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First Example of a Third Generation Nitrone Cycloaddition

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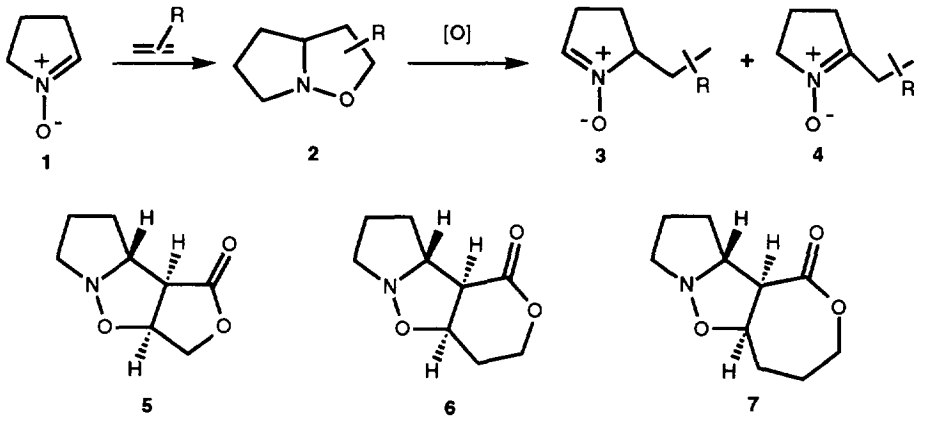
Abstract: Compounds **5** and **6**, derived from the cycloadditions of a nitrone to α,β-unsaturated lactones, were oxidized with *m*-chloroperbenzoic acid affording regiospecifically aldonitrones, **8** and **14**, respectively. These second generation nitrones were reacted with several dipolarophiles yielding cycloadducts **9-13**, **15**, and **16**. A repeated sequence of oxidation-cycloaddition applied to compound **12** allowed the isolation of the first example of a third generation cycloadduct, **17**. During this work a series of new highly functionalized pyrrolidines have been prepared.

The cycloaddition of the five membered cyclic nitrone 3,4-dihydro-2*H*-pyrrole 1-oxide, **1**, to olefins gives cycloadducts that contain in their structure a pyrrolidine, a widespread heterocyclic system in nature, and also an isoxazolidine ring (Scheme 1). According to the pioneering work of LeBel and Spurlock, the latter heterocycle may be oxidized with peracids to afford a new nitrone.[1] The oxidation of perhydropyrrolo[1,2-*b*]isoxazole systems of type **2** is under certain conditions regiospecific affording the less substituted aldonitrone **3**, without formation of the ketonitrone **4**.[2] The main feature in this sequence of nitrone cycloaddition-oxidation is that the second generation nitrone **3** is formally the result of an α alkylation of the original nitrone. This strategy has been also applied to other cyclic nitrones[3] and has found several synthetic applications.[2,3]

As part of a synthetic programme, we have prepared a series of new compounds derived from the cycloaddition of nitrone **1** to several α,β-unsaturated carboxylic acid derivatives.[4] With the aim of exploring the potential synthetic utility of these products, we decided to test their oxidation by peracid and to study the reactivity of the corresponding second generation nitrones. Herein we present the results on the cycloaddition chemistry of the nitrones derived from the oxidation of compounds **5**, **6**, and **7**.[4a] Included in this work is also the first example of a third generation nitrone cycloadduct.

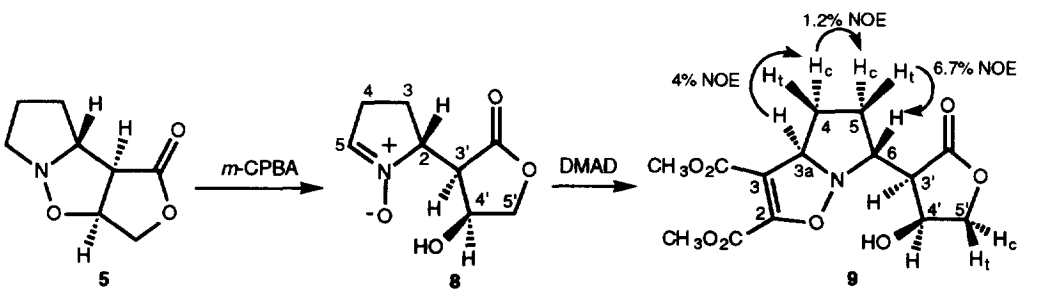
According to the mechanistic studies of Ali and coworkers[2d-f] the oxidation of **2** with *m*-chloroperbenzoic acid (*m*-CPBA) affords the aldonitrone as the sole product if it is conducted in an aprotic solvent. A preliminary oxidation experiment was run with **5** using one equivalent of anhydrous *m*-CPBA in $CDCl_3$ in an NMR tube to examine the regioselectivity of this reaction. After *ca.* 5 minutes of reaction we observed in the ^{1}H-NMR spectrum only one product, which was identified as **8** (Scheme 2) since it presented a singlet absorption at δ 7.28, characteristic of aldonitrones and a multiplet at δ 4.60, that was attributed to the

proton at C_2. When the oxidation of **5** was conducted in a protic solvent, d_4-methanol, we obtained a complex mixture useless for subsequent synthetic applications.



Scheme 1

Then, a methylene chloride solution of nitrone **8** was allowed to react with dimethyl acetylenedicarboxylate (DMAD) and a sole adduct **9** could be isolated as a solid in 70% yield (Scheme 2). The IR spectrum of **9** shows absorptions at 3544, 1763, 1709, and 1650 cm^{-1} due to the presence of a hydroxyl group, a butanolide, a conjugated ester, and an olefin, respectively. With the help of 1D- and 2D-NMR experiments all the proton and carbon atom signals of the spectra of **9** could be assigned. The α-carbonylic proton $H_{3'}$ absorbs as a double doublet at δ 2.60 and it correlates in the COSY spectrum with protons $H_{4'}$ and H_6. The relative stereochemistry of H_{3a} and H_6 was determined through NOE experiments. Presaturation of H_{3a} (δ 4.98) produces enhancement of only one of the signals corresponding to the protons at C_4, namely H_{4cis} (δ 2.35). When the latter is irradiated, only one of the absorptions of the protons at C_5 is affected (H_{5cis} at δ 1.63) and, finally, when the other proton at C_5, H_{5trans} (δ 2.57) is irradiated, the proton at C_6 (δ 3.62) is strongly affected (6.7% NOE). The *trans* relationship between H_{3a} and H_6 indicates that the dipolarophile has approached the nitrone from its less hindered face affording a *trans*-disubstituted pyrrolidine system. The high field absorption of H_{5cis} and the value of $J_{3',6}$=9.5 Hz indicate that in the preferred conformation of **9** both protons $H_{3'}$ and H_6 must be almost in an antiperiplanar arrangement and proton H_{5cis} is therefore shielded by the anisotropic cone of the carbonyl group.



Scheme 2

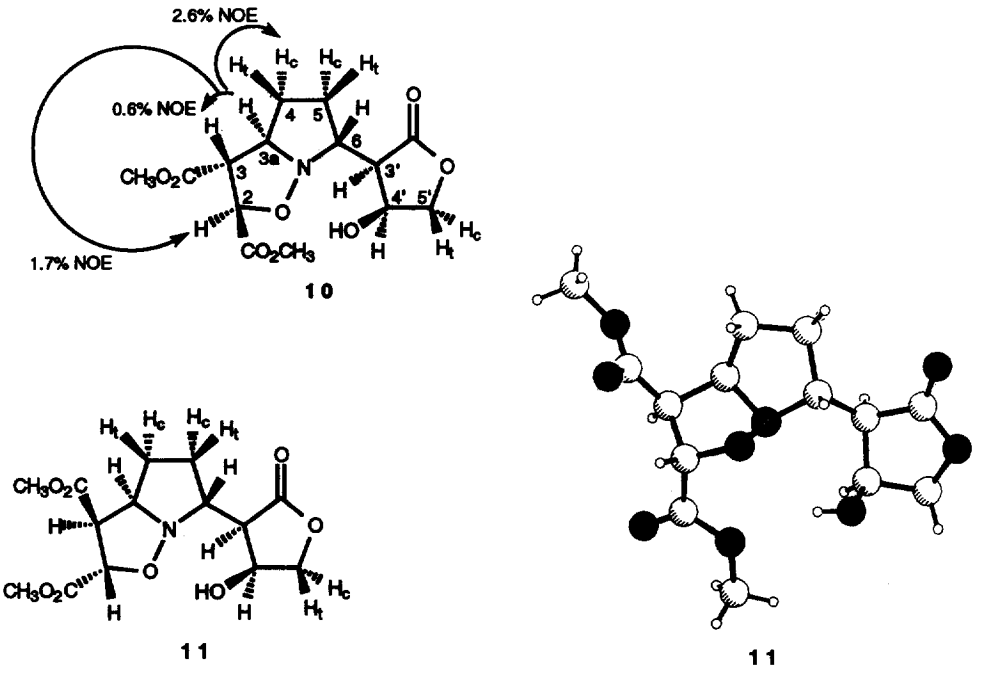
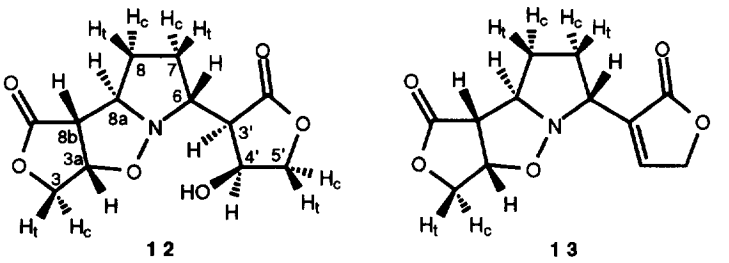


Figure 1

The reaction of nitrone **8** with dimethyl fumarate in CH_2Cl_2 at room temperature afforded two crystalline cycloadducts, identified as **10** and **11** in 43% and 41% yield, respectively (Figure 1). The same reaction conducted in toluene at the reflux temperature gave 57% and *ca.* 15% yield of adducts **10** and **11**, respectively. The relative stereochemistry at centers C_3-C_{3a} of **10** (*exo/endo* referred to the ester group at C_3) is based on a NOE experiment. Presaturation of H_{3a} (δ 3.92) gives the following NOEs: 2.6% on H_{4cis} (δ 2.12), 1.7% on H_2 (δ 5.00), and 0.6% on H_3 (δ 3.26). This result can only be explained if H_{3a} and H_2 are *cis* to each other and they present pseudoaxial positions, indicating that the cycloaddition has proceeded through an *exo* transition state. The *anti* stereochemistry of **10**, that is the relative configuration of H_6 and H_{3a}, was established as described previously for adduct **9**. Also as in compound **9**, the high field resonance of H_{5cis} (δ 1.77) and the value of $J_{3',6}$=9.8 Hz are according with a preferred conformation with protons 3' and 6 almost antiperiplanar. Unfortunately, in the ^{1}H-NMR spectrum of cycloadduct **11**, the absorptions of several protons crucial for the stereochemical assignment present very similar chemical shifts, precluding the realization of NOE experiments. Therefore, the *endo-anti* stereochemistry of compound **11** was established by an X-ray diffraction analysis (Figure 1).

In an effort to introduce two lactone residues as substituents of the pyrrolidine ring, we performed the reaction between nitrone **8** and 2(5*H*)-furanone. This cycloaddition did not evolve at room temperature and it was necessary to run it at 110 °C. We isolated two crystalline products **12** and **13** in 62% and 12% yield, respectively (Figure 2). The IR spectrum of the more polar and major product **12** presents absorptions at 3529, 1774, and 1757 cm^{-1} assignable to the hydroxyl group and the two γ-lactones, respectively. The value of the coupling constant $J_{8a,8b}$=2.2 Hz demonstrates the *trans* relationship between H_{8a} and H_{8b},[4a] according

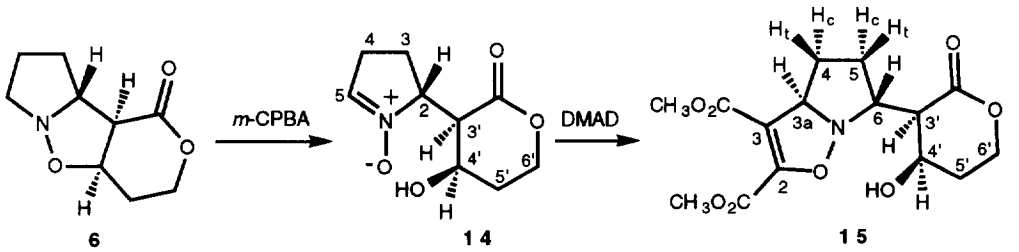


12 **13**

Figure 2

to the *exo* stereochemistry of the transition state. The less polar and minor compound was identified by its spectroscopic data and elemental analysis as **13**. A molecular weight of 251, which is 18 units smaller than the corresponding to **12**, points out to the elimination of a water molecule from the primary cycloadduct. Thus, the IR spectrum of **13** does not show hydroxyl stretching, and two signals at 1760 and 1735 cm^{-1} indicate the presence of a saturated and an α,β-unsaturated γ-lactones, respectively. The presence of the double bond is also demonstrated by a singlet at δ 7.55 and absorptions at δ 134.0 and 146.0 in the ^1H- and ^{13}C-NMR spectra, respectively. The small value of $J_{8a,8b}$=1.8 Hz indicates again that these protons are almost orthogonal to each other,[4a] and therefore the adduct must derive from the major product **12**. For both, **12** and **13**, the *trans* relationship between H_{8a} and H_6 is assumed considering the results of the previous cycloadditions to DMAD and dimethyl fumarate.

Next we tried the preparation of the second generation cycloadducts derived from tricyclic compound **6** (Scheme 3). An assay of oxidation of **6** with *m*-CPBA in $CDCl_3$ revealed the formation of a sole aldonitrone **14**, as demonstrated by the singlet at δ 7.28 in the ^1H-NMR spectrum. Treatment of a CH_2Cl_2 solution of **14** with DMAD at room temperature afforded a solid cycloadduct **15** in 73% yield. The ^1H-NMR spectrum of **15** correlates perfectly with that of **9**, and therefore we assign also the *anti* stereochemistry to this product.



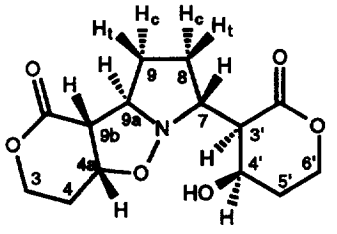
6 **14** **15**

Scheme 3

The reaction of nitrone **14** with α,β-pentenolide[5] in toluene at the reflux temperature gave a new product **16** in 47% yield. The stereochemistry of **16** was assessed by an X-ray diffraction analysis which indicated that **16** derives from an *exo* transition state with an antifacial approach of the reactants (Figure 3). The solid state conformer of **16** presents an antiperiplanar arrangement for H_7 and $H_{3'}$ and the carbonyl group of the hydroxylactone lies below the proton H_{8cis}.

The oxidation of **7** was also undertaken, but we did not observe the presence of the desired nitrone.

So far we have described seven cycloadducts, **9-13**, **15**, and **16**, derived from second generation nitrones. They all contain *trans*-2,5-disubstituted pyrrolidines that derive from an *anti* approach of the educts.



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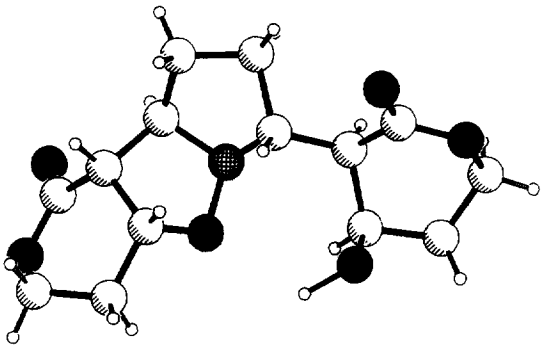
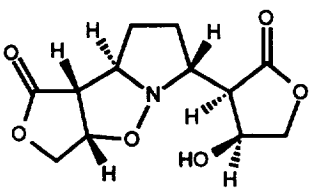


16

Figure 3



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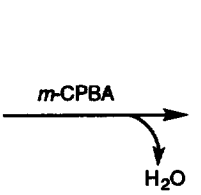

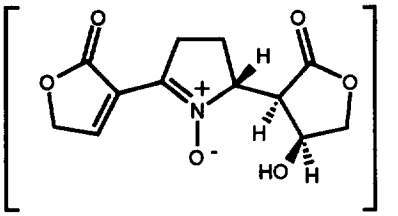

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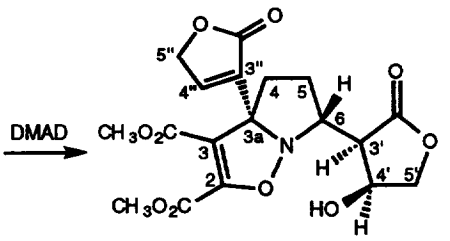

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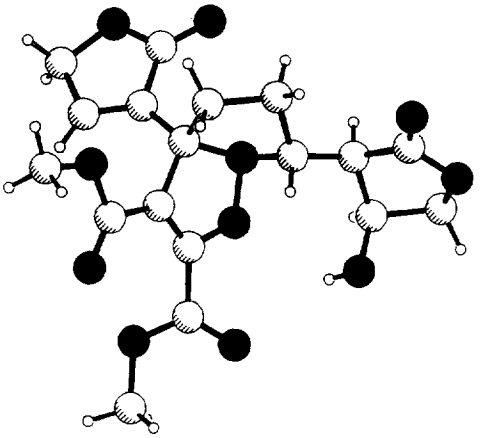

17

Scheme 4

Ali and coworkers[2e,2f] described the first example of a third generation nitrone, but they do not use it as a 1,3-dipole in the following transformation. Among the adducts available, we chose compound **12** to perform

the *m*-CPBA oxidation, since the formation of the nitrone will not present regioselectivity problems. The oxidation product was then treated with DMAD and we isolated one crystalline compound, **17**, in 34% yield (Scheme 4), whose structure was established by its spectroscopic data. In particular, a signal in the IR spectrum at 3516 cm^{-1} indicates the presence of the hydroxyl group and the ^{1}H-NMR spectrum shows a very deshielded ethylenic proton at δ 7.34, characteristic for an α,β-butenolide. The α-carbonylic proton $H_{3'}$ absorbs as a double doublet (δ 2.87) revealing that the dehydration has occurred at the lactone ring attached to C_{3a}. Most probably the elimination of the water molecule should be previous to the cycloaddition to afford the conjugated nitrone **18**.

The stereochemistry of **17** at the quaternary center C_{3a} could not be established from the NMR data, but considering the previous results it can be predicted that the cycloaddition should proceed through an *anti* approach and consequently the lactones should be in *cis* disposition. The X-ray analysis of **17** confirmed the prediction (Scheme 4).

Finally, we also tried the cycloaddition of nitrone **18** to 2(5*H*)-furanone, but the reaction did not evolve at room temperature after seven days, and when we heated it at 70 °C, a tlc analysis showed the formation of a very complex mixture.

In conclusion, we have described here the formation of several nitrone-dipolarophile cycloadducts of second generation and the first example of an adduct of third generation. All these compounds are highly functionalized pyrrolidines useful for synthetic purposes.

EXPERIMENTAL SECTION

In all cases commercial *m*-CPBA of 95% purity was employed and it was dried over $MgSO_4$ before its use. Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15-20 Torr. Column chromatographies were performed by using silica gel (230-400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC-250-WB or AM-400-WB instruments and chemical shifts are given in δ values. Mass spectra were performed on a Hewlett-Packard 5985B instrument at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments. Compounds **5**, **6**, and **7** were prepared according to previously described methods.[4a]

Oxidation assays of compounds 5 and 6 with m-CPBA

The described oxidation assays were realized in an NMR tube at 0 °C with one equivalent of *m*-CPBA in $CDCl_3$ as solvent. The reaction time was 5 min.

The oxidation of **5** yielded nitrone **8**: ^{1}H-RMN (250 MHz, $CDCl_3$): δ 2.40-2.90 (m, 5H: 2xH_3, 2xH_4, $H_{3'}$), 4.35 (dd, $J_{5',5'}$=11.0 Hz, $J_{5',4'}$=3.6 Hz, 1H: $H_{5'}$), 4.42 (d, $J_{5',5'}$=11.0 Hz, 1H: $H_{5'}$), 4.60 (m, 1H: H_2), 4.92 (t, $J_{4',3'}\approx J_{4',5'}\approx$5.5 Hz, 1H: $H_{4'}$), 5.30 (s, 1H: OH), 7.28 (s, 1H: H_5).

The oxidation of **6** yielded nitrone **14**: ^{1}H-RMN (250 MHz, $CDCl_3$): δ 1.90-2.70 (m, 6H: 2xH_3, 2xH_4, 2x$H_{5'}$), 3.00 (dd, J=7.8 Hz, J=4.7 Hz, 1H: $H_{3'}$), 4.25 (m, 1H: $H_{6'}$), 4.55 (m, 2H: $H_{6'}$, H_2), 4.65 (dd, J=9.9 Hz, J=5.6 Hz, 1H: $H_{4'}$), 7.28 (s, 1H: H_5).

Dimethyl (3aRS,6RS)-3a,4,5,6-tetrahydro-6-[(3RS,4SR)-dihydro-4-hydroxy-2(3H)-oxo-3-furyl]-pyrrolo[1,2-b]isoxazole-2,3-dicarboxylate, **9**

A solution of **5** (100 mg, 0.59 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen atmosphere was treated with a solution of *m*-CPBA (117 mg, 0.65 mmol) in the same solvent (3 mL). The mixture was left at 0 °C for 15 min. Then, DMAD (70 µl, 0.56 mmol) was added and the reaction mixture was kept at 20 °C for 5 h. Flash chromatography of the crude material (340 mg) using methylene chloride-ether 4:1 as eluent afforded the following fractions: i) *m*-chlorobenzoic acid (137 mg); and ii) adduct **9** (134 mg, 0.41 mmol, 70% yield) as a solid. **9**: mp 105-107 °C (CH_2Cl_2-pentane); IR (KBr): 3544, 3008, 2960, 2916, 2860, 1763, 1709, 1650, 1328, 1142 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 1.63 (dtd, $J_{5c,5t}$=13.4 Hz, $J_{5c,4t}$=$J_{5c,6}$=10.4 Hz, $J_{5c,4c}$=7.9 Hz, 1H: H_{5c}), 2.03 (dddd, $J_{4t,4c}$=13.7 Hz, $J_{4t,5c}$=10.4 Hz, $J_{4t,5t}$=8.2 Hz, $J_{4t,3a}$=6.1 Hz, 1H: H_{4t}), 2.35 (dtd, $J_{4c,4t}$=13.7 Hz, $J_{4c,3a}$=$J_{4c,5c}$=7.9 Hz, $J_{4c,5t}$=2.1 Hz, 1H: H_{4c}), 2.57 (dddd, $J_{5t,5c}$=13.4 Hz, $J_{5t,4t}$=8.2 Hz, $J_{5t,6}$=6.1 Hz, $J_{5t,4c}$=2.1 Hz, 1H: H_{5t}), 2.60 (dd, $J_{3',6}$=9.5 Hz, $J_{3',4'}$=4.6 Hz, 1H: $H_{3'}$), 3.43 (broad s, 1H: OH), 3.62 (td, $J_{6,5c}$≈$J_{6,3'}$≈10.0 Hz, $J_{6,5t}$=6.1 Hz, 1H: H_6), 3.76 (s, 3H: OMe), 3.88 (s, 3H: OMe), 4.30 (dd, $J_{5'c,5't}$=10.1 Hz, $J_{5'c,4'}$=3.7 Hz, 1H: $H_{5'c}$), 4.36 (d, $J_{5't,5'c}$=10.1 Hz, 1H: $H_{5't}$), 4.77 (dd, $J_{4',3'}$=4.6 Hz, $J_{4',5'c}$=3.7 Hz, 1H: $H_{4'}$), 4.98 (t, $J_{3a,4c}$≈$J_{3a,4t}$≈7.0 Hz, 1H: H_{3a}); ^{13}C-RMN (100 MHz, $CDCl_3$): δ 24.0 (C_5), 28.0 (C_4), 48.4 ($C_{3'}$), 50.7 (OMe), 52.1 (OMe), 63.7 (C_6), 67.3 (C_{3a}), 68.3 ($C_{4'}$), 72.4 ($C_{5'}$), 110.4 (C_3), 147.3 (C_2), 157.4/160.6 (2xCO), 173.2 ($C_{2'}$); MS (*m/z*) 327 (M^+, 4), 268 (8), 166 (32), 69 (29), 68 (20), 59 (44), 55 (32), 45 (100), 43 (68), 42 (37), 41 (52). Anal. Calcd for $C_{14}H_{17}NO_8$: C, 51.38; H, 5.24; N, 4.28. Found: C, 51.37; H, 5.38; N, 4.27.

Dimethyl (2RS,3RS,3aRS,6RS)-hexahydro-6-[(3RS,4SR)-dihydro-4-hydroxy-2(3H)-oxo-3-furyl]-pyrrolo[1,2-b]isoxazole-2,3-dicarboxylate, **10**, *and its (2RS,3RS,3aSR,6SR,3'SR,4'RS)-isomer,* **11**

A solution of **5** (200 mg, 1.18 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen atmosphere was treated with a solution of *m*-CPBA (235 mg, 1.30 mmol) in the same solvent (5 mL). The mixture was left at 0 °C for 15 min. Then, dimethyl fumarate (187 mg, 1.30 mmol) was added and the reaction mixture was kept at 20 °C for 19 h. Flash chromatography of the crude material (602 mg) using methylene chloride-ether 4:1 as eluent afforded the following fractions: i) *m*-chlorobenzoic acid (205 mg); ii) adduct **10** (168 mg, 0.51 mmol, 43% yield) as a solid; and iii) 158 mg (0.48 mmol, 41% yield) of a solid identified as **11**.

The same reaction was performed in toluene at reflux for 3 h affording 57% yield of adduct **10** and 20% yield of a 2.75:1 mixture of **11** and an unidentified compound.

10: mp 146-148 °C (CH_2Cl_2-pentane); IR (KBr): 3469, 2966, 2896, 1759, 1739, 1234 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 1.77 (dtd, $J_{5c,5t}$=13.7 Hz, $J_{5c,6}$≈$J_{5c,4c}$≈10.3 Hz, $J_{5c,4t}$=7.3 Hz, 1H: H_{5c}), 1.98 (dddd, $J_{4t,4c}$=12.8 Hz, $J_{4t,5t}$=10.0 Hz, $J_{4t,5c}$=7.3 Hz, $J_{4t,3a}$=3.0 Hz, 1H: H_{4t}), 2.12 (dddd, $J_{4c,4t}$=12.8 Hz, $J_{4c,5c}$=10.6 Hz, $J_{4c,3a}$=7.4 Hz, $J_{4c,5t}$=3.7 Hz, 1H: H_{4c}), 2.51 (dd, $J_{3',6}$=9.8 Hz, $J_{3',4}$=4.3 Hz, 1H: $H_{3'}$), 2.73 (dddd, $J_{5t,5c}$=13.7 Hz, $J_{5t,4t}$=10.0 Hz, $J_{5t,6}$=7.6 Hz, $J_{5t,4c}$=3.7 Hz, 1H: H_{5t}), 3.26 (t, $J_{3,3a}$=$J_{3,2}$=9.2 Hz, 1H: H_3), 3.36 (td, $J_{6,5c}$≈$J_{6,3}$≈10.3 Hz, $J_{6,5t}$=7.6 Hz, 1H: H_6), 3.75 (s, 3H: OMe), 3.76 (s, 3H: OMe), 3.92 (ddd, $J_{3a,3}$=9.2 Hz, $J_{3a,4c}$=7.4 Hz, $J_{3a,4t}$=3.0 Hz, 1H: H_{3a}), 4.24 (dd, $J_{5'c,5't}$=9.8 Hz, $J_{5'c,4'}$=3.1 Hz, 1H: $H_{5'c}$), 4.34 (d, $J_{5't,5'c}$=9.8 Hz, 1H: $H_{5't}$), 4.75 (t, $J_{4',3'}$≈$J_{4',5'c}$≈3.7 Hz, 1H: $H_{4'}$), 5.00 (d, $J_{2,3}$=9.2 Hz, 1H: H_2); ^{13}C-RMN (62.5 MHz, $CDCl_3$): δ 24.3 (C_4), 26.9 (C_5), 52.8/52.9/53.4 ($C_{3'}$/OMe/OMe), 57.1 (C_3), 61.4 (C_6), 68.8 (C_{3a}), 69.3 ($C_{4'}$), 73.8 ($C_{5'}$), 81.8 (C_2), 169.7/172.4 (2xCO), 175.1 ($C_{2'}$); MS (*m/z*) 329

(M^+, 15), 270 (11), 228 (100), 168 (24), 150 (25), 113 (34), 108 (58), 84 (26), 59 (20). Anal. Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 50.70; H, 5.99; N, 4.22.

11: mp 80-82 °C (CH_2Cl_2-pentane); IR (KBr): 3531, 2961, 2903, 1738, 1255, 1184 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 1.60-1.70 (m, 2H: H_4, H_5), 1.90 (m, 1H: H_4), 2.45 (dd, $J_{3',6}$=10.1 Hz, $J_{3',4'}$=4.9 Hz, 1H: $H_{3'}$), 2.62 (m, 1H: H_5), 3.66 (m, 1H: H_6), 3.75 (s, 3H: OMe), 3.76 (s, 3H: OMe), 3.80 (dd, $J_{3,3a}$=9.1 Hz, $J_{3,2}$=6.1 Hz, 1H: H_3), 3.93 (m, 1H: H_{3a}), 4.26 (dd, $J_{5'c,5't}$=9.8 Hz, $J_{5'c,4'}$=3.7 Hz, 1H: $H_{5'c}$), 4.32 (d, $J_{5't,5'c}$=9.8 Hz, 1H: $H_{5't}$), 4.70 (t, $J_{4',3'}\approx J_{4',5'c}$=4.3 Hz, 1H: $H_{4'}$), 4.91 (d, $J_{2,3}$=6.1 Hz, 1H: H_2); ^{13}C-RMN (62.5 MHz, $CDCl_3$): δ 27.1 (C_4), 30.8 (C_5), 50.1 (C_3), 52.4/52.7/53.4 ($C_{3'}$/OMe/OMe), 63.6/65.8 (C_6/C_{3a}), 69.8 ($C_{4'}$), 73.6 ($C_{5'}$), 76.1 (C_2), 169.7/169.9 (2xCO), 175.4 ($C_{2'}$); MS (*m/z*) 329 (M^+, 14), 270 (8), 228 (100), 168 (39), 150 (54), 132 (28), 113 (81), 108 (79), 85 (55), 84 (50), 80 (28), 68 (24), 59 (32), 53 (27). Anal. Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 51.11; H, 5.89; N, 4.26.

Reaction of nitrone **8** *with 2(5H)-furanone*

A solution of **5** (1.00 g, 5.9 mmol) in CH_2Cl_2 (40 mL) at 0 °C under nitrogen atmosphere was treated with a solution of *m*-CPBA (1.07 g, 5.9 mmol) in the same solvent (10 mL). The mixture was left at 0 °C for 15 min. Then, the solution was concentrated to 25 mL and toluene (40 mL) was added; the rest of the CH_2Cl_2 was afterwards removed. 2(5*H*)-Furanone (500 mg, 5.9 mmol) was added to the toluene solution and the reaction mixture was heated at 110 °C for 4 h. Flash chromatography of the crude material (2.50 g) using methylene chloride-ether 1:1 as eluent afforded the following fractions: i) *m*-chlorobenzoic acid (935 mg); ii) 2(5*H*)-furanone (79 mg); iii) starting product **5** (132 mg); iv) a solid (159 mg, 0.58 mmol, 10% yield) identified as (3a*RS*,6*SR*,8a*SR*,8b*SR*)-octahydro-6-[2(5*H*)-oxo-3-furyl]furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **13**. Using ethyl acetate-CH_2Cl_2 as mobile phase were eluted 38 mg of an unidentified material. Finally, (3a*RS*,6*SR*,8a*SR*,8b*SR*)-octahydro-6-[(3*SR*,4*RS*)-dihydro-4-hydroxy-2(3*H*)-oxo-3-furyl]furo[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **12** (874 mg, 3.18 mmol, 54% yield), was obtained using ethyl acetate as eluent.

Considering the recovered compound **5** the yields are 62% and 12% for **12** and **13**, respectively.

12: mp 191-192 °C (methanol); IR (KBr): 3529, 2951, 2893, 1774, 1757 cm^{-1}; ^{1}H-RMN (400 MHz, d_4-MeOH): δ 1.80 (dtd, $J_{7c,7t}$=12.9 Hz, 2xJ=10.1 Hz, J'=7.6 Hz, 1H: H_{7c}), 1.91 (m, 1H: H_{8t}), 2.35 (dtd, $J_{8c,8t}$=12.9 Hz, 2xJ≈7.6 Hz, J'=2.9 Hz, 1H: H_{8c}), 2.50 (m, 1H: H_{7t}), 2.77 (dd, $J_{3',6}$=8.6 Hz, $J_{3',4'}$=4.7 Hz, 1H: $H_{3'}$), 3.51 (dd, $J_{8b,3a}$=5.8 Hz, $J_{8b,8a}$=2.2 Hz, 1H: H_{8b}), 3.63 (m, 1H: H_6), 4.01 (td, $J_{8a,8t}\approx J_{8a,8c}$≈7.4 Hz, $J_{8a,8b}$=2.2 Hz, 1H: H_{8a}), 4.25 (d, $J_{5't,5'c}$=10.0 Hz, 1H: $H_{5't}$), 4.37 (dd, $J_{5'c,5't}$=10.0 Hz, $J_{5'c,4'}$=3.2 Hz, 1H: $H_{5'c}$), 4.38 (d, $J_{3c,3t}$=10.9 Hz, 1H: H_{3c}), 4.50 (dd, $J_{3t,3c}$=10.9 Hz, $J_{3t,3a}$=4.0 Hz, 1H: H_{3t}), 4.71 (t, $J_{4',3'}\approx J_{4',5'c}$≈4.2 Hz, 1H: $H_{4'}$), 5.08 (dd, $J_{3a,8b}$=5.8 Hz, $J_{3a,3t}$=4.0 Hz, 1H: H_{3a}); ^{13}C-RMN (62.5 MHz, d_6-DMSO): δ 27.2/29.2 (C_7/C_8), 49.0 ($C_{3'}$), 55.1 (C_{8b}), 60.7 (C_{8a}), 67.5 (C_6), 68.8/70.9 (C_3/$C_{5'}$), 74.6 ($C_{4'}$), 77.0 (C_{3a}), 176.0/177.5 ($C_{2'}$/C_1); MS (*m/z*) 269 (M^+, 3), 168 (100), 84 (20), 68 (22), 55 (25). Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.51; H, 5.62; N, 5.20. Found: C, 53.42; H, 5.56; N, 5.21.

13: mp 123-125 °C (CH_2Cl_2-pentane); IR (KBr): 2958, 2921, 2866, 1760, 1735 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 1.64 (dtd, $J_{8t,8c}$=12.7 Hz, $J_{8t,7t}\approx J_{8t,7c}$≈9.8 Hz, $J_{8t,8a}$=7.8 Hz, 1H: H_{8t}), 1.87 (m, 1H: H_{7c}), 2.37 (m, 2H: H_{8c}, H_{7t}), 3.30 (dd, $J_{8b,3a}$=5.8 Hz, $J_{8b,8a}$=1.8 Hz, 1H: H_{8b}), 3.97 (broad t, $J_{8a,8c}\approx J_{8a,8t}$≈7.3 Hz, 1H: H_{8a}), 4.14 (broad t, $J_{6,7t}\approx J_{6,7c}$≈7.6 Hz, 1H: H_6), 4.38 (d, $J_{3c,3t}$=11.0 Hz, 1H: H_{3c}), 4.46 (dd, $J_{3t,3c}$=11.0 Hz, $J_{3t,3a}$=4.1 Hz, 1H: H_{3t}), 4.84 (m, 2H: 2x$H_{5'}$), 5.00 (dd, $J_{3a,8b}$=5.8 Hz, $J_{3a,3t}$=4.1 Hz, 1H: H_{3a}), 7.55 (s , 1H: $H_{4'}$); ^{13}C-RMN (62.5 MHz, $CDCl_3$): δ 29.5/30.4 (C_7/C_8), 55.6

(C_{8b}), 61.7 (C_{8a}), 68.0 (C_6), 70.4 (C_3), 70.7 ($C_{5'}$), 76.7 (C_{3a}), 134.0 ($C_{3'}$), 146.0 ($C_{4'}$), 173.0 ($C_{2'}$), 176.2 (C_1); MS (CI/NH_3) (*m/z*) 269 (M^++18, 10), 252 (M^++1, 100). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.27; H, 5.18; N, 5.55.

Dimethyl (3aRS,6RS)-3a,4,5,6-tetrahydro-6-[(3RS,4RS)-tetrahydro-4-hydroxy-2-oxo-2H-3-pyranyl]-pyrrolo[1,2-b]isoxazole-2,3-dicarboxylate, **15**

A solution of **6** (51 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen atmosphere was treated with a solution of *m*-CPBA (55 mg, 0.30 mmol) in the same solvent (3 mL). The mixture was left at 0 °C for 15 min. Then, DMAD (34 µl, 0.27 mmol) was added and the reaction mixture was kept at 20 °C for 5 h. Flash chromatography of the crude material (156 mg) using methylene chloride-ether 4:1 as eluent afforded the following fractions: i) *m*-chlorobenzoic acid (47 mg); and ii) adduct **15** (69 mg, 0.20 mmol, 73% yield) as a solid. **15**: mp 97-99 °C (CH_2Cl_2-pentane); IR (KBr): 3464, 2955, 2940, 1729, 1708 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 1.51 (dtd, $J_{5c,5t}$=13.0 Hz, $J_{5c,6}$=$J_{5c,4t}$=10.9 Hz, $J_{5c,4c}$=7.8 Hz, 1H: H_{5c}), 2.03 (m, 1H: H_{4t}), 2.05 (m, 1H: $H_{5'}$) 2.20 (dddd, $J_{5',5'}$=12.7 Hz, J=10.8 Hz, J'=7.8 Hz, J''=5.4 Hz, 1H: $H_{5'}$), 2.33 (dtd, $J_{4c,4t}$=13.3 Hz, $J_{4c,3a}$=$J_{4c,5c}$=7.8 Hz, $J_{4c,5t}$=2.2 Hz, 1H: H_{4c}), 2.46 (dd, $J_{3',6}$=8.3 Hz, $J_{3',4'}$=3.0 Hz, 1H: $H_{3'}$), 2.48 (dddd, $J_{5t,5c}$=13.0 Hz, $J_{5t,4t}$=8.2 Hz, $J_{5t,6}$=5.6 Hz, $J_{5t,4c}$=2.2 Hz, 1H: H_{5t}), 3.75 (s, 3H: OMe), 3.85 (m, 1H: H_6), 3.86 (s, 3H: OMe), 4.24 (ddd, $J_{6',6'}$=11.5 Hz, $J_{6',5'}$=6.8 Hz, $J_{6',5'}$=5.5 Hz, 1H: $H_{6'}$), 4.56 (ddd, $J_{6',6'}$=11.5 Hz, $J_{6',5'}$=7.3 Hz, $J_{6',5'}$=5.5 Hz, 1H: $H_{6'}$), 4.72 (dt, $J_{4',5'}$=5.2 Hz, $J_{4',5'}$≈$J_{4',3'}$≈3.0 Hz, 1H: $H_{4'}$), 4.87 (t, $J_{3a,4c}$≈$J_{3a,4t}$≈7.0 Hz, 1H: H_{3a}); ^{13}C-RMN (100 MHz, $CDCl_3$): 27.2 (C_5), 29.3 (C_4), 29.9 ($C_{5'}$), 50.0 ($C_{3'}$), 51.6 (OMe), 52.9 (OMe), 64.2 ($C_{4'}$), 64.6 ($C_{6'}$), 66.9 (C_6), 68.7 (C_{3a}), 110.8 (C_3), 148.4 (C_2), 158.2 (2xCO), 170.5 ($C_{2'}$); MS (*m/z*) 341 (M^+, 0.8), 282 (2), 60 (22), 59 (60), 45 (100). Anal. Calcd for $C_{15}H_{19}NO_8$: C, 52.79; H, 5.61; N, 4.10. Found: C, 52.84; H, 5.81; N, 4.05.

(4aRS,7RS,9aRS,9bRS)-octahydro-7-[(3RS,4RS)-tetrahydro-4-hydroxy-2-oxo-2H-3-pyranyl]-1H-pyrano[3,4-b]pyrrolo[1,2-b]isoxazol-1-one, **16**

A solution of **6** (103 mg, 0.57 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen atmosphere was treated with a solution of *m*-CPBA (101 mg, 0.58 mmol) in the same solvent (3 mL). The mixture was left at 0 °C for 15 min. Then, the solution was concentrated to 6 mL and toluene (15 mL) was added; the rest of the CH_2Cl_2 was afterwards removed. 5,6-Dihydro-2*H*-pyran-2-one (48 µl, 0.56 mmol) was added to the toluene solution and the reaction mixture was heated at 110 °C for 4 h. Flash chromatography of the crude material (267 mg) using methylene chloride-ether 1:1 as eluent afforded the following fractions: i) *m*-chlorobenzoic acid (90 mg); and ii) **16** (78 mg, 0.26 mmol, 47% yield) as a solid. **16**: mp 172-173 °C (CH_2Cl_2-pentane); IR (KBr): 3532, 2964, 2935, 1725, 1271 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 1.71 (ddt, $J_{8c,8t}$=13.2 Hz, $J_{8c,7}$=10.3 Hz $J_{8c,9t}$≈$J_{8c,9c}$≈8.8 Hz, 1H: H_{8c}), 1.90 (m, 1H: H_4), 1.92 (m, 1H: H_{9t}), 2.00-2.10 (m, 2H: 2x$H_{5'}$), 2.15 (m, 1H: H_4), 2.25 (m, 1H: H_{9c}), 2.35 (m, 1H: H_{8t}), 2.38 (dd, $J_{3',7}$=5.8 Hz, $J_{3',4'}$=3.4 Hz, 1H: $H_{3'}$), 3.16 (dd, $J_{9b,4a}$=8.5 Hz, $J_{9b,9a}$=5.7 Hz, 1H: H_{9b}), 3.85 (dt, $J_{7,8c}$=10.3 Hz, $J_{7,8t}$≈$J_{7,3'}$≈7.0, 1H: H_7), 3.96 (dt, $J_{9a,9}$=7.1 Hz, $J_{9a,9b}$≈$J_{9a,9}$≈5.3 Hz, 1H: H_{9a}), 4.21 (m, 1H: H_3), 4.25 (m, 1H: $H_{6'}$), 4.41 (ddd, $J_{3,3}$=11.5 Hz, $J_{3,4}$=9.6 Hz, $J_{3,4}$=3.2 Hz, 1H: H_3), 4.63 (ddd, $J_{6',6'}$=11.1 Hz, $J_{6',5'}$=9.0 Hz, $J_{6',5'}$=4.7 Hz, 1H: $H_{6'}$), 4.67 (q, 3xJ≈4.0 Hz, 1H: $H_{4'}$), 4.79 (dt, $J_{4a,9b}$=8.5 Hz, $J_{4a,4}$≈$J_{4a,4}$≈4.3 Hz, 1H: H_{4a}); ^{13}C-RMN (100 MHz, $CDCl_3$): δ 26.3 (C_4), 27.5 (C_8), 27.8 (C_9), 30.3 ($C_{5'}$), 48.9 ($C_{3'}$), 53.2 (C_{9b}), 62.2 (C_7), 63.9 ($C_{4'}$),

64.5 (C_3), 65.0 ($C_{6'}$), 68.4 (C_{9a}), 72.5 (C_{4a}), 169.9/170.3 ($C_1/C_{2'}$); MS (*m/z*) 297 (M^+, 4), 182 (100). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.40; H, 6.44; N, 4.68.

Dimethyl (3aRS,6SR)-3a,4,5,6-tetrahydro-6-[(3SR,4RS)-dihydro-4-hydroxy-2(3H)-oxo-3-furyl]-3a-[2(5H)-oxo-3-furyl]pyrrolo[1,2-b]isoxazole-2,3-dicarboxylate, **17**

A solution of **12** (210 mg, 0.78 mmol) in CH_2Cl_2 (4 mL) at 0 °C under nitrogen atmosphere was treated with a solution of *m*-CPBA (155 mg, 0.85 mmol) in the same solvent (2 mL). The mixture was left at 0 °C for 15 min. Then, DMAD (190 µl, 1.56 mmol) was added and the reaction mixture was kept at 20 °C for 3 d. Flash chromatography of the crude material (560 mg) using ethyl acetate-hexane 4:1 as eluent afforded the following fractions: i) *m*-chlorobenzoic acid (142 mg); and ii) adduct **17** (107 mg, 0.26 mmol, 34% yield) as a solid. **17**: mp 160-162 °C (CH_2Cl_2-pentane); IR (KBr): 3516, 2953, 1762, 1725, 1639 cm^{-1}; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 2.23 (dq, $J_{5,5}\approx$13.6 Hz, 3xJ≈8.7 Hz, 1H: H_5), 2.47 (dt, $J_{4,4}\approx$13.4 Hz, 2xJ≈8.7 Hz, 1H: H_4), 2.63 (m, 2H: H_4, H_5), 2.87 (dd, $J_{3',6}$=9.7 Hz, $J_{3',4}$=4.5 Hz, 1H: $H_{3'}$), 3.20 (broad s, 1H: OH), 3.78 (td, $J_{6,5}\approx J_{6,3'}\approx$9.8 Hz, $J_{6,5}$=5.8 Hz, 1H: H_6), 3.82 (s, 3H: OMe), 3.93 (s, 3H: OMe), 4.34 (dd, $J_{5'c,5't}$=10.2 Hz, $J_{5'c,4'}$=3.2 Hz, 1H: $H_{5'c}$), 4.38 (d, $J_{5't,5'c}$=10.2 Hz, 1H: $H_{5't}$), 4.81 (broad t, $J_{4',3''}\approx J_{4',5'c}\approx$3.8 Hz, 1H: $H_{4'}$), 4.82 (dd, $J_{5'',5''}$=18.3 Hz, $J_{5'',4''}$=1.8 Hz, 1H: $H_{5''}$), 4.87 (dd, $J_{5'',5''}$=18.3 Hz, $J_{5'',4''}$=1.6 Hz, 1H: $H_{5''}$), 7.34 (broad s, 1H: $H_{4''}$); ^{13}C-RMN (62.5 MHz, $CDCl_3$): δ 26.1 (C_5), 32.1 (C_4), 49.5 ($C_{3'}$), 52.4/53.6 (2xOMe), 66.0 (C_6), 69.6 (C_{3a}), 69.8 ($C_{4'}$), 73.6 ($C_{5'}$), 75.8 ($C_{5''}$), 110.8 (C_3), 134.1 ($C_{3''}$), 148.0 (C_2), 151.0 ($C_{4''}$), 158.6/162.0 (2xCO), 170.8 ($C_{2''}$), 174.6 ($C_{2'}$); MS (CI/NH_3) (*m/z*) 427 (M^++18, 37), 410 (M^++1, 75), 366 (38), 348 (40), 306 (64), 252 (41), 239 (22), 222 (72), 188 (20), 178 (100), 122 (26). Anal. Calcd for $C_{18}H_{19}NO_{10}$: C, 52.82; H, 4.68; N, 3.42. Found: C, 52.93; H, 4.58; N, 3.26.

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