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# Cycloadditions of Highly Functionalized $C_6$-Synthons to Cyclic Nitrones

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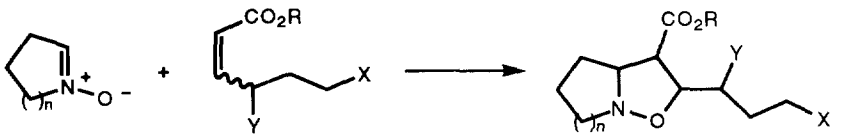
***Abstract:*** The 1,3-dipolar cycloaddition of cyclic nitrones to several $C_6$ α,β-unsaturated esters and lactones with different functionalities has been studied. All these olefins have shown high stereoselectivity, with a predominance of the *exo* or *endo* transition state for the *cis* or *trans* dipolarophiles, respectively. The antifacial approach is favoured in the reactions with γ-substituted hexenolides and also with the substituted nitrone **21**. © 1997 Elsevier Science Ltd.

The 1,3-dipolar cycloaddition of nitrones to olefins is a widely used method for the preparation of isoxazolidines. Great advantages of employing this reaction are the high regio- and stereoselectivity often achieved in the process and the synthetic versatility of the adducts, which can be readily converted into cyclic or acyclic polyfunctionalized compounds.[1] When 1,2-disubstituted olefins in which one of the substituents is an electron-withdrawing group are used as the dipolarophile component, a high degree of regiocontrol is usually observed, leading to isoxazolidine adducts with the electron-withdrawing substituent attached to the 4 position,[1a,c,2] in agreement with the FMO theory.[1a] Less predictable is the stereoselectivity of the process, since it depends on both electronic and steric factors. Only a careful consideration of the competitive *endo* and *exo* transition states for each particular reaction may allow an explanation of the experimental results.

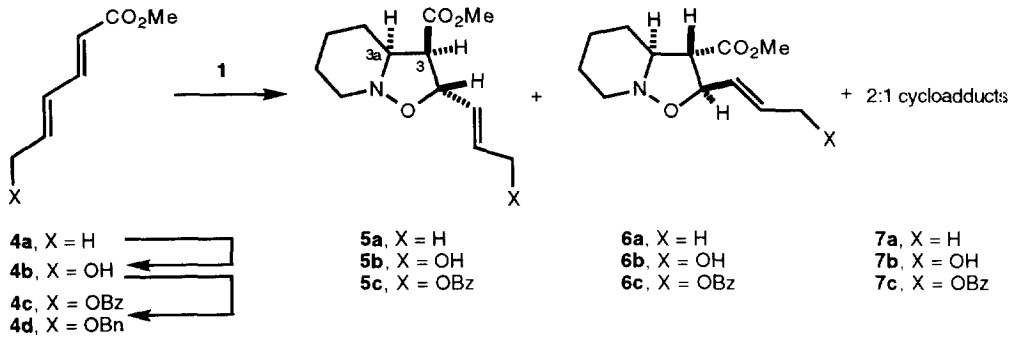
As part of a program on alkaloid synthesis, we have been interested in the reaction of five and six-membered cyclic nitrones with α,β-unsaturated esters and lactones of different degrees of functionality.[2d-k] Among these dipolarophiles, particularly interesting for our synthetic purposes, are those with a $C_6$ skeleton substituted at the γ and/or ω positions, **3**, (Scheme 1).We have already described the cycloaddition of 2,3,4,5-tetrahydropyridine 1-oxide, **1**, to several α,β-unsaturated lactones[2e,g] and esters[2h,i] of type **3** and also the reactions of 3,4-dihydro-2*H*-pyrrole 1-oxide, **2**, with the same esters.[2h,i] To complete those studies we have prepared new dipolarophiles equivalent to **3** and their cycloadditions to **1** and **2** have been performed. The results of these and other closely related reactions are reported herein.

The 6-oxy derivatives of sorbic acid, **4b-d**, (Scheme 2) look to be easily accessible compounds synthetically equivalent to **3**, but we had previously studied the cycloaddition of nitrone **1** to methyl sorbate, **4a**, and found this reaction to have poor chemoselectivity, yielding 2:1 cycloadducts as major products.[2d]




Scheme 1

Nevertheless, a report dealing with the use of β-cyclodextrin in the cycloaddition of a nitrile oxide to a vinylpyridine[3] encouraged us to prepare the derivatives **4c,d** in order to study their cycloaddition to nitrone **1**. The presence of a phenyl group in these substrates should facilitate their inclusion in the cavity of the cyclodextrin and hence favour the higher reactivity of the α,β- in relation to the γ,δ-double bond, the last being much more sterically demanding. On the other hand, there was a possibility that the chiral environment produced by the cyclodextrin in the proximity of the reaction site could induce enantioselectivity in the cycloaddition process.




Scheme 2

A preparation of **4b** had been described in a three step sequence,[4] that involved allylic bromination of methyl sorbate,[5] followed by a nucleophilic substitution reaction with silver acetate and subsequent selective hydrolysis of the acetate, but we have improved this preparation by performing directly the hydrolysis of the bromide.[6] The benzoyl derivative **4c** was easily obtained in 77% yield by reaction of **4b** with benzoyl chloride in pyridine. On the contrary, **4d** could only be obtained in very low yield by treatment of **4b** with benzyl trichloroacetimidate,[7] since the benzylation of **4b** by standard procedures failed. Therefore we decided to study only the dipolar cycloadditions of nitrone **1** to **4b** and **4c**. The results are collected in Table 1.

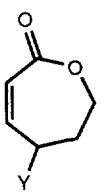
The cycloadditions were first performed in organic solvent at two different temperatures, under similar conditions to those previously used with methyl sorbate.[2d,h] In all cases, a 20% excess of the dipolarophile was used. The reactions between nitrone **1** and the hydroxy derivative **4b** gave complex mixtures from which the major component was separated by column chromatography and identified as a 2:1 cycloadduct, **7b**. By repeated chromatographies, analytical samples of the two 1:1 cycloadducts, **5b** and **6b**, resulting from the addition of the nitrone to the α,β-double bond of **4b**, were also obtained. The stereochemistry of these adducts was elucidated considering the value of the coupling constant $J_{3,3a}$, that is 8.0 Hz for the *endo* isomer, **5b**, and 10.2 Hz for the *exo*, **6b**, as in closely related compounds previously described.[2h,i] Similar results were

Table 1. Cycloadditions of nitrone **1** to sorbic acid derivatives **4b,c**.

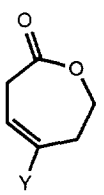
| dipolarophile | conditions | *endo*-adduct (yield) | *exo*-adduct (yield) | 2:1 adducts (yield) |
|---|---|---|---|---|
| **4b** | $CH_2Cl_2$, 4 °C, 6.5 months | **5b** + **6b** (11%) | | **7b** (18%) |
| **4b** | $CHCl_3$, 60 °C, 7 d | **5b** + **6b** (9%) | | **7b** (20%) |
| **4c** | $CH_2Cl_2$, 4 °C, 2 months | **5c** (14%) | **6c** (8%) | **7c** (18%) |
| **4c** | $CHCl_3$, 60 °C, 24 h | **5c** (18%) | **6c** (11%) | **7c** (19%) |
| **4c** | $H_2O$, β-HPCD, 4 °C, 58 d | --- | --- | *a* |

[a] Some 2:1 cycloadduct was obtained, but it was contaminated with the dimer of the nitrone.

obtained in the cycloaddition of nitrone **1** to the benzoyloxy derivative **4c**. In this case, the two 1:1 cycloadducts *endo*, **5c**, and *exo*, **6c**, could be quantitatively separated and their stereochemistry assigned as above according to the value of $J_{3,3a}$. The hydroxy derivative **4b** was fairly soluble in water, while the benzoyloxy derivative **4c** was not. Therefore, the cycloaddition in water in the presence of a twofold molar excess of β-hydroxypropylcyclodextrin was only intended with **4c**. Unfortunately, after 2 months at 4 °C, most of the nitrone was recovered (partially as the dimer) and only traces of 2:1 cycloaddition products were detected. Several trials in other conditions were also unsuccessful and the study was abandoned.



**8a**, Y = H
**8b**, Y = Br
**8c**, Y = OAc
**8d**, Y = SAc
**8e**, Y = SPh
**8f**, Y = SOPh
**8g**, Y = OTs

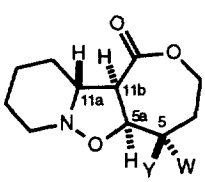


**9e**, Y = SPh
**9f**, Y = SOPh

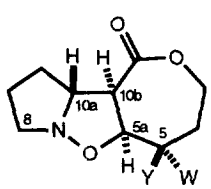
Figure 1

Another kind of synthon equivalent to **3** are α,β-hexenolides with an heteroatom at the γ position, **8** (Figure 1). In previous studies we had found that the 1,3-dipolar cycloadditions of nitrone **1** to **8a-d** gave exclusively *exo* cycloadducts with a very high *anti* selectivity.[2g] We thought that the phenylthiolactone **8e** could open the access to enantiopure molecules of type **8** through the asymmetric oxidation to the corresponding sulfoxide. Treatment of bromolactone **8b** with thiophenol in the presence of triethylamine in acetone at -78 °C produced the new lactone **8e** in 90% yield, along with a 3% of its β,γ-unsaturated isomer, **9e**. The oxidation of **8e** with MCPBA in $CHCl_3$ gave the expected sulfoxide **8f**, as was evidenced by the presence in its $^1$H-NMR spectrum of a double doublet at δ 6.30 and a doublet at δ 6.20, corresponding to the olefinic β and α protons respectively, but all attempts to purify this compound lead to its β,γ-unsaturated isomer, **9f**, which was isolated in 76% yield and presented only one olefinic proton at δ 6.54 with a high multiplicity due to vicinal and allylic couplings. With the aim of improving the leaving group capacity of the γ-substituent, the preparation of **8g** was also intended. With this purpose, lactone **8b** was treated with silver tosylate in ether at room temperature for 24 h.[8] The $^1$H-NMR spectrum of the reaction crude showed two absorptions at δ 6.18 and 6.03 for the ethylenic protons, one signal at δ 5.21 for the allylic proton and a methyl group at δ 2.45. These data are consistent with the structure of **8g**, but this compound was not stable enough to be isolated and it was used for the 1,3-dipolar cycloaddition without further purification.

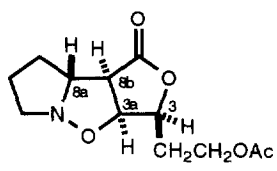
The cycloadditions of nitrones **1** and **2** to the hexenolides were performed in refluxing toluene, with a twofold molar excess of nitrone and their evolution was controlled by tlc. After 9 h of reaction between nitrone **1** and phenylthiolactone **8e**, purification by flash column chromatography over silica gel afforded the *exo-anti* cycloadduct, **10**, as major product (72%) and a minor percentage of the *exo-syn* isomer, **11**, (Figure 2). The cycloaddition of nitrone **1** to crude lactone **8g**, after 45 min of reaction, allowed the isolation of the *exo-anti* adduct, **12**, as the only product, although in low yield (12% for the two consecutive steps). In the $^1$H-NMR spectra of adducts **10** and **12** in chloroform solution, only one set of signals corresponding to the *trans*-invertomer is observed, while for adduct **11** a 9:1 relation for the *trans/cis* fusion can be mesured. The *exo* stereochemistry of all these adducts is deduced from the value of $J_{11a,11b}$, which is 9.8 Hz for the three compounds, while the *anti* or *syn* geometry is evidenced by $J_{5,5a}$: 11.6 and 11.0 Hz for **10** and **12** respectively, where $H_5$ and $H_{5a}$ are *trans* to each other, and 2.9 Hz for **11**, where these two protons are *cis*.[2g]



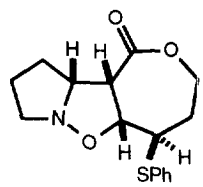

**10**, Y = H W = SPh
**11**, Y = SPh W = H
**12**, Y = H W = OTs




**13**, Y = H W = OAc
**14**, Y = OAc W = H
**16**, Y = H W = SAc
**17**, Y = SAc W = H
**18**, Y = H W = SPh
**19**, Y = SPh W = H




**15**




**20**

Figure 2

From the reaction between nitrone **2** and acetoxylactone **8c** two cycloadducts, **13** and **14**, were isolated in 77% and 12% yield, respectively, and also a 5% of a third product that was identified as **15**. As above, the *anti* geometry of the major product **13** was assigned according to the observed value of 10.4 Hz for the coupling constant between $H_5$ ($\delta$ 5.00) and $H_{5a}$ ($\delta$ 4.52). The *exo* stereochemistry was established by a NOE experiment: presaturation of the signal corresponding to $H_{5a}$ produces enhancement on the absorption of one of the methylenic protons $\alpha$ to the nitrogen atom, $H_8$ ($\delta$ 3.15). The proximity of $H_{5a}$ and $H_8$ is only possible in an *exo* isomer. Cycloadduct **14** presents a $J_{5,5a}$ of 1.8 Hz, in agreement with its *syn* stereochemistry. The structural and stereochemical elucidation of the third compound, **15**, was based on its spectroscopic data. In the IR spectrum it presents an absorption at 1764 cm$^{-1}$ characteristic for a $\gamma$-lactone. Its $^1$H-NMR spectrum shows a doublet for $H_{8b}$ ($\delta$ 3.46) with $J_{8b,3a}$ = 6.7 Hz, meaning that the coupling constant between $H_{8b}$ and $H_{8a}$ is 0 Hz and consequently these two protons should be *trans*,[2e] and $H_{3a}$ appears as a double doublet at $\delta$ 4.77 with $J_{3a,3}$ = 4.9 Hz, in agreement with a *cis* disposition for $H_{3a}$ and $H_3$. The stereochemistry assigned to **15** was also confirmed by NOE experiments. Compound **15** derives formally from nitrone **2** and $\gamma$-acetoxyethyl-$\alpha,\beta$-butenolide, but since it presents *exo-syn* stereochemistry we believe that it is most probably formed through a reorganisation of the major *exo-anti* cycloadduct **13**.

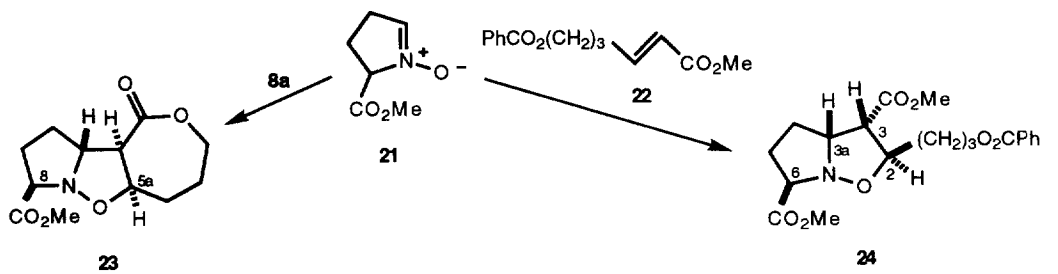
When acetylthiolactone **8d** was treated with nitrone **2**, after 4 h of reaction the overall yield of cycloadducts was 53%, some starting lactone (16%) being recovered unchanged, but prolonged reaction times did not improve this result. Two cycloadducts, **16** and **17**, could be isolated and fully characterized. In the

cycloaddition of **2** to phenylthiolactone **8e**, the cycloadducts **18** and **19** were obtained in 69% and 7% yield, respectively, and we isolated another compound that was identified as the *endo-anti* adduct, **20** (1%). The $^1H$ and $^{13}C$ chemical shifts of the major adducts **16** and **18** and the value of their coupling constants $J_{10a,10b}$ and $J_{5a,5}$ correlate perfectly with those of **13** (Table 2), therefore they were assigned as *exo-anti*. The stereochemistry of the minor adducts **14**, **17** and **19** was determined also to be *exo*, through NOE experiments performed for each compound. Therefore they should necessarily come from a *syn* approach of the reactants in the transition state, resulting in a *cis* relationship between $H_{5a}$ and $H_5$. Accordingly all three compounds present a small value of $J_{5a,5}$.

Table 2. Significant $^1H$ and $^{13}C$-NMR data of compounds **13**, **14** and **16-20**.

| compound | δ $H_8$ | δ $H_{10a}$ | δ $H_{10b}$ | δ $H_{5a}$ | δ $H_5$ | $J_{10a,10b}$ | $J_{5a,5}$ |
|---|---|---|---|---|---|---|---|
| **13** | 3.15 | 4.28 | 3.50 | 4.52 | 5.00 | 3.7 Hz | 10.4 Hz |
| **14** | 2.82 and 3.23 | 4.13 | 3.39 | 4.73 | 5.35 | 7.3 Hz | 1.8 Hz |
| **16** | 3.09 and 3.16 | 4.34 | 3.53 | 4.56 | 3.57 | 4.3 Hz | 11.0 Hz |
| **17** | 2.87 and 3.25 | 4.14 | 3.42 | 4.77 | 4.21 | 6.7 Hz | 2.7 Hz |
| **18** | 3.11 | 4.32 | 3.49 | 4.27 | 3.25 | 3.2 Hz | 11.1 Hz |
| **19** | 2.82 and 3.21 | 4.15 | 3.33 | 4.77 | 3.59 | 6.8 Hz | 2.1 Hz |
| **20** | 2.93 and 3.35 | 3.68 | 4.50 | 4.20 | 3.16 | 6.5 Hz | 11.3 Hz |

We were also interested in testing the facial selectivity of the cycloaddition reaction between our $C_6$ dipolarophiles and a five membered cyclic nitrone substituted at position 2. As representative examples we studied the cycloadditions of the known nitrone **21**[9] to the parent hexenolide **8a** and to methyl (*E*)-6-benzoyloxy-2-hexenoate, **22**,[10] (Scheme 3). With the less reactive *cis* dipolarophile **8a**, after 5 h of reaction in refluxing toluene, we isolated only one cycloadduct (52%) that was identified as *exo-anti*, **23**, on the basis of a strong NOE between $H_{5a}$ (δ 4.44) and $H_8$ (δ 3.70) With the more reactive *trans* dipolarophile **22**, the reaction was performed in refluxing $CHCl_3$ and, after 72 h, again a single product, **24**, was obtained in 81% yield. The *endo* stereochemistry of **24** was demonstrated by the NOE between $H_3$ (t at δ 3.15) and $H_{3a}$ (q at δ 4.10) and the *anti* geometry by the NOE between $H_2$ (ddd at δ 4.22) and $H_6$ (t at δ 3.80).




Scheme 3

In conclusion, all the α,β-hexenolides and α,β-unsaturated esters have demonstrated a high stereoselectivity in their 1,3-dipolar cycloadditions to cyclic nitrones. For the *cis* dipolarophiles the *exo*

transition state predominates over the *endo*, while for the *trans* dipolarophiles the opposite preference is observed. The antifacial approach is favoured in the reactions with γ-substituted hexenolides and also in the reactions with the substituted nitrone, regardless of *endo* or *exo* adducts are formed. Further synthetic transformations with the cycloadducts described here are being investigated.

## EXPERIMENTAL SECTION

The following products were prepared according to previously described methods: **1**,[11] **2**,[12] **4a**,[13] **8a**,[14] **8b-d**,[2g] **21**[9] and **22**.[10] 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 Merck silica gel (230-400 mesh). Tlc were performed by using 0.25 mm Alugram Sil plates, Macherey-Nägel. Distillation of small amounts were effected on a Büchi KRV 65/30 rotary still (only oven temperature given). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. $^1$H-NMR and $^{13}$C-NMR spectra were recorded by *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona* on Bruker AC-250-WB or AM-400-WB instruments. $CDCl_3$ is used as solvent for the NMR experiments. 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.

*Methyl (2E,4E)-6-hydroxy-2,4-hexadienoate,* **4b**

A mixture of acetone (24 mL), aqueous $NaHCO_3$ sat. solution (16 mL) and methyl (2*E*,4*E*)-6-bromo-2,4-hexadienoate[5] (2.0 g, 9.8 mmol) was heated at reflux for 5 h. After neutralization with 5% HCl and removal of the acetone under vacuum, a two layer residue was obtained. The aqueous phase was extracted with EtOAc (6 x 25 mL) and the organic phase disolved in EtOAc (250 mL) . The combined organic extracts were washed with water and concentrated to dryness to give 401 mg of a solid material that was crystallised from hexane yielding 856 mg (62%) of **4b** (mp. 52-54 °C; lit.[4] *ca* 55-56 °C).

*Methyl (2E,4E)-6-benzoyloxy-2,4-hexadienoate,* **4c**

Benzoyl chloride (1.2 mL, 10.0 mmol) was added to a cold solution of **4b** (980 mg, 6,9 mmol) in pyridine (15 mL) and the mixture was stirred at 0 °C for 30 min. Then 25 mL of $CH_2Cl_2$ were added and the resultiong solution was washed with 5% HCl (6 x 25 mL) and water (25 mL). Evaporation of the solvent under vacuum gave a residue that was crystallised from hexane to yield 1.31 g (77%) of **4c**: mp 90-91 °C; IR (KBr): 2938, 1710, 1648, 1614, 1450, 1390, 1274, 1118 cm$^{-1}$; $^1$H-NMR (400 MHz): δ 3.73 (s, 3H: OC$H_3$), 4.91 (d, $J_{6,5}$=5.5 Hz, 2H: 2H$_6$), 5.92 (d, $J_{2,3}$=15.3 Hz, 1H: H$_2$), 6.23 (dt, $J_{5,4}$=15.3 Hz, $J_{5,6}$=5.5 Hz, 1H: H$_5$), 6.45 (dd, $J_{4,5}$=15.3 Hz, $J_{4,3}$=11.0 Hz, 1H: H$_4$), 7.28 (dd, $J_{3,2}$=15.3 Hz, $J_{3,4}$=11.0 Hz, 1H: H$_3$), 7.43 (t, J=7.3 Hz, 2H: 2H$_{m\text{-Ph}}$), 7.56 (t, $J_{p,m}$=7.3 Hz, 1H: H$_{p\text{-Ph}}$), 8.04 (d, $J_{o,m}$=7.3 Hz, 2H: 2H$_{o\text{-Ph}}$); $^{13}$C-NMR (62.5 MHz): δ 51.5 (O$CH_3$), 64.1 ($C_6$), 122.0 ($C_2$), 128.4/129.6/129.7/130.4/133.1 ($C_4$/Ph), 135.4 ($C_5$), 143.2 ($C_3$), 165.9 (OCOPh), 167.0 ($C_1$); MS (CI, $NH_3$) (*m/z*) 264 ($M^+$+18, 100), 247 ($M^+$+1, 13). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.45; H, 5.74.

*Methyl (2E,4E)-6-benzyloxy-2,4-hexadienoate,* **4d**

To a stirred solution of benzyl 2,2,2-trichloroacetimidate (200 μL, 1.1 mmol) and two drops of triflic acid in a 2/1 mixture of cyclohexane and $CH_2Cl_2$ (3 mL), a solution of **4b** (60 mg, 0.4 mmol) in the same solvent (9 mL) was added dropwise and the mixture was stirred at rt for 2 d, following its evolution by tlc

(hexane/EtOAc 4/1). The reaction mixture was washed with $NaHCO_3$ sat. solution (5 mL) and water (5 mL) and the solvent removed to give a crude material (375 mg) that was purified by flash chromatography using hexane/EtOAc 10/1 as eluent. A second flash chromatography eluting with hexane/$CH_2Cl_2$ 1/1 allowed the isolation of pure **4d** (23 mg, 24%) as an oil: IR (film): 3064 , 3037, 2951, 2924, 2858, 1723, 1656, 1616, 1457, 1437, 1277, 1171, 1118 $cm^{-1}$; $^1$H-NMR (250 MHz): δ 3.73 (s, 3H: OC$H_3$), 4.12 (dd, $J_{6,5}$=5.1 Hz, $J_{6,6}$=1.5 Hz, 2H: $2H_6$), 4.53 (s, 2H: C$H_2$Ph), 5.87 (d, $J_{2,3}$=15.4 Hz, 1H: $H_2$), 6.16 (dt, $J_{5,4}$=15.4 Hz, $J_{5,6}$=5.1 Hz, 1H: $H_5$), 6.41 (dd, $J_{4,5}$=15.4 Hz, $J_{4,3}$=11.0 Hz, 1H: $H_4$), 7.28 (dd, $J_{3,2}$=15.4 Hz, $J_{3,4}$=11.0 Hz, 1H: $H_3$), 7.33 (m, 5H: Ph); $^{13}$C-NMR (62.5 MHz): δ 51.6 (O$CH_3$), 69.6 ($C_6$), 72.7 (C$H_2$Ph), 121.0 ($C_2$), 127.76/127.80/128.5/129.1/137.9 (Ph/$C_4$), 138.8 ($C_5$), 144.0 ($C_3$), 167.4 ($C_1$).

*Reaction of Nitrone* **1** *with* **4b**

To a solution of nitrone **1** (2.4 mmol) in $CH_2Cl_2$ (20 mL) was added a solution of **4b** (346 mg, 2.9 mmol) in the same solvent (5 mL) and the mixture was kept at 4 °C for 6.5 months following its evolution by tlc ($CHCl_3$/MeOH 9/1). Removal of the solvent gave a crude material (591 mg) that was purified by flash chromatography. Using hexane/EtOAc 1/6 as eluent, the following fractions were obtained: 127 mg (37%) of starting **4b**; 66 mg (11%) of a mixture of methyl (2*RS*,3*SR*,3a*RS*)-2-[(*E*)-3-hydroxy-1-propenyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **5b**, and its (2*RS*,3*SR*,3a*SR*) isomer, **6b**. Changing the eluent to EtOAc/MeOH 20/1, another fraction containing a mixture of 2:1 cycloadducts, **7b**, (74 mg, 18%) was obtained. Repeated flash chromatographies allowed the isolation of analytical samples of **5b** and **6b**.

**5b**: IR (film): 3395 (br), 2945, 2861, 1736, 1441, 1202, 1173, 991 $cm^{-1}$; $^1$H-NMR (250 MHz): δ 1.20-1.93 (m, 6H: $2H_4$, $2H_5$, $2H_6$), 2.44 (m, 2H: $H_{7ax}$, $H_{3a}$), 3.02 (dd, $J_{3,3a}$=8.0 Hz, $J_{3,2}$=5.5 Hz, 1H: $H_3$), 3.50 (m, 1H: $H_{7eq}$), 3.70 (s, 3H: OC$H_3$), 4.12 (d, J=6.6 Hz, 2H: $2H_{3'}$), 4.86 (br t, $J_{2,3}$=$J_{2,1'}$=5.5 Hz, 1H: $H_2$), 5.72 (dd, J=15.7 Hz, J'=7.3 Hz, 1H: $H_{1'}$), 5.97 (dt, J=15.7 Hz, J'=4.8 Hz, 1H: $H_{2'}$); $^{13}$C-NMR (62.5 MHz): δ 23.6 ($C_5$), 24.3 ($C_6$), 26.7 ($C_4$), 51.9 (O$CH_3$), 55.5 ($C_7$), 56.4 ($C_3$), 62.6 ($C_{3'}$), 69.5 ($C_{3a}$), 78.9 ($C_2$), 128.1/134.1 ($C_{1'}$/$C_{2'}$), 171.7 (*C*O); MS (*m/z*) 242 ($M^+$+1, 1), 100 (58), 99 (100), 69 (49), 55 (52), 41 (83).

**6b**: IR (film): 3395 (br), 2945, 2854 , 1736, 1441, 1272, 1202, 1173 $cm^{-1}$; $^1$H-NMR (250 MHz): δ 1.20-2.00 (m, 6H: $2H_4$, $2H_5$, $2H_6$), 2.40 (m, 2H: $H_{7ax}$, $H_{3a}$), 2.85 (dd, $J_{3,3a}$=10.2 Hz, $J_{3,2}$=6.2 Hz, 1H: $H_3$), 3.37 (m, 1H: $H_{7eq}$), 3.69 (s, 3H: OC$H_3$), 4.11 (d, J=3.3 Hz, 2H: $2H_{3'}$), 4.64 (t, $J_{2,3}$=$J_{2,1'}$=5.8 Hz, 1H: $H_2$), 5.85 (m, 2H: $H_{1'}$, $H_{2'}$); $^{13}$C-NMR (62.5 MHz): δ 23.2 ($C_5$), 24.4 ($C_6$), 28.6 ($C_4$), 52.2 (O$CH_3$), 55.2 ($C_7$), 58.7 ($C_3$), 62.7 ($C_{3'}$), 70.4 ($C_{3a}$), 78.4 ($C_2$), 131.1/131.6 ($C_{1'}$/$C_{2'}$), 171.6 (*C*O); MS (*m/z*) 242 ($M^+$+1, 1), 100 (58), 99 (100), 69 (43), 55 (42), 41 (60).

**7b**: Anal. Calcd for $C_{17}H_{28}N_2O_5$: C, 59.89; H, 8.29; N, 8.23. Found: C, 59.98; H, 8.32; N, 8.18.

When the same reaction was performed in $CHCl_3$ (25 mL) at reflux for 7 d, from 3.0 mmol of nitrone **1** and 3.6 mmol of olefin **4b**, after purification of the crude material by flash chromatography the following fractions were obtained: **4b** (22%); a mixture of **5b** and **6b** (5%); pure **6b** (4%); **7b** (20%).

*Reaction of Nitrone* **1** *with* **4c**

To a solution of nitrone **1** (2.7 mmol) in $CH_2Cl_2$ (20 mL) was added a solution of **4c** (800 mg, 3.3 mmol) in the same solvent (5 mL) and the mixture was kept at 4 °C for 2 months following its evolution by tlc ($CHCl_3$/MeOH 9/1). Removal of the solvent gave a crude material (1.09 g) that was purified by flash chromatography. Using hexane/EtOAc 4/1 as eluent, the following fractions were obtained: 488 mg (60%) of starting **4c**; 12 mg of the dimer of the nitrone; 76 mg (8%) of methyl (2*RS*,3*SR*,3a*SR*)-2-[(*E*)-3-benzoyloxy-1-propenyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **6c**. Changing the eluent to hexane/EtOAc 1/1, the following fractions were separated: 129 mg (14%) of the (2*RS*,3*SR*,3a*RS*) isomer, **5c**; 106 mg (18%)

of a mixture of 2:1 cycloadducts, **7c**. Finally, with $CHCl_3$/MeOH 9/1 a last fraction consisting of 113 mg (41%) of nitrone **1** was recovered.

**5c**: IR (film): 3070, 2947, 2856, 2828, 1722, 1603, 1445, 1271, 1193, 1175, 1113 $cm^{-1}$; $^1$H-NMR (250 MHz): δ 1.15-1.30 (m, 2H), 1.50-1.85 (m, 3H), 1.90 (m, 1H), 2.44 (m, 2H: $H_{7ax}$, $H_{3a}$), 3.03 (dd, $J_{3,3a}$=8.1 Hz, $J_{3,2}$=5.5 Hz, 1H: $H_3$), 3.50 (m, 1H: $H_{7eq}$), 3.70 (s, 3H: $OCH_3$), 4.79 (d, J=4.8 Hz, 2H: $2H_{3'}$), 4.88 (t, $J_{2,3}$=$J_{2,1'}$=6.0 Hz, 1H: $H_2$), 5.82 (dd, J=15.7 Hz, J'=7.0 Hz, 1H: $H_{1'}$), 6.01 (dt, J=15.7 Hz, J'=5.1 Hz, 1H: $H_{2'}$), 7.41 (t, $J_{m,o}$=$J_{m,p}$=7.3 Hz, 2H: $2H_{m\text{-}Ph}$), 7.53 (t, $J_{p,m}$=7.3 Hz, 1H: $H_{p\text{-}Ph}$), 8.01 (d, $J_{o,m}$=7.0 Hz, 2H: $2H_{o\text{-}Ph}$); $^{13}$C-NMR (62.5 MHz): δ 23.5 ($C_5$), 24.2 ($C_6$), 26.6 ($C_4$), 51.9 ($OCH_3$), 55.4 ($C_7$), 56.2 ($C_3$), 64.1 ($C_{3'}$), 69.3 ($C_{3a}$), 78.6 ($C_2$), 128.3/128.5/129.6/129.9 (Ph), 130.9/133.0 ($C_{1'}$/$C_{2'}$), 166.1 (*C*OPh), 171.5 ($CO_2$Me); MS (CI, $NH_3$) (*m/z*) 346 ($M^+$+1, 100). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.07; H, 6.83; N, 4.01.

**6c**: IR (film): 3070, 2946, 2856, 1725, 1603, 1444, 1272, 1174, 1113 $cm^{-1}$; $^1$H-NMR (250 MHz): δ 1.10-1.85 (m, 5H: $2H_5$, $2H_6$, $H_4$), 2.05 (m, 1H: $H_4$), 2.43 (m, 2H: $H_{3a}$, $H_{7ax}$), 2.88 (dd, $J_{3,3a}$≈10.2 Hz, $J_{3,2}$=6.2 Hz, 1H: $H_3$), 3.40 (m, 1H: $H_{7eq}$), 3.70 (s, 3H: $OCH_3$), 4.69 (t, $J_{2,3}$=$J_{2,1'}$=6.2 Hz, 1H: $H_2$), 4.79 (d, J=4.8 Hz, 2H: $2H_{3'}$), 5.89 (dt, J=15.7 Hz, J'=4.8 Hz, 1H: $H_{2'}$), 6.01 (dd, J=15.7 Hz, J'=6.2 Hz, 1H: $H_{1'}$), 7.40 (t, $J_{m,o}$=$J_{m,p}$=7.3 Hz, 2H: $2H_{m\text{-}Ph}$), 7.53 (t, $J_{p,m}$=7.3 Hz, 1H: $H_{p\text{-}Ph}$), 8.02 (d, $J_{o,m}$=7.3 Hz, 2H: $2H_{o\text{-}Ph}$); $^{13}$C-NMR (62.5 MHz): δ 23.2 ($C_5$), 24.3 ($C_6$), 28.5 ($C_4$), 52.2 ($OCH_3$), 55.2 ($C_7$), 58.6 ($C_3$), 64.4 ($C_{3'}$), 70.4 ($C_{3a}$), 78.1 ($C_2$), 126.0/128.3/129.6/130.0 (Ph), 132.9/134.1 ($C_{1'}$/$C_{2'}$), 166.2 (*C*OPh), 171.5 ($CO_2$Me). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.01; H, 6.80; N, 4.14.

**7c**: Anal. Calcd for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.65; H, 7.23; N, 6.23.

When the same reaction was performed in $CHCl_3$ (25 mL) at reflux for 24 h, from 1.7 mmol of nitrone **1** and 2.0 mmol of olefin **4c**, after purification of the crude material by flash chromatography the following fractions were obtained: **4c** (56%); **6c** (11%); **5c** (18%); **7c** (19%).

*3,3-Diphenylseleno-2-oxepanone*: mp 118-119 °C ($CHCl_3$/hexane); IR (KBr): 2960, 2928, 2864, 1680, 1216, 1168 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.76 (m, 1H), 1.84 (m, 1H), 2.14 (m, 1H), 4.64 (t, J=5.1 Hz, 1H), 7.36 (m, 2H), 7.43 (m, 1H), 7.74 (m, 2H); $^{13}$C-NMR (62.5 MHz): δ 24.7, 28.5, 35.7, 60.4, 68.7, 128.3, 128.8, 129.5, 137.2, 170.6; MS (*m/z*) 426 ($M^+$, 3), 314 (45), 312 (41), 269 (40), 157 (100), 77 (69). Anal. Calcd for $C_{18}H_{18}O_2Se_2$: C, 50.71; H, 4.26. Found: C, 50.86; H, 4.22.

*5-Phenylthio-6,7-dihydro-2(5H)-oxepinone*, **8e**

To a solution of **8b** (751 mg, 3.9 mmol) in acetone (60 mL) at -78 °C, triethylamine (550 μL, 3.9 mmol) and then thiophenol (400 μL, 3.9 mmol) were added slowly. The low temperature was maintained for 1 h, then the cooling bath was removed and the reaction mixture let to reach room temperature. The resulting suspension was filtered, the solid washed with acetone and the solvent evaporated to give a yellow oil (951 mg). Purification of this crude material by flash chromatography using hexane/EtOAc 2/1 as eluent gave the following fractions: 780 mg (90%) of an oil identified as 5-phenylthio-6,7-dihydro-2(5*H*)-oxepinone, **8e**; 26 mg (3%) of an oil identified as 5-phenylthio-6,7-dihydro-2(3*H*)-oxepinone, **9e**.

**8e**: IR (film): 3058, 2988, 2952, 2917, 1701, 1476, 1405, 1293, 1223, 1202, 1075 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 2.20 (br dt, $J_{6,6}$=15.8 Hz, $J_{6,7}$≈$J_{6,5}$≈7.6 Hz, 1H: $H_6$), 2.44 (dddd, $J_{6,6}$=15.8 Hz, $J_{6,7'}$≈7.5 Hz, $J_{6,5}$≈6.3 Hz, $J_{6,7}$≈1.5 Hz, 1H: $H_6$), 4.02 (tdd, $J_{5,6}$≈$J_{5,6}$≈6.3 Hz, $J_{5,4}$≈4.3 Hz, $J_{5,3}$=1.8 Hz, 1H: $H_5$), 4.22 (ddd, $J_{7,7}$=12.7 Hz, $J_{7,6}$≈7.5 Hz, $J_{7,6}$≈1.2 Hz, 1H: $H_7$), 4.38 (ddd, $J_{7,7}$=12.7 Hz, $J_{7,6}$≈8.1 Hz, $J_{7,6}$≈1.2 Hz, 1H: $H_7$), 5.94 (dd, $J_{3,4}$=12.5 Hz, $J_{3,5}$=1.8 Hz, 1H: $H_3$), 6.39 (dd, $J_{4,3}$=12.5 Hz, $J_{4,5}$=4.3 Hz, 1H: $H_4$), 7.32 (m, 3H: $3H_{Ph}$), 7.42 (m, 2H: $2H_{Ph}$); $^{13}$C-NMR (62.5 MHz): δ 33.2 ($C_6$), 47.9 ($C_5$), 64.7 ($C_7$), 121.0 ($C_3$), 128.3/129.1/131.9/133.2 (Ph), 142.2 ($C_4$), 167.3 ($C_2$); MS (*m/z*) 220 ($M^+$, 62), 110

(100), 81 (48), 67 (46), 53 (60), 43 (53). Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.44; H, 5.50; S, 14.53. Found: C, 65.44; H, 5.56; S, 14.40.

**9e**: IR (film): 3058, 2981, 2917, 1750, 1476, 1279, 1244, 1145, 1082, 1054 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 2.60 (m, 2H: $2H_6$), 3.42 (m, 2H: $2H_3$), 4.40 (m, 2H: $2H_7$), 5.77 (tt, $J_{4,3}$≈5.8 Hz, $J_{4,6}$≈1.7 Hz, 1H: $H_4$), 7.32 (m, 5H: Ph); $^{13}$C-NMR (62.5 MHz): δ 33.8/34.5 ($C_3$/$C_6$), 65.2 ($C_7$), 120.1 ($C_4$), 127.8/129.2/132.1/132.4 (Ph), 135.8 ($C_5$), 171.9 ($C_2$); MS (*m/z*) 220 ($M^+$, 53), 218 (83), 178 (39), 128 (33), 109 (100), 65 (58), 43 (42). Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.44; H, 5.50; S, 14.53. Found: C, 65.41; H, 5.45; S, 14.46.

*5-Phenylsulfinyl-6,7-dihydro-2(3H)-oxepinone*, **9f**

A solution of lactone **8e** (67 mg, 0.3 mmol) in $CHCl_3$ (15 mL) was treated with MCPBA (55 mg, 0.3 mmol) at rt for 2 h. The reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with $NaHSO_3$ and then with $NaHCO_3$ solution. Evaporation of the solvent gave a yellow oil, which was purified by flash chromatography using $Et_2O$/pentane 7/3 as eluent. A white solid (55 mg, 76%) was obtained and identified as 5-phenylsulfinyl-6,7-dihydro-2(3*H*)-oxepinone, **9f**: mp 78-80 °C (EtOAc); IR (KBr): 3072, 3051, 2995, 2931, 2903, 1729, 1279, 1152, 1082, 1054, 1033 $cm^{-1}$; $^1$H-NMR (250 MHz): δ 2.15 (m, $J_{6,6}$≈19.0 Hz, 1H: $H_6$), 2.62 (m, $J_{6,6}$≈19.0 Hz, 1H: $H_6$), 3.48 (ddt, $J_{3,3}$=17.2 Hz, $J_{3,4}$=6.6 Hz, $J_{3,6}$≈$J_{3,6}$≈1.8 Hz, 1H: $H_3$), 3.69 (ddt, $J_{3,3}$=17.2 Hz, $J_{3,4}$=4.4 Hz, $J_{3,6}$≈$J_{3,6}$≈2.7 Hz, 1H: $H_3$), 4.38 (m, 2H: $2H_7$), 6.54 (ddt, $J_{4,3}$=6.6 Hz, $J_{4,3}$=4.4 Hz, $J_{4,6}$≈$J_{4,6}$≈1.5 Hz, 1H: $H_4$), 7.49 (m, 5H: Ph); $^{13}$C-NMR (62.5 MHz): δ 24.6 ($C_6$), 33.7 ($C_3$), 64.7 ($C_7$), 123.7/124.5/129.4/131.4 (Ph), 141.3/146.5 ($C_4$/$C_5$), 170.7 ($C_2$); MS (*m/z*) 218 (94), 185 (22), 154 (29), 109 (100), 65 (32). Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.54. Found: C, 61.01; H, 5.07; S, 13.45.

*5-Tosyloxy-6,7-dihydro-2(5H)-oxepinone*, **8g**

A solution of **8b** (352 mg, 1.8 mmol) in anhydrous ether (50 mL) was poured into a light protected flask containing dry AgTsO (1.07 g, 3.7 mmol) and the mixture was stirred at rt for 1 d. Filtration, followed by solvent removal, gave 508 mg of an oil in which compound **8g** was identified, but all attempts to isolate it were fruitless. $^1$H-NMR (250 MHz): δ 2.22-2.50 (m, 2H: $2H_6$), 2.45 (s, 3H: $CH_3$), 4.20 (m, 1H: $H_7$), 4.32 (m, 1H: $H_7$), 5.21 (m, 1H: $H_5$), 6.03 (dd, $J_{3,4}$=12.2 Hz, $J_{3,5}$≈2.0 Hz, 1H: $H_3$), 6.18 (dd, $J_{4,3}$=12.2 Hz, $J_{4,5}$≈3.7 Hz, 1H: $H_4$), 7.37 (d, J=8.1 Hz, 2H: $2H_{Ar}$), 7.78 (d, $J_{o,m}$=8.1 Hz, 2H: $2H_{Ar}$).

*Reaction of* **1** *with* **8e**.

To a cold (0 °C) solution of *N*-hydroxypiperidine (1.00 g, 9.9 mmol) in $CH_2Cl_2$ (100 mL) under nitrogen, yellow HgO (6.43 g, 29.7 mmol) was added in three portions during 10 min. The mixture was stirred until tlc analysis indicated the disappearance of *N*-hydroxypiperidine, then it was filtered through *Celite*® and the filtrate concentrated under vacuum. The oily residue was disolved in toluene (80 mL), added to a solution of **8e** (1.09 g, 4.9 mmol) in toluene (20 mL) and the mixture heated at reflux until tlc analysis showed no evolution (9 h). Then the solvent was removed to give 2.54 g of crude material that was purified by flash chromatography. Using hexane/EtOAc 1/1 as eluent, the following fractions were obtained: 182 mg (17%) of **9e**; 90 mg of the dimer of the nitrone; 1.14 g (72%) of (5*RS*,5a*RS*,11a*SR*,11b*SR*)-5-phenylthiodecahydro-1*H*-oxepino[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **10**. Changing the eluent to $Et_2O$/EtOAc 1/1 another fraction was separated: 127 mg (8%) of the (5*RS*,5a*SR*,11a*RS*,11b*RS*) isomer, **11**.

**10**: mp 130-134 °C ($CHCl_3$/hexane); IR (KBr): 2952, 2938, 2917, 2854, 2833, 1736, 1441, 1293, 1216, 1187, 1181, 1159, 1054 $cm^{-1}$; $^1$H-NMR (400 MHz): *trans*-invertomer δ 1.36 (m, 2H: $H_{10}$, $H_{11}$), 1.65 (m, 2H: $H_9$, $H_{10}$), 1.73 (m, 1H: $H_9$), 1.83 (m, 1H: $H_4$), 2.14 (m, 1H: $H_{11}$), 2.38 (tt, $J_{4,4}$≈$J_{4,3}$≈13.4 Hz, $J_{4,5}$≈$J_{4,3}$≈6.7 Hz, 1H: $H_4$), 2.53 (ddd, $J_{8ax,9ax}$=12.2 Hz, $J_{8ax,8eq}$≈9.2 Hz, $J_{8ax,9eq}$≈3.1 Hz, 1H: $H_{8ax}$), 2.73

(td, $J_{11a,11ax}$≈$J_{11a,11b}$≈10.4 Hz, $J_{11a,11eq}$≈1.8 Hz, 1H: $H_{11a}$), 3.03 (td, $J_{5,5a}$≈$J_{5,4}$≈11.3 Hz, $J_{5,4}$≈6.4 Hz, 1H: $H_5$), 3.28 (t, $J_{11b,11a}$=$J_{11b,5a}$=9.8 Hz, 1H: $H_{11b}$), 3.54 (dt, $J_{8eq,8ax}$≈8.2 Hz, $J_{8eq,9ax}$≈$J_{8eq,9eq}$≈2.7 Hz, 1H: $H_{8eq}$), 4.04 (td, $J_{3,3}$≈$J_{3,4}$≈12.8 Hz, $J_{3,4}$=3.7 Hz, 1H: $H_3$), 4.05 (dd, $J_{5a,5}$=11.6 Hz, $J_{5a,11b}$=9.8 Hz, 1H: $H_{5a}$), 4.18 (dd, $J_{3,3}$=12.8 Hz, $J_{3,4}$=6.7 Hz, 1H: $H_3$), 7.29 (m, 3H: $3H_{Ph}$), 7.53 (m, 2H: $2H_{Ph}$); $^{13}$C-NMR (62.5 MHz): *trans*-invertomer δ 23.6 ($C_{10}$), 24.6 ($C_9$), 29.2 ($C_{11}$), 31.8 ($C_4$), 44.7 ($C_5$), 55.1 ($C_8$, $C_{11b}$), 63.9 ($C_3$), 69.4 ($C_{11a}$), 75.8 ($C_{5a}$), 128.3/128.9/131.3/134.8 (Ph), 171.5 ($C_1$); MS (*m/z*) 319 ($M^+$, 61), 210 (21), 124 (100), 100 (76), 84 (75), 55 (64), 41 (82). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39; S, 10.02. Found: C, 63.90; H, 6.68; N, 4.36; S, 10.07.

**11**: mp 158-161 °C ($CHCl_3$/hexane); IR (KBr): 2959, 2924, 2861, 2826, 1729, 1483, 1187, 1166, 1089, 1026 $cm^{-1}$; $^1$H-NMR (400 MHz): *trans*-invertomer δ 1.33 (m, 2H: $H_{10}$, $H_{11}$), 1.60 (m, 1H: $H_9$), 1.75 (m, 2H: $H_9$, $H_{10}$), 2.20-2.40 (m, 4H: $2H_4$, $H_{8ax}$, $H_{11}$), 2.84 (td, $J_{11a,11b}$≈$J_{11a,11ax}$≈9.9 Hz, $J_{11a,11eq}$≈1.8 Hz, 1H: $H_{11a}$), 3.25 (dd, $J_{11b,5a}$=$J_{11b,11a}$=9.8 Hz, 1H: $H_{11b}$), 3.32 (m, 1H: $H_{8eq}$), 3.95 (ddd, $J_{5,4}$≈7.9 Hz, $J_{5,5a}$≈2.4 Hz, $J_{5,4}$≈1.5 Hz, 1H: $H_5$), 4.21 (td, $J_{3,3}$=$J_{3,4}$=12.8 Hz, $J_{3,4}$≈3.8 Hz, 1H: $H_3$), 4.33 (br dd, $J_{3,3}$=12.8 Hz, $J_{3,4}$≈5.7 Hz, 1H: $H_3$), 4.57 (dd, $J_{5a,11b}$≈9.6 Hz, $J_{5a,5}$≈2.9 Hz, 1H: $H_{5a}$), 7.24 (m, 3H: $3H_{Ph}$), 7.47 (m, 2H: $2H_{Ph}$); $^{13}$C-NMR (62.5 MHz): *trans*-invertomer δ 23.3 ($C_{10}$), 24.7 ($C_9$), 29.4/30.3 ($C_{11}$/$C_4$), 45.7 ($C_5$), 54.3 ($C_{11b}$), 54.8 ($C_8$), 64.4 ($C_3$), 69.7 ($C_{11a}$), 76.4 ($C_{5a}$), 127.2/128.8/132.2/135.7 (Ph), 171.9 ($C_1$); MS (*m/z*) 319 ($M^+$, 100), 220 (19), 210 (22), 124 (99), 117 (94), 100 (83), 41 (81). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39; S, 10.02. Found: C, 63.82; H, 6.62; N, 4.31; S, 9.90.

*Reaction of* **1** *with* **8g**.

Nitrone **1**, prepared as above from *N*-hydroxypiperidine (549 mg, 5.4 mmol) and yellow HgO (3.53 g, 16.3 mmol), was disolved in toluene (80 mL) and treated with **8g** (458 mg of crude material) at reflux for 45 min. The cold reaction mixture was filtered, giving a residue (294 mg) of unidentifiable products. The filtrate was evaporated to dryness yielding 771 mg of a brown oil that was purified by flash chromatography. Using EtOAc/hexane 1/1 as eluent, a fraction containing the dimer of nitrone **1** (54 mg) was obtained. Elution with EtOAc/hexane 2/1 gave 77 mg (12% for the two consecutive steps) of a compound identified as (5*RS*,5a*RS*,11a*SR*,11b*SR*)-5-tosyloxydecahydro-1*H*-oxepino[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **12**: IR (film): 2931, 2861, 1743, 1363, 1195, 1173, 984, 857 $cm^{-1}$; $^1$H-NMR (400 MHz): *trans*-invertomer δ 1.25 (m, 2H), 1.53 (m, 1H), 1.69 (m, 2H), 1.91 (m, 1H: $H_4$), 2.02 (ddd, J=12.2 Hz, J'=9.2 Hz, J''=3.1 Hz, $H_{8ax}$), 2.09 (m, 1H), 2.37 (td, $J_{11a,11b}$=$J_{11a,11ax}$=11.0 Hz, $J_{11a,11eq}$=3.1 Hz, 1H: $H_{11a}$), 2.41 (s, 3H: $CH_3$), 2.74 (tt, $J_{4,4}$≈$J_{4,3}$≈13.7 Hz, $J_{4,3}$≈$J_{4,5}$≈6.9 Hz, 1H: $H_4$), 3.16 (m, 1H: $H_{8eq}$), 3.17 (t, $J_{11b,5a}$=$J_{11b,11a}$=9.8 Hz, 1H: $H_{11b}$), 4.13 (td, $J_{3,3}$=$J_{3,4}$=12,8 Hz, $J_{3,4}$=3.7 Hz, 1H: $H_3$), 4.20 (dd, $J_{5a,5}$=11.0 Hz, $J_{5a,11b}$=9.8 Hz, 1H: $H_{5a}$), 4.25 (ddd, $J_{3,3}$≈13.4 Hz, $J_{3,4}$=6.7 Hz, $J_{3,4}$=1.2 Hz, 1H: $H_3$), 4.36 (ddd, $J_{5,5a}$=11.0 Hz, $J_{5,4}$=9.2 Hz, $J_{5,4}$=7.3 Hz, 1H: $H_5$), 7.28 (d, $J_{m,o}$≈8.1 Hz, 2H: $2H_{m\text{-}Ph}$), 7.76 (d, $J_{o,m}$=8.1 Hz, 2H: $2H_{o\text{-}Ph}$); $^{13}$C-NMR (62.5 MHz): *trans*-invertomer δ 21.5 ($CH_3$), 23.1 ($C_{10}$), 24.4 ($C_9$), 28.8 ($C_{11}$), 31.4 ($C_4$), 52.8 ($C_{11b}$), 54.7 ($C_8$), 62.4 ($C_3$), 69.1 ($C_{11a}$), 74.2/77.6 ($C_5$/$C_{5a}$), 128.3/129.4/133.3/144.7 (Ph), 170.6 ($C_1$); MS (*m/z*) 381 ($M^+$, 1), 227 (19), 210 (7), 99 (100), 84 (80), 69 (53), 55 (54), 41 (76).

*Reaction of* **2** *with* **8c**

A solution of **8c** (880 mg, 5.2 mmol) in toluene (10 mL) was added to a solution of nitrone **2** (880 mg, 10.4 mmol) in the same solvent (40 mL) and the mixture was heated at reflux until tlc analysis (EtOAc/hexane 1/1) showed complete conversion of **8c** (4 d). Evaporation of the solvent gave a brown oil (1.75 g) that was purified by flash chromatography, using EtOAc as eluent, and yielded the following fractions: 32 mg (4%) of **8c**; 65 mg (5%) of a solid identified as (3*RS*,3a*RS*,8a*SR*,8b*SR*)-3-(2-acetoxy)ethylhexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-one, **15**; 1.02 g (77%) of (5*RS*,5a*RS*,10a*SR*,10b*SR*)-5-

acetoxyoctahydrooxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-one, **13**; 25 mg (2%) of a mixture of **13** and its (5*RS*,5a*SR*,10a*RS*,10b*RS*) isomer, **14**; 154 mg (12%) of **14**.

**13**: mp 132-134 °C ($CHCl_3$/hexane); IR (KBr): 2987, 2945, 2903, 2875, 1729, 1370, 1244, 1209, 1145, 1054, 1012 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.63 (dddd, $J_{4,4}$=14.0 Hz, $J_{4,5}$=9.2 Hz, $J_{4,3}$=4.3 Hz, $J_{4,3}$=1.8 Hz, 1H: $H_4$), 2.02 (m, 1H: $H_9$), 2.06 (s, 3H: C$H_3$COO), 2.12 (m, 1H: $H_{10}$), 2.18 (m, 2H: $H_9$, $H_{10}$), 2.66 (ddt, $J_{4,4}$=14.0 Hz, $J_{4,3}$=12.2 Hz, $J_{4,3}$≈$J_{4,5}$≈7.3 Hz, 1H: $H_4$), 3.15 (m, 2H: 2$H_8$), 3.50 (dd, $J_{10b,5a}$=9.8 Hz, $J_{10b,10a}$=3.7 Hz, 1H: $H_{10b}$), 4.24 (td, $J_{3,3}$=$J_{3,4}$=12.8 Hz, $J_{3,4}$=4.3 Hz, 1H: $H_3$), 4.28 (dt, J≈8.5 Hz, 2xJ≈4.3 Hz, 1H: $H_{10a}$), 4.31 (ddd, $J_{3,3}$=12.8 Hz, $J_{3,4}$=7.3 Hz, $J_{3,4}$=1.8 Hz, 1H: $H_3$) 4.52 (t, $J_{5a,5}$≈$J_{5a,10b}$≈10.0 Hz, 1H: $H_{5a}$), 5.00 (ddd, $J_{5,5a}$=10.4 Hz, $J_{5,4}$=8.8 Hz, $J_{5,4}$=7.0 Hz, 1H: $H_5$); $^{13}$C-NMR (62.5 MHz): δ 20.9 (*C*$H_3$COO), 23.2 ($C_9$), 29.1 ($C_{10}$), 29.5 ($C_4$), 54.8 ($C_{10b}$), 54.9 ($C_8$), 62.6 ($C_3$), 67.9 ($C_{10a}$), 69.5 ($C_5$), 75.9 ($C_{5a}$), 169.6/170.6 ($C_1$/$CH_3$*C*OO); MS (*m/z*) 255 ($M^+$, 7), 213 (7), 212 (2), 196 (6), 184 (5), 110 (100), 85 (40), 55 (37), 43 (86). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.45; H, 6.72; N, 5.49. Found: C, 56.21; H, 6.86; N, 5.28.

**14**: mp 183-185 °C ($CHCl_3$/hexane); IR (KBr): 2976, 2928 , 2880, 1744, 1376, 1280, 1248, 1232, 1200, 1168, 1136, 1104, 1056, 1024 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.85 (m, 1H: $H_{10}$), 1.88 (m, 1H: $H_9$), 1.94 (m, 1H: $H_4$), 1.98 (m, 1H: $H_9$), 2.02 (s, 3H: C$H_3$COO), 2.22 (m, 1H: $H_{10}$), 2.25 (m, 1H: $H_4$), 2.82 (dt, $J_{8,8}$≈11.0 Hz, $J_{8,9}$≈$J_{8,9}$=8.6 Hz, 1H: $H_8$), 3.23 (ddd, $J_{8,8}$≈11.0 Hz, $J_{8,9}$≈7.7 Hz, $J_{8,9}$≈4.0 Hz, 1H: $H_8$), 3.39 (dd, $J_{10b,5a}$=10.4 Hz, $J_{10b,10a}$=7.3 Hz, 1H: $H_{10b}$), 4.13 (td, $J_{10a,10b}$=$J_{10a,10}$=7.3 Hz, $J_{10a,10}$≈2.0 Hz, 1H: $H_{10a}$), 4.30 (m, 2H: 2$H_3$), 4.73 (dd, $J_{5a,10b}$≈10.4 Hz, $J_{5a,5}$≈1.8 Hz, 1H: $H_{5a}$), 5.35 (dt, $J_{5,4}$≈5.5 Hz, $J_{5,5a}$≈$J_{5,4}$≈1.5 Hz, 1H: $H_5$); $^{13}$C-NMR (62.5 MHz): δ 20.8 (*C*$H_3$COO), 21.4 ($C_{10}$), 27.1 ($C_4$), 29.8 ($C_9$), 53.0 ($C_8$), 53.8 ($C_{10b}$), 63.7 ($C_3$), 68.1 ($C_{10a}$), 69.5 ($C_5$), 75.9 ($C_{5a}$), 169.7/171.5 ($C_1$/$CH_3$*C*OO); MS (*m/z*) 255 ($M^+$, 13), 213 (7), 196 (9), 110 (100), 86 (34), 43 (47). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.45; H, 6.72; N, 5.49. Found: C, 56.55; H, 6.80; N, 5.49.

**15**: mp 78-80 °C ($CHCl_3$/hexane); IR (KBr): 2973, 2875, 1764, 1736, 1391, 1370, 1244, 1180, 1047 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.63 (m, 1H: $H_8$), 1.78 (m, 1H: $H_7$), 2.03 (s, 3H: C$H_3$COO), 1.96-2.29 (m, 4H: 2$H_{1'}$, $H_7$, $H_8$), 3.01 (dt, $J_{6,6}$=14.0 Hz, $J_{6,7}$=$J_{6,7}$=8.2 Hz, 1H: $H_6$), 3.35 (ddd, $J_{6,6}$=14.0 Hz, $J_{6,7}$=7.3 Hz, $J_{6,7}$=3.7 Hz, 1H: $H_6$), 3.46 (d, $J_{8b,3a}$=6.7 Hz, 1H: $H_{8b}$), 3.86 (t, $J_{8a,8}$≈$J_{8a,8}$≈7.9 Hz, 1H: $H_{8a}$), 4.17 (ddd, $J_{2',2'}$≈11.3 Hz, $J_{2',1'}$≈7.9 Hz, $J_{2',1'}$≈5.2 Hz, 1H: $H_{2'}$), 4.29 (dt, $J_{2',2'}$≈11.0 Hz, $J_{2',1'}$≈$J_{2',1'}$≈6.1 Hz, 1H: $H_{2'}$), 4.57 (dt, $J_{3,1'}$=8.5 Hz, $J_{3,3a}$≈$J_{3,1'}$≈5.3 Hz, 1H: $H_3$), 4.77 (dd, $J_{3a,8b}$=6.7 Hz, $J_{3a,3}$=4.9 Hz, 1H: $H_{3a}$); $^{13}$C-NMR (62.5 MHz): δ 20.7 (*C*$H_3$COO), 24.1 ($C_7$), 28.1 ($C_{1'}$), 29.6 ($C_8$), 55.9 ($C_{8b}$), 56.5 ($C_6$), 61.0 ($C_{2'}$), 70.2 ($C_{8a}$), 77.8 ($C_{3a}$), 80.3 ($C_3$), 171.6 ($C_1$), 176.6 ( $CH_3$*C*OO); MS (*m/z*) 256 ($M^+$+1, 1), 212 (1), 196 (6), 86 (30), 70 (100), 55 (33), 43 (37). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.45; H, 6.72; N, 5.49. Found: C, 56.35; H, 6.79; N, 5.44.

*Reaction of* **2** *with* **8d**

A solution of **8d** (500 mg, 2.7 mmol) in toluene (10 mL) was added to a solution of nitrone **2** (468 mg, 5.5 mmol) in the same solvent (40 mL) and the mixture was heated at reflux for 4 h. Evaporation of the solvent gave a brown oil (969 mg) that was purified by flash chromatography. Using EtOAc/hexane 1/1 as eluent, a fraction containing 82 mg (16%) of 5-acetylthio-6,7-dihydro-2(3*H*)-oxepinone[2g] was separated. Elution with EtOAc yielded the following fractions: 223 mg (31%) of a solid identified as (5*RS*,5a*RS*,10a*SR*,10b*SR*)-5-acetylthiooctahydrooxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-one, **16**; 29 mg (14%) of a mixture of **16** and its (5*RS*,5a*SR*,10a*RS*,10b*RS*) isomer, **17**; 58 mg (8%) of **17**.

**16**: mp 162-164 °C ($CHCl_3$/hexane); IR (KBr): 2992, 2944, 2880, 1744 , 1680, 1392, 1360, 1280, 1200, 1152, 1136, 1104, 1072 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.78 (m, 2H: $H_9$, $H_{10}$), 1.96 (m, 2H: $H_9$, $H_4$), 2.14 (m, 1H: $H_{10}$), 2.31 (s, 3H: C$H_3$COS), 2.55 (ddt, $J_{4,4}$=14.0 Hz, $J_{4,3}$=12.2 Hz, $J_{4,3}$≈$J_{4,5}$≈6.7 Hz, 1H: $H_4$), 3.09 (m, 1H: $H_8$), 3.16 (m, 1H: $H_8$), 3.53 (dd, $J_{10b,5a}$=9.1 Hz, $J_{10b,10a}$=4.3 Hz, 1H: $H_{10b}$), 3.57 (dd,

$J_{5,5a}$=11.0 Hz, $J_{5,4}$=6.7 Hz, 1H: $H_5$), 4.23 (td, $J_{3,4}$=$J_{3,3}$=12.8 Hz, $J_{3,4}$=4.3 Hz, 1H: $H_3$), 4.29 (ddd, $J_{3,3}$=12.8 Hz, $J_{3,4}$=7.9 Hz, $J_{3,4}$≈1.5 Hz, 1H: $H_3$), 4.34 (dt, $J_{10a,10}$≈8.0 Hz, $J_{10a,10}$≈$J_{10a,10b}$≈4.3 Hz, 1H: $H_{10a}$), 4.56 (dd, $J_{5a,10b}$=9.1 Hz, $J_{5a,5}$=11.0 Hz, 1H: $H_{5a}$); $^{13}$C-NMR (62.5 MHz): δ 22.9 ($C_9$), 29.0 ($C_{10}$), 30.5/30.7 ($C_4$/$CH_3$COS), 41.5 ($C_5$), 54.5 ($C_8$), 56.6 ($C_{10b}$), 63.6 ($C_3$), 67.7 ($C_{10a}$), 74.8 ($C_{5a}$), 170.8 ($C_1$), 193.7 ($CH_3$*C*OS); MS (*m/z*) 271 ($M^+$, 3), 229 (3), 110 (34), 86 (100), 43 (83). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.17; S, 11.79. Found: C, 53.36; H, 6.13; N, 5.08; S, 11.86.

**17**: mp 164-166 °C ($CHCl_3$/hexane); IR (KBr): 2951, 2945, 2924, 2882, 1736, 1694, 1370, 1286, 1251, 1181, 1138, 1117, 1096, 1033, 977 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.90 (m, 3H: $2H_9$, $H_{10}$), 2.18 (m, 2H: $H_4$, $H_{10}$), 2.33 (s, 3H: C*H*$_3$COS), 2.37 (m, 1H: $H_4$), 2.87 (dt, $J_{8,8}$=11.0 Hz, $J_{8,9}$=$J_{8,9}$=7.9 Hz, 1H: $H_8$), 3.25 (ddd, $J_{8,8}$=11.0 Hz, $J_{8,9}$=7.9 Hz, $J_{8,9}$=4.9 Hz, 1H: $H_8$), 3.42 (dd, $J_{10b,5a}$=10.4 Hz, $J_{10b,10a}$=6.7 Hz, 1H: $H_{10b}$), 4.14 (td, $J_{10a,10b}$=$J_{10a,10}$=6.7 Hz, $J_{10a,10}$=2.1 Hz, 1H: $H_{10a}$), 4.21 (ddd, $J_{5,4}$=7.3 Hz, $J_{5,4}$=4.3 Hz, $J_{5,5a}$=2.7 Hz, 1H: $H_5$), 4.23 (ddd, $J_{3,3}$=12.8 Hz, $J_{3,4}$=9.8 Hz, $J_{3,4}$=4.9 Hz, 1H: $H_3$), 4.48 (dt, $J_{3,3}$=12.8 Hz, $J_{3,4}$=$J_{3,4}$=5.2 Hz, 1H: $H_3$), 4.77 (dd, $J_{5a,10b}$=10.4 Hz, $J_{5a,5}$=2.7 Hz, 1H: $H_{5a}$); $^{13}$C-NMR (62.5 MHz): δ 21.5 ($C_9$), 27.8 ($C_{10}$), 30.3/30.5 ($C_4$/$CH_3$COS), 39.9 ($C_5$), 53.3 ($C_8$), 56.6 ($C_{10b}$), 64.4 ($C_3$), 67.9 ($C_{10a}$), 76.2 ($C_{5a}$), 171.5 ($C_1$), 193.5 ($CH_3$COS); MS (*m/z*) 272 ($M^+$+1, 23), 228 (13), 196 (4), 110 (46), 86 (77), 70 (36), 43 (100), 41 (31). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.17; S, 11.79. Found: C, 53.14; H, 6.38; N, 5.03; S, 11.70.

*Reaction of* **2** *with* **8e**

A solution of **8e** (1.22 g, 5.54 mmol) in toluene (10 mL) was added to a solution of nitrone **2** (0.95 g, 11.2 mmol) in the same solvent (40 mL) and the mixture was heated at reflux for 19 h. Evaporation of the solvent gave a brown oil (1.94 g) that was purified by flash chromatography. Using EtOAc/hexane 1/1 as eluent, the following fractions were obtained: 59 mg (5%) of **9e**; 188 mg (15%) of **8e**; 1.17 g (69%) of a solid that was identified as (5*RS*,5a*RS*,10a*SR*,10b*SR*)-5-phenylthiooctahydrooxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-one, **18**. Elution with EtOAc/$Et_2O$ 1/1 yielded the following fractions: 113 mg (7%) of the (5*RS*,5a*SR*,10a*RS*,10b*RS*) isomer, **19**; 23 mg (1%) of a solid identified as the (5*RS*,5a*RS*,10a*RS*,10b*SR*) isomer, **20**.

**18**: mp 89-90 °C ($CHCl_3$/hexane); IR (KBr): 3066, 2980, 2952, 2917, 2875, 1743, 1476, 1391, 1286, 1265, 1202, 1159, 1054 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.68 (m, 3H), 1.78 (m, 1H), 1.96 (m, 1H), 2.09 (m, 1H), 2.44 (m, 1H: $H_4$), 3.11 (m, 2H: $2H_8$), 3.25 (td, $J_{5,5a}$=$J_{5,4}$=11.3 Hz, $J_{5,4}$=6.1 Hz, 1H: $H_5$), 3.49 (dd, $J_{10b,5a}$=9.0 Hz, $J_{10b,10a}$≈3.2 Hz, 1H: $H_{10b}$), 4.12 (td, $J_{3,3}$≈$J_{3,4}$≈13.2 Hz, $J_{3,4}$≈4.4 Hz, 1H: $H_3$), 4.19 (dd, $J_{3,3}$≈13.2 Hz, $J_{3,4}$=8.1 Hz, 1H: $H_3$), 4.27 (dd, $J_{5a,5}$=11.1 Hz, $J_{5a,10b}$=9.0 Hz, 1H: $H_{5a}$), 4.32 (ddd, $J_{10a,10}$≈8.4 Hz, $J_{10a,10}$=5.7 Hz, $J_{10a,10b}$=3.2 Hz, 1H: $H_{10a}$), 7.24 (m, 3H: $3H_{Ph}$), 7.40 (m, 2H: $2H_{Ph}$); $^{13}$C-NMR (62.5 MHz): δ 23.3 ($C_9$), 29.3 ($C_{10}$), 31.4 ($C_4$), 45.1 ($C_5$), 54.6 ($C_8$), 56.5 ($C_{10b}$), 63.6 ($C_3$), 67.9 ($C_{10a}$), 77.2 ($C_{5a}$), 127.6/128.7/132.7/133.4 (Ph), 171.0 ($C_1$); MS (*m/z*) 305 ($M^+$, 40), 220 (18), 196 (23), 117 (48), 111 (28), 110 (100), 86 (79), 70 (99), 41 (49). Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.28; N, 4.59; S, 10.48. Found: C, 63.04; H, 6.30; N, 4.44; S, 10.49.

**19**: mp 185-186 °C ($CHCl_3$/hexane); IR (KBr): 2959, 2875, 1721, 1483, 1363, 1293, 1244, 1173, 1089, 1026 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.77 (m, 1H), 1.87 (m, 2H), 2.15 (m, 1H), 2.21 (m, 1H: $H_4$), 2.26 (m, 1H: $H_4$), 2.82 (dt, $J_{8,8}$=11.0 Hz, $J_{8,9}$=$J_{8,9}$=8.4 Hz, 1H: $H_8$), 3.21 (ddd, $J_{8,8}$=11.0 Hz, $J_{8,9}$=7.7 Hz, $J_{8,9}$=4.6 Hz, 1H: $H_8$), 3.33 (dd, $J_{10b,5a}$=9.8 Hz, $J_{10b,10a}$=6.8 Hz, 1H: $H_{10b}$), 3.59 (ddd, $J_{5,4}$=7.6 Hz, $J_{5,4}$=5.7 Hz, $J_{5,5a}$=2.1 Hz, 1H: $H_5$), 4.15 (td, $J_{10a,10b}$≈$J_{10a,10}$≈7.0 Hz, $J_{10a,10}$=1.8 Hz, 1H: $H_{10a}$), 4.17 (ddd, $J_{3,3}$=12.8 Hz, $J_{3,4}$=7.6 Hz, $J_{3,4}$=5.2 Hz, 1H: $H_3$), 4.49 (dt, $J_{3,3}$=12.8 Hz, $J_{3,4}$≈$J_{3,4}$≈5.8 Hz, 1H: $H_3$), 4.77 (dd, $J_{5a,10b}$=9.8 Hz, $J_{5a,5}$=2.1 Hz, 1H: $H_{5a}$), 7.22 (m, 3H: $3H_{Ph}$), 7.42 (m, 2H: $2H_{Ph}$); $^{13}$C-NMR (62.5 MHz): δ 21.7 ($C_9$), 28.6 ($C_{10}$), 30.8 ($C_4$), 45.9 ($C_5$), 53.8 ($C_8$), 58.0 ($C_{10b}$), 64.6 ($C_3$), 68.6 ($C_{10a}$), 77.3 ($C_{5a}$), 127.6/129.0/132.6/134.8 (Ph), 171.8 ($C_1$); MS (*m/z*) 305 ($M^+$, 20), 220 (14), 196 (23), 149

(70), 110 (100), 86 (78), 70 (62), 41 (52). Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.28; N, 4.59; S, 10.48. Found: C, 62.86; H, 6.36; N, 4.52; S, 10.40.

**20**: mp 141-143 °C; IR (KBr): 2980, 2952, 2882, 1743, 1483, 1384 , 1272, 1223, 1166, 1096, 1061, 969 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.63 (m, 4H), 2.22 (m, 1H), 2.46 (tt, $J_{4,4}\approx J_{4,3}\approx 13.1$ Hz, $J_{4,3}\approx J_{4,5}\approx 6.4$ Hz, 1H: $H_4$), 2.93 (dt, $J_{8,8}=14.3$ Hz, $J_{8,9}=J_{8,9}=8.8$ Hz, 1H: $H_8$), 3.16 (td, $J_{5,5a}=J_{5,4}=11.3$ Hz, $J_{5,4}=6.4$ Hz, 1H: $H_5$), 3.35 (ddd, $J_{8,8}=14.3$ Hz, $J_{8,9}=7.7$ Hz, $J_{8,9}=3.7$ Hz, 1H: $H_8$), 3.68 (td, $J_{10a,10}=J_{10a,10}=9.1$ Hz, $J_{10a,10b}=6.5$ Hz, 1H: $H_{10a}$), 4.20 (dd, $J_{5a,5}=11.3$ Hz, $J_{5a,10b}=9.6$ Hz, 1H: $H_{5a}$), 4.21 (dd, $J_{3,3}=13.4$ Hz, $J_{3,4}=5.8$ Hz, 1H: $H_3$), 4.30 (td, $J_{3,3}=J_{3,4}=13.4$ Hz, $J_{3,4}=3.7$ Hz, 1H: $H_3$), 4.50 (dd, $J_{10b,5a}=9.6$ Hz, $J_{10b,10a}=6.5$ Hz, 1H: $H_{10b}$), 7.26 (m, 3H: $3H_{Ph}$), 7.49 (m, 2H: $2H_{Ph}$); $^{13}$C-NMR (62.5 MHz): δ 23.3 ($C_9$), 28.3 ($C_{10}$), 31.5 ($C_4$), 46.9 ($C_5$), 54.98/55.00 ($C_8/C_{10b}$), 64.1 ($C_3$), 69.9 ($C_{10a}$), 77.4 ($C_{5a}$), 128.0/128.8/133.1/134.0 (Ph), 171.0 ($C_1$); MS (*m/z*) 305 ($M^+$, 20), 220 (13), 196 (25), 110 (41), 86 (100), 55 (29), 41 (39).

*Reaction of Nitrone* **21** *with* **8a**

Lactone **8a** (68 mg, 0.61 mmol) was added to a solution of nitrone **21** (95 mg, 0.66 mmol) in toluene (3 mL) and the mixture was heated at reflux for 5 h. Evaporation of the solvent gave a brown oil that was purified by flash chromatography using $CH_2Cl_2/Et_2O$ 9/1 as eluent. The following fractions were obtained: 25 mg (37%) of **8a**; 83 mg (52%) of a solid identified as (5a*RS*,8*RS*,10a*RS*,10b*RS*)-8-methoxycarbonyldecahydro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1-one, **23**.

**23**: mp 116-117 °C (EtOAc/pentane); IR (KBr): 2959, 2924, 1743, 1483, 1441, 1391, 1300, 1251, 1209, 1166, 1089, 1019 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.52 (m, 1H: $H_5$), 1.66 (m, 1H: $H_4$), 1.82 (m, 1H: $H_{10}$), 1.98-2.11 (m, 3H: $H_4$, $H_5$, $H_9$), 2.18 (m, 1H: $H_9$), 2.27 (m, 1H: $H_{10}$), 3.33 (dd, $J_{10b,5a}=9.2$ Hz, $J_{10b,10a}=6.1$ Hz, 1H: $H_{10b}$), 3.70 (t, $J_{8,9}=J_{8,9}=8.5$ Hz, 1H: $H_8$), 3.71 (s, 3H: $CH_3O$), 4.16 (td, $J_{3,3}=J_{3,4}=12.8$ Hz, $J_{3,4}=4.3$ Hz, 1H: $H_3$), 4.24 (dd, $J_{3,3}=12.8$ Hz, $J_{3,4}=7.3$ Hz, 1H: $H_3$), 4.41 (ddd, $J_{10a,10}=9.2$ Hz, $J_{10a,10b}=6.1$ Hz, $J_{10a,10}=3.1$ Hz, 1H: $H_{10a}$), 4.44 (ddd, $J_{5a,5}=12.2$ Hz, $J_{5a,10b}=9.2$ Hz, $J_{5a,5}=3.1$ Hz, 1H: $H_{5a}$); $^{13}$C-NMR (62.5 MHz): δ 22.4 ($C_4$), 25.4 ($C_5$), 26.4 ($C_9$), 27.8 ($C_{10}$), 52.3 ($OCH_3$), 56.9 ($C_{10b}$), 64.9 ($C_3$), 65.6 ($C_8$), 67.3 ($C_{10a}$), 74.6 ($C_{5a}$), 171.2/172.2 ($C_1/C_{1'}$); MS (*m/z*) 255 ($M^+$, 7), 196 (100), 126 (21), 111 (24), 108 (35), 71 (41). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.51; H, 6.71; N, 5.40.

*Reaction of Nitrone* **21** *with* **22**

A solution of **22** (393 mg, 1.6 mmol) in $CHCl_3$ (5 mL) was added to a solution of nitrone **21** (340 mg, 2.3 mmol) in the same solvent (10 mL) and the mixture was heated at reflux for 70 h. Evaporation of the solvent gave an oil that was purified by flash chromatography using EtOAc/hexane 1/1 as eluent. The following fractions were obtained: 27 mg (7%) of **22**; 504 mg (81%) of an oil identified as methyl (2*RS*,3*SR*,3a*RS*,6*RS*)-2-(3-benzoyloxy-1-propyl)-6-methoxycarbonylhexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **24**.

**24**: bp 180 °C (0.03 Torr); IR (film): 2952, 1736, 1722, 1602, 1441, 1370, 1314, 1279, 1202 , 1180, 1117, 1068, 1026 $cm^{-1}$; $^1$H-NMR (400 MHz): δ 1.59-1.96 (m, 7H: $2H_{1'}$, $2H_{2'}$, $2H_4$, $H_5$), 2.17 (m, 1H: $H_5$), 3.15 (t, $J_{3,2}=J_{3,3a}=9.1$ Hz, 1H: $H_3$), 3.65 (s, 3H: $CH_3O$), 3.70 (s, 3H: $CH_3O$), 3.80 (t, $J_{6,5}\approx J_{6,5}\approx 8.2$ Hz, 1H: $H_6$), 4.10 (q, $J_{3a,3}\approx J_{3a,4}\approx J_{3a,4}\approx 8.2$ Hz, 1H: $H_{3a}$), 4.22 (ddd, $J_{2,3}\approx 9.7$ Hz, $J_{2,1'}\approx 7.3$ Hz, $J_{2,1'}\approx 3.0$ Hz, 1H: $H_2$), 4.27 (t, $J_{3',2'}=J_{3',2'}=5.8$ Hz, 2H: $2H_{3'}$), 7.37 (t, J=7.3 Hz, 2H: $2H_{m\text{-Ph}}$), 7.49 (t, J=7.3 Hz, 1H: $H_{p\text{-Ph}}$), 7.96 (d, J=7.3 Hz, 2H: $2H_{o\text{-Ph}}$); $^{13}$C-NMR (62.5 MHz): δ 25.2/27.2/28.6 ($C_4/C_{1'}/C_{2'}$), 27.9 ($C_5$), 51.9 ($OCH_3$), 52.2 ($OCH_3$), 55.8 ($C_3$), 64.4 ($C_{3'}$), 66.3 ($C_{3a}$), 69.1 ($C_6$), 76.3 ($C_2$), 128.2 ($C_{m\text{-Ph}}$), 129.4 ($C_{o\text{-Ph}}$), 130.1 ($C_{ipso\text{-Ph}}$), 132.7 ($C_{p\text{-Ph}}$), 166.4 (Ph*C*O), 170.3 (*C*O), 172.2 (*C*O); MS (*m/z*) 391 ($M^+$, 1),

332 (25), 210 (27), 149 (36), 108 (35), 105 (100), 77 (37). Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 60.85; H, 6.57; N, 3.53.

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