DOI: 10.1002/ejoc.200700171

Synthesis of Methyleneisoxazolidine Nucleoside Analogues by Microwave-Assisted Nitrone Cycloaddition

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Keywords: 1,3-Dipolar cycloaddition / Nucleosides / Microwave irradiation / Semiempirical calculations

A new series of conformationally locked N,O-nucleoside analogues was synthesized by exploiting allenic nucleobases as dipolarophiles in 1,3-dipolar nitrone cycloadditions. The regio- and sitoselectivity of the reaction were rationalized according to the frontier orbital treatment of the nitrone cycloaddition by AM1 calculations.

Introduction

In the search for effective antiviral and/or anticancer agents, the modification of natural nucleosides has emerged as a focal research area in medicinal chemistry.[1] A lot of structural modifications have been developed that affect the nucleobase, the sugar unit, or both.[2] Heterocyclic nucleosides have gained considerable attention in recent years.[3] In this context, our research group has disclosed a new series of modified nucleosides containing an isoxazolidine or a pyrrolidine spacer unit instead of the sugar moiety.[4] These nucleoside analogues have shown interesting physiological activities as inhibitors of HIV reverse transcriptase or as anti-HCV agents.[5]

The antiviral activity exhibited by nucleoside analogues has been correlated to some extent to conformational preferences of the drug during the formation of the enzyme-inhibitor complex, which temporarily inhibits DNA strand proliferation. Unmodified nucleoside rings, as described by the pseudorotation cycle,[6] exist in S-type (2′-*endo*/3′-*exo*) or N-type (2′-*exo*/3′-*endo*) conformations. The observation that reverse transcriptase (RT) is able to discriminate between two conformationally locked nucleosides[7] prompted us to pursue synthetic strategies aimed at locking the isoxazolidine ring in one of the two conformations.

Recently, we reported the synthesis of a new series of alkylidene isoxazolidinyl nucleosides **1**–**3** as potential anti-HIV agents. In these analogues, the sugar spacer is replaced by the more rigid methyleneisoxazolidine group (Figure 1).[8] The rationale for this choice is that the introduction of a rigid structural element could increase the selectivity towards viral polymerases relative to those of the cellular ones. Furthermore, this modification could increase the lipophilicity of the molecule, which would facilitate its interaction with the hydrophobic pocket of the RT binding site.

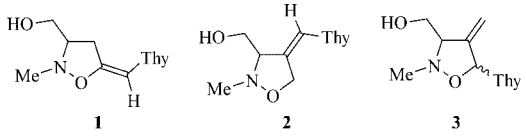

Figure 1. Alkylidene isoxazolidinyl nucleosides.

In this paper, we extended our interest towards the construction of conformationally controlled modified nucleosides, and we report the synthesis of N,O-nucleoside analogues **4** and **5**, which are characterized by the insertion of a methyleneisoxazolidine spacer unit between the nucleobase and the hydroxymethyl group. This spacer could control the conformational mobility of the system. An important structural feature of these compounds is the favorable arrangement and relative distance of the nucleobase and the hydroxymethyl group; the biological effects of modified nucleosides are strictly linked to the ability of these groups to interact with enzymes.[1f]

Results and Discussion

From a retrosynthetic perspective, allenic derivatives of nucleobases can be used as starting materials, and the isoxazolidine nucleus can be constructed by a 1,3-dipolar cycloaddition process (Scheme 1).

We therefore investigated the cycloaddition reaction of *C*-ethoxycarbonyl-*N*-methylnitrone (**6**) with protected thymallene **7**.[9] The reaction, performed in CCl_4 at reflux for 8 h with a dipole/dipolarophile ratio of 5:1, appears to pro-

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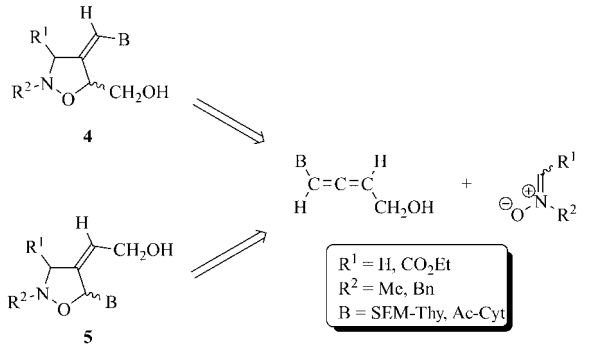


Scheme 1. Retrosynthetic analyses to isoxazolidines **4** and **5**.

ceed with high C-2–C-3 sitoselectivity and affords a diastereomeric mixture of compounds **8** and **9** in a 1:1 ratio (total yield 20%; Table 1, Entry 1) along with traces of 3-methoxyethoxytrimethylsilylthymine (SEM-thymine) **11**.[10] Better results were obtained when the cycloaddition process was performed under microwave irradiation. In fact, under these conditions the reaction time was reduced to 45 min and the yields of the cycloadducts increased to 50% (Scheme 2; Table 1, Entry 2).

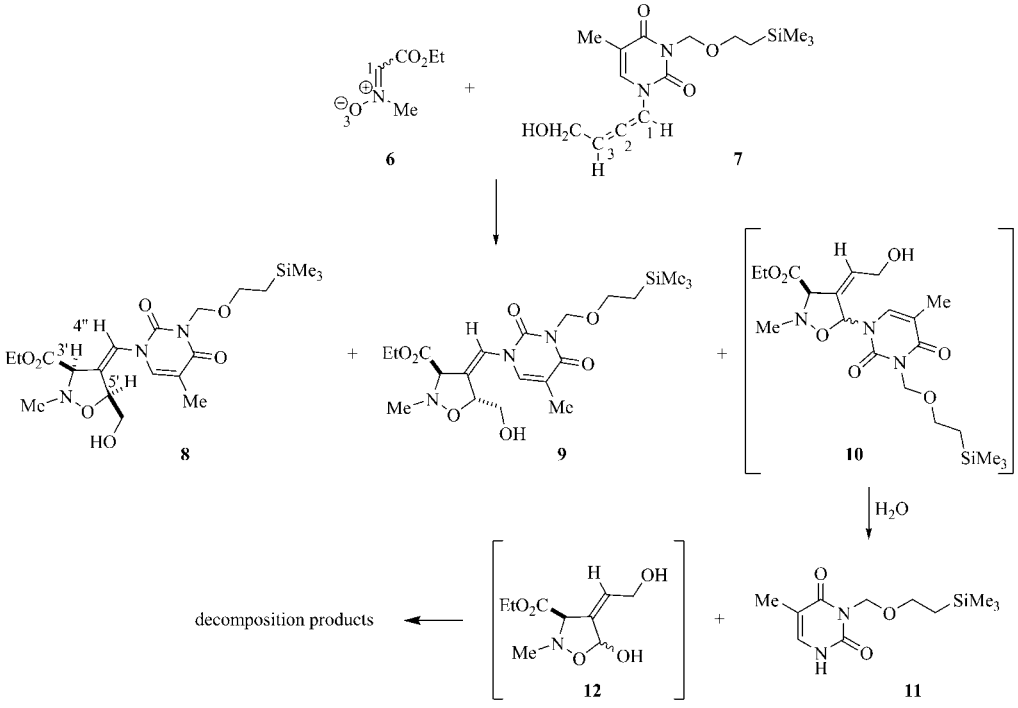
The structure of the cycloadducts was determined by ^{1}H NMR spectroscopic experiments. Thus, compound **8** shows the diagnostic resonance of the exocyclic methine proton 4"-H as a doublet of doublets at δ = 6.68 ppm, whereas the 5′-H proton resonates as a doublet of doublet of doublets at δ = 4.92 ppm and the 3′-H proton gives rise to a doublet of doublets at δ = 4.14 ppm. For compound **9**, the diagnostic resonance of the methine proton 4"-H appears at δ = 6.66 ppm, whereas the 5′-H proton resonates at δ = 4.82 ppm and the 3′-H proton produces a set of signals at δ = 4.04 ppm.

The identification of the individual diastereomers was established on the basis of ^{1}H–^{1}H NOE difference experiments. In particular, for *cis* adduct **8**, irradiation of the 4"-H proton induced a positive NOE effect on 3′-H; likewise, irradiation of 3′-H gave rise to NOE enhancements for 4"-

Table 1. Cycloaddition between nitrones **6**, **17** and **18** and protected allenyl nucleobases **7** and **13**.

Entry	Nitrone	Allene	Solvent	Temp. [°C]	MW [W][a]	Time [min]	Compounds	Ratio	Yield [%][b]
1	**6**	**7**	CCl_4	80[c]	n/a	480	**8/9**[d]	1:1	20
2	**6**	**7**	CCl_4	80	80	45	**8/9**	1:1	50
3	**6**	**13**	EtOH	70	80	10	**14/15**	1:1	50
4	**17**	**7**	CCl_4	70	80	15	**19a/20a**	1:2	69
5	**18**	**13**	EtOH	70	80	15	**19b/20b**	1:2	72
6	**17**	**7**	CCl_4	70	80	15	**21a/22a**	2:1	60
7	**18**	**13**	EtOH	70	80	15	**21b/22b**	2:1	45

[a] MW: microwave; the reactions were carried out in a microwave reactor by using a 3:1 ratio of dipole/dipolarophile. [b] Isolated yield. [c] Reaction performed in a sealed tube under conventional heating by using a 5:1 ratio of dipole/dipolarophile. [d] The reaction mixture also contained traces of **11**.

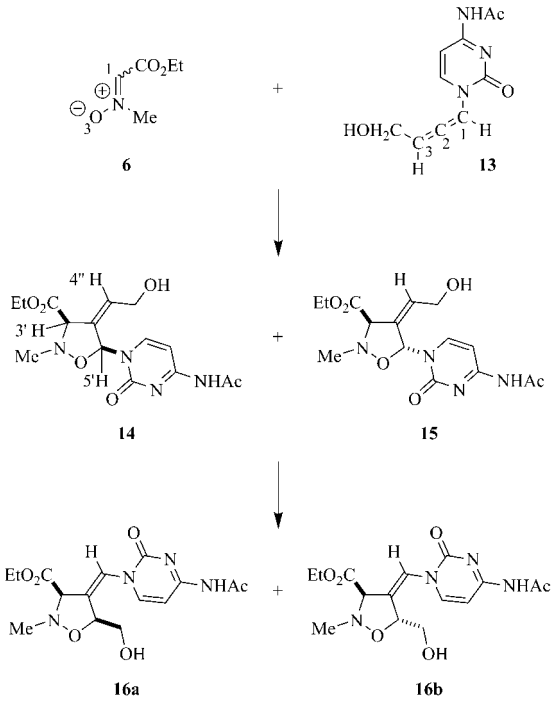


Scheme 2. Preparation of isoxazolidines **8** and **9**.

H and 5′-H. Moreover, when 6-H of thymine was irradiated, a positive NOE effect was observed on 5′-H. These data unambiguously support a *cis* relationship between 5′-H and 3′-H and, moreover, support a (*Z*) configuration between the thymine unit and the hydroxymethyl group present at C-5 of the isoxazolidine ring.

For *trans* adduct **9**, irradiation of the 4"-H proton produced a moderate enhancement for 3′-H, whereas irradiation of 5′-H gave rise to a positive NOE effect on 6-H. These results are clearly indicative of a *trans* relationship between 5′-H and 3′-H and a (*Z*) configuration between the thymine unit and the hydroxymethyl group.

We next explored the cycloaddition reaction of nitrone **6** with *N*-acetylcytallene **13**.[11] Under conditions of microwave irradiation in ethanol, the reaction was complete in only 10 min (Table 1, Entry 3). The cycloaddition process shows a different sitoselectivity with the attack of the dipole occurring at C-1–C-2 of the dipolarophile; we isolated a 1:1 mixture of compounds **14** and **15**, which have the nucleobase attached at C-5 of the isoxazolidine ring (Scheme 3).



Scheme 3. Synthesis of compounds **14**–**16**.

The assignment of the structures was made possible by ^{1}H NMR spectroscopic analysis. Compounds **14** and **15** show the diagnostic resonance of the aminalic 5′-H proton in the range 7.08–7.16 ppm, and the NOE enhancement observed between 3′-H and 5′-H in **14** is clearly indicative of a *syn* relationship between these protons. Furthermore, the (*Z*) configuration for both compounds was supported by the NOE enhancement observed for the methylene protons of the hydroxymethyl group when the 5′-H proton was irradiated.

The experimental results were explained according to the frontier orbital treatment of the nitrone cycloaddition. AM1 calculations indicate that the reaction is controlled by HOMO dipolarophile–LUMO dipole interactions (Table 2). The largest HOMO coefficients on protected thymallene **7** and protected cytallene **13** reside on the central atom of the allene and the next largest reside on the position bearing the protected pyrimidine. For the nitrone, the largest coefficient resides on C-1 and the lowest on the oxygen atom. Consequently, the cycloaddition should proceed with good sitoselectivity, and the reaction should afford adducts that contain the nucleobase at the C-5 position of the isoxazolidine ring.

Table 2. HOMO and LUMO energies [eV] and orbital coefficients for nitrones **6**, **17**, and **18**, and allenes **7** and **13** calculated at the AM1 level.

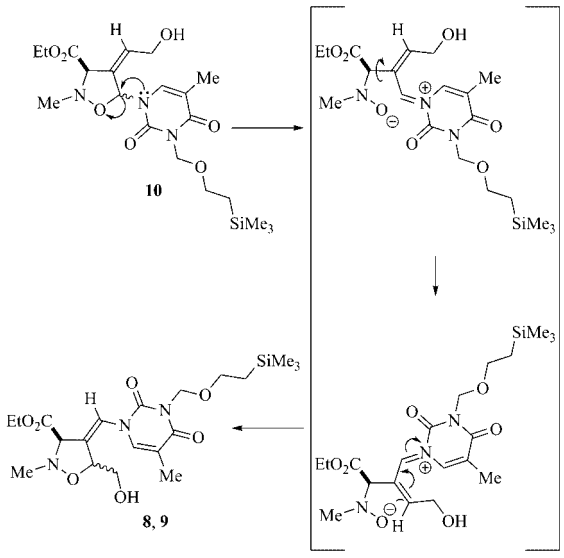
	(*E*)-**6**	(*Z*)-**6**	**7**	**13**	**17**	**18**
E_{HOMO}	–9.770	–9.699	–9.168	–9.093	–9.227	–9.183
C-1	0.699	0.701	0.257	–0.291	–0.687	–0.678
C-2			0.422	–0.442		
C-3 or O-3	–0.605	–0.602			0.679	0.088
E_{LUMO}	–0.628	–0.517	–0.366	–0.792	0.489	–0.015
C-1	0.428	0.463	0.284	0.197	0.633	0.684
C-2			–0.313	–0.267		
C-3 or O-3	0.427	0.443			0.402	0.047

This theory is confirmed for the cycloaddition reaction involving cytallene as the dipolarophile, which affords adducts **14** and **15**. This prediction is not, however, in agreement with the experimental results obtained for the reaction involving thymallene as the dipolarophile (Scheme 2); thus, the formation of adducts **8** and **9** must be related to other factors.

A possible explanation is that these compounds are actually derived from cycloadducts **10**, which are the expected compounds according to FMO treatment. These compounds can undergo an extremely facile thermally promoted rearrangement. In fact, as previously reported for similar systems,[12] the presence of a lone pair of electrons on the aza group of the pyrimidine nucleobase could facilitate a [1,3] sigmatropic shift involving ring opening and ring closing (Scheme 4).

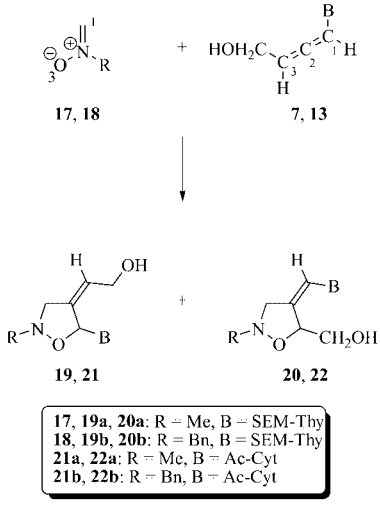
As a confirmation of this hypothesis, compounds **14** and **15** were converted into a mixture of compounds **16** after prolonged heating in ethanol (Scheme 3). This is parallel to the rearrangement suggested for the isomerization of compounds **10** into compounds **8** and **9**.

In the same context, the formation of SEM-thymine **11**, a byproduct present in small amounts in the reaction mixture of **6** with **7**, can easily be rationalized on the basis of the initial formation of cycloadduct **10**. This compound is readily hydrolyzed by the small quantities of water present in the system, giving rise to compound **11** and isoxazolidine derivative **12**. The aminol character of **12** is consistent with its total decomposition under the experimental conditions, leaving no characterizable products (Scheme 2).



Scheme 4. Rearrangement process for isoxazolidine **10**.

We next examined the regio- and stereochemical aspects of the cycloaddition of *N*-methyl- and *N*-benzylnitrone **17** and **18**, respectively, with allenes **7** and **13**. The reactions, performed under microwave irradiation in CCl_4 at 70 °C, gave rise to a mixture of both isoxazolidines **19/21** and **20/22** in 15 min. Product ratios depended on the nitrones and nucleobases employed (Table 1; Scheme 5).



Scheme 5. Cycloaddition reaction of nitrones **17** and **18** with allenes **7** and **13**.

These reactions can be explained by HOMO dipole–LUMO dipolarophile interactions, in agreement with the FMO treatment (see Table 2). However, the obtained distribution of compounds can also be rationalized by the initial formation of cycloadducts **19/21**, which could then undergo a thermally promoted ring-opening reaction and subsequent rearrangement to derivatives **20/22**.

Conclusions

A new series of conformationally locked N,O-nucleoside analogues were synthesized by exploiting allenic nucleobases as dipolarophiles in 1,3-dipolar cycloaddition reactions with nitrones. Biological tests to determine the antiviral activity of these analogues are currently in progress.

Experimental Section

General: Melting points were determined with a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer elemental analyzer. NMR spectra were recorded with a Varian instrument; chemical shifts are given in ppm from TMS as internal standard. NOE difference spectra were obtained by subtracting right-off-resonance free induction decays (FIDS) from right-on-resonance FIDS. The microwave reactions were carried out with a Discover Focused Microwave System (CEM Corporation). Thin-layer chromatographic separations were performed on Merck silica gel 60-F_{254} precoated aluminium plates. Preparative separations were performed by flash chromatography using Merck silica gel 0.035–0.070 mm, or by centrifugally accelerated radial thin-layer chromatography (PCAR-TLC) with a Chromatotron Model 7924 T instrument (Harrison Research, Palo Alto, CA, USA); the rotors were coated with Merck grade silica gel type 7749 (2 or 4-mm layer thickness, 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 1.5–3.5 mL/min. Preparative HPLC was performed with a microsorb silica DYNAMAX-100 Å (21 × 250 mm) column at a flow rate of 21 mL/min with a Varian Pro Star instrument. Nitrones[13] and allenyl nucleobases[9,11] were prepared as reported in the literature.

General Procedure: A solution of nitrone **6**, **17**, or **18** (3.0 mmol) and allene **7** or **13** (1.0 mmol) in the appropriate solvent (2 mL; see Table 1) was irradiated under microwave conditions at 80 W for 10–45 min. Removal of the solvent in vacuo afforded a crude material, which was purified by PCAR-TLC (cyclohexane/2-propanol, 9:1). For compounds **8**, **9**, **14**, and **15** the PCAR-TLC was followed by preparative HPLC.

Preparation of Compounds 8 and 9

Ethyl (3*RS*,4*Z*,5*SR*)-5-(Hydroxymethyl)-2-methyl-4-{[2,4-dioxo-5-methyl-3-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydropyrimidin-1(2*H*)-yl]methylene}isoxazolidine-3-carboxylate (8): Yield: 113.9 mg (25%), yellow oil. HPLC (*n*-hexane/2-propanol, 97:3): t_R = 17.65 min. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 0.01 (s, 9 H, Si-Me_3), 0.85–0.88 (m, 2 H, CH_2-Si), 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, OCH_2-CH_3), 1.96 (d, $^4J_{H,H}$ = 1.3 Hz, 3 H, Me-Thy), 2.58 (br. s, 1 H, OH), 2.80 (s, 3 H, N-Me), 3.59 (dd, $^3J_{H,H}$ = 4.2 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, C*H*-OH), 3.66–3.70 (m, 2 H, CH_2-O), 3.73 (dd, $^3J_{H,H}$ = 2.5 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, C*H*-OH), 4.14 (dd, $^4J_{H,H}$ = 0.5, 1.9 Hz, 1 H, 3′-H), 4.26 (dq, $^3J_{H,H}$ = 7.2 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, CH-OCO), 4.29 (dq, $^3J_{H,H}$ = 7.2, $^2J_{H,H}$ = 10.8 Hz, 1 H, CH-OCO), 4.92 (dddd, $^4J_{H,H}$ = 0.5, 2.4 Hz, $^3J_{H,H}$ = 2.5, 4.2 Hz, 1 H, 5′-H), 5.41 (s, 2 H, N-CH_2-O) 6.68 (dd, $^4J_{H,H}$ = 1.9, 2.4 Hz, 1 H, 4′′-H), 7.07 (q, $^4J_{H,H}$ = 1.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 1.5, 13.0, 14.1, 18.1, 44.4, 61.4, 62.2, 67.6, 70.3, 72.2, 78.3, 111.2, 121.1, 137.1, 139.1, 149.9, 163.1, 168.4 ppm. $C_{20}H_{33}N_3O_7Si$ (455.58): calcd. C 52.73, H 7.30, N 9.22; found C 52.89, H 7.28, N 9.20. HRMS: calcd. for $C_{20}H_{33}N_3O_7Si$ 455.2088; found 455.2090.

Ethyl (3*RS*,4*Z*,5*RS*)-5-(Hydroxymethyl)-2-methyl-4-{[2,4-dioxo-5-methyl-3-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydropyrimidin-1(2*H*)-yl]methylene}isoxazolidine-3-carboxylate (9): Yield: 113.9 mg (25%), yellow oil. HPLC (*n*-hexane/2-propanol, 97:3): t_R = 10.20 min. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = –0.01 (s, 9 H, Si-Me$_3$), 0.94–0.98 (m, 2 H, CH$_2$-Si), 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, OCH$_2$-C*H*$_3$), 1.95 (d, $^4J_{H,H}$ = 1.3 Hz, 3 H, Me-Thy), 2.32 (br. s, 1 H, OH), 2.85 (s, 3 H, N-Me), 3.57 (dd, $^3J_{H,H}$ = 4.7 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, C*H*-OH), 3.66–3.68 (m, 2 H, CH$_2$-O), 3.72 (dd, $^3J_{H,H}$ = 1.3 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, C*H*-OH), 4.04 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 3′-H), 4.28 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH$_2$OCO), 4.82 (ddd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 1.3, 4.7 Hz, 1 H, 5′-H), 5.38–5.43 (m, 2 H, N-CH$_2$-O), 6.66 (t, $^4J_{H,H}$ = 2.4 Hz, 1 H, 4′′-H), 6.96 (q, $^3J_{H,H}$ = 1.3 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = –1.5, 13.1, 14.2, 18.1, 44.0, 61.0, 62.1, 67.7, 70.4, 72.5, 79.6, 111.7, 120.2, 137.0, 139.6, 150.8, 163.0, 167.5 ppm. $C_{20}H_{33}N_3O_7Si$ (455.58): calcd. C 52.73, H 7.30, N 9.22; found C 52.39, H 7.32, N 9.26. HRMS: calcd. for $C_{20}H_{33}N_3O_7Si$ 455.2088; found 455.2085.

Cycloaddition of Nitrone 6 with Allene 13

Ethyl (3*RS*,4*Z*,5*SR*)-5-[4-(Acetylamino)-2-oxopyrimidin-1(2*H*)-yl]-4-(2-hydroxyethylidene)-2-methylisoxazolidine-3-carboxylate (14): Yield: 88.0 mg (25%), colorless oil. HPLC (*n*-hexane/2-propanol, 85:15): t_R = 20.0 min.. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.28 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH$_2$-C*H*$_3$), 2.17 (s, 3 H, CO-CH$_3$), 2.72 (s, 3 H, N-Me), 3.61 (br. s, 1 H, OH), 3.83–3.86 (m, 1 H, 3′-H), 4.04–4.12 (m, 2 H, C*H*$_2$OH), 4.25 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH$_2$OCO), 5.91–5.94 (m, 1 H, 4′′-H), 7.16 (s, 1 H, 5′-H), 7.29 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 5-H), 8.22 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 9.69 (br. s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 14.2, 24.9, 44.2, 59.6, 62.2, 73.2, 83.1, 97.1, 129.3, 137.0, 147.5, 156.4, 162.9, 168.5, 171.2 ppm. $C_{15}H_{20}N_4O_6$ (352.14): calcd. C 51.13, H 5.72, N 15.90; found C 51.38, H 5.70, N 15.93. HRMS: calcd. for $C_{15}H_{20}N_4O_6$ 352.1383; found 352.1376.

Ethyl (3*RS*,4*Z*,5*RS*)-5-[4-(Acetylamino)-2-oxopyrimidin-1(2*H*)-yl]-4-(2-hydroxyethylidene)-2-methylisoxazolidine-3-carboxylate (15): Yield: 88.0 mg (25%), colorless oil. HPLC (*n*-hexane/2-propanol, 85:15): t_R = 22.3 min. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.25 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH$_2$-C*H*$_3$), 2.19 (s, 3 H, CO-CH$_3$), 2.76 (s, 3 H, N-Me), 4.02 (dd, $^3J_{H,H}$ = 1.8 Hz, $^2J_{H,H}$ = 15.2 Hz, 1 H, C*H*$_2$OH), 3.54 (br. s, 1 H, OH), 4.07 (dd, $^3J_{H,H}$ = 5.5 Hz, $^2J_{H,H}$ = 15.2 Hz, 1 H, C*H*$_2$OH), 4.17 (dq, $^3J_{H,H}$ = 7.3 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, CH$_2$OCO), 4.21 (dq, $^3J_{H,H}$ = 7.3 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, CH$_2$OCO), 4.33–4.35 (m, 1 H, 3′-H), 6.00 (dt, $^3J_{H,H}$ = 1.8, 5.5 Hz, 1 H, 4′′-H), 7.08 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, 5′-H), 7.33 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 5-H), 7.83 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 9.93 (br. s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 14.2, 24.9, 40.7, 59.2, 61.6, 70.2, 83.2, 97.4, 129.5, 138.0, 147.6, 156.3, 161.0, 168.0, 171.3 ppm. $C_{15}H_{20}N_4O_6$ (352.14): calcd. C 51.13, H 5.72, N 15.90; found C 51.33, H 5.71, N 15.92. HRMS: calcd. for $C_{15}H_{20}N_4O_6$ 352.1383; found 352.1387.

Cycloaddition of Nitrones 17 and 18 with Allene 7

1-[(4*Z*,5*SR*)-4-(2-Hydroxyethylidene)-2-methylisoxazolidin-5-yl]-5-methyl-3-{[2-(trimethylsilyl)ethoxy]methyl}pyrimidine-2,4(1*H*,3*H*)-dione (19a): Yield: 88.2 mg (23%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = –0.01 (s, 9 H, Si-Me$_3$), 0.94–0.98 (m, 2 H, CH$_2$-Si), 1.85 (br. s, 1 H, OH), 1.91 (d, $^4J_{H,H}$ = 1.1 Hz, 3 H, Me-Thy), 2.75 (s, 3 H, N-Me), 3.23 (dd, $^4J_{H,H}$ = 1.5 Hz, $^2J_{H,H}$ = 12.2 Hz, 1 H, 3′-H), 3.66–3.70 (m, 2 H, CH$_2$-O), 4.00 (d, $^2J_{H,H}$ = 12.2 Hz, 1 H, 3′-H), 4.05 (dd, $^3J_{H,H}$ = 6.4 Hz, $^2J_{H,H}$ = 13.9 Hz, 1 H, C*H*$_2$OH), 4.08 (dd, $^3J_{H,H}$ = 6.4 Hz, $^2J_{H,H}$ = 13.9 Hz, 1 H, C*H*$_2$OH), 5.40 (s, 2 H, N-CH$_2$-O), 5.90 (ddt, $^4J_{H,H}$ = 1.5, 2.5 Hz, $^3J_{H,H}$ = 6.4 Hz, 1 H, 4′′-H), 6.89 (d, $^4J_{H,H}$ = 2.5 Hz, 1 H, 5′-H), 7.43 (q, $^4J_{H,H}$ = 1.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = –1.4, 13.3, 18.1, 45.4, 59.3, 62.0, 67.5, 70.3, 82.0, 110.3, 125.7, 136.3, 140.0, 151.7, 163.3 ppm. $C_{17}H_{29}N_3O_5Si$ (383.51): calcd. C 53.24, H 7.62, N 10.96; found C 53.57, H 7.59, N 10.99. HRMS: calcd. for $C_{17}H_{29}N_3O_5Si$ 383.1876; found 383.1879.

1-{(*Z*)-[(5*SR*)-5-(Hydroxymethyl)-2-methylisoxazolidin-4-ylidene]methyl}-5-methyl-3-{[2-(trimethylsilyl)ethoxy]methyl}-pyrimidine-2,4(1*H*,3*H*)-dione (20a): Yield: 176.4 mg (46%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = –0.01 (s, 9 H, Si-Me$_3$), 0.94–0.97 (m, 2 H, CH$_2$-Si), 1.95 (d, $^4J_{H,H}$ = 1.0 Hz, 3 H, Me-Thy), 2.09 (br. s, 1 H, OH), 2.73 (s, 3 H, N-Me), 3.35 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, 3′-H), 3.62 (m, 2 H, CH$_2$OH), 3.63–3.67 (m, 2 H, CH$_2$-O), 3.97 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, 3′-H), 4.81 (m, 1 H, 5′-H), 5.40 (s, 2 H, N-CH$_2$-O), 6.43 (d, $^4J_{H,H}$ = 1.5 Hz, 1 H, 4′′-H), 7.01 (q, $^4J_{H,H}$ = 1.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = –1.5, 13.1, 18.2, 50.0, 61.3, 62.6, 67.7, 70.4, 78.3, 111.2, 117.8, 137.4, 141.9, 151.2, 163.1 ppm. $C_{17}H_{29}N_3O_5Si$ (383.51): calcd. C 53.24, H 7.62, N 10.96; found C 53.42, H 7.61, N 10.94. HRMS: calcd. for $C_{17}H_{29}N_3O_5Si$ 383.1876; found 383.1878.

1-[(4*Z*,5*SR*)-2-Benzyl-4-(2-hydroxyethylidene)isoxazolidin-5-yl]-5-methyl-3-{[2-(trimethylsilyl)ethoxy]methyl}pyrimidine-2,4(1*H*,3*H*)-dione (19b): Yield: 110.3 mg (24%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = –0.02 (s, 9 H, Si-Me$_3$), 0.95–0.97 (m, 2 H, CH$_2$-Si), 1.65 (br. s, 1 H, OH), 1.93 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, Me-Thy), 3.38 (dd, $^4J_{H,H}$ = 1.7 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, 3′-H), 3.66–3.69 (m, 2 H, CH$_2$-O), 3.88–3.91 (m, 2 H, 2′′-H and 3′-H), 4.04 (dd, $^3J_{H,H}$ = 6.3 Hz, $^2J_{H,H}$ = 13.5 Hz, 1 H, C*H*$_2$OH), 4.11 (dd, $^3J_{H,H}$ = 6.3 Hz, $^2J_{H,H}$ = 13.5 Hz, 1 H, C*H*$_2$OH), 4.20 (d, $^2J_{H,H}$ = 12.7 Hz, 1 H, 2′′-H), 5.40 (s, 2 H, N-CH$_2$-O), 5.88 (dt, $^4J_{H,H}$ = 1.7 Hz, $^3J_{H,H}$ = 6.3 Hz, 1 H, 4′′-H), 6.94 (s, 1 H, 5′-H), 7.28–7.35 (m, 5 H, Ar-H), 7.52 (q, $^4J_{H,H}$ = 1.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = –1.4, 13.3, 18.1, 59.2, 59.5, 62.4, 67.5, 70.4, 81.9, 115.2, 117.8, 126.0, 127.8, 128.5, 128.9, 135.6, 136.2, 139.6, 163.3 ppm. $C_{23}H_{33}N_3O_5Si$ (459.61): calcd. C 60.10, H 7.24, N 9.14; found C 60.45, H 7.22, N 9.10. HRMS: calcd. for $C_{23}H_{33}N_3O_5Si$ 459.2189; found 459.2184.

1-{(*Z*)-[(5*SR*)-2-Benzyl-5-(hydroxymethyl)isoxazolidin-4-ylidene]methyl}-5-methyl-3-{[2-(trimethylsilyl)ethoxy]methyl}-pyrimidine-2,4(1*H*,3*H*)-dione (20b): Yield: 220.6 mg (48%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = –0.01 (s, 9 H, Si-Me$_3$), 0.95–0.98 (m, 2 H, CH$_2$-Si), 1.74 (br. s, 1 H, OH), 1.94 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, Me-Thy), 3.51–3.54 (m, 1 H, 2′′-H), 3.56–3.58 (m, 1 H, 3′-H), 3.66–3.79 (m, 3 H, CH$_2$-O, and 3′-H), 3.87–3.92 (m, 2 H, C*H*$_2$OH), 4.10–4.13 (m, 1 H, 2′′-H), 4.84 (m, 1 H, 5′-H), 5.41 (s, 2 H, N-CH$_2$-O), 6.41 (d, $^4J_{H,H}$ = 1.5 Hz, 1 H, 4′′-H), 6.97 (q, $^4J_{H,H}$ = 1.2 Hz, 1 H, 6-H), 7.28–7.36 (m, 5 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = –1.5, 13.0, 18.1, 29.6, 64.5, 63.6, 62.6, 67.6, 70.3, 76.7, 111.2, 117.8, 122.0, 127.8, 128.5, 129.0, 136.0, 137.4, 153.3, 163.1 ppm. $C_{23}H_{33}N_3O_5Si$ (459.61): calcd. C 60.10, H 7.24, N 9.14; found C 60.35, H 7.22, N 9.17. HRMS: calcd. for $C_{23}H_{33}N_3O_5Si$ 459.2189; found 459.2193.

Cycloaddition of Nitrones 17 and 18 with Allene 13

***N*-{1-[(4*Z*,5*SR*)-4-(2-Hydroxyethylidene)-2-methylisoxazolidin-5-yl]-2-oxo-1,2-dihydropyrimidin-4-yl}acetamide (21a):** Yield: 112.1 mg (40%), white solid, m.p. 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 2.23 (s, 3 H, CO-CH$_3$), 2.74 (s, 3 H, N-Me), 3.23 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H, 3′-H), 3.84 (br. s, 1 H, OH), 3.99 (d, $^2J_{H,H}$ = 11.5 Hz, 1 H, 3′-H), 4.04 (dd, $^3J_{H,H}$ = 4.5 Hz, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$OH), 4.11 (dd, $^3J_{H,H}$ = 4.5 Hz, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$OH), 5.90–5.92 (m, 1 H, 4′′-H), 7.11 (s, 1 H, 5′-H), 7.34 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 5-H), 8.05 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 6-H), 9.30 (br. s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$,

27 °C): δ = 24.8, 45.1, 59.3, 61.8, 83.1, 97.1, 126.2, 138.4, 146.9, 156.2, 162.9, 171.4 ppm. $C_{12}H_{16}N_4O_4$ (280.28): calcd. C 51.42, H 5.75, N 19.99; found C 51.60, H 5.74, N 19.95. HRMS: calcd. for $C_{12}H_{16}N_4O_4$ 280.1172; found 280.1175.

***N*-(1-{(*Z*)-[(5*SR*)-5-(Hydroxymethyl)-2-methylisoxazolidin-4-ylidene]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (22a):** Yield: 56.0 mg (20%), white solid, m.p. 134–137 °C. ^{1}H NMR (500 MHz, CD_3OD, 27 °C) δ = 2.17 (s, 3 H, CO-CH_3), 2.69 (s, 3 H, N-Me), 3.36 (dd, $^3J_{H,H}$ = 2.9 Hz, $^2J_{H,H}$ = 11.5 Hz, 1 H, 5′′-H), 3.49 (dd, $^3J_{H,H}$ = 6.2 Hz, $^2J_{H,H}$ = 11.5 Hz, 1 H, 5′′-H), 3.52 (dd, $^4J_{H,H}$ = 0.6 Hz, $^2J_{H,H}$ = 13.4 Hz, 1 H, 3′-H), 3.96 (dd, $^4J_{H,H}$ = 0.6 Hz, $^2J_{H,H}$ = 13.4 Hz, 1 H, 3′-H), 4.91–4.95 (m, 1 H, 5′-H), 6.70 (dt, $^4J_{H,H}$ = 0.5, 0.6 Hz, 1 H, 4′′-H), 7.47 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, 5-H), 8.05 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, CD_3OD, 27 °C): δ = 24.5, 45.1, 61.7, 62.1, 79.5, 98.5, 120.7, 143.3, 149.8, 157.2, 164.8, 173.0 ppm. $C_{12}H_{16}N_4O_4$ (280.28): calcd. C 51.42, H 5.75, N 19.99; found C 51.67, H 5.73, N 20.03. HRMS: calcd. for $C_{12}H_{16}N_4O_4$ 280.1172; found 280.1176.

***N*-{1-[(4*Z*,5*SR*)-2-Benzyl-4-(2-hydroxyethylidene)isoxazolidin-5-yl]-2-oxo-1,2-dihydropyrimidin-4-yl}acetamide (21b):** Yield: 106.9 mg (30%), white solid, m.p. 139–141 °C. ^{1}H NMR (500 MHz, CD_3OD, 27 °C) δ = 2.13 (s, 3 H, CO-CH_3), 3.43 (dd, $^4J_{H,H}$ = 2.1 Hz, $^2J_{H,H}$ = 12.3 Hz, 1 H, 3′-H), 3.93 (dd, $^3J_{H,H}$ = 3.5 Hz, $^2J_{H,H}$ = 14.4 Hz, 1 H, CH_2OH), 3.98 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, 2′′-H), 4.00 (dd, $^3J_{H,H}$ = 6.4 Hz, $^2J_{H,H}$ = 14.4 Hz, 1 H, CH_2OH), 4.03 (dd, $^4J_{H,H}$ = 2.1 Hz, $^2J_{H,H}$ = 12.3 Hz, 1 H, 3′-H), 4.11 (d, $^2J_{H,H}$ = 13.1 Hz, 1 H, 2′′-H), 5.92 (dddt, $^4J_{H,H}$ = 0.3, 2.1 Hz, $^3J_{H,H}$ = 3.5, 6.4 Hz, 1 H, 4′′-H), 7.03 (d, $^4J_{H,H}$ = 0.3 Hz, 1 H, 5′-H), 7.23–7.32 (m, 5 H, Ar-H), 7.37 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, 5-H), 8.16 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, CD_3OD, 27 °C): δ = 24.5, 60.5, 63.0, 84.4, 98.1, 127.4, 127.6, 128.6, 129.4, 130.2, 137.6, 139.6, 148.3, 155.4, 164.8, 172.8 ppm. $C_{18}H_{20}N_4O_4$ (356.38): calcd. C 60.66, H 5.66, N 15.72; found C 60.87, H 5.64, N 15.75. HRMS: calcd. for $C_{18}H_{20}N_4O_4$ 356.1485; found 356.1481.

***N*-(1-{(*Z*)-[(5*SR*)-2-Benzyl-5-(hydroxymethyl)isoxazolidin-4-ylidene]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (22b):** Yield: 53.5 mg (15%), white solid, m.p. 145–146 °C. ^{1}H NMR (500 MHz, CD_3OD, 27 °C) δ = 2.17 (s, 3 H, CO-CH_3), 3.43–3.50 (m, 2 H, 2′′-H), 3.63–3.72 (m, 1 H, 3′-H), 3.84–3.91 (m, 2 H, 3′-H and CH_2OH), 4.05–4.10 (m, 1 H, CH_2OH), 4.94–4.99 (m, 1 H, 5′-H), 6.67–6.71 (m, 1 H, 4′′-H), 7.20–7.40 (m, 5 H, Ar-H), 7.47 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 5-H), 7.98 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, CD_3OD, 27 °C): δ = 24.5, 55.0, 61.1, 62.2, 80.0, 98.5, 118.2, 121.2, 128.7, 129.4, 130.5, 140.5, 150.0, 156.8, 166.7, 172.0 ppm. $C_{18}H_{20}N_4O_4$ (356.38): calcd. C 60.66, H 5.66, N 15.72; found C 60.48, H 5.68, N 15.69. HRMS: calcd. for $C_{18}H_{20}N_4O_4$ 356.1485; found 356.1479.

Synthesis of Compounds 16a,b

A solution of **14** and **15** (0.2 mmol, 70.5 mg) in ethanol (2 mL) was placed in a pressure tube equipped with a stir bar. This was heated at 100 W for 90 min in a Discover Microwave System apparatus (internal temperature 100–110 °C). The solvent was evaporated, and the resulting oil was purified by flash chromatography on silica gel (dichloromethane/methanol, 80:20) to give **16b** and **16a**, respectively.

Ethyl (3*RS*,4*Z*,5*SR*)-4-{[4-(Acetylamino)-2-oxopyrimidin-1(2*H*)-yl]methylene}-5-(hydroxymethyl)-2-methylisoxazolidine-3-carboxylate (16a): Second eluted product: R_f = 0.16. Yield: 21.1 mg (30%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.16 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, OCH_2-CH_3), 2.15 (s, 3 H, CO-CH_3), 2.82 (s, 3 H, N-Me), 3.47 (dd, $^3J_{H,H}$ = 4.1 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, CH_2OH), 3.70 (dd, $^3J_{H,H}$ = 2.8 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, CH_2OH), 3.86 (br. s, 1 H, OH), 4.24 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, 3′-H), 4.21 (dq, $^3J_{H,H}$ = 7.2 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, OCH_2-CH_3), 4.29 (dq, $^3J_{H,H}$ = 7.2 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, OCH_2-CH_3), 4.81 (ddd, $^4J_{H,H}$ = 2.4 Hz, $^3J_{H,H}$ = 2.8, 4.1 Hz, 1 H, 5′-H), 6.72 (dd, $^4J_{H,H}$ = 1.8, 2.4 Hz, 1 H, 4′′-H), 7.31 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 5-H), 8.15 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 9.68 (br. s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 14.7, 24.8, 42.0, 61.0, 66.2, 67.0, 75.3, 96.6, 118.8, 125.0, 141.1, 152.7, 164.3, 169.3, 171.9 ppm. $C_{15}H_{20}N_4O_6$ (352.34): calcd. C 51.13, H 5.72, N 15.90; found C 50.97, H 5.73, N 15.93. HRMS: calcd. for $C_{15}H_{20}N_4O_6$ 352.1383; found 352.1384.

Ethyl (3*RS*,4*Z*,5*RS*)-4-{[4-(Acetylamino)-2-oxopyrimidin-1(2*H*)-yl]methylene}-5-(hydroxymethyl)-2-methylisoxazolidine-3-carboxylate (16b): First eluted product: R_f = 0.21. Yield: 24.7 mg (35%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.19 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, OCH_2-CH_3), 2.14 (s, 3 H, CO-CH_3), 2.80 (s, 3 H, N-Me), 3.61 (dd, $^3J_{H,H}$ = 3.8 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, CH_2OH), 3.75 (dd, $^3J_{H,H}$ = 2.1 Hz, $^2J_{H,H}$ = 12.5 Hz, 1 H, CH_2OH), 3.80 (br. s, 1 H, OH), 4.23 (dq, $^3J_{H,H}$ = 7.2 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, OCH_2-CH_3), 4.28 (d, $^4J_{H,H}$ = 1.5 Hz, 1 H, 3′-H), 4.31 (dq, $^3J_{H,H}$ = 7.2 Hz, $^2J_{H,H}$ = 10.8 Hz, 1 H, OCH_2-CH_3), 4.85 (ddd, $^4J_{H,H}$ = 1.9 Hz, $^3J_{H,H}$ = 2.1, 3.8 Hz, 1 H, 5′-H), 6.78 (dd, $^4J_{H,H}$ = 1.5, 1.9 Hz, 1 H, 4′′-H), 7.35 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 5-H), 8.10 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 9.73 (br. s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 14.7, 24.7, 42.4, 61.6, 66.1, 68.1, 74.8, 97.2, 119.8, 126.5, 140.2, 153.9, 165.0, 169.9, 170.7 ppm. $C_{15}H_{20}N_4O_6$ (352.34): calcd. C 51.13, H 5.72, N 15.90; found C 51.33, H 5.70, N 15.96. HRMS: calcd. for $C_{15}H_{20}N_4O_6$ 352.1383; found 352.1379.

Acknowledgments

This work was partially supported by M.I.U.R. (progetto P.R.I.N. 2005 and 2006).

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Received: February 23, 2007
Published Online: July 30, 2007

