



Diastereoselective synthesis of *N,O*-psiconucleosides via 1,3-dipolar cycloadditions

Ugo Chiacchio,^{a,*} Antonino Corsaro,^a Daniela Iannazzo,^b Anna Piperno,^b Antonio Rescifina,^a Roberto Romeo^b and Giovanni Romeo^{b,*}

^a*Dipartimento di Scienze Chimiche, Università di Catania, Catania, Italy*

^b*Dipartimento Farmaco-Chimico, Università di Messina, Messina, Italy*

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Abstract—A flexible synthetic procedure to access a new and biologically interesting class of *N,O*-psiconucleosides by 1,3-dipolar cycloaddition of *C*-ethoxycarbonyl-*N*-methyl nitrone with ethyl 2-(acetyloxy)acrylate, followed by Vörbruggen nucleosidation and sodium borohydride reduction, is described. © 2001 Elsevier Science Ltd. All rights reserved.

The chemical modification of nucleic acid fragments offers a continuous challenge for organic chemists in search of compounds with antiviral and anticancer activity.¹ Accordingly, considerable efforts have been made in the last few years to develop new nucleoside analogs² likely to exhibit improved activity or decreased toxicity with respect to 3'-azido-5'-deoxythymidine (AZT), the first anti-HIV drug. In this context, the design of novel 'ribose' rings has resulted in the discovery of effective biologically active agents; in particular, promising results have been obtained from a new generation of nucleoside analogs where the ribose moiety has been replaced by alternative heterocyclic rings.³

The ever-growing interest for compounds with no cross resistance and low cytotoxicity has led, in recent years, to the investigation of the relatively unexplored, but potentially interesting area of nucleosides branched at the C_{1'} position, i.e. the so called psicofuranosyl nucleosides which carry an hydroxymethyl group at the anomeric carbon atom.⁴ Typical examples are angustmycin A and angustmycin C (**1**) (Fig. 1) which show interesting antimicrobial and antiviral properties, and

hydantodycin, a spironucleoside, which shows herbicide feature able to regulate plant growth.⁵

In connection with our studies on the exploitation of nitrones for the synthesis of biologically interesting nitrogenated compounds, we have recently designed a new synthetic route to *N,O*-nucleosides **2** via 1,3-dipolar cycloaddition of *C*-alkoxycarbonyl nitrones to vinyl acetate, followed by glycosylation with silylated nucleobases.⁶ The asymmetric version of the process has been successfully investigated through the use of chiral dipoles containing a chiral center α to the nitron functionality or a chiral auxiliary on the nitrogen atom.⁷

On this basis, we realized that the application of our methodology could serve as a strategy for the synthesis of modified psiconucleosides **3**, in which the sugar unit is replaced by an isoxazolidine ring. This paper describes a reaction route, of general applicability, which leads to *N,O*-psiconucleosides **3**, and we report here the first synthesis of purine and pyrimidine modified nucleosides, branched at the anomeric posi-

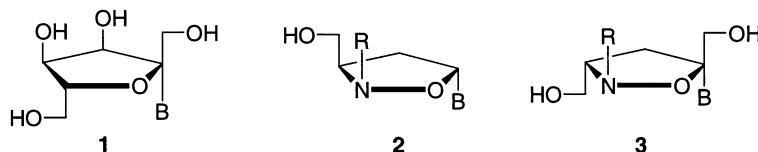


Figure 1.

* Corresponding authors. Fax: +39 095 580138; e-mail: uchiacchio@dipchi.unict.it

tion. In fact, to the best of our knowledge, no example of this kind of compound has been reported in literature, until now.

Results and discussion

The synthetic design requires the acquisition of the enol acetate **5** derived from ethyl pyruvate. Thus, ethyl pyruvate in acetic anhydride was heated under reflux for 20 h with *p*-toluenesulphonic acid; subsequent distillation under vacuum afforded the enol-acetate in 70% yield.⁸

The 1,3-dipolar cycloaddition reaction of **5** with alkoxy carbonylnitrone **4** took place in anhydrous ether at room temperature to give a mixture of epimeric isoxazolidines **6** and **7** in an isomeric ratio of ca. 8.6:1 and a combined yield of 96% (Scheme 1). The crude mixture was purified by flash chromatography (chloroform/methanol 99:1 as eluant) and the main cycloadduct **6** was obtained in pure form.⁹ The *cis/trans* stereochemistry of this adduct was readily deduced by means of NOE measurements. Thus, irradiation of H_{4a} (δ 2.87) produced strong enhancements for H₃ (δ 3.70; 11%) and H_{4b} (δ 3.17; 20%), together with a minor enhancement of the methyl group of the acetyl moiety at C₅ (δ 2.06). Conversely, when H_{4b} was irradiated, a positive NOE effect was observed only for H_{4a}, so indicating the *cis* relationship between H_{4b} and the CO₂Et groups at C₃ and C₅.

The crude mixture of epimeric isoxazolidines **6** and **7** was then transformed into two isoxazolidine nucleoside analogs as depicted in Scheme 1. The condensation with silylated thymine, using the glycosylation methodology developed by Vörbruggen,¹⁰ resulted in nucleoside products consisting of α -(**9a**) and β -(**8a**) anomers (1:1) which were isolated in 57% combined yield. The anomers could be separated by flash chromatography, the *cis* isomer (β) showing the lower *R_f*.¹¹

The anomeric configuration of **8a** and **9a** was assigned on the basis of ¹H NMR and NOE experiments in which irradiation of H_{2'a} (δ 2.83) in **8a** increased the

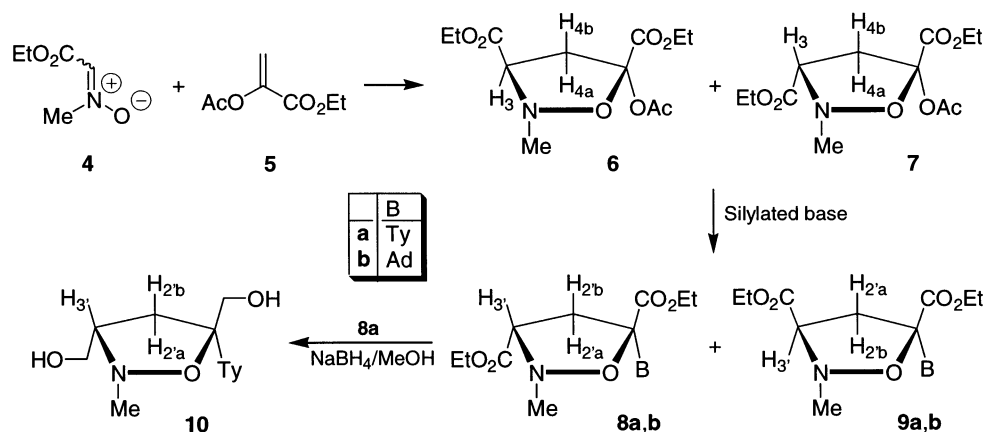
proton signals of H_{2'b} (δ 3.80) and H₆ (δ 7.46) by 32 and 3%, respectively. Conversely, when H_{2'b} was irradiated, strong NOE effects were observed for H_{3'} (δ 3.56) and H_{2'a}, so indicating that the thymine moiety at C_{1'}, H_{2'a} and the CO₂Et group at C_{3'} are in a topologically *cis* relationship. Similarly, in compound **9a**, upon irradiation of H_{2'a} (δ 2.97), the signal of H_{2'b} (δ 3.81) was enhanced, but no NOE effect was observed for the H_{3'} proton (δ 4.18) as well as for the resonance of H₆ in the thymine moiety; while irradiation of H_{2'b} induced an enhancement of H_{3'} and H₆ in the thymine group. As a consequence, the relative configuration of the CO₂Et groups at C_{1'} and C_{3'} must be *cis*.

Several attempts to optimize the reaction yield and conditions, in favor of formation of the β -isomer **8a**, were carried out by varying the temperature and the nature of the catalyst. The results are summarized in Table 1. As can be seen in entries 2–4, the use of higher temperatures (45–80°C) with respect to entry 1 (25°C) resulted in a better diastereoselectivity, leading to the exclusive formation of the β -isomer **8a**. In particular, the best yields were obtained using 0.4 equiv. of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst and a temperature of 45°C (see entry 3).

The results obtained can be rationalized by assuming that equilibration of the products is possible under the reaction conditions.¹² As reported, nucleosidation can proceed under kinetic or thermodynamic control through an intermediate oxonium ion: in our case, **8a** appears to be the thermodynamically controlled compound.

As confirmation, compound **9a** was heated at 45°C in acetonitrile, in the presence of TMSOTf and silylated thymine: the result was the complete formation of the isomer **8a**.

The initial goal of the design of a synthetic approach to a new class of *N,O*-psiconucleosides was then reached by NaBH₄ reduction of **8a** in a 1:1 dioxane/water solution at 0°C for 30 min. Thus, **8a**, as the selected model, furnished the expected compound **10** in 80% yield.¹³



Scheme 1.

Table 1. *N*-Glycosidation of **6** and **7** with silylated thymine and adenine in acetonitrile

Entry	Base	Conditions	B/I/C ^a	α : β Ratio	Combined yield (%)
1	Thymine	TMSOTf, 25°C, 24 h	2:1:1	1:1	57
2	Thymine	TMSOTf, 45°C, 10 h	2:1:1	0:1	70
3	Thymine	TMSOTf, 45°C, 10 h	2:1:0.4	0:1	80
4	Thymine	TMSOTf, 80°C, 6 h	2:1:1	0:1	40
5	Thymine	SnCl ₄ , 25°C, 24 h	2:1:0.3	1:1	10
6	Thymine	SnCl ₄ , 45°C, 10 h	2:1:0.3	0:1	30
7	Adenine	TMSOTf, 25°C, 24 h	2:1:0.4	1:1	30
8	Adenine	TMSOTf, 45°C, 10 h	2:1:0.4	0:1	50
9	Adenine	TMSOTf, 25°C, 24 h	2:1:1	NI ^b	25
10	Adenine	TMSOTf, 45°C, 10 h	2:1:1	NI ^b	35

^a Molar ratio of the base (B), isoxazolidine (I) and catalyst (C).^b Inseparable mixture.

The generality of this synthetic approach was tested with a purine nucleobase, by reaction of the mixture of isoxazolidines **6** and **7** with silylated adenine.

The results obtained are shown in Table 1. Also in this case, an increase in temperature leads to the formation of only the β -isomer **8b**.¹⁴ Control of the amount of catalyst appears to be essential to produce the desired nitrogen substitution product (N₉): when the amount of TMSOTf is more than 0.4 equiv., a complex and not a separable mixture of different derivatives was obtained which probably originates from nucleosidation at the other nitrogen atoms (N₇, N₁, N₃).¹²

In conclusion, we have described a flexible synthetic procedure to access a new and biologically interesting class of *N,O*-psiconucleosides: the methodology is applicable to purine and pyrimidine derivatives. The synthesis of both D- and L-isomers, using homochiral nitrones, is also in progress.

Acknowledgements

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References

- Kuritzkes, D. *HIV Clinical Management*; Medscape Inc., 1999; Vol. 13.
- (a) Schinazi, R. F.; Mead, J. R.; Feorino, P. M. *AIDS Res. Hum. Retrovir.* **1992**, *8*, 963; (b) Bonnet, P.; Robins, R. K. *J. Med. Chem.* **1995**, *36*, 635; (c) Chiacchio, U.; Iannazzo, D.; Rescifina, A.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28–36.
- (a) Gi, H. J.; Xiang, Y.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 88–92; (b) Merino, P.; del Alamo, E. M.; Franco, S.; Merchan, F. L.; Simon, A.; Tejero, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1543–1554; (c) Chiacchio, U.; Corsaro, A.; Gumina, G.; Iannazzo, D.; Rescifina, A.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321–9327.
- (a) Tronchet, J. M. J.; Zsely, M.; Brenas, L.; Lassout, O.; Grand, E.; Seuret, P.; Grigorov, M.; Rivara-Minten, E.; Geoffroy, M. *Nucleosides Nucleotides* **1999**, *18*, 1077–1078; (b) Jorgensen, P. N.; Wengel, J. *Structure and Chemistry*, Part E. 1997; Vol 19, 511–547; (c) Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem.* **1995**, *60*, 656–662.
- Prisbe, E. J.; Smejkal, J.; Verheyden, J. P. H.; Moffat, J. G. *J. Org. Chem.* **1976**, *41*, 1836–1846.
- Chiacchio, U.; Gumina, G.; Rescifina, A.; Romeo, R.; Uccella, N.; Piperno, A.; Romeo, G. *Tetrahedron* **1996**, *52*, 8889–8898.
- (a) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Romeo, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2045–2048; (b) *Eur. J. Org. Chem.*, in press.
- Monnin, J. *Helv. Chim. Acta* **1956**, *39*, 1721–1724.
- Compound 6**: 86% yield; yellow oil. ¹H NMR: (CDCl₃, 500 MHz) δ 1.19 (t, 6H, $J=6.2$ Hz), 2.06 (s, 3H), 2.87 (dd, 1H, $J=7.5$ and 13.5 Hz, H_{4a}), 2.91 (s, 3H, *N*-Me), 3.17 (dd, 1H, $J=9.0$ and 13.5 Hz, H_{4b}), 3.70 (dd, 1H, $J=7.5$ and 9.0 Hz, H₃), 4.11–4.20 (m, 4H). ¹³C NMR: (CDCl₃, 125 MHz) δ 13.81, 14.02, 20.95, 42.98, 45.30, 61.81, 62.62, 67.62, 104.59, 168.02, 168.37, 169.48.
Compound 7: 10% yield; yellow oil. ¹H NMR: (CDCl₃, 500 MHz) δ 1.23 (t, 6H, $J=6.2$ Hz), 2.01 (s, 3H), 2.85 (dd, 1H, $J=8.6$ and 14.0 Hz, H_{4a}), 2.86 (s, 3H, *N*-Me), 3.27 (dd, 1H, $J=8.5$ and 14.0 Hz, H_{4b}), 3.46 (dd, 1H, $J=8.5$ and 8.6 Hz, H₃), 4.15–4.21 (m, 4H). ¹³C NMR: (CDCl₃, 125 MHz) δ 13.81, 14.03, 25.62, 44.00, 45.26, 61.82, 62.62, 69.12, 103.47, 168.05, 168.37, 169.50.
- Vörbruggen, H.; Kvolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255.
- Compound 8a**: 80% yield; white solid: mp 145°C. ¹H NMR: (CDCl₃, 500 MHz) δ 1.20 (t, 6H, $J=7.1$ Hz), 1.90 (d, 3H, $J=1.3$ Hz), 2.83 (dd, 1H, $J=9.0$ and 13.9 Hz, H_{2a}), 2.90 (s, 3H, *N*-Me), 3.56 (dd, 1H, $J=8.2$ and 9.0 Hz, H₃), 3.80 (dd, 1H, $J=8.2$ and 13.9 Hz, H_{2b}), 4.16 (m, 4H), 7.46 (q, 1H, $J=1.3$ Hz, H₆), 8.07 (bs, 1H, NH). ¹³C NMR: (CDCl₃, 125 MHz) δ 12.68, 13.82, 14.01, 45.08, 45.35, 61.89, 63.25, 69.68, 92.93, 109.50, 134.65, 150.45, 164.20, 165.32, 167.91.13.
Compound 9a: 28.5% yield; white solid: mp 147–150°C. ¹H NMR: (CDCl₃, 500 MHz) δ 1.20 (t, 3H, $J=7.1$ Hz), 1.21 (t, 3H, $J=7.1$ Hz), 1.91 (d, 3H, $J=1.3$ Hz), 2.94 (s, 3H, *N*-Me), 2.97 (m, 1H, H_{2a}), 3.81 (m, 1H, H_{2b}), 4.18 (m, 1H, H₃), 4.20 (m, 4H), 7.45 (q, 1H, $J=1.3$ Hz, H₆),

- 8.82 (bs, 1H, NH). ^{13}C NMR: (CDCl_3 , 125 MHz) δ 12.76, 13.83, 14.20, 43.89, 45.38, 61.59, 63.23, 69.69, 93.62, 109.74, 134.74, 150.30, 164.28, 165.47, 166.34, 168.50.
12. Wilson, L. J.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis* **1995**, 1465–1479.
13. *Compound 10*: 80% yield; sticky oil. ^1H NMR: ($\text{CDCl}_3/\text{CD}_3\text{OD}$ 9:1, 500 MHz) δ 1.81 (d, 3H, $J=1.2$ Hz), 2.33 (m, 2H, $\text{H}_{2'}$), 2.73 (s, 3H, $N\text{-Me}$), 3.44 (m, 1H, $\text{H}_{3'}$), 3.65 (bs, 2H, OH), 4.05 (m, 2H, $\text{H}_{3''}$), 4.21 (m, 1H, $\text{H}_{1''\text{a}}$), 4.24 (m, 1H, $\text{H}_{1''\text{b}}$), 7.54 (q, 1H, $J=1.2$ Hz, H_6), 8.41 (bs, 1H, NH). ^{13}C NMR: ($\text{CDCl}_3/\text{CD}_3\text{OD}$ 9:1, 125 MHz) δ 26.04, 30.88, 46.10, 60.68, 61.30, 69.40, 102.78, 131.36, 136.26, 158.04, 166.18.
14. *Compound 8b*: 50% yield; yellow oil. ^1H NMR: (CDCl_3 , 500 MHz) δ 1.09 (t, 3H, $J=7.2$ Hz), 1.14 (t, 3H, $J=7.2$ Hz), 2.92 (s, 3H, $N\text{-Me}$), 3.74 (m, 2H, $\text{H}_{2'}$), 3.99 (m, 1H, $\text{H}_{3'}$), 4.16 (m, 4H), 6.03 (bs, 2H, NH_2), 8.10 (s, 1H), 8.26 (s, 1H). ^{13}C NMR: (CDCl_3 , 125 MHz) δ 13.80, 14.10, 41.82, 45.72, 61.88, 63.46, 68.18, 92.73, 120.19, 149.24, 152.74, 155.44, 164.20, 168.02, 168.05.