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Application of Chiral Cyclic Nitrones to the Diastereoselective Synthesis of Bicyclic Isoxazolidine Nucleoside Analogues

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APPLICATION OF CHIRAL CYCLIC NITRONES TO THE DIASTEREOSELECTIVE SYNTHESIS OF BICYCLIC ISOXAZOLIDINE NUCLEOSIDE ANALOGUES

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□ New bicyclic isoxazolidine nucleoside analogues are synthesized through 1,3-dipolar cycloaddition of enantiopure cyclic nitrones to appropriate vinyl nucleobases. The reactions are diastereoselective, giving as the main or the sole product the exo-Re cycloadducts. The diastereoselectivity depends on both the kind of the base and the substitution pattern of the nitrone.

Keywords Isoxazolidines; nucleoside analogues; cyclic nitrones; vinyl nucleobases

INTRODUCTION

In the last two decades nucleoside analogues in which the furanose ring has been replaced by a different carbo- or heterocyclic ring have attracted special interest by virtue of their biological action as antiviral and anticancer agents.^[1] Among them isoxazolidine nucleosides have emerged as an important class of nucleoside analogues with potential pharmacological activity and several approaches for their synthesis have been reported.^[2] For construction of the heterocyclic ring the well-known convenient 1,3-dipolar cycloaddition approach has been applied in most cases.

Between the several parameters concerning the structure–activity relationship, of immense importance is the conformational behavior of natural as well as modified nucleosides, since conformational preferences are observed in the several enzymatic steps. Especially, nucleoside analogues with restricted conformational flexibility induced by a second ring are target compounds in many cases as potent inhibitors of HIV reverse transcriptase.^[3] Thus, the incorporation of isoxazolidine rings into

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conformationally restrained nucleoside analogues should be of considerable interest. However, to the best of our knowledge only two examples of bicyclic N,O-nucleoside analogues have been recently appeared in the literature.^[4] As targeted isoxazolidine analogues we have planned compounds of the general structure A, where the isoxazolidine ring mimics the sugar moiety and the second five membered ring induces restricted conformational mobility. Moreover the stereochemical outcome can be manipulated by the spatial disposition of the functional groups on the cyclopentane ring. The synthesis of these compounds can be easily achieved using cyclic nitrones in the 1,3-dipolar cycloaddition approach. Regarding the attachment of the nucleobase, it may be done either before the formation of the heterocyclic ring, by applying vinyl derivatives of pyrimidine and purine nucleobases as dipolarophiles, or after the cycloaddition step via nucleophilic substitution of a suitable preexisting on the starting materials leaving group by a nucleobase. The application of chiral cyclic nitrones in the above reaction sequences seems to be of particular importance, since it allows the creation of multiple stereocenters in a single step with complete control of their relative configuration.



In connection with our previous studies on the synthesis of modified nucleosides^[5] we report in this paper the synthesis of new bicyclic isoxazolidine nucleoside analogues of the general structure **A** applying 1,3-dipolar cycloaddition approach with chiral cyclic nitrones.

RESULTS AND DISCUSSION

For the purposes of our study we have used the previously prepared chiral polysubstituted nitrones 1 and 2 possessing two different stereochemical patterns of substituents. Nitrone 1 was prepared from D-ribose and its synthesis and applications to the preparation of pyrrolidine and pyrrolizidine derivatives have been previously described by us.^[6] Nitrone 2 was prepared from D-arabinose and its synthesis and application as intermediate for the total synthesis of pyrrolizidine alkaloids hyacinthacine A₂ and 7-deoxycasuarine have been previously described by research groups of Carmona,^[7a] Goti,^[7b] and Sardine.^[7c]



The required vinyl bases **3** were prepared by known alkylation followed by elimination procedures.^[8] The reactions between nitrone **1** and vinylbases **3** were carried out by refluxing equimolecular amounts of the reactants in toluene under an argon atmosphere until the disappearance of the starting compounds. From the reactions there were obtained the two diastereoisomers **4** and **5** in high total yields (96–99%) and in ratio 4.5:1 from the reaction with vinyladenine and 2.3:1 from the reactions with vinylthymine and vinyluracil (Scheme 1).

The structure elucidation of the obtained cycloadducts was mainly based on their spectral data. ¹H NMR assignments, where it was possible, were confirmed by double-resonance experiments, and selected values, useful for diagnostic purposes, are given in Table 1. The proposed regiochemistry is in accordance to the well-established regiochemistry of cycloadditions



SCHEME 1

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| Comp. | 3a-H | 4-H | H-7 | 8 ¹ -H | 8 ² -H | 8α-H | H-48 |
| 4a | 4,81 (t) $J = 6.4 \mathrm{Hz}$ | 3.80 br. q | 6.44 (dd) J = 7.7, 3.2 Hz | 3.00 (ddd) J = 13.1, 9.4.3.2 Hz | 3.16 (ddd) J = 13.1, 7.7.1.3 Hz | 4.03 br d | 4.65 (dd) $J = 6.4$, 3.2 Hz |
| 5a | 4.73 -4 .82 (m)* | $3.97-4.05 (m)^*$ | 6.40–6.47 (m)* | 2.66 (ddd) J = 14.0, 7.9, 2.9 Hz | 3.40 (ddd) J = 14.0, 7.7, 1.5 Hz | 4.19 (t) $J = 7.8$ Hz | 4.73–4.82 (m)* |
| 4b | 4.78 (t) $J = 7.0 \text{ Hz}$ | 3.67–3.75 (m)* | $6.09 (\mathrm{dd}) J = 7.0,$ $3.2 \mathrm{Hz}$ | 2.67 (ddd) J = 14.3, 7.7, 3.2 Hz | 3.12 (dd) J = 14.3, 7.0 Hz | 3.88 (dd) J = 7.7, 3.2 Hz | 4.58 (dd) $J = 7.0$, 3.2 Hz |
| 5b | 4.70–4.77 (m)* | 3.88 br. q | 6.09 (dd) J = 7.1, 3.2 Hz | 2.36–2.48 (m)* | 3.32 (dd) J = 13.9, 7.1 Hz | 4.23 (t) $J = 7.7$ Hz | 4.70–4.77 (m)* |
| 4c | 4.76 (t) $J = 6.7 \mathrm{Hz}$ | 3.67–3.78 (m)* | 6.09 (dd) J = 7.7, 3.6 Hz | 2.67 (ddd) J = 14.1, 7.7, 3.6 Hz | 3.11 (dd) J = 14.1, 7.7 Hz | 3.89 (dd) J = 7.7, 3.6 Hz | 4.60 (dd) f = 6.7, 3.6 Hz |
| 5c | 4.67–4.78 (m)* | 3.85 br. q | 6.09 (dd) J = 7.7, 2.6 Hz | 2.30–2.48 (m)* | 3.29 (dd) f = 13.5, 7.7 Hz | 4.22 (t) $J = 7.7$ Hz | 4.67–4.78 (m)* |
| | | | | | | | |

*overlapped multipets.



SCHEME 2

of nitrones with monosubstituted alkenes as dipolarophiles where the formation of 5-substituted isoxazolidines predominates^[9] and it is strongly supported by the chemical shift of the next to isoxazolidine oxygen 7-H proton, which appears as a doublet of doublets at the higher δ value.

For 5-substituted isoxazolidines there are four possible diastereomers arising from the *exo/endo* approach of dipolarophile and also from the *Re* and the *Si* face of the reacting nitrone, as depicted in Scheme 2 for the nitrone **1**. Between these four possible diastereomeric structures the major products **4** were assigned as *exo-Re* cycloadducts (Scheme 2, structure I), whereas the minor products **5** were assigned as *exo-Si* cycloadducts (structure III).

The data of Table 1 show that each of the methylene 8-H protons exhibits, besides their geminal coupling constant ($J_{8}1_{.8}2 = 13.1-14.3$ Hz), a large one (J = 7.0-9.4 Hz) and a small or zero one (J = 0-3.6 Hz). This shows that each of the 8-H is *trans* to one of its neighboring 7-H and 8a-H and *cis* to the other, which holds only in structures I and III. Futhermore, in the minor isomer 5 8a-H exhibits two large coupling constants (J = 7.7-7.8 Hz), indicating that, besides to one of the 8-H, it is also *cis* to 8b-H as it holds in structure III. Therefore, on the basis of the values of coupling constants, structures I and III were assigned for the major and minor isomers, respectively. The proposed structure for the major isomer



FIGURE 1 NOE enhancements measured on compound 4a.

was further supported by NOE measurements performed on compound **4a** as depicted in Figure 1. The mutual NOE enhancements observed between 8-H² with both 7-H and 8b-H show that these protons are on the same side of the plane. Similarly, the significant positive NOE observed between 8a-H with both 4-H and 8-H¹ shows also that these protons are on the same side above the rings. These spatial arrangements of protons are possible only in structure I.

The reactions between the nitrone 2 and the vinyl bases 3 were also performed by refluxing equimolecular amounts of the reactants in toluene until the disappearance of the starting compounds. The reaction with vinyladenine gave only isomer 6 in 60% yield, whereas reactions with vilyluracil and vilylthymine gave the two diastereoisomers 6 and 7 in a ratio 10:1 and 75–80% total yield (Scheme 3).

The structure elucidation of the obtained cycloadducts was based on their spectral data. ¹H NMR assignments, where it was possible, were confirmed by double-resonance experiments, and selected values, useful for diagnostic purposes, are given in Table 2.

As in the case of the reactions of nitrone 1, the obtained cycloadducts were safely assigned as 5-substituted regioisomers on the basis the chemical shift of the next to isoxazolidine oxygen 2-H proton, which appears as a doublet of doublets at the higher δ (6.08–6.51). The four possible diastereomers arising from the *exo/endo* approach of dipolarophile and from the *Re/Si* face of the nitrone 2 are given in Scheme 4. The values of Table 2 show that the *cis* to the base more shielded 3-H¹ exhibits a small coupling constant with 2-H (2.2–3.4 Hz) and a larger one (7.3–7.9) with 3a-H indicative that it is *trans* to 2-H and *cis* to 3a-H. This arrangement holds only in structures I and III. Futhermore, in the major isomer **6** the 4-H exhibits two equal rather small coupling constants (J = 4.4-4.6 Hz) with 3a-H and 5-H, indicative that it is *trans* to both of them. Between structures



I and III this arrangement holds only in structure I. In the minor isomer 7 the less protected 3-H² *trans* to the base moiety and *cis* to 2-H exhibits a zero coupling constant with 3a-H showing their *trans* arrangement. Therefore, similarly to the cycloadducts 4 and 5 of nitrone 1, the major products 6 are assigned as *exo-Re* cycloadducts (structure I), whereas the minor products 7 are assigned as *exo-Si* cycloadducts (structure III).

The proposed structures are further supported by NOE measurements performed on compounds **6c** and **7c** as depicted in Figures 2 and 3, respectively. In compound **6c** the significant NOE enhancement observed between the *trans* to the base 3-H^2 and 4-H shows that they are at the same side. Similarly, in compound **7c** the remarkable NOE between the 3-H^2 and one of the methylene CH₂OBn protons shows that these protons are on the same side. In accordance with the proposed structure, a significant positive NOE is also developed on one of CH₂OBn upon saturation of 2-H. However, it should be noted that the more informative for the structure determination NOE measurements, between 3a-H and its neighboring protons, were not possible since in all compounds 3a-H appears as multiplet overlapped with other chemical shifts.

The observed diastereoselectivity of the reactions of nitrones 1 and 2 is in accordance with molecular model predictions. Thus, in all cases the stereochemically favored *exo* adducts are formed with predominance of the *exo-Re* adduct, which comes from the less sterically hindered transition state. These findings are also in line with the well-documented behavior of cyclic nitrones to react via *exo* transition states^[10] and our previous results on the reactions of nitrone 1 with several dipolarophiles.^[6b] Between the two nitrones studied, nitrone 2 has a more restricted *Si* phase since besides the substituent at the 5-position bears also a substituent at the 3-position towards this phase. Thus, nitrones of this type have been referred to show almost

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| IABLE 2 | Selected values for C | memical shirts and Coupi | ung constants of compo | unas o ana / | | | |
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| Comp. | 2-H | $3-H^1$ | $3-H^2$ | 3a-H | 4-H | 5-H | H-9 |
| 6a | 6.51 (dd) $J = 5.7$, 3.1 Hz | 2.82–2.92 (m) | 2.82–2.92 (m) | 3.92 (m) | 4.14 (t) $J = 4.4$ Hz | 4.21 (t) $J = 4,4$ Hz | 3.57–3.77 (m)* |
| 6b | 6.25 (dd) $J = 6.5$, 2.2 Hz | 2.43 (ddd) J = 13.9, 7.7, 2.2 Hz | 2.81 (dt) $J = 13.9$, 6.5 Hz | 3.53–3.73 (m)* | 4.07 (t) $J = 4.6$ Hz | 4.12 (t) $J = 4.6$ Hz | 3.53–3.73 (m)* |
| 7b | 6.07 (dd) J = 7.1, 3.0 Hz | 2.39 (ddd) $J = 13.5$, 7.9, 3.0 Hz | 3.20 (dd) J = 13.5, 7.1 Hz | 3.88–4.19 (m)* | 3,88–4.19 (m)* | 3,88–4.19 (m)* | 3.52–3.62 (m) |
| 6 c | 6.25 (dd) $J = 6.6$, 2.6 Hz | 2.49 (ddd) J = 13.6, 7.5, 2.6 Hz | 2.81 (dt) $J = 13.6$, 6.6 Hz | 3.57–3.73 (m)* | 4.07(t) J = 4.4 Hz | 4.15 (t) $J = 4.4$ Hz | 3.57–3.73 (m)* |
| 7c | 6.08 (dd) $J = 7.5$, 3.4 Hz | 2.37 (ddd) $J = 13.6$, 7.3, 3.4 Hz | 3.18 (dd) J = 13.6, 7.5 Hz | 3.89–4.16 (m)* | 3.89–4.16 (m)* | $3.89-4.16 (m)^{*}$ | 3.48–3.58 (m) |
| (| | | | | | | |

TABLE 2 Selected Values for Chemical Shifts and Coupling Constants of Compounds 6 and 7

*Overlapped multiplets.



SCHEME 4

perfect discrimination of the two faces affording products only from the *Re*-face with the *exo-Re* as the major or the sole product and the *endo-Re* as the minor one.^[7a,7b,10d] However, in our experiments with nitrone **2** and vinyl bases the above described evidence supports structure **7** for the minor isomer resulting from an *exo-Si* approach. Nevertheless, the increased steric hindrance results in a higher diastereoselectivity of nitrone **2** giving rise exclusively or higher ratios of the major *exo-Re* adducts. An interesting point is also the influence of the base on the diastereoselectivity of the reactions. Thus, the bulkier vinyladenine **3a** increases the steric hindrance and induces higher diastereoselectivity in the reactions with both nitrones **1** and **2**. So, the reaction of the nitrone **1** with **3a** gives the major adduct **4** in a higher ratio (4.5:1 compared to 2.3:1 with **3b** and **3c**), whereas the reaction of **2** with **3a** gives exclusively the major adduct **6**.

In conclusion, the cycloaddition reactions of the chiral cyclic nitrones **1** and **2** with vinyl nucleic bases can lead conveniently to asymmetric bicyclic isoxazolidine nucleoside analogues. All the reactions are diastereoselective giving the *exo-Re* cycloadducts as the main or the sole product. The diastereoselectivity is dictated by steric factors and it is mainly determined by the nitrone configuration enhanced further by the magnitude of the nucleic base in the olefin moiety. These results, together with the possibility to use sugar-derived cyclic nitrones with known and desirable configuration, allow



FIGURE 2 NOE enhancements measured on compound 6c.

access to bicyclic nucleoside analogues, as possible candidates for biological applications, in a stereocontrolled and predictable manner.

EXPERIMENTAL

Mps are uncorrected and were determined on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin-Elmer 297 spectrometer. ¹H NMR spectra were recorded at 300 MHz on a Bruker 300 AM spectrometer and ¹³C NMR spectra at 75.5 MHz on the same spectrometer, and are quoted relative to tetramethylsilane as internal reference, in deuteriochloroform solutions. Mass spectra (EI) were performed on a VG-250 spectrometer with ionization energy maintained at 70 eV. High-resolution mass spectra (HRESI) were obtained with a 7 T APEX II spectrometer. Microanalyses were performed on a Perkin-Elmer 2400-II element analyzer. Column



7c (B = T)

FIGURE 3 NOE enhancements measured on compound 7c.

chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use.

General Procedure for the Cycloaddition Reactions

A solution of the nitrone 1 or 2 (0.5 mmol) and the dipolarophile 3 (0.5 mmol) in toluene (5 mL) was heated to reflux under an argon atmosphere and the reaction was monitored by TLC until the consumption of the starting reagents. This took about 2 days for the reactions of nitrone 1 and 8–10 hours for the reactions of nitrone 2. Then the heating was stopped and after evaporation of the solvent the residue was chromatographed on a silica gel column with ethyl acetate–methanol 95:5 (for the reaction of 1 with 3a), ethyl acetate (for the reactions of 1 with 3b and 3c and 2 with 3a) and ethyl acetate–hexane 2:1 (for the reactions of 2 with 3b and 3c) as the eluents. With the exception of 5a and 7b in all other cases it was possible to isolate from the column fractions with separated pure isomers. The given yields are the total yields as they were calculated from the pure fractions and the estimated consistency of the mixtures by ¹H NMR.

9-{(3a*S,4S,7R,*8a*R,*8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2dimethylhexahydro [1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazol-7-yl}adenine (4a)

This compound was obtained from the reaction of nitrone **1** with 9-vinyadenine (**3a**) in 81% yield as an solid mp 185–187°C; Rf (EtOAc/MeOH, 95:5) 0.47; ¹H NMR (CDCl₃) δ : 1.36 (s, 3H, CH₃), 1.56 (s, 3H, CH₃), 2.79 (dd, J = 15.4, 5.8 Hz, 1H, $CH_2CO_2CH_3$), 2.93 (dd, J = 15.4, 8.9 Hz, 1H, $CH_2CO_2CH_3$), 3.00 (ddd, J = 13.1, 9.4, 3.2 Hz, 1H, 8-H), 3.16 (ddd, J = 13.1, 7.7, 1.3 Hz, 1H, 8-H), 3.71 (s, 3H, OCH₃), 3.80 (br q, 1H, 4-H), 4.03 (br d, 1H, 8a-H), 4.65 (dd, J = 6.4, 3.2 Hz, 1H, 8b-H), 4.81 (t, J = 6.4 Hz, 1H, 3a-H), 5.89 (br s, 2H, NH₂), 6.44 (dd, J = 7.7, 3.2 Hz, 1H, 7-H), 8.17 (s, 1H, Ad-H), 8.33 (s, 1H, Ad-H); ¹³C NMR (CDCl₃) δ : 25.1 and 27.4 (CH₃), 34.4 and 42.9 ($CH_2CO_2CH_3$ and C-8), 51.9 (OCH₃), 69.7, 70.2, 81.1, 85.6, and 88.3 (C-3a, C-4, C-7, C-8a, and C-8b), 115.3 ($C(CH)_3$), 119.2, 138.8, 149.3, 152.8, and 155.4 (C-Ad), 171.3 (C=O);MS: m/z (%): 391(32) [M+H⁺]. Anal. calcd. for C₁₇H₂₂N₆O₅ (315.33): C, 52.30; H, 5.68; N, 21.53. Found: C, 52.56; H, 5.90; N, 21.23.

9-{(3a*S*,4*S*,7*S*,8a*S*,8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2dimethylhexahydro [1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazol-7-yl}adenine (5a)

This compound was obtained from the reaction of nitrone 1 with 9vinyladenine (3a) as a mixture with the isomer 4a and it was characterized only from its NMR data assigned in the mixture (yield 18%). ¹H NMR (CDCl₃) δ : 1.30 (s, CH₃), 1.33 (s, CH₃), 2.52 (d, J = 7.0 Hz, $CH_2CO_2CH_3$), 2.66 (ddd, J = 14.0, 7.9, 2.9 Hz, 8-H), 3.40 (ddd, J = 14.0, 7.7, 1.5 Hz, 8-H), 3.74 (s, OCH₃), 3.97–4.05 (m, 4-H superimposed with 8a-H of the **4a** isomer), 4.19 (t, J = 7.8 Hz, 8a-H), 4.73–4.82 (m, 3a-H, 8b-H superimposed with 3a-H of **4a** isomer), 6.30 (br s, NH₂), 6.40–6.47 (m, 7-H, superimposed with 7-H of **4a** isomer), 8.17 (s, 1H, Ad-H), 8.33 (s, 1H, Ad-H); ¹³C NMR (CDCl₃) δ : 24.2 and 26.6 (CH₃), 36.7 and 38.1 ($CH_2CO_2CH_3$ and C-8), 52.0 (OCH₃), 67.4, 68.1, 82.3, 82.7, and 87.1 (C-3a, C-4, C-7, C-8a, and C-8b), 113.4 ($C(CH)_3$), 119.4, 138.7, 149.3, 152.9, and 155.4 (C-Ad), 171.3 (C=O).

1-{(3a*S,4S,7R,*8a*R,*8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2dimethylhexahydro [1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazol-7-yl}uracil (4b)

This compound was obtained from the reaction of nitrone **1** with 1vinyuracil (**3b**) in 67% yield as an oil; Rf (EtOAc) 0.47; ¹H NMR (CDCl₃) δ : 1.33 (s, 3H, CH₃), 1.53 (s, 3H, CH₃), 2.67 (ddd, J = 14.3, 7.7, 3.2 Hz, 1H, 8-H), 2.80 (dd, J = 14.8, 5.8 Hz, 1H, $CH_2CO_2CH_3$), 2.90 (dd, J = 14.8, 9.6 Hz, 1H, $CH_2CO_2CH_3$), 3.12 (dd, J = 14.3, 7.0 Hz, 1H, 8-H), 3.67–3.75 (overlapped s and m, 4H, OCH₃, and 4-H), 3.88 (dd, J = 7.7, 3.2 Hz, 1H, 8a-H), 4.58 (dd, J = 7.0, 3.2 Hz, 1H, 8b-H), 4.78 (t, J = 7.0 Hz, 1H, 3a-H), 5.69 (d, J = 8.3 Hz, 1H, Ur-H), 6.09 (dd, J = 7.0, 3.2 Hz, 1H, 7-H), 7.73 (d, J = 8.3 Hz, 1H, Ur-H), 9.37 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ : 25.0 and 27.3 (CH₃), 34.4 and 43.2 ($CH_2CO_2CH_3$ and C-8), 51.9 (OCH₃), 70.1, 70.5, 83.2, 85.4, and 87.7 (C-3a, C-4, C-7, C-8a and C-8b), 101.9 (C-Ur), 115.4 (C(CH)₃), 140.0, 150.4, and 163.4 (C-Ur), 171.3 (C=O); HRESIMS for C₁₆H₂₁N₃O₇ (M+Na)⁺: calcd. 390.1272, found 390.1274. Anal. calcd. for C₁₆H₂₁N₃O₇: C, 52.31; H, 5.76; N, 11.44. Found: C, 51.95; H, 5.78; N, 11.28.

1-{(3a*S*,4*S*,7*S*,8a*S*,8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2dimethylhexahydro [1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazol-7-yl}uracil (5b)

This compound was obtained from the reaction of nitrone **1** with 1vinyuracil (**3b**) in 29% yield as an oil; Rf (EtOAc) 0.36; ¹H NMR (CDCl₃) δ : 1.30 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 2.36–2.48 (m, 2H, 8-H and $CH_2CO_2CH_3$), 2.54 (dd, J = 15.4, 7.1 Hz, 1H, $CH_2CO_2CH_3$), 3.32 (dd, J = 13.9, 7.1 Hz, 1H, 8-H), 3.71 (s, 3H, OCH₃), 3.88 (br q, 1H, 4-H), 4.23 (t, J = 7.7 Hz, 1H, 8a-H), 4.70–4.77 (m, 2H, 3a-H, and 8b-H), 5.69 (d, J = 8.4 Hz, Hz, 1H, Ur-H), 6.09 (dd, J = 7.1, 3.2 Hz, 1H, 7-H), 7.76 (d, J = 8.4 Hz, 1H, Ur-H), 8.66 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ : 24.1 and 26.5 (CH₃), 36.4 and 38.8 ($CH_2CO_2CH_3$ and C-8), 52.1 (OCH₃), 67.9, 68.6, 82.6, 85.5, and 87.1 (C-3a, C-4, C-7, C-8a, and C-8b), 101.9 (C-Ur), 113.4 (C(CH)₃), 140.2, 150.3, and 163.3 (C-Ur), 170.7 (C=O). HRESIMS for $C_{16}H_{21}N_3O_7$ (M+Na)⁺: calcd. 390.1272, found 390.1270. Anal. calcd. for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.18; H, 5.95; N, 11.49.

1-{(3a*S,4S,7R,*8a*R,*8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2dimethylhexahydro [1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazol-7-yl}thymine (4c)

This compound was obtained from the reaction of nitrone **1** with 1vinythymine (**3c**) in 68% yield as a solid mp 182–184°C; Rf (EtOAc) 0.52; ¹H NMR (CDCl₃) δ : 1.34 (s, 3H, CH₃), 1.54 (s, 3H, CH₃), 1.94 (s, 3H, CH₃), 2.67 (ddd, J = 14.1, 7.7, 3.6 Hz, 1H, 8-H), 2.83 (dd, J = 15.3, 5.8 Hz, 1H, $CH_2CO_2CH_3$), 2.92 (dd, J = 15.3, 9.5 Hz, 1H, $CH_2CO_2CH_3$), 3.11 (dd, J = 14.1, 7.7 Hz, 1H, 8-H), 3.67–3.78 (overlapped s and m, 4H, OCH₃, and 4-H), 3.89 (dd, J = 7.7, 3.6 Hz, 1H, 8a-H), 4.60 (dd, J = 6.7, 3.6 Hz, 1H, 8b-H), 4.76 (t, J = 6.7 Hz, 1H, 3a-H), 6.09 (dd, J = 7.7, 3.6 Hz, 1H, 7-H), 7.58 (s, 1H, Thy-H), 9.40 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ : 12.4, 25.0, and 27.2 (CH₃), 34.4 and 43.1 ($CH_2CO_2CH_3$ and C-8), 51.9 (OCH₃), 70.1, 70.5, 83.0, 85.5, and 87.7 (C-3a, C-4, C-7, C-8a, and C-8b), 110.4 (C-Thy), 115.4 (C(CH)₃), 135.8, 150.5, and 164.0 (C-Thy), 171.3 (C = O). HRESIMS for C₁₇H₂₃N₃O₇ (M+Na)⁺: calcd. 404.1428, found 404.1430. Anal. calcd. for C₁₇H₂₃N₃O₇: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.19; H, 5.94; N, 10.78.

1-{(3a*S*,4*S*,7*S*,8a*S*,8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2dimethylhexahydro [1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazol-7-yl}thymine (5c)

This compound was obtained from the reaction of nitrone **1** with 1vinythymine (**3c**) in 30% yield as an oil; Rf (hexane/EtOAc, 3:1) 0.41; ¹H NMR (CDCl₃) δ : 1.31 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 1.92 (s, 3H, CH₃), 2.30–2.48 (m, 2H, 8-H, and CH₂CO₂CH₃), 2.58 (dd, J = 16.0, 7.1 Hz, 1H, CH₂CO₂CH₃), 3.29 (dd, J = 13.5, 7.7 Hz, 1H, 8-H), 3.73 (s, 3H, OCH₃), 3.85 (br q, 1H, 4-H), 4.22 (t, J = 7.7 Hz, 1H, 8a-H), 4.67–4.78 (m, 2H, 3a-H, and 8b-H), 6.09 (dd, J = 7.7, 2.6 Hz, 1H, 7-H), 7.57 (s, 1H, Thy-H), 8.68 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ : 12.6, 24.6, and 26.5 (CH₃), 36.6 and 38.8 (CH₂CO₂CH₃ and C-8), 52.0 (OCH₃), 67.7, 68.5, 82.6, 84.5, and 87.2 (C-3a, C-4, C-7, C-8a, and C-8b), 110.2 (C-Thy), 113.4 (C(CH)₃), 136.1, 159.3, and 163.9 (C-Thy), 170.7 (C=O). HRESIMS for C₁₇H₂₃N₃O₇: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.41; H, 6.12; N, 10.83.

9-{(*2R,3aR,4R,5R,6R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]hexahydro pyrrolo[1,2-*b*]isoxazol-2-yl}adenine (6a)

This compound was obtained from the reaction of nitrone **2** with 9vinyadenine (**3a**) in 60% yield as an oil; Rf (EtOAc) 0.12; ¹H NMR (CDCl₃) δ : 2.80–2.92 (m, 2H, 3-H), 3.57–3.77 (m, 3H, 6-H, CH₂OCH₂Ph), 3.92 (m, 1H, 3a-H), 4.14 (t, J = 4.4 Hz, 1H, 4-H) 4.21(t, J = 4.4 Hz, 1H, 5-H), 4.46–4.65 (m, 6H, CH₂OCH₂Ph), 6.32 (br s, 2H, NH₂), 6.51 (dd, J = 5.7, 3.1 Hz, 1H, 2-H), 7.11–7.47 (m, 15H, Ph-H), 8,24 (s, 1H, Ad-H), 8.31 (s, 1H, Ad-H); ¹³C NMR (CDCl₃) δ : 41.4 (C-3), 67.5, 69.7, 71.4, 72.2, 72.4, 73.4, 83.6, 85.5, and 87.9 (C-2, C-3a, C-4, C-5, C-6, and CH₂), 119.6 (C-Ad), 127.7, 127.9, 128.0, 128.5, 137.4, 137.8, and 138.1 (C-Ph), 138.9, 149.1, 152.9, and 155.6 (C-Ad); HRESIMS for C₃₃H₃₄N₆O₄: C, 68.49; H, 5.92; N, 14.52. Found: C, 68.55; H, 6.07; N, 14.22.

1-{(*2R,3aR,4R,5R,6R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]hexahydro pyrrolo[1,2-*b*]isoxazol-2-yl}uracil (6b)

This compound was obtained from the reaction of nitrone **2** with 9vinyuracil (**3b**) in 68% yield as an oil; Rf (hexane/EtOAc, 1:2) 0.40; ¹H NMR (CDCl₃) δ : 2.43 (ddd, J = 13.9, 7.7, 2.2 Hz, 1H, 3-H), 2.81 (dt, J =13.9, 6.5 Hz, 1H, 3-H), 3.53–3.73 (m, 4H, 3a-H, 6-H, CH₂OCH₂Ph), 4.07 (t, J = 4.6 Hz, 1H, 4-H), 4.12 (t, J = 4.6 Hz, 1H, 5-H), 4.45–4.60 (m, 6H, CH₂OCH₂Ph), 5.68 (d, J = 8.6 Hz, 1H, Ur-H), 6.25 (dd, J = 6.5, 2.2 Hz, 1H, 2-H), 7.19–7.41 (m, 15H, Ph-H), 7.68 (d, J = 8.6 Hz, 1H, Ur-H), 10.00 (s, 1H, NH); ¹³C NMR (CDCl₃) δ : 41.9 (C-3), 67.0, 69.4, 71.3, 72.1, 73.2, 85.1, 85.4, and 87.9 (C-2, C-3a, C-4, C-5, C-6, and CH₂), 101.7 (C-Ur), 127.5, 127.6, 127.7, 127.9, 128.3, 128.4, 137.3, 137.6, and 137.8 (C-Ph), 140.1, 150.3, and 163.8 (C-Ur); HRESIMS for C₃₂H₃₃N₃O₆: C, 69.17; H, 5.99; N, 7.56. Found: C, 69.18; H, 6.08; N, 7.74.

1-{(*2S,3aS,4R,5R,6R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]hexahydro pyrrolo[1,2-*b*]isoxazol-2-yl}uracil (7b)

This compound was obtained from the reaction of nitrone **2** with 9vinyuracil (**3b**) only as a mixture with the isomer **6b** and it was characterized only from its NMR data assigned in the mixture (yield 7%). ¹H NMR (CDCl₃) δ : 2.39 (ddd, J = 13.5, 7.9, 3.0 Hz, 1H, 3-H), 3.20 (dd, J = 13.5, 7.1 Hz, 3-H), 3.52–3.62 (m, 6-H), 3.75 (dd, J = 10.0, 4.8 Hz, CH₂OCH₂Ph), 3.89–4.19 (m, 3a-H, 4-H, 5-H, CH_2OCH_2Ph), 4.45–4.65 (m, CH_2OCH_2Ph), 5.62 (d, J = 8.3 Hz. 1H, Ur-H), 6.07 (dd, J = 7.1, 3.0 Hz, 2-H), 7.19–7.41 (m, Ph-H), 7.85 (d, J = 8.3 Hz. 1H, Ur-H), 9.20 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ : 39.9 (C-3), 66.5, 68.1, 69.0, 72.7, 72.9, 73.3, 84.5, 85.5, and 87.6 (C-2, C-3a, C-4, C-5, C-6, and CH_2), 101.6 (C-Ur), 127.7, 127.8, 127.9, 128, 128.4, 128.6, 129.7, 137.2, 137.5, and 137.7 (C-Ph), 140.6, 150.4, and 163.8 (C-Ur).

1-{(*2R,3aR,4R,5R,6R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]hexahydro pyrrolo[1,2-*b*]isoxazol-2-yl}thymine (6c)

This compound was obtained from the reaction of nitrone **2** with 9vinythymine (**3c**) in 73% yield as a solid mp 139–141°C; Rf (hexane/EtOAc, 1:2) 0.59; ¹H NMR (CDCl₃) δ : 1.91 (s, 3H, CH₃), 2.49 (ddd, J = 13.6, 7.5,2.6 Hz, 1H, 3-H), 2.81 (dt, J = 13.6, 6.6 Hz, 1H, 3-H), 3.57–3.73 (m, 4H, 3a-H, 6-H, CH₂OCH₂Ph), 4.07 (t, J = 4.4 Hz, 1H, 4-H), 4.15 (t, J = 4.4 Hz, 1H, 5-H), 4.43–4.68 (m, 6H, CH₂OCH₂Ph), 6.25 (dd, J = 6.6, 2.6 Hz, 1H, 2-H), 7.19–7.41 (m, 15H, Ph-H), 7.48 (s, 1H, Thy-H), 9.22 (s, 1H, NH); ¹³C NMR (CDCl₃) δ : 12.4 (CH₃), 41.6 (C-3), 67.2, 69.5, 71.4, 72.1, 73.2, 84.9, 85.2, and 87.9 (C-2, C-3a, C-4, C-5, C-6, and CH₂), 110.4 (C-Thy), 127.5, 127.7, 127.9, 128.2, 128.4, and 128.5 (C-Ph), 135.7 (C-Thy), 137.3, 137.6, and 137.0 (C-Ph), 150.3 and 164.2 (C-Thy); HRESIMS for C₃₃H₃₅N₃O₆: (M+H)⁺: calcd. 570.2599, found 570.2593. Anal. calcd. for C₃₃H₃₅N₃O₆: C, 69.58; H, 6.19; N, 7.38. Found: C, 69.59; H, 6.26; N, 7.46.

1-{(*2S,3aS,4R,5R,6R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]hexahydro pyrrolo[1,2-*b*]isoxazol-2-yl}thymine (7c)

This compound was obtained from the reaction of nitrone **2** with 9vinythymine (**3c**) in 7% yield as an oil; Rf (hexane/EtOAc, 1:2) 0.44; ¹H NMR (CDCl₃) δ : 1.84 (s, 3H, CH₃), 2.37 (ddd, J = 13.6, 7.3, 3.4 Hz, 1H, 3-H), 3.18 (dd, J = 13.6, 7.5 Hz, 1H, 3-H), 3.48–3.58 (m, 1H, 6-H), 3.75 (dd, J = 9.5, 4.6 Hz, 1H, CH₂OCH₂Ph), 3.89–4.16 (m, 4H, 3a-H, 4-H, 5-H, CH₂OCH₂Ph), 4.45–4.65 (m, 6H, CH₂OCH₂Ph), 6.08 (dd, J = 7.5, 3.4 Hz, 1H, 2-H), 7.19–7.41 (m, 15H, Ph-H), 7.67 (s, 1H, Thy-H), 8.38 (s, 1H, NH); ¹³C NMR (CDCl₃) δ : 12.5 (CH₃), 38.1 (C-3), 67.0, 68.0, 69.4, 72.8, 73.0, 73.4, 84.4, 85.3, and 87.5 (C-2, C-3a, C-4, C-5, C-6, and CH₂), 110.2 (C-Thy), 127.7 127.9, 128.1, 128.5, and 128.6 (C-Ph), 136.2 (C-Thy), 137.3, 137.6, and 137.0 (C-Ph), 150.2 and 163.8 (C-Thy); HRESIMS for C₃₃H₃₅N₃O₆: C, 69.58; H, 6.19; N, 7.38. Found: C, 69.20; H, 6.34; N, 7.17.

REFERENCES

- (a) Crimmins, M.T. New developments in the enantioselactive synthesis of cyclopentyl carbocyclic nucleosides. *Tetrahedron* 1998, 54, 9229–9272. (b) Yokoyama, M.; Momotake, A. Synthesis and biological activity of azanucleosides. *Synthesis* 1999, 1541–1554. (c) Chu, C.K.; Ma, L.; Olgen, S.; Pierra, C.; Du, J.; Gumina, G.; Gullen, E.; Cheng, Y.-C.; Schinazi, R.F. Synthesis and antiviral activity of oxaselenonane nucleosides. *J. Med. Chem.* 2000, 43, 3906–3912. (d) Ichikawa, I.; Kato, K. Sugar-modified nucleosides in the past 10 years, a review. *Curr. Med. Chem.* 2001, 8, 385–423. (e) Moon, H.R.; Kim, H.O.; Lee, S.K.; Choi, W.J.; Chun, M.W.; Jeong L.S. Synthesis and biological evaluation of novel thioapio dideoxynucleosides. *Bioorg. Med. Chem.* 2002, 10, 1499–1507. (f) Choi, Y.; Choo, H.; Chong, Y.; Lee, S.; Olgen, S.; Schinazi, R.F.; Chu, C.K. Synthesis and potent anti-HIV activity of L-2',3'-dideoxy-2'-fluoro-4'-thiocytidine. *Org. Lett.* 2002, 4, 305–307. (g) Rodriguez, J.B.; Comin, M.J. New progresses in the enantioselective synthesis and biological properties of carbocyclic nucleosides. *Mini-Rev. Med. Chem.* 2003, 3, 95–114.
- (a) Pan, S.; Amankulor, N.M.; Zhao, K. Syntheses of isoxazolinyl and isoxazolidinyl nucleoside 2. analogues. Tetrahedron 1998, 54, 6587-6604. (b) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. Homochiral α -D and β -isoxazolidinylthymidines by 1,3-dipolar cycloaddition. J. Org. Chem. 1999, 64, 9321-9327. (c) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Procopio, A.; Rescifina, A.; Romeo, G.; Romeo, R. A stereoselective approach to isoxazolidinyl nucleosides. Eur. J. Org. Chem. 2001, 1893-1898. (d) Colacino, E.; Converso, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. Simple and efficient routes for the preparation of isoxazolidinyl nucleosides containing cytosine and 5-methyl-cytosine as new potential anti-HIV drugs. Tetrahedron 2001, 57, 8551-8557. (e) Dalpozzo, R.; De Nino, A.; Maiuolo L.; Procopio, A.; De Munno, G.; Sindona, G. 9-Vinylguanine: an easy access to aza-analogs of 2',3'-dideoxyguanosine. Tetrahedron 2001, 57, 4035-4038. (f) Fischer, R.; Drucková, A.; Fišera, L.; Rybár, A.; Hametner, C.; Cyrański, M.K. New chiral nitrones in the synthesis of modified nucleosides. Synlett 2002, 1113–1117. (g) Colacino, E.; De Luca, G.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. Reactivity models of 1-N-vinyluracil and synthesis of a new class of potential antiviral agents by the use of 1,3-dipolar cycloaddition reactions. Nucleosides Nucleotides & Nucleic acids 2003, 22, 743–745. (h) Merino, P.; Tejero, T.; Laguna, M.; Cerrada, E.; Moreno, A.; Lopez, J.A. An investigation of the Lewis acid mediated 1,3-dipolar cycloaddition between N-benzyl-C-(2-pyridyl)nitrone and allylic alcohol: direct entry to isoxazolidinyl C-nucleosides. Org. Biomol. Chem. 2003, 1, 2336-2342. (i) Chiacchio, U.; Genovese, F.; Iannazzo, D.; Piperno, A.; Quadrelli, P.; Antonino, C.; Romeo, R.; Valveri, V.; Mastino, A. 4'- α -C-Branched N,O-nucleosides: synthesis and biological properties. Bioorg. Med. Chem., 2004, 12, 3903–3909. (j) Romeo, G.; Jannazzo, D.; Piperno, A.; Romeo, R.; Corsaro, A.; Rescifina, A.; Chiacchio, U. C-Alkoxycarbonyl nitrones: building blocks for the synthesis of butenolides, lactams and modified nucleosides. Mini-Rev. Org. Chem 2005, 2, 59-77. (k) Chiacchio, U.; Saita, M.G.; Crispino, L.; Gumina, G.; Mangiafico, S.; Pistarà, V.; Romeo, G.; Piperno, A.; De Clercq, E. Enantioselective synthesis of homocarbocyclic-2'-oxo-3'-azanucleosides. Tetrahedron 2006, 62, 1171-1181.
- 3. (a) Shin, K.J.; Moon, H.R.; George, C.; Marquez, V.E. Construction of the bicyclo[3.1.0] hexane template of a conformationally locked carbocyclic adenosine via an olefin keto-carbene cycloaddition. J. Org. Chem. 2000, 65, 2172-2178. (b) Wang G. Conformationally locked nucleosides: synthesis of 3 (R,S)-(adenin-9-yl)-1- and 3(R,S)-(cytosin-1-yl)-1- hydroxymethylbicyclo[2.1.1]hexanes. Tetrahedrom Lett. 2000, 41, 7139–7143. (c) Bhushan, R.G.; Vince, R. Synthesis of conformationally restricted 2'-3'-exo-methylene carbocyclic nucleosides built on a bicyclo[2.1.1]hexane template. Bioorg. Med. Chem. 2002, 10, 2325-2333. (d) Lin, W.Y.; Li, K.; Moore, B.M.; Doughty, M.B. Conformational properties of nucleotide-based template-competitive HIV-1 reverse transcriptase inhibitors: analysis of enzyme binding modes. Nucleosides Nucleotides Nucleic Acids 2003, 22, 283-297. (e) Choi, Y.; Moon, H.R.; Yoshimura, Y.; Marquez, V.E. Recent advances in the synthesis of conformationally locked nucleosides and their success in probing the critical question of conformational preferences by their biological targets. Nucleosides Nucleotides Nucleic acids 2003, 22, 547-557. (f) Kifli, N.; Htar, T.T.; De Clercq, E.; Balzarini, J.; Simons, C. Novel bicyclic sugar modified nucleosides: synthesis, conformational analysis and antiviral evaluation. Bioorg. Med. Chem., 2004, 12, 3247–3257. (g) Hrdlicka, P.J.; Andersen, N.K.; Jepsen, J.S.; Hansen, F.G.; Haselmann, K.F.; Nielsen, C.; Wengel, J. Synthesis and antiviral evaluation of branched and conformationally restricted analogs of the

anticancer compounds 3'-C-ethynyluridine (EUrd) and 3'-C-ethynylcytidine (ECyd). Bioorg. Med. Chem. 2005, 13, 2597–2621.

- (a) Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. Stereoselective synthesis of new bicyclic *N*,*O*-iso-homonucleoside analogues. *Tetrahedron* **2003**, 59, 5231–5240. (b) Procopio, A.; Alcaro, S.; De Nino, A.; Maiuolo, L.; Ortuso, F.; Sindona, G. New conformationally locked bicyclic *N*,*O*-nucleoside analogues of antiviral drugs. *Bioorg. Med. Chem. Lett.* **2005**, 15, 545–550.
- (a) Coutouli-Argyropoulou, E.; Pilanidou, P. An entry to new isoxazoline analogues of dideoxynucleosides by bromonitrile oxide 1,3-dipolar cycloaddition. *Tetrahedron Lett.* 2003, 44, 3755–3758.
 (b) Coutouli-Argyropoulou, E.; Lianis, P.; Giannoulis, A.; Mitakou, M.; Nowak, J. 1,3-Dipolar cycloaddition approach to isoxazole, isoxazoline and isoxazolidine analogues of *C*-nucleosides related to pseudouridine. *Tetrahedron* 2006, 62, 1494–1501.
- (a) Argyropoulos, N.G.; Panagiotidis, T.; Gallos, I. Synthesis of enantiomerically pure hydroxylated pyrroline *N*-oxides from p-ribose. *Tetrahedron: Asymmetry* **2006**, 17, 829–836. (b) Argyropoulos, N.G.; Panagiotidis, T.; Coutouli-Argyropoulou, E., Raptopoulou, C. Asymmetric nitrone cycloadditions and their application to the synthesis of enantiopure pyrrolidine and pyrrolizidine derivatives. *Tetrahedron* **2007**, 63, 321–330.
- (a) Carmona, A.T.; Whigtman, R.H.; Robina, I.; Vogel, P. Synthesis and glycosidase inhibitory activity of 7-deoxycasuarine. *Helv. Chim. Acta* 2003, 86, 3066–3073. (b) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. Total syntheses of hyacinthacine A₂ and 7-deoxycasuarine by cycloaddition to a carbohydrate derived nitrone. *Tetrahedron Lett.* 2003, 44, 2315–2318. (c) Desvergnes, S.; Sandrine, P.; Vallée, Y. Total synthesis of (+)-hyacinthacine A₂ based on SmI₂–induced nitrone umpolung. *J. Org. Chem.* 2005, 70, 1459–1462.
- (a) D'Auria, M.; Vantaggi, A. Photochemical reactivity of 9-vinyladenine with diethyl fumarate. J. Heterocyclic Chem., 1994, 31, 375–376. (b) Qiu, Y.L.; Ksebati, M.B.; Ptak, R.G.; Fan, B.Y.; Breitenbach, J.M.; Lin, J.S.; Cheng, Y.C.; Kern, E.R.; Drach, J.C.; Zemlicka, J. (Z)- and (E)-2-((hydroxymethyl)cyclopropylidene)methyladenine and –guanine: new nucleoside analogues with broad-spectrum antiviral activity. J. Med. Chem. 1998, 41, 10–23. (c) Adams, D.R.; Boyd, A.S.F.; Ferguson, R.; Grierson, D.S.; Monneret, C. Heterocyclic nucleoside analogues by cycloaddition reactions of 1-vinylthymine with 1,3-dipoles. Nucleosides Nucleotides, 1998, 17, 1053-1075.
- (a) Padwa, A.; Fisera, L.; Koehler, K.F.; Rodriguez, A.; Wong, G.S.K. Regioselectivity associated with the 1,3-dipolar cycloaddition of nitrones with electron-deficient dipolarophiles. *J. Org. Chem.* **1984**, 49, 276–281 (b) Ali, S.A.; Almuallem, H. 1,3-Dipolar cycloaddition reactions of a heterocyclic nitrone. *Tetrahedron* **1992**, 48, 5273–5282. (c) Tejero, T.; Dondoni, A.; Rojo, I.; Merchán, F.L.; Merino, P. 1,3-Dipolar cycloaddition of *C*-(2-thiazolyl)nitrones to chiral acrylates. Synthesis of enantiopure α-amino-2-alkylthiazoles and 5-formylpyrrolidin-2-ones. *Tetrahedron* **1997**, 53, 3301–3318. (d) Ishar, M.P.S.; Singh, G.; Kumar, K.; Singh, R. Investigations on peri-, regio- and stereoselectivities in thermal cycloadditions involving *C*-(4-Oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrones: role of steric factors and secondary interactions in 1,3-dipolar cycloadditions. *Tetrahedron* **2000**, 56, 7817–7828.
- (a) Tufariello, J.J. Alkaloids from nitrones. Acc. Chem. Res. 1979, 12, 396–403. (b) Tufariello, J.J.; Puglis, J.M. The stereochemistry of nitrone-diene cycloadditions: synthesis of the alkaloids of darlingia darlingiana. Tetrahedron Lett. 1986, 27, 1265–1268. (c) Ali, S. A.; Khan, J.H.; Wazeer, M.I.M. The regiochemistry and stereochemistry of 1,3-dipolar cycloaddition of cyclic nitrones. Tetrahedron 1988, 44, 5911–5920. (d) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. Synthesis and asymmetric [3 + 2] cycloaddition reactions of chiral cyclic nitrone: a novel system providing maximal facial bias for both nitrone and dipolarophile. Angew. Chem. Int. Ed. Engl. 1996, 35, 1863–1864. (e) Hall, A.; Meldrum, K.P.; Therond, P.R.; Wightman, R.H. Synthesis of hydroxylated pyrrolizidines related to alexine using cycloaddition reactions of functionalized cyclic nitrones. Synlett 1997, 123–125.