8.6 Hz), 3.68 (dd, 1H, J = 5.0, 11.7 Hz), 3.79 (dd, 1H, J = 3.3, 11.7 Hz), 3.92 (d, 1H, J = 13.9 Hz), 4.32 (d, 1H, J = 13.9 Hz), 5.99 (dd, 1H, J = 3.6, 7.4 Hz), 7.23–7.50 (m, 6H), 8.47 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 40.7, 61.5, 61.6, 66.3, 83.3, 109.7, 127.8, 128.5, 128.9, 136.0, 136.7, 150.5, 164.2. Anal. calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.61; H, 5.88; N, 13.37.

Acknowledgements

The authors gratefully acknowledge the financial support by the Direccion General de Enseñanza Superior (Project PB97-1014, MEC, Madrid, Spain).

References

1. (a) Nguyen-Ba, N.; Brown, W. L.; Chan, L.; Lee, N.; Brasili, L.; Lafleur, D.; Zacharie, B. *Chem. Commun.* **1999**, 1245. (b) Lin, J.-S.; Kira, T.; Gullen, E.; Choi, Y.; Qu, F.; Chu, C. K.; Cheng, Y.-C. *J. Med. Chem.* **1999**, *42*, 2212. (c) Westwood, N. B.; Walker, R. T. *Tetrahedron* **1998**, *54*, 13391. (d) Mansour, T. S.; Evans, C. A.; Charron, M.; Korba, B. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 303. (e) Perry, C. M.; Faulds, D. *Drugs* **1997**, *53*, 657. (f) Deng, L.; Scharer, O. D.; Verdine, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 7865. (g) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782. (h) Peterson, M. L.; Vince, R. *J. Med. Chem.* **1991**, *34*, 2787.
2. For a review, see: Pan, S.; Amankulor, N. M.; Zhao, K. *Tetrahedron* **1998**, *54*, 6587.
3. For recent accounts, see: (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442. (b) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. In *Recent Research Developments in Synthetic Organic Chemistry*; Pandalai, S. G., Ed.; Transworld Research Network: Trivandrum, India, 1998; Vol. 1, p. 109.
4. Merino, P.; Franco, S.; Garces, N.; Merchan, F. L.; Tejero, T. *Chem. Commun.* **1998**, 493.
5. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett.* **1998**, *39*, 6411.
6. Xiang, Y.; Gi, H.-J.; Niu, D.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 7430. This approach has also been exemplified in our laboratory in synthesis of isoxazolidin-5-ones, useful precursors to a number of analogues of type **1b**. See: Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3945.
7. (a) Xiang, Y.; Chen, J.; Schinazi, R. F.; Zhao, K. *Tetrahedron Lett.* **1995**, *36*, 7193. (b) Xiang, Y.; Gong, Y.; Zhao, K. *Tetrahedron Lett.* **1996**, *37*, 4877.
8. Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9322. For 1,3-dipolar cycloadditions leading to racemic compounds, see: Li, P.; Gi, H.-J.; Sun, L.; Zhao, K. *J. Org. Chem.* **1998**, *63*, 366. Chiacchio, U.; Gumina, G.; Rescifina, A.; Romeo, R.; Uccella, N.; Casuscelli, F.; Piperno, A.; Romeo, G. *Tetrahedron* **1996**, *52*, 8889.
9. (a) DeShong, P.; Li, W.; Kennington Jr., J. W.; Ammon, H. L.; Leginus, J. M. *J. Org. Chem.* **1991**, *56*, 1364. (b) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598. (c) Xu, Z.; Johannes, C. W.; La, D. S.; Hofilena, G. E.; Hoveyda, A. H. *Tetrahedron* **1997**, *53*, 16377.

10. In this work we use the *syn*/*anti* nomenclature according to Masamune convention, see: Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557 and Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.
11. The importance of L-nucleoside analogues has been pointed out; see: (a) Furman, P. A.; Wilson, J. E.; Reardon, J. E.; Painter, G. R. *Antiviral Chemistry & Chemotherapy* **1995**, *6*, 345. (b) Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017. (c) Wang, P.; Gullen, B.; Newton, M. G.; Cheng, Y.-C.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 3390. (d) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1999**, *64*, 4173. (e) Varaprasad, C. V.; Averett, D. A.; Ramasamy, K. S.; Wu, J. *Tetrahedron* **1999**, *55*, 13345.
12. The 1,3-dipolar cycloaddition between a nitrone and a vinyl base has been applied to the synthesis of isoxazolidinyl nucleosides, but there was until now no example of the synthesis of homochiral compounds by such an approach; see: (a) Leggio, A.; Liguori, A.; Procopio, Siciliano, C.; Sindona, G. *Tetrahedron Lett.* **1996**, *37*, 1277. (b) Leggio, A.; Liguori, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Nucleosides and Nucleotides* **1997**, *16*, 1515. (c) Leggio, A.; Liguori, A.; Maiuolo, L.; Napoli, A.; Procopio, A.; Siciliano, C.; Sindona, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3097. (d) Adams, D. R.; Boyd, A. S. F.; Ferguson, R.; Grierson, D. S.; Monneret, C. *Nucleosides and Nucleotides* **1998**, *17*, 1053. (e) Colacino, E.; Converso, A.; De Nino, A.; Leggio, A.; Liguori, A.; Maiuolo, L.; Napoli, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Nucleosides and Nucleotides* **1999**, *18*, 581.
13. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489.
14. Desai, H. K.; Joshi, B. S.; Panu, A. M.; Pelletier, S. W. *J. Chromatogr.* **1985**, *322*, 223. Separation was carried out in a Chromatotron®, Harrison Research, Palo Alto, CA, USA.
15. For synthetic purposes it is possible to use the mixture of *cis*/*trans anti* isomers for the *N*-glycosylation step.
16. Niahimura, T.; Iwai, T. *Chem. Pharm. Bull.* **1964**, *12*, 352.
17. Vörbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
18. Semiempirical geometry optimizations were carried out at the PM3 level of theory as implemented in WINMOPAC 2.0, Fujitsu Limited, 1998. For simplicity the *N*-benzyl group of the nitrone **2** was replaced by a methyl group.
19. Ab initio calculations were performed using Gaussian 98, Revision A.3, M. Frisch, J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, USA, 1998.