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On the Regioselectivity in Nitrone Cycloadditions to γ-Oxo α,β-Unsaturated Esters

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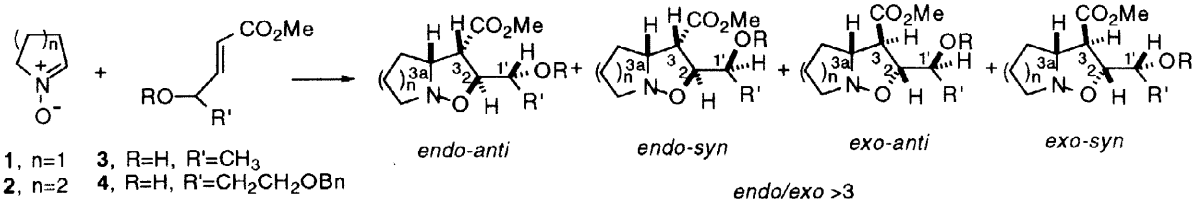
Abstract: The 1,3-dipolar cycloadditions of the cyclic nitrones **1** and **2** to several γ-oxo α,β-unsaturated esters, **5-10**, are reported. A strong predominance of the regioisomers with the oxygen atom of the dipole attached to the β-ester position is observed. This high regioselectivity is attributed to steric factors. The reduction of the carbonyl group of some of the major cycloadducts is a good yielding procedure for the preparation of some hydroxylic derivatives that are not formed or obtained only as minor stereoisomers in the cycloadditions of the same nitrones to the corresponding γ-hydroxy α,β-unsaturated esters.

INTRODUCTION

The 1,3-dipolar cycloaddition of nitrones to electron-deficient olefins is a reaction that has been of considerable use in organic chemistry.[1] Using it as the key step, a wide variety of natural products have been synthesized, including amino sugars,[2] β-amino acids,[3] alkaloids,[4] and β-lactams[5] among others.

In some cases, the intermolecular version of this process suffers from a lack of regioselectivity, which is one of its most severe limitations. Thus, electron-deficient monosubstituted olefins give rise to mixtures of 4- and 5-substituted isoxazolidines.[1a,6] Much luckily, when 1,2-disubstituted olefins in which one of the substituents is an electron-withdrawing group are used as the dipolarophile component, a high regioselectivity is usually observed that favors the isoxazolidine adducts with the electron-withdrawing substituent attached to the 4-position.[1a,1c,3b,4a,5b,6c,7,8] The dominant FMO interaction for the addition of nitrones to electron-poor olefins is HOMO(dipole)-LUMO(dipolarophile). Nevertheless, since the HOMO terminal coefficients of the nitrone are very similar, it has been suggested that its LUMO, with a much larger coefficient on the carbon atom, controls the regioselectivity in some cases.[9] There is also enough experimental evidence to consider that steric factors may play too an important role in the regiochemical outcome of these cycloadditions.[1a,6c]



1, n=1 **3**, R=H, R'=CH_3
2, n=2 **4**, R=H, R'=CH_2CH_2OBn

Scheme 1

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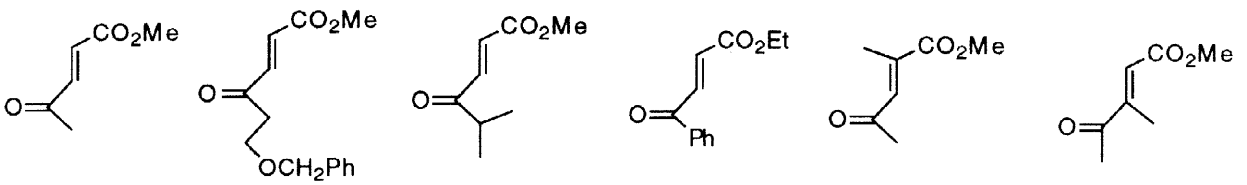
We have recently described the reactions of nitrones **1** and **2** to several γ-oxy α,β-unsaturated esters, among them alcohols **3** and **4**[8] (Scheme 1). In these cycloadditions up to four diastereoisomers (*endo-anti*, *endo-syn*, *exo-anti*, and *exo-syn*) were formed, but a high *endo* selectivity was always observed. In connection with an ongoing program on the synthesis of alkaloids, we wanted to prepare some of the minor (or not found) diastereoisomeric cycloadducts and the reduction of the corresponding ketones seemed a convenient way to do it. Since γ-oxo α,β-unsaturated esters have been scarcely used as dipolarophiles, we decided to undertake a study on the reaction of nitrones **1** and **2** with these olefins. This study would extend the knowledge of the regio- and stereochemical outcome of nitrone cycloadditions to electron-deficient olefins and, depending on the adducts obtained, it would give us an access to the minor (or not found) products of the cycloadditions already performed with γ-oxy α,β-unsaturated esters.[8]

When using 1,2-disubstituted olefins with electron-withdrawing groups attached to both ends of the double bond as dipolarophiles, one should expect *a priori* poor regioselectivity, since the coefficients of both olefinic carbon atoms in the FMO are almost identical.[10] Also, according to Bastide and Henry-Rousseau,[11] these reactions should give rise to both regioisomers in equal amounts.

To the best of our knowledge, examples of 1,3-dipolar cycloadditions of this class of olefins have been described only for two dipoles, namely diazoalkanes[12] and azomethine imines,[13] and the regioselectivity was always low (< 3:1). In these examples the major regioadduct has the nucleophilic end of the dipole (carbon atom for diazoalkanes and nitrogen atom for the reported azomethine imines) linked to the carbon atom at the α-ester position. These results could be explained as a consequence of the greater electron-withdrawing character of the ketone group compared with that of the ester group.[14]



5 **6** **7** **8** **9** **10**

Figure 1

Herein we report the 1,3-dipolar cycloadditions between nitrones **1** and **2** and several (*E*)-γ-oxo α,β-unsaturated esters, **5-10** (Figure 1), in which a remarkably high regioselectivity has been found. We also describe the reduction of some keto cycloadducts, leading to those hydroxy derivatives that could not be prepared in significant yields through the cycloadditions with the corresponding γ-hydroxy α,β-unsaturated esters.

RESULTS AND DISCUSSION

Cycloaddition reactions. In this study we have used the cyclic nitrones **1**[17] and **2**,[6c,18] as in the previous work with γ-oxy α,β-unsaturated esters.[8] These nitrones are incapable of *E/Z* isomerization, therefore the stereochemistry of the products can be related to the *endo/exo* selectivity of the cycloaddition process, if a kinetic control is operating.

Methyl (*E*)-4-oxo-2-pentenoate, **5**, and methyl (*E*)-6-(benzyloxy)-4-oxo-2-hexenoate, **6**, were selected as dipolarophiles because they should afford cycloadducts that could be chemically correlated with those previously obtained from the allylic alcohols **3** and **4** and, eventually, provide an access to the minor *exo* stereoisomers. Methyl (*E*)-5-methyl-4-oxo-2-hexenoate, **7**, ethyl (*E*)-4-oxo-4-phenyl-2-butenoate, **8**, methyl (*E*)-2-methyl-4-oxo-2-pentenoate, **9**, and methyl (*E*)-3-methyl-4-oxo-2-pentenoate, **10**, were chosen to evaluate the influence of steric factors when the carbonyl group or the double bond are differently substituted. The keto esters **5**[12,19] and **8** are commercially available. The new compound **6** was obtained by PCC oxidation of methyl (*E*)-6-(benzyloxy)-4-hydroxy-2-hexenoate.[20] Although **7** was described in the literature,[21] we prepared it in a much simple way by allylic oxidation of methyl (*E*)-5-methyl-2-hexenoate[22] with chromic anhydride in acetic acid/acetic anhydride.[23] Compounds **9**[19c] and **10**[24] were synthesized by Wittig olefination of methyl pyruvate and 2,3-butanedione, respectively.

The results of the cycloadditions of nitrones **1** and **2** to olefins **5-10** are summarized in Figure 2 and Table 1. The yields are referred to pure products isolated by flash chromatography. For each cycloadduct ^{1}H and ^{13}C NMR absorptions were fully assigned with the help of DEPT, COSY, and $^{1}H/^{13}C$-correlation experiments. The *endo/exo* stereochemistry was deduced from the value of the coupling constant $J_{3,3a}$ or by NOE measurements and the regiochemistry[25] was based on HMBC[26] experiments along with the chemical shift values of C_2 and C_3. These diagnostic data are collected in Table 2.

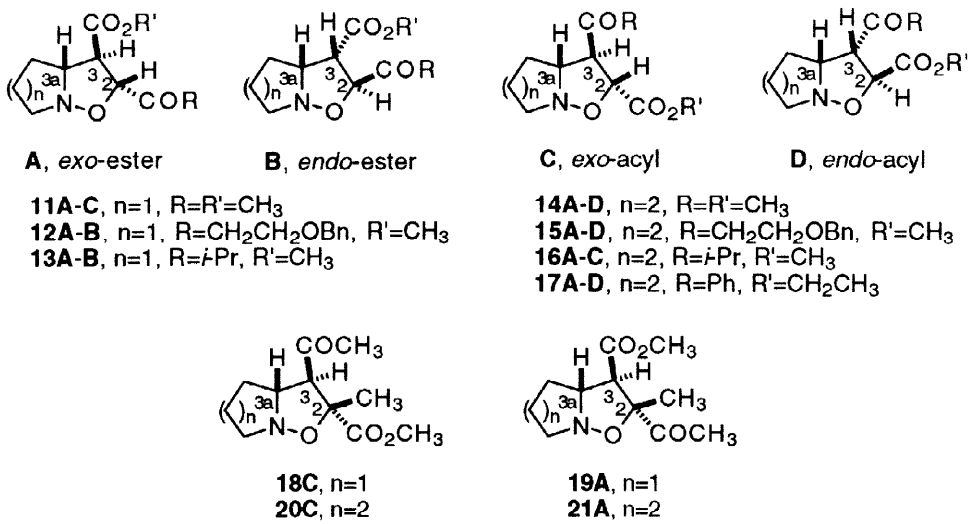


Figure 2

From the reaction of nitrone **1** with olefin **5** at room temperature (Table 1, entry 1), we isolated three adducts that were identified as **11A** (*exo*-ester, 56%), **11B** (*endo*-ester, 27%) and **11C** (*exo*-acyl, 4%). All these products contain the perhydropyrrolo[1,2-*b*]isoxazole system. When this heterocycle is *trans* disubstituted at C-2 and C-3, a coupling constant $J_{3,3a}$ of 8.0 Hz, as in compound **11B**, evidences a *cis* relationship between H-3 and H-3a, while smaller values around 5 Hz, as in **11A** and **11C**, indicate that these two protons are *trans*.[7k,8] HMBC experiments, that show proton-carbon connectivities through two and three bonds, revealed that the methyl protons of the acetyl group in compounds **11A** and **11B** correlate with C-2 at δ 84.9 and 82.2, respectively, while the same protons in **11C** correlate with C-3 at δ 65.4. Due to the higher deshielding effected by the carbonyl group compared to the ester group, the value of Δδ (C-2, C-3) is *ca.* 30 ppm in compounds **11A**

Table 1. Isolated Yields in the Cycloadditions of Nitrones 1 and 2 to Olefins 5-10

entry	nitrone	olefin	temp[a]	*exo*-ester (%)	*endo*-ester (%)	*exo*-acyl (%)	*endo*-acyl (%)	A+B/C+D
1	**1**	**5**	rt	**11A** (56)	**11B** (27)	**11C** (4)		21:1
2	**1**	**5**	110 °C	**11A** (40)	**11B** (35)	**11C** (5)		15:1
3	**1**	**6**	rt	**12A** (65)	**12B** (22)	traces		> 30:1
4	**1**	**7**	rt	**13A** (60)	**13B** (21)			> 30:1
5	**2**	**5**	rt	**14A** (40)	**14B** (36)	**14C** (11)	**14D** (3)	5.4:1
6	**2**	**5**	110 °C	**14A** (78)	**14B** (6)	**14C** (4)		21:1
7	**2**	**6**	rt	**15A** (38)	**15B** (34)	**15C** (12)	**15D** (3)	4.8:1
8	**2**	**6**	110 °C	**15A** (70)	**15B** (6)	**15C** (7)		11:1
9	**2**	**7**	rt	**16A** (42)	**16B** (35)	**16C** (8)	traces	9.5:1
10	**2**	**8**	rt	**17A** (39)	**17B** (31)	**17C** (8)	**17D** (3)	6.4:1
11	**1**	**9**	rt			**18C** (87)		
12	**1**	**10**	rt	**19A** (86)				
13	**2**	**9**	rt			**20C** (91)		
14	**2**	**10**	rt	**21A** (90)				

[a]All the reactions performed at rt were run in CH_2Cl_2 and those at 110 °C in toluene.

and **11B** but only *ca.* 15 ppm in the regioadduct **11C**. This difference will be a criterion for the regiochemical assignment of the rest of cycloadducts.

The high regioselectivity (*ca.* 20:1) observed, with the predominance of the pair **A-B** over the pair **C-D**, indicates that the nucleophilic oxygen atom of the nitrone attaches preferentially to the β-ester position, conversely to what could be expected on the basis of electronic effects and previous results.[12,13] When the same reaction was performed at 110 °C (Table 1, entry 2), we observed a slight decrease in the regioselectivity but a significant difference on the proportion of stereoisomers **11A** and **11B**. At this temperature the reaction is under thermodynamic control, since a sample of pure **11B** heated at 110 °C afforded a mixture of **11A-C** in similar proportions to those of entry 2. The adducts derived from nitrone **1** present a flexible isoxazolidine ring and both

Table 2. Significant NMR Data for Adducts 11-21[a]

Adduct	**11A**	**11B**	**11C**	**12A**	**12B**	**13A**	**13B**	**14A**	**14B**	**14C**	**14D**
$J_{3,3a}$ (Hz)	4.7	8.0	5.1	5.0	8.0	5.1	8.0	9.8	7.9	9.9	8.0
δC_2	84.9	82.2	78.3	84.9	82.2	82.8	80.7	82.0	83.0	75.1	75.7
δC_3	55.3	53.3	65.4	55.3	53.2	55.2	53.2	54.6	52.4	63.6	61.0

Adduct	**15A**	**15B**	**15C**	**15D**	**16A**	**16B**	**16C**	**17A**	**17B**	**17C**	**18C**	**19A**	**20C**	**21A**
$J_{3,3a}$ (Hz)	9.9	8.0	9.9	-	9.7	8.4	9.9	9.9	8.0	9.5	7.1	7.1	10.5	9.6
δC_2	81.8	82.6	75.1	75.6	80.8	81.6	76.1	79.2	79.8	76.7	83.9	88.7	80.4	86.4
δC_3	54.4	52.3	63.5	60.7	54.5	52.6	61.2	53.1	51.8	58.0	66.8	58.6	64.0	56.7

[a]These data correspond to the *trans*-invertomer in the adducts derived from nitrone **2**.

substituents can always be accommodated in pseudoequatorial positions. Therefore, both adducts **A** and **B** must have similar stabilities.

The cycloaddition between nitrone **1** and olefin **6** at room temperature (Table 1, entry 3) allowed us the isolation and characterization of compounds **12A** (65%) and **12B** (22%), whose NMR data match those of **11A,B** (Table 2). Traces of the *exo*-acyl regioisomer could only be detected. From the reaction with dipolarophile **7** (Table 1, entry 4) we could isolate and identify only cycloadducts **13A** and **13B** in 60% and 21% yield, respectively. These results indicate that higher regio- and stereoselectivity are found when bulkier substituents are bounded to the ketone carbon atom of the dipolarophile.

The reaction between the six-membered nitrone **2** and olefin **5** at room temperature (Table 1, entry 5) afforded all four possible adducts: **14A** (*exo*-ester, 40%), its diastereoisomer **14B** (*endo*-ester, 36%) and the regioisomers **14C** (*exo*-acyl, 11%) and **14D** (*endo*-acyl, 3%). The NMR spectra of adducts **14A** and **14C** show a single set of well defined signals attributed to the almost exclusive presence of the *trans* invertomer of the perhydroisoxazolo[2,3-*a*]pyridine ring.[7g,8] These two compounds present values of $J_{3,3a}$ close to 10 Hz (Table 2), indicative of a *trans* relationship between H-3 and H-3a.[8] An HMBC experiment, that showed a correlation between H-3a and the carbon atom of the ester group demonstrated the regiochemistry of **14A** and proved that the chemical shifts of C-2 and C-3 show the same trend as above. These δ values were then used to establish the regiochemistry of **14B-D**. The NMR spectra of compounds **14B** and **14D** show two series of signals corresponding to the presence of the *trans* and *cis* invertomers in a *ca.* 2:1 relation and the value of $J_{3,3a}$ close to 8 Hz in the *trans* invertomer demonstrates the *cis* geometry of H-3 and H-3a in these adducts.[8] Under kinetic control nitrone **2** is clearly less regio- and stereoselective than nitrone **1**. The same tendency in the stereoselectivity was observed when using γ-oxy α,β-unsaturated esters as dipolarophiles.[8] At 110 °C both the regio- and stereoselectivity dramatically improved and adduct **14A** was clearly predominant (Table 1, entry 6). At this temperature the product distribution corresponds to the thermodynamic stability, since a sample of pure **14C** in the same conditions was converted into a mixture of **14A-C** in similar proportions to those of entry 6. The greater stability of adduct **14A** may be due to the fact that in its preferred rigid *trans*-fused invertomer[7g] both substituents at C-2 and C-3 are allocated in pseudoequatorial positions, meanwhile for isomer **14B** they are in pseudoaxial orientation.

At room temperature the reaction of **2** with **6** (Table 1, entry 7) gave four compounds: **15A** (*exo*-ester, 38%), **15B** (*endo*-ester, 34%), **15C** (*exo*-acyl, 12%) and **15D** (*endo*-acyl, 3%). Their structural and stereochemical assignment was based on the same evidences as before (Table 2). Under thermodynamic control (Table 1, entry 8), the regio- and stereoselectivity of this cycloaddition was also considerably improved and **15A** was obtained in 70% yield.

The reaction between **2** and **7** (Table 1, entry 9) at room temperature yielded three new adducts, **16A-C**, in 42%, 35%, and 8% yield, respectively, and only traces of the *endo*-acyl isomer were detected. The cycloaddition of nitrone **2** to olefin **8** (Table 1, entry 10) gave a similar result and adducts **17A-D** were obtained in 39%, 31%, 8%, and 3% yield, respectively.

The results so far obtained indicate that in these reactions electronic effects are overwhelmed by steric interactions. Thus, the less sterically demanding oxygen end of the nitrone has been mainly linked to the more crowded α-ketone carbon atom of the alkene. In all the cases a slight preference for the formation of isomer **A** *vs.* **B** is observed. When the ester group is *endo* orientated (TS leading to **B**) it lies directly above/below the methylene group adjacent to the carbon atom of the dipole. If the ester group is *exo* orientated (TS leading to **A**)

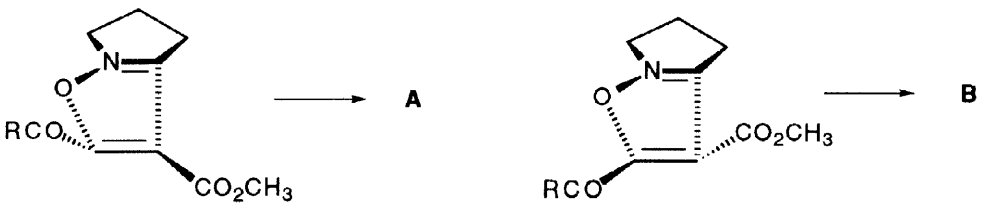
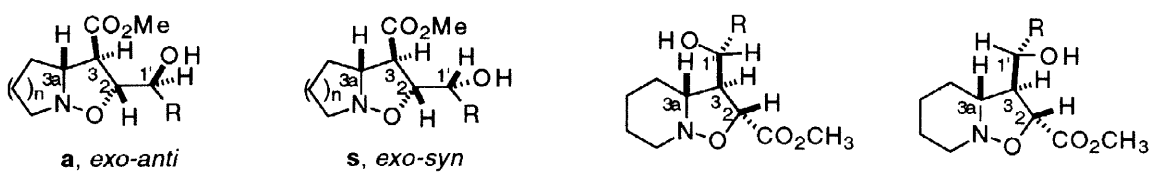


Figure 3

the ketone substituent lies away from the nitrone ring (Figure 3). Since both competitive transition states benefit from a favorable secondary orbital interaction, the observed preference must be explained considering sterical factors.

Nitrones **1** and **2** were also added to the trisubstituted olefins **9** and **10** (Table 1, entries 11-14) and, in each case, only one product was formed in very high yield. We exclusively isolated regioadducts in which the oxygen end of the dipole has attached to the more substituted olefinic carbon atom. The regiochemistry of **18C**, **19A**, **20C**, and **21A**, is evidenced by the NMR absorption of H-3 as a doublet at δ *ca.* 3.5. The *exo* stereochemistry for **18C** and **19A** was proven by the observation of NOE on H-3a when the methyl group at C-2 was irradiated and for **20C** and **21A** by the value of $J_{3,3a} \approx 10.0$ Hz.

Carbonyl reduction of some cycloadducts. The high regioselectivities encountered in the cycloadditions of the γ-oxo esters brought us to consider the reduction of the carbonyl group for some of the cycloadducts. The reduction of the type **A** major adducts could give access to *exo-anti* and/or *exo-syn* hydroxylic derivatives that were not formed (from nitrone **1**) or obtained only as minor products (from nitrone **2**) through the cycloadditions of these nitrones to the corrresponding allylic alcohols like **3** or **4**.[8] The reduction of *endo* adducts of type **B** would furnish the stereoisomers obtained as major products in the cycloadditions with the allylic alcohols; therefore this alternative would not represent a synthetic improvement and it was excluded. The reduction of the minor *exo* adducts of type **C** could provide new products with the structure of the regioisomers that were never observed in the cycloadditions with the corresponding allylic alcohols. The reduction studies were performed with oxo cycloadducts derived from the keto esters **5** and **6**. The results are shown in Table 3.



11Aa	n=1, R=CH_3	**11As**
12Aa	n=1, R=CH_2CH_2OBn	**12As**
14Aa	n=2, R=CH_3	**14As**
15Aa	n=2, R=CH_2CH_2OBn	**15As**

Figure 4

Treatment of **11A** with $NaBH_4$ (Table 3, entry 1) gave an inseparable 1:1.5 mixture of the unknown alcohols **11Aa**, *exo-anti*, and **11As**, *exo-syn*, in 88% overall yield (Figure 4). Changing the reducing agent by lithium tri-*tert*-butoxyaluminohydride (LTBA) or L-Selectride® (Table 3, entries 2 and 3) the *anti/syn* ratio could be modified from 1.5:1 to 1:4, respectively. The reduction of **12A** with the same hydrides (Table 3, entries 4-6)

Table 3. Reductions of the Carbonyl Group of several Adducts

Entry	Ketone	Method[a]	Products (%)		*anti/syn*
1	**11A**	A	**11Aa**[b] (35)	**11As**[b] (53)	1:1.5
2	**11A**	B	**11Aa**[b] (50)	**11As**[b] (33)	1.5:1
3	**11A**	C	**11Aa**[b] (17)	**11As**[b] (69)	1:4
4	**12A**	A	**12Aa**[b] (36)	**12As**[b] (54)	1:1.5
5	**12A**	B	**12Aa**[b] (47)	**12As**[b] (39)	1.2:1
6	**12A**	C	**12Aa**[b] (10)	**12As**[b] (74)	1:7
7	**14A**	A	**14Aa**[c] (40)	**14As**[c] (48)	1:1.2
8	**15A**	A	**15Aa**[c] (39)	**15As**[c] (47)	1:1.2
9	**15A**	B	**15Aa**[c] (21)	**15As**[c] (63)	1:3
10	**15A**	C	**15Aa**[c] (14)	**15As**[c] (69)	1:5
11	**15A**	D	**15Aa**[c] (10)	**15As**[c] (52)	1:5
12	**14C**	A	**22**[b] (38)	**23**[b] (46)	
13	**14C**	B	**22**[b] (36)	**23**[b] (44)	
14	**14C**	C	**22**[b] (23)	**23**[b] (54)	
15	**15C**	A	**24**[b] (40)	**25**[b] (40)	
16	**15C**	B	**24**[b] (36)	**25**[b] (46)	
17	**15C**	C	**24**[b] (21)	**25**[b] (64)	

[a]Method A: $NaBH_4$, CH_2Cl_2/MeOH (1:1), rt; Method B: LTBA, THF, -78 °C; Method C: L-Selectride®, THF, -78 °C; Method D: NB-Enantride®, THF, -78 °C. [b]new compound. [c]previously described compound.[8]

furnished the new alcohols **12Aa** and **12As** also in good yields and variable *anti/syn* ratios. The assignment of the relative *anti/syn* configuration is based on earlier observations regarding the relative polarity and some NMR data of these kind of stereoisomers.[7k,8] Particularly, the *anti* isomer is less polar and it shows higher chemical shifts for H-2, H-1', C-2, and C-1'and a greater value of $J_{2,1'}$.

Treatment of **14A** with $NaBH_4$ (Table 3, entry 7) yielded the known compounds **14Aa** and **14As** in 40% and 48% yield, respectively. The reduction of **15A** (Table 3, entries 8-11) afforded the also known alcohols **15Aa** and **15As** in good yields and *anti/syn* ratios from 1:1.2 to 1:5. With this substrate the reduction with NB-Enantride® was also performed, but the stereoselectivity was not further improved. Since the oxo adducts **14A** and **15A** may be obtained in excellent yields (Table 1, entries 6 and 8), this route represents a much superior synthesis of the four alcohols **14-15Aa/s** than the cycloaddition between nitrone **2** and the allylic alcohols **3** and **4**, in which only small percentages of these hydroxy adducts were obtained.[8]

Finally, we undertook the reduction of ketones **14C** (Table 3, entries 12-14) and **15C** (Table 3, entries 15-17). As with the former substrates, the highest stereoselectivities were obtained with L-Selectride®. The assignment of the relative configuration at C-3/C-1' for each couple of products **22/23** and **24/25** (Figure 4) was based on NOE experiments. Upon irradiation of H-1', the enhancement of the signal corresponding to H-2 is greater for alcohols **22** and **24** than for alcohols **23** and **25**, and the opposite happens with the signal of H-3a. Examination of molecular models shows that in the less hindered rotamer of the former isomers H-1' is close to H-2, while in the latter H-1' is close to H-3a.[27]

In conclusion, we have shown that the cycloadditions of cyclic nitrones to γ-oxo α,β-unsaturated esters present an unexpectedly high regioselectivity, that must be attributed to steric factors. Under kinetic control, the *endo/exo* stereoselectivity is low, but it can be spectacularly improved under thermodynamic conditions. The reduction of the major regioisomers is a good yielding procedure for the preparation of some hydroxylic derivatives that are not formed or obtained only as minor stereoisomers in the cycloadditions of the same nitrones to the corresponding γ-hydroxy α,β-unsaturated esters.

EXPERIMENTAL SECTION

General Procedures. See ref 7g. THF was dried by distillation over sodium benzophenone ketyl. NMR spectra were recorded by *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona*. $CDCl_3$ was used as solvent for NMR experiments. Keto esters **5** and **8** are commercially available. Nitrones **1**[17] and **2**[6c,18] were prepared according to previously described methods.

Methyl (E)-6-(benzyloxy)-4-oxo-2-hexenoate, **6**

To a suspension of pyridium chlorochromate (1.81 g, 8.4 mmol) in CH_2Cl_2 (25 mL) was added a solution of methyl (*E*)-6-(benzyloxy)-4-hydroxy-2-hexenoate[20] (1.45 g, 5.8 mmol) in CH_2Cl_2 (4 mL) and the resulting mixture was stirred for 8 h. Ether (60 mL) was added, the solid filtered off and rinsed with ether. The solvent was evaporated and the residue was purified by flash chromatography using hexane-EtOAc (5:1) as eluent yielding 1.17 g (4.7 mmol, 84% yield) of methyl (*E*)-6-(benzyloxy)-4-oxo-2-hexenoate, **6**, as a white solid. **6**: mp 37-9 °C (ethyl acetate-pentane); IR (KBr) 1730, 1678 cm^{-1}; ^1H NMR (250 MHz) δ 7.35-7.20 (m, 5 H, Ph), 7.07 (d, $J_{3,2}$ = 15.9 Hz, 1 H, H-3), 6.67 (d, $J_{2,3}$ = 15.9 Hz, 1 H, H-2), 4.49 (s, 2 H, CH_2Ph), 3.79 (s, 3 H, OMe), 3.77 (t, $J_{6,5}$ = 6.2 Hz, 2 H, H-6), 2.90 (t, $J_{5,6}$ = 6.2 Hz, 2 H, H-5); ^{13}C NMR (100 MHz) δ 197.8 (C=O), 165.9 (C=O), 139.5 (C-3), 137.9 (Ph), 130.7 (C-2), 128.4 (Ph), 127.7 (Ph), 73.3 (CH_2Ph), 64.8 (C-6), 52.3 (OMe), 41.6 (C-5); MS *m/z* 157 (3), 156 (33), 124 (62), 114 (72), 91 (100). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.65; H, 6.50.

Methyl (E)-5-methyl-4-oxo-2-hexenoate, **7**

To an ice-cooled mixture of acetic acid (36 mL) and acetic anhydride (18 mL) was added chromic anhydride (3.52 mg, 35.2 mmol) in small portions. The mixture was diluted with benzene (40 mL) and a solution of methyl (*E*)-5-methyl-2-hexenoate[22] (1.00 g, 7.0 mmol) in benzene (5 mL) was added dropwise. After 1 h stirring at 0 °C, water (100 mL) was added, the mixture was neutralized with 20% NaOH, and extracted with ether. The solvent was removed and the residue was purified by flash chromatography using hexane-ether (2:1) as eluent to afford 560 mg (3.60 mmol, 51% yield) of methyl (*E*)-5-methyl-4-oxo-2-hexenoate, **7**, as a colorless oil, whose spectroscopic data matched with those previously published.[21] For larger amounts of material a minor modification is useful: direct extraction with ether of the reaction mixture without previous neutralization, followed by distillation of the acetic acid or neutralization with solid $NaHCO_3$.

Reaction between nitrone **1** *and olefin* **5**

A solution of nitrone **1** (796 mg, 9.36 mmol) and methyl (*E*)-4-oxo-2-pentenoate, **5**, (600 mg, 4.68 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 3 d following its evolution by tlc (hexane-EtOAc 1:1). Removal

of the solvent and flash chromatography using hexane-EtOAc (from 2:1 to 1:1) as eluent afforded the following fractions: (i) 274 mg (1.29 mmol, 27% yield) of methyl (2*RS*,3*RS*,3a*SR*)-2-acetylhexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **11B**, as a colorless oil; (ii) 555 mg (2.60 mmol, 56% yield) of its (2*RS*,3*RS*,3a*RS*)-isomer, **11A**, as a colorless oil; and (iii) 40 mg (0.19 mmol, 4% yield) of methyl (2*RS*,3*RS*,3a*RS*)-3-acetylhexahydropyrrolo[1,2-*b*]isoxazole-2-carboxylate, **11C**, as a colorless oil. **11A**: IR (film) 2954, 2928, 1720, 1674 cm^{-1}; ^1H NMR (250 MHz) δ 4.69 (d, $J_{2,3}$ = 7.3 Hz, 1 H, H-2), 3.86 (dt, $J_{3a,4}$ = 7.5 Hz, $J_{3a,3}$ = $J_{3a,4}$ = 4.7 Hz, 1 H, H-3a), 3.72 (s, 3 H, OMe), 3.29 (dd, $J_{3,2}$ = 7.3 Hz, $J_{3,3a}$ = 4.7 Hz, 1 H, H-3), 3.22 (m, 1 H, H-6), 2.99 (dt, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = $J_{6,5}$ = 7.6 Hz, 1 H, H-6), 2.24 (s, 3 H, H-2'), 2.05-1.93 (m, 2 H, H-5, H-4), 1.81-1.67 (m, 2 H, H-5, H-4); ^{13}C NMR (100 MHz) δ 204.2 (C=O), 171.2 (C=O), 84.9 (C-2), 69.5 (C-3a), 55.9 (C-6), 55.3 (C-3), 52.2 (OMe), 29.6 (C-4), 26.8 (C-2'), 23.1 (C-5); MS *m/z* 213 (23), 182 (1), 170 (5), 110 (100), 85 (43), 70 (35), 43 (79). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.33; H, 7.34; N, 6.35. **11B**: IR (film) 2955, 1741, 1719, 1439 cm^{-1}; ^1H NMR (250 MHz) δ 4.67 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 3.96 (dd, $J_{3,3a}$ = 8.0 Hz, $J_{3,2}$ = 4.8 Hz, 1 H, H-3), 3.76 (q, $J_{3a,3} \approx J_{3a,4} \approx J_{3a,4} \approx$ 8.0 Hz, 1 H, H-3a), 3.71 (s, 3 H, OMe), 3.44 (ddd, $J_{6,6}$ = 14.2 Hz, $J_{6,5}$ = 8.0 Hz, $J_{6,5}$ = 3.6 Hz, 1 H, H-6), 2.99 (dt, $J_{6,6}$ = 14.2 Hz, $J_{6,5}$ = $J_{6,5}$ = 8.0 Hz, 1 H, H-6), 2.29 (s, 3 H, H-2'), 2.08 (m, 1 H, H-5), 1.85-1.70 (m, 2 H, H-5, H-4), 1.57 (m, 1 H, H-4); ^{13}C NMR (100 MHz) δ 209.9 (C=O), 170.9 (C=O), 82.2 (C-2), 68.1 (C-3a), 55.8 (C-6), 53.3 (C-3), 52.0 (OMe), 26.6 (C-4), 25.6 (C-2'), 24.2 (C-5); MS *m/z* 213 (18), 182 (1), 170 (15), 110 (93), 86 (39), 85 (53), 43 (100). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.24; H, 7.13; N, 6.34. **11C**: IR (film) 2955, 2927, 1716, 1679 cm^{-1}; ^1H NMR (250 MHz) δ 4.73 (d, $J_{2,3}$ = 7.3 Hz, 1 H, H-2), 3.73 (m, 1 H, H-3a), 3.72 (s, 3 H, OMe), 3.42 (dd, $J_{3,2}$ = 7.3 Hz, $J_{3,3a}$ = 5.1 Hz, 1 H, H-3), 3.31 (m, 1 H, H-6), 2.98 (dt, $J_{6,6}$ = 13.1 Hz, $J_{6,5}$ = $J_{6,5}$ = 7.5 Hz, 1 H, H-6), 2.23 (s, 3 H, H-2'), 2.10-1.90 (m, 2 H, H-5, H-4), 1.75-1.55 (m, 2 H, H-5, H-4); ^{13}C NMR (100 MHz) δ 203.9 (C=O), 170.2 (C=O), 78.3 (C-2), 68.9 (C-3a), 65.4 (C-3), 56.2 (C-6), 52.6 (OMe), 30.2 (C-4), 26.5 (C-2'), 23.4 (C-5); MS *m/z* 213 (22), 170 (3), 112 (34), 110 (55), 85 (94), 55 (78), 43 (100).

The same reaction was performed in toluene at 110 °C for 10 h yielding **11A** (40% yield), **11B** (35% yield), and **11C** (5% yield). A similar composition mixture of **11A-C** was obtained when heating an analytical sample of **11B** in toluene at 110 °C overnight.

Reaction between nitrone **1** *and olefin* **6**

A solution of nitrone **1** (624 mg, 7.34 mmol) and methyl (*E*)-6-(benzyloxy)-4-oxo-2-hexenoate, **6**, (912 mg, 3.67 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 2 d following its evolution by tlc (hexane-EtOAc 4:1). Removal of the solvent and flash chromatography using hexane-EtOAc (from 2:1 to 1:1) as eluent afforded the following fractions: (i) 264 mg (0.79 mmol, 22% yield) of methyl (2*RS*,3*RS*,3a*SR*)-2-[3-(benzyloxy)-1-oxopropyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **12B**, as a colorless oil; and (ii) 795 mg (2.39 mmol, 65% yield) of its (2*RS*,3*RS*,3a*RS*)- isomer, **12A**, as a colorless oil. **12A**: IR (film) 2953, 2871, 1739, 1451 cm^{-1}; ^1H NMR (250 MHz) δ 7.40-7.26 (m, 5 H, Ph), 4.74 (d, $J_{2,3}$ = 6.9 Hz, 1 H, H-2), 4.49 (s, 2 H, C*H*$_2$-Ph), 3.86 (m, 1 H, H-3a), 3.80-3.65 (m, 2 H, H-3'), 3.72 (s, 3 H, OMe), 3.36 (dd, $J_{3,2}$ = 6.9 Hz, $J_{3,3a}$ = 5.0 Hz, 1 H, H-3), 3.21 (ddd, $J_{6,6}$ = 12.8 Hz, $J_{6,5}$ = 6.6 Hz, $J_{6,5}$ = 4.4 Hz, 1 H, H-6), 3.05-2.75 (m, 3 H, H-6, 2 H-2'), 2.09-1.84 (m, 2 H, H-4, H-5), 1.80-1.60 (m, 2 H, H-5, H-4); ^{13}C NMR (62.5 MHz) δ 205.0 (C=O), 171.4 (C=O), 137.9/128.3/127.6 (Ph), 84.9 (C-2), 73.1 (*C*H$_2$-Ph), 69.6 (C-3a), 64.6 (C-3'), 56.1 (C-6), 55.3 (C-3), 52.4 (OMe), 39.7 (C-2'), 29.6 (C-4), 23.2 (C-5); MS *m/z* 333 (5), 114 (28), 110 (49), 91

(100), 85 (23). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.81; H, 7.05; N, 4.21. **12B**: IR (film) 2953, 2871, 1739, 1451 cm^{-1}; ^1H NMR (250 MHz) δ 7.30-7.20 (m, 5 H, Ph), 4.70 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 4.47 (s, 2 H: CH_2Ph), 3.98 (dd, $J_{3,3a}$ = 8.0 Hz, $J_{3,2}$ = 4.8 Hz, 1 H, H-3), 3.76-3.67 (m, 3 H, H-3a, 2 H-3'), 3.68 (s, 3 H, OMe), 3.40 (ddd, $J_{6,6}$ = 14.3 Hz, $J_{6,5}$ = 8.0 Hz, $J_{6,5}$ = 3.3 Hz, 1 H, H-6), 3.12-2.92 (m, 3 H, 2 H-2', H-6), 2.04 (m, 1 H, H-5), 1.82-1.63 (m, 2 H, H-5, H-4), 1.54 (m, 1 H, H-4); ^{13}C NMR (100 MHz) δ 209.9 (C=O), 171.0 (C=O), 138.1/128.2/127.6/127.4 (Ph), 82.2 (C-2), 73.0 (CH_2Ph), 68.2 (C-3a), 64.9 (C-3'), 55.8 (C-6), 53.2 (C-3), 52.1 (OMe), 38.4 (C-2'), 26.7 (C-4), 24.3 (C-5); MS *m/z* 334 (M^++1, 4), 110 (38), 91 (100), 70 (58). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.82; H, 7.03; N, 4.20.

Reaction between nitrone **1** *and olefin* **7**

A solution of nitrone **1** (930 mg, 10.94 mmol) and methyl (*E*)-5-methyl-4-oxo-2-hexenoate, **7**, (853 mg, 5.46 mmol) in CH_2Cl_2 (36 mL) was stirred at rt for 3 d following its evolution by tlc (hexane-EtOAc 1:1). Removal of the solvent and flash chromatography using hexane-EtOAc (from 3:1 to 1:1) as eluent afforded the following fractions: (i) 281 mg (1.16 mmol, 21% yield) of methyl (2*RS*,3*RS*,3a*SR*)-2-(2-methyl-1-oxopropyl)hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **13B**, as a colorless oil; and (ii) 788 mg (3.27 mmol, 60% yield) of its (2*RS*,3*RS*,3a*RS*)- isomer, **13A**, as a colorless oil. **13A**: IR (film) 2971, 2876, 1741, 1719 cm^{-1}; ^1H NMR (250 MHz) δ 4.85 (d, $J_{2,3}$ = 7.3 Hz, 1 H, H-2), 3.86 (m, 1 H, H-3a), 3.72 (s, 3 H, OMe), 3.34 (dd, $J_{3,2}$ = 7.3 Hz, $J_{3,3a}$ = 5.1 Hz, 1 H, H-3), 3.20 (m, 1 H, H-6), 2.97 (m, 2 H, H-6, H-2'), 2.08-1.88 (m, 2 H), 1.82-1.64 (m, 2 H), 1.12 (d, $J_{Me,2'}$ = 6.9 Hz, 3 H, Me), 1.08 (d, $J_{Me,2'}$ = 6.9 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 209.3 (C=O), 171.0 (C=O), 82.8 (C-2), 69.2 (C-3a), 55.7 (C-6), 55.2 (C-3), 51.8 (OMe), 37.6 (C-2'), 29.3 (C-4), 22.7 (C-5), 17.8 (Me), 16.8 (Me); MS *m/z* 242 (M^++1, 5), 241 (12), 110 (100), 85 (32). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.36; H, 7.83; N, 5.80. **13B**: IR (film) 2971, 2875, 1742, 1716 cm^{-1}; ^1H NMR (250 MHz) δ 4.83 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 4.02 (dd, $J_{3,3a}$ = 8.0 Hz, $J_{3,2}$ = 4.8 Hz, 1 H, H-3), 3.77 (q, $J_{3a,3}$ = $J_{3a,4}$ = $J_{3a,4}$ = 8.0 Hz, 1 H, H-3a), 3.72 (s, 3 H, OMe), 3.41 (ddd, $J_{6,6}$ = 13.9 Hz, $J_{6,5}$ = 7.7 Hz, $J_{6,5}$ = 3.3 Hz, 1 H, H-6), 3.20 (heptet, $J_{2',Me}$ = 6.9 Hz, 1 H, H-2'), 3.00 (dt, $J_{6,6}$ = 13.9 Hz, $J_{6,5}$ = $J_{6,5}$ = 8.0 Hz, 1 H, H-6), 2.16-1.98 (m, 1 H, H-5), 1.84-1.66 (m, 2 H, H-4, H-5), 1.68-1.48 (m, 1 H, H-4), 1.12 (d, $J_{Me,2'}$ = 6.9 Hz, 3 H, Me), 1.05 (d, $J_{Me,2'}$ = 6.9 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 214.6 (C=O), 171.1 (C=O), 80.7 (C-2), 68.0 (C-3a), 55.8 (C-6), 53.2 (C-3), 52.0 (OMe), 35.7 (C-2'), 26.6 (C-4), 24.2 (C-5), 18.7 (Me), 17.1 (Me); MS *m/z* 242 (M^++1, 8), 241 (14), 156 (1), 119 (100), 85 (26). Anal. Cald for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.74; H, 7.74; N, 5.85.

Reaction between nitrone **2** *and olefin* **5**

To a solution of nitrone **2** (prepared from *N*-hydroxypiperidine (592 mg, 5.86 mmol) and yellow HgO (3.810 g, 17.58 mmol)) in CH_2Cl_2 (25 mL) was added a solution of methyl (*E*)-4-oxo-2-pentenoate, **5**, (500 mg, 3.90 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at rt for 18 h following its evolution by tlc (hexane-EtOAc 3:1). Removal of the solvent and flash chromatography using hexane-EtOAc (from 3:1 to 1:1) as eluent afforded the following fractions: (i) 355mg (1.56 mmol, 40% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-acetylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **14A**, as a colorless oil; (ii) 320 mg (1.41 mmol, 36% yield) of its (2*RS*,3*RS*,3a*SR*)- isomer, **14B**, as a colorless oil; (iii) 95 mg (0.42 mmol, 11% yield) of

methyl (2*RS*,3*RS*,3a*RS*)-3-acetylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate, **14C**, as a colorless oil; and (iv) 27 mg (0.12 mmol, 3% yield) of its (2*RS*,3*RS*,3a*SR*)- isomer, **14D**, as a colorless oil. **14A**: IR (film) 2950, 2863, 1727, 1437 cm^{-1}; ^1H NMR (400 MHz) δ 4.48 (d, $J_{2,3}$ = 4.4 Hz, 1 H, H-2), 3.70 (s, 3 H: OMe), 3.43 (m, 1 H, H-7eq), 3.24 (dd, $J_{3,3a}$ = 9.8 Hz, $J_{3,2}$ = 4.4 Hz, 1 H, H-3), 2.48 (ddd, $J_{7ax,6ax}$ = 12.2 Hz, $J_{7ax,7eq}$ = 8.9 Hz, $J_{7ax,6eq}$ = 3.0 Hz, 1 H, H-7ax), 2.28 (m, 1 H, H-3a), 2.27 (s, 3 H, H-2'), 2.07 (br d, J = 12.2 Hz, 1 H, H-4eq), 1.78-1.65 (m, 2 H, H-5eq, H-6eq), 1.55 (qt, $J_{6ax,6eq} \approx J_{6ax,7ax} \approx J_{6ax,5ax}$ ≈ 13.1 Hz, $J_{6ax,7eq} \approx J_{6ax,5eq}$ ≈ 4.0 Hz, 1 H, H-6ax), 1.34 (qd, $J_{4ax,4eq} \approx J_{4ax,5ax} \approx J_{4ax,3a}$ ≈ 12.5 Hz, $J_{4ax,5eq}$ = 3.7 Hz, 1 H, H-4ax), 1.18 (qt, $J_{5ax,5eq} \approx J_{5ax,4ax} \approx J_{5ax,6ax}$ ≈ 13.0 Hz, $J_{5ax,6eq} \approx J_{5ax,4eq}$ ≈ 4.0 Hz, 1 H, H-5ax); ^{13}C NMR (62.5 MHz) δ 210.7 (C=O), 171.7 (C=O), 82.0 (C-2), 70.1 (C-3a), 54.8 (C-7), 54.6 (C-3), 52.2 (OMe), 28.6 (C-4), 25.6 (C-2'), 24.1 (C-6), 23.1 (C-5); MS *m/z* 227 (14), 196 (1), 184 (2), 124 (87), 99 (68), 84 (38), 55 (57), 43 (100). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.20; H, 7.56; N, 6.17. **14B**: IR (film) 2949, 2858, 1740, 1721, 1439 cm^{-1}; ^1H NMR (400 MHz) δ (*ca.* 67% *trans*-invertomer) δ 4.82 (d, $J_{2,3}$ = 4.9 Hz, 1 H, H-2), 3.70 (s, 3 H, OMe), 3.48 (m, 1 H, H-7eq), 3.38 (dd, $J_{3,3a}$ = 7.9 Hz, $J_{3,2}$ = 4.9 Hz, 1 H, H-3), 2.43 (ddd, $J_{7ax,6ax}$ = 12.2 Hz, $J_{7ax,7eq}$ = 9.5 Hz, $J_{7ax,6eq}$ = 3.0 Hz, 1 H, H-7ax), 2.35 (t, J ≈ 8.2 Hz, 1 H, H-3a), 2.22 (s, 3 H, H-2'), 1.95 (br d, J = 12.5 Hz, 1 H, H-4eq), 1.82-1.48 (m, 3 H, H-5eq, H-6eq, H-6ax), 1.38-1.12 (m, 2 H, H-4ax, H-5ax); (*ca.* 33% *cis*-invertomer, observable signals) δ 4.69 (d, $J_{2,3}$ = 5.5 Hz, 1 H, H-2), 3.70 (m, 1 H, H-3), 3.69 (s, 3 H, OMe), 2.95 (br t, J ≈ 12.0 Hz, 1 H, H-7), 2.25 (s, 3 H, H-2'); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 205.1 (C=O), 170.9 (C=O), 83.0 (C-2), 68.8 (C-3a), 55.4 (C-7), 52.4 (C-3), 52.0 (OMe), 27.0 (C-2'), 26.6 (C-4), 24.1 (C-6), 23.2 (C-5); (*cis*-invertomer, observable signals) δ 211.0 (C=O), 170.5 (C=O), 81.4 (C-2), 60.8 (C-3a), 54.8 (C-3), 50.5 (C-7), 25.7 (C-2'), 22.1/21.7/19.2 (C-6/ C-5/ C-4); MS *m/z* 228 (M^++1, 100), 227 (46), 196 (1), 184 (12), 124 (38), 84 (28), 43 (92). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.13; H, 7.56; N, 6.21. **14C**: IR (film) 2948, 2856, 1761, 1716, 1439 cm^{-1}; ^1H NMR (250 MHz) δ 4.69 (d, $J_{2,3}$ = 5.5 Hz, 1 H, H-2), 3.76 (s, 3 H, OMe), 3.47 (dd, $J_{3,3a}$ = 9.9 Hz, $J_{3,2}$ = 5.5 Hz, 1 H, H-3), 3.50 (m, 1 H, H-7eq), 2.48 (ddd, $J_{7ax,6ax}$ = 12.1 Hz, $J_{7ax,7eq}$ = 9.1 Hz, $J_{7ax,6eq}$ = 3.5 Hz, 1 H, H-7ax), 2.29 (m, 1 H, H-3a), 2.26 (s, 3 H, H-2'), 2.02 (m, 1 H, H-4eq), 1.82-1.56 (m, 3 H, H-5eq, H-6eq, H-6ax), 1.50 (qd, $J_{4ax,4eq} \approx J_{4ax,5ax} \approx J_{4ax,3a}$ ≈ 12.0 Hz, $J_{4ax,5eq}$ = 3.7 Hz, 1 H, H-4ax), 1.21 (m, 1 H, H-5ax); ^{13}C NMR (62.5 MHz) δ 204.5 (C=O), 172.3 (C=O), 75.1 (C-2), 69.9 (C-3a), 63.6 (C-3), 55.0 (C-7), 52.5 (OMe), 30.5 (C-2'), 28.6 (C-4), 24.0 (C-6), 23.1 (C-5); MS *m/z* 227 (3), 184 (2), 99 (26), 55 (28), 43 (100). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.95; H, 7.50; N, 6.15. **14D**: IR (film) 2934, 2855, 1719, 1439 cm^{-1}; ^1H NMR (250 MHz) (*ca.* 67% *trans*-invertomer) δ 4.92 (d, $J_{2,3}$ = 5.1 Hz, 1 H, H-2), 3.74 (s, 3 H, OMe), 3.59 (dd, $J_{3,3a}$ = 8.0 Hz, $J_{3,2}$ = 5.1 Hz, 1 H, H-3), 3.55 (m, 1 H, H-7eq), 2.60-2.43 (m, 2 H, H-3a, H-7ax), 2.24 (s, 3 H, H-2'), 1.95 (br d, J ≈ 11.0 Hz, 1 H, H-4eq), 1.90-1.05 (m, 5 H, H-5eq, H-6eq, H-6ax, H-4ax, H-5ax); (*ca.* 33% *cis*-invertomer, observable signals) δ 5.00 (d, $J_{2,3}$ = 6.2 Hz, 1 H, H-2), 3.73 (s, 3 H, OMe), 2.97 (br t, J ≈ 11.8 Hz, 1 H, H-7), 2.21 (s, 3 H, H-2'); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 204.8 (C=O), 170.4 (C=O), 75.7 (C-2), 68.4 (C-3a), 61.0 (C-3), 55.3 (C-7), 52.4 (OMe), 31.2 (C-2'), 26.5 (C-4), 24.1 (C-6), 23.4 (C-5); (*cis*-invertomer, observable signals) δ 73.6 (C-2), 64.0 (C-3a), 60.6 (C-3), 50.8 (C-7), 29.6 (C-2'), 22.3/21.6/18.7 (C-4/C-5/C-6); MS *m/z* 227 (15), 184 (4), 124 (24), 99 (100), 69 (32), 43 (54). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.90; H, 7.36; N, 6.16.

The same reaction was performed in toluene at 110 °C for 6 h affording **14A** (78% yield), **14B** (6% yield), and **14C** (4% yield). A similar composition mixture of **14A-C** was obtained when heating an analytical sample of **14B** in toluene at 110 °C overnight.

Reaction between nitrone **2** *and olefin* **6**

To a solution of nitrone **2** (prepared from *N*-hydroxypiperidine (281 mg, 2.78 mmol) and yellow HgO (1.808 g, 8.35 mmol)) in CH_2Cl_2 (25 mL) was added a solution of methyl (*E*)-6-(benzyloxy)-4-oxo-2-hexenoate, **6**, (460 mg, 1.85 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at rt for 18 h following its evolution by tlc (hexane-EtOAc 2:1). Flash chromatography of the crude material using hexane-EtOAc (from 4:1 to 1:1) as eluent gave the following fractions: (i) 243 mg (0.70 mmol, 38% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-[3-(benzyloxy)-1-oxopropyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **15A**, as a colorless oil; (ii) 219 mg (0.63 mmol, 34% yield) of its (2*RS*,3*RS*,3a*SR*)- isomer, **15B**, as a colorless oil; (iii) 76 mg (0.22 mmol, 12% yield) of methyl (2*RS*,3*RS*,3a*RS*)-3-[3-(benzyloxy)-1-oxopropyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate, **15C**, as a colorless oil; and (iv) 21 mg (0.06 mmol, 3% yield) of its (2*RS*,3*RS*,3a*SR*)- isomer, **15D**, as a colorless oil. **15A**: IR (film) 2933, 2858, 1736, 1442 cm^{-1}; ^1H NMR (250 MHz) δ 7.30-7.20 (m, 5 H, Ph), 4.54 (d, $J_{2,3}$ = 4.4 Hz, 1 H, H-2), 4.48 (s, 2 H, CH_2Ph), 3.75 (t, $J_{3',2'}$ = 6.4 Hz, 2 H, H-3'), 3.71 (s, 3 H, OMe), 3.42 (m, 1 H, H-7eq), 3.30 (dd, $J_{3,3a}$ = 9.9 Hz, $J_{3,2}$ = 4.4 Hz, 1 H, H-3), 3.01 (t, $J_{2',3'}$ = 6.4 Hz, 2 H, H-2'), 2.47 (ddd, $J_{7ax,6ax}$ = 12.1 Hz, $J_{7ax,7eq}$ = 9.2 Hz, $J_{7ax,6eq}$ = 3.0 Hz, 1 H, H-7ax), 2.30 (ddd, $J_{3a,4ax}$ = 11.0 Hz, $J_{3a,3}$ = 9.9 Hz, $J_{3a,4eq}$ = 2.2 Hz, 1 H, H-3a), 2.07 (br d, J ≈ 12.3 Hz, 1 H, H-4eq), 1.80-1.60 (m, 2 H, H-5eq, H-6eq), 1.51 (qt, $J_{6ax,6eq} \approx J_{6ax,7ax} \approx J_{6ax,5ax}$ ≈ 12.8 Hz, $J_{6ax,7eq} \approx J_{6ax,5eq}$ ≈ 4.0 Hz, 1 H, H-6ax), 1.35 (m, 1 H, H-4ax), 1.15 (qt, $J_{5ax,5eq} \approx J_{5ax,4ax} \approx J_{5ax,6ax}$ ≈ 12.6 Hz, $J_{5ax,6eq} \approx J_{5ax,4eq}$ ≈ 4.0 Hz, 1 H, H-5ax); ^{13}C NMR (62.5 MHz) δ 210.2 (C=O), 171.5 (C=O), 138.0/128.1/127.4/127.3 (Ph), 81.8 (C-2), 72.8 (CH_2Ph), 70.1 (C-3a), 64.7 (C-3'), 54.7 (C-7), 54.4 (C-3), 52.1 (OMe), 38.1 (C-2'), 28.5 (C-4), 24.1 (C-6), 23.1 (C-5); MS *m/z* 347 (1), 316 (1), 256 (9), 124 (46), 99 (27), 91 (100), 84 (80). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.63; H, 7.24; N, 3.99. **15B**: IR (film) 2949, 2858, 1739, 1450 cm^{-1}; ^1H NMR (400 MHz) (*ca.* 70% *trans*-invertomer) δ 7.40-7.20 (m, 5 H, Ph), 4.88 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 4.48 (s, 2 H, CH_2Ph), 3.82-3.70 (m, 2 H, H-3'), 3.71 (s, 3 H, OMe), 3.50 (m, 1 H, H-7eq), 3.44 (dd, $J_{3,3a}$ = 8.0 Hz, $J_{3,2}$ = 4.8 Hz, 1 H, H-3), 2.95-2.75 (m, 2 H, H-2'), 2.43 (ddd, $J_{7ax,6ax}$ = 11.7 Hz, $J_{7ax,7eq}$ = 9.1 Hz, $J_{7ax,6eq}$ = 2.6 Hz, 1 H, H-7ax), 2.34 (m, 1 H, H-3a), 1.92 (m, 1 H, H-4eq), 1.80-1.50 (m, 3 H, H-5eq, H-6eq, H-6ax), 1.40-1.10 (m, 2 H, H-4ax, H-5ax); (*ca.* 30% *cis*-invertomer, observable signals) δ 4.75 (d, $J_{2,3}$ = 5.1 Hz, 1 H, H-2), 3.72 (m, 1 H, H-3), 3.70 (s, 3 H, OMe), 3.50 (m, 2 H, H-3a, H-3'), 3.25 (m, 1 H, H-7), 3.05-2.90 (m, 3 H, 2 H-2', H-3'), 2.58 (m, 1 H, H-7); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 205.4 (C=O), 170.7 (C=O), 137.8/128.0/127.3/127.2 (Ph), 82.6 (C-2), 72.9 (CH_2Ph), 68.5 (C-3a), 64.6 (C-3'), 55.3 (C-7), 52.3 (C-3), 51.8 (OMe), 39.6 (C-2'), 26.5 (C-4), 24.0 (C-6), 23.1 (C-5); (*cis*-invertomer, observable signals) δ 210.5 (C=O), 170.3 (C=O), 81.2 (C-2), 60.6 (C-3a), 54.5 (C-3), 52.3 (C-7), 50.3 (C-3'), 38.2 (C-2'), 22.0/21.7/19.1 (C-4/C-5/C-6); MS *m/z* 347 (2), 316 (1), 256 (8), 114 (34), 100 (25), 99 (34), 91 (100), 55 (26). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.53; H, 7.29; N, 4.07. **15C**: IR (film) 2933, 2858, 1735, 1443 cm^{-1}; ^1H NMR (250 MHz) δ 7.35-7.20 (m, 5 H, Ph), 4.72 (d, $J_{2,3}$ = 5.5 Hz, 1 H, H-2), 4.48 (s, 2 H, CH_2Ph), 3.82-3.72 (m, 2 H, H-3'), 3.74 (s, 3 H, OMe), 3.51 (m, 1 H, H-7eq), 3.51 (dd, $J_{3,3a}$ = 9.9 Hz, $J_{3,2}$ = 5.5 Hz, 1 H, H-3), 2.90-2.72 (m, 2 H, H-2'), 2.48 (ddd, $J_{7ax,6ax}$ = 11.7 Hz, $J_{7ax,7eq}$ = 9.1 Hz, $J_{7ax,6eq}$ = 3.3 Hz, 1 H, H-7ax),

2.33 (ddd, $J_{3a,4ax}$ = 11.5 Hz, $J_{3a,3}$ = 9.9 Hz, $J_{3a,4eq}$ = 2.2 Hz, 1 H, H-3a), 2.02 (br d, J ≈ 12.4 Hz, 1 H, H-4eq), 1.80-1.60 (m, 3 H, H-6eq, H-5eq, H-6ax), 1.45 (m, 1 H, H-4ax), 1.20 (m, 1 H, H-5ax); ^{13}C NMR (62.5 MHz) δ 205.4 (C=O), 172.3 (C=O), 137.9/128.3/127.6 (Ph), 75.1 (C-2), 73.3 (CH_2Ph), 69.9 (C-3a), 65.0 (C-3'), 63.5 (C-3), 55.1 (C-7), 52.5 (OMe), 43.3 (C-2'), 28.6 (C-4), 24.1 (C-6), 23.1 (C-5); MS *m/z* 347 (2), 316 (1), 256 (9), 114 (31), 100 (27), 99 (34), 91 (100), 55 (25). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.63; H, 7.20; N, 3.99. **15D**: IR (film) 2944, 2859, 1723, 1443 cm^{-1}; ^{1}H NMR (250 MHz) (*ca.* 67% *trans*-invertomer) δ 7.35-7.20 (m, 5 H, Ph), 4.94 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 4.48 (s, 2 H, CH_2Ph), 3.82-3.73 (m, 2 H, H-3'), 3.73 (s, 3 H, OMe), 3.68-3.50 (m, 2 H, H-7eq, H-3), 2.85-2.70 (m, 2 H, H-2'), 2.59-2.42 (m, 2 H, H-7ax, H-3a), 1.93 (m, 1 H, H-4eq), 1.80-1.08 (m, 5 H, H-5eq, H-6eq, H-6ax, H-4ax, H-5ax); (*ca.* 33% *cis*-invertomer, observable signals) δ 5.02 (d, $J_{2,3}$ = 6.2 Hz, 1 H, H-2), 2.97 (br t, J ≈ 12.0 Hz, 1 H, H-7); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 205.6 (C=O), 170.5 (C=O), 138.0/128.4/127.6 (Ph), 75.6 (C-2), 73.3 (CH_2Ph), 68.8 (C-3a), 65.1 (C-3'), 60.7 (C-3), 55.4 (C-7), 52.5 (OMe), 44.3 (C-2'), 26.6 (C-4), 24.1 (C-6), 23.4 (C-5); (*cis*-invertomer, observable signals) δ 203.2, 172.9, 73.7, 64.9, 63.7, 61.0, 50.9, 43.7, 22.4, 21.8, 18.9; MS *m/z* 347 (2), 256 (8), 114 (47), 99 (43), 91 (100), 82 (28), 55 (25).

The same reaction was performed in toluene at 110 °C overnight affording **15A** (70% yield), **15B** (6% yield), and **15C** (7% yield).

Reaction between nitrone **2** *and olefin* **7**

To a solution of nitrone **2** (prepared from *N*-hydroxypiperidine (777 mg, 7.69 mmol) and yellow HgO (4.998 g, 23.08 mmol)) in CH_2Cl_2 (25 mL) was added a solution of methyl (*E*)-5-methyl-4-oxo-2-hexenoate, **7**, (800 mg, 5.13 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at rt for 18 h following its evolution by tlc (hexane-EtOAc 3:1). Flash chromatography of the crude material using hexane-EtOAc (from 3:1 to 1:1) as eluent afforded the following fractions: (i) 549 mg (2.15 mmol, 42% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-(2-methyl-1-oxopropyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **16A**, as a colorless oil; (ii) 458 mg (1.80 mmol, 35% yield) of its (2*RS*,3*RS*,3a*SR*)- isomer, **16B**, as a colorless oil; (iii) 102 mg (0.40 mmol, 8% yield) of methyl (2*RS*,3*RS*,3a*RS*)-3-(2-methyl-1-oxopropyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate, **16C**, as a colorless oil; and (iv) 15 mg of a mixture containing the *endo*-acyl regioisomer. **16A**: IR (film) 2947, 2880, 1740, 1718, 1441 cm^{-1}; ^{1}H NMR (250 MHz) δ 4.60 (d, $J_{2,3}$ = 4.7 Hz, 1 H, H-2), 3.67 (s, 3 H, OMe), 3.37 (dt, $J_{7eq,7ax}$ = 9.2 Hz, $J_{7eq,6ax} \approx J_{7eq,6eq}$ ≈ 4.2 Hz, 1 H, H-7eq), 3.28 (dd, $J_{3,3a}$ = 9.7 Hz, $J_{3,2}$ = 4.7 Hz, 1 H, H-3), 3.14 (heptet, $J_{2',Me}$ = 7.0 Hz, 1 H, H-2'), 2.43 (ddd, $J_{7ax,6ax}$ = 12.0 Hz, $J_{7ax,7eq}$ = 9.2 Hz, $J_{7ax,6eq}$ = 3.1 Hz, 1 H, H-7ax), 2.26 (td, $J_{3a,3} \approx J_{3a,4ax}$ ≈ 9.7 Hz, $J_{3a,4eq}$ ≈ 2.5 Hz, 1 H, H-3a), 2.03 (br d, J ≈ 12.0 Hz, 1 H, H-4eq), 1.75-1.60 (m, 2 H, H-5eq, H-6eq), 1.50 (qt, $J_{6ax,6eq} \approx J_{6ax,7ax} \approx J_{6ax,5ax}$ ≈ 12.0 Hz, $J_{6ax,7eq} \approx J_{6ax,5eq}$ ≈ 4.2 Hz, 1 H, H-6ax), 1.31 (qd, $J_{4ax,4eq} \approx J_{4ax,5ax} \approx J_{4ax,3a}$ ≈ 12.0 Hz, $J_{4ax,5eq}$ = 3.5 Hz, 1 H, H-4ax), 1.13 (m, 1 H, H-5ax), 1.08 (d, $J_{Me,2'}$ = 7.0 Hz, 3 H, Me), 0.99 (d, $J_{Me,2'}$ = 7.0 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 215.4 (C=O), 171.9 (C=O), 80.8 (C-2), 70.3 (C-3a), 54.8 (C-7), 54.5 (C-3), 52.1 (OMe), 35.4 (C-2'), 28.6 (C-4), 24.2 (C-6), 23.2 (C-5), 18.7 (Me), 17.3 (Me); MS *m/z* 255 (19), 224 (2), 184 (5), 124 (82), 99 (41), 43 (100). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.17; H, 8.44; N, 5.48. **16B**: IR (film) 2946, 2860, 1741, 1717, 1441 cm^{-1}; ^{1}H NMR (250 MHz) (*ca.* 75% *trans*-invertomer) δ 4.93 (d, $J_{2,3}$ = 4.7 Hz, 1 H, H-2), 3.68 (s, 3 H, OMe), 3.47 (m, 1 H, H-7eq), 3.38 (dd, $J_{3,3a}$ = 8.4 Hz, $J_{3,2}$ = 4.7 Hz, 1 H, H-3), 2.91 (heptet, $J_{2',Me}$ = 7.0 Hz, 1 H, H-2'), 2.39 (m, 1 H, H-7ax), 2.33 (m, 1

H, H-3a), 1.91 (m, 1 H, H-4eq), 1.74-1.45 (m, 3 H, H-5eq, H-6eq, H-6ax), 1.35-1.10 (m, 2 H, H-4ax, H-5ax), 1.09 (d, $J_{Me,2'}$ = 7.0 Hz, 3 H, Me), 1.01 (d, $J_{Me,2'}$ = 7.0 Hz, 3 H, Me); (*ca.* 25% *cis*-invertomer, observable signals) δ 4.80 (d, $J_{2,3}$ = 5.5 Hz, 1 H, H-2), 3.71 (dd, $J_{3,3a}$ = 7.0 Hz, $J_{3,2}$ = 5.5 Hz, 1 H, H-3), 3.67 (s, 3 H, OMe), 3.10 (heptet, $J_{2',Me}$ = 7.0 Hz, 1 H, H-2'), 2.91 (m, 1 H, H-7); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 210.6 (C=O), 171.2 (C=O), 81.6 (C-2), 68.8 (C-3a), 55.5 (C-7), 52.6 (C-3), 52.0 (OMe), 37.5 (C-2'), 26.7 (C-4), 24.2 (C-6), 23.3 (C-5), 18.2 (Me), 17.4 (Me); MS *m/z* 255 (12), 224 (1), 184 (18), 124 (62), 99 (54), 84 (39), 43 (100). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.19; H, 8.37; N, 5.48. **16C**: IR (film) 2945, 2859, 1740, 1718, 1441 cm^{-1}; ^{1}H NMR (250 MHz) δ 4.56 (d, $J_{2,3}$ = 5.9 Hz, 1 H, H-2), 3.70 (s, 3 H, OMe), 3.59 (dd, $J_{3,3a}$ = 9.9 Hz, $J_{3,2}$ = 5.9 Hz, 1 H, H-3), 3.44 (m, 1 H, H-7eq), 2.66 (heptet, $J_{2',Me}$ = 7.0 Hz, 1 H, H-2'), 2.46 (ddd, $J_{7ax,6ax}$ = 12.1 Hz, $J_{7ax,7eq}$ = 9.5 Hz, $J_{7ax,6eq}$ = 3.3 Hz, 1 H, H-7ax), 2.27 (td, $J_{3a,3} \approx J_{3a,4ax} \approx$ 11.0 Hz, $J_{3a,4eq} \approx$ 2.2 Hz, 1 H, H-3a), 1.87 (br d, J ≈ 11.0 Hz, 1 H, H-4eq), 1.75-1.53 (m, 3 H, H-5eq, H-6eq, H-6ax), 1.43 (qd, $J_{4ax,4eq} \approx J_{4ax,5ax} \approx J_{4ax,3a} \approx$ 12.4 Hz, $J_{4ax,5eq}$ = 3.7 Hz, 1 H, H-4ax), 1.16 (m, 1 H, H-5ax), 1.08 (d, $J_{Me,2'}$ = 7.0 Hz, 3 H, Me), 1.05 (d, $J_{Me,2'}$ = 7.0 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 211.0 (C=O), 172.2 (C=O), 76.1 (C-2), 70.9 (C-3a), 61.2 (C-3), 55.0 (C-7), 52.4 (OMe), 41.4 (C-2'), 28.4 (C-4), 24.0 (C-6), 23.1 (C-5), 17.8 (Me), 17.3 (Me); MS *m/z* 255 (24), 224 (2), 184 (6), 124 (90), 99 (43), 84 (52), 55 (38), 43 (100). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.02; H, 8.33; N, 5.41.

Reaction between nitrone **2** *and olefin* **8**

To a solution of nitrone **2** (prepared from *N*-hydroxypiperidine (743 mg, 7.35 mmol) and yellow HgO (4.780 g, 22.06 mmol)) in CH_2Cl_2 (25 mL) was added a solution of ethyl (*E*)-4-oxo-4-phenyl-2-butenoate, **8**, (1.00 g, 4.90 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at rt for 16 h following its evolution by tlc (hexane-EtOAc 3:1). Flash chromatography of the crude material using hexane-EtOAc (from 3:1 to 1:1) as eluent afforded the following fractions: (i) 573 mg (1.89 mmol, 39% yield) of ethyl (2*RS*,3*RS*,3a*RS*)-2-benzoylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **17A**, as a solid; (ii) 457 mg (1.51 mmol, 31% yield) of its (2*RS*,3*RS*,3a*SR*)- isomer, **17B**, as a solid; (iii) 121 mg (0.40 mmol, 8% yield) of ethyl (2*RS*,3*RS*,3a*RS*)-3-benzoylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate, **17C**, as a colorless oil; and (iv) 50 mg (0.16 mmol, 3% yield) of its (2*RS*,3*RS*,3a*SR*)- isomer, **17D**, as a colorless oil. **17A**: mp 110-2 °C (ethyl acetate-hexane); IR (KBr) 2943, 2857, 1733, 1689 cm^{-1}; ^{1}H NMR (250 MHz) (*ca.* 80% *trans*-invertomer) δ 8.03 (d, J = 7.3 Hz, 2 H, Ph), 7.54 (t, J = 7.3 Hz, 1 H, Ph), 7.43 (t, J = 7.3 Hz, 2 H, Ph), 5.39 (d, $J_{2,3}$ = 5.1 Hz, 1 H, H-2), 4.18 (q, J = 7.3 Hz, 2 H, OCH_2), 3.77 (dd, $J_{3,3a}$ = 9.9 Hz, $J_{3,2}$ = 5.1 Hz, 1 H, H-3), 3.36 (m, 1 H, H-7eq), 2.60-2.35 (m, 2 H, H-7ax, H-3a), 2.13 (br d, J ≈ 13.2 Hz, 1 H, H-4eq), 1.80-1.35 (m, 4 H, H-6eq, H-6ax, H-5eq, H-4ax), 1.25 (t, J = 7.3 Hz, 3 H, Me), 1.20 (m, 1 H, H-5ax); (*ca.* 20% *cis*-invertomer, observable signals) δ 5.55 (d, $J_{2,3} \approx$ 5.1 Hz, 1 H, H-2), 2.97 (m, 1 H, H-7); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 196.6 (C=O), 171.5 (C=O), 135.0/133.1/129.2/128.5 (Ph), 79.2 (C-2), 70.6 (C-3a), 61.2 (OCH_2), 55.1 (C-7), 53.1 (C-3), 28.8 (C-4), 24.2 (C-6), 23.2 (C-5), 14.3 (Me); (*cis*-invertomer, observable signals) δ 133.6, 83.6, 65.3, 51.8, 48.9, 24.5, 23.8, 18.7; MS *m/z* 303 (13), 258 (2), 198 (7), 105 (100), 99 (39), 77 (60). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.32; H, 7.03; N, 4.69. **17B**: mp 63-4 °C (ethyl acetate-hexane); IR (KBr) 2938, 2857, 1734, 1690, 1447 cm^{-1}; ^{1}H NMR (250 MHz) (*ca.* 90% *trans*-invertomer) δ 8.02 (d, J = 7.3 Hz, 2 H, Ph), 7.53 (t, J = 7.3 Hz, 1 H, Ph), 7.41 (t, J = 7.3 Hz, 2 H, Ph), 5.66 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 4.30-4.10 (m, 2 H, OCH_2), 3.74 (dd, $J_{3,3a}$ = 8.0 Hz,

$J_{3,2}$ = 4.8 Hz, 1 H, H-3), 3.51 (br d, J ≈ 9.5 Hz, 1 H, H-7eq), 2.52-2.35 (m, 2 H, H-7ax, H-3a), 2.01 (br d, J ≈ 12.1 Hz, 1 H, H-4eq), 1.78-1.50 (m, 3 H, H-6eq, H-6ax, H-5eq), 1.40-1.10 (m, 2 H, H-4ax, H-5ax), 1.24 (t, J = 7.3 Hz, 3 H, Me); (*ca.* 10% *cis*-invertomer, observable signals) δ 5.62 (d, $J_{2,3}$ = 5.5 Hz, 1 H, H-2), 3.35 (m, 1 H, H-7), 2.95 (m, 1 H, H-7); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 194.0 (C=O), 171.0 (C=O), 135.0/133.7/129.3/128.5 (Ph), 79.8 (C-2), 69.0 (C-3a), 61.0 (OCH_2), 55.5 (C-7), 51.8 (C-3), 26.9 (C-4), 24.3 (C-6), 23.4 (C-5), 14.2 (Me); (*cis*-invertomer, observable signals) δ 78.7 (C-2), 50.6 (C-7), 22.2/21.9/19.7 (C-6/C-5/C-4); MS *m/z* 303 (3), 258 (1), 198 (6), 131 (26), 105 (100), 99 (27), 77 (58), 41 (41). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.32; H, 7.01; N, 4.74. **17C**: IR (film) 2940, 2858, 2832, 1734, 1690, 1597 cm^{-1}; ^{1}H NMR (250 MHz) (*ca.* 95% *trans*-invertomer) δ 7.98 (d, J = 7.3 Hz, 2 H, Ph), 7.59 (t, J = 7.3 Hz, 1 H, Ph), 7.47 (t, J = 7.3 Hz, 2 H, Ph), 4.83 (d, $J_{2,3}$ = 5.7 Hz, 1 H, H-2), 4.43 (dd, $J_{3,3a}$ = 9.5 Hz, $J_{3,2}$ = 5.7 Hz, 1 H, H-3), 4.30-4.05 (m, 2 H, OCH_2), 3.55 (m, 1 H, H-7eq), 2.63-2.35 (m, 2 H, H-7ax, H-3a), 1.80-1.40 (m, 5 H, H-4eq, H-6eq, H-6ax, H-5eq, H-4ax), 1.23-1.05 (m, 1 H, H-5ax), 1.20 (t, J = 7.3 Hz, 3 H, Me); ^{13}C NMR (100 MHz) (*trans*-invertomer) δ 197.3 (C=O), 171.8 (C=O), 136.9/133.8/128.8/128.7 (Ph), 76.7 (C-2), 71.8 (C-3a), 61.5 (OCH_2), 58.0 (C-3), 55.3 (C-7), 28.7 (C-4), 24.2 (C-6), 23.2 (C-5), 14.1 (Me); MS *m/z* 303 (1), 131 (23), 198 (1), 105 (100), 99 (22), 77 (54), 41 (38). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.28; H, 7.03; N, 4.64. **17D**: IR (film) 2942, 2857, 2828, 1733, 1689, 1447 cm^{-1}; ^{1}H NMR (250 MHz) (*ca.* 50% *trans*- + *ca.* 50% *cis*-invertomer) δ 7.97 (m, 2 H, Ph), 7.57 (t, J = 7.3 Hz, 1 H, Ph), 7.45 (t, J = 7.3 Hz, 2 H, Ph), 5.25 (br s) + 5.18 (d, $J_{2,3}$ = 4.8 Hz) (1 H, H-2), 4.72 (br t, J ≈ 6.0 Hz) + 4.50 (br t, J ≈ 6.0 Hz) (1 H, H-3), 4.25-4.10 (m, 2 H, OCH_2), 3.78-3.50 (m) + 2.97 (br t, J ≈ 13.0 Hz) + 2.68 (br t, J ≈ 9.1 Hz) + 2.50 (br t, J ≈ 9.3 Hz) (3 H, 2 H-7, H-3a), 1.80-0.70 (m, 6 H, 2 H-6, 2 H-5, 2 H-4), 1.18 (t, J = 7.3 Hz, 3 H, Me); MS *m/z* 303 (2), 105 (100), 99 (32), 77 (46). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.20; H, 7.07; N, 4.59.

Reaction between nitrone **1** *and olefin* **9**

A solution of nitrone **1** (1.37 g, 16.1 mmol) and methyl (*E*)-2-methyl-4-oxo-2-pentenoate, **9**, (1.14 g, 8.01 mmol) in CH_2Cl_2 (38 mL) was stirred at rt for 14 d following its evolution by tlc (hexane-EtOAc 2:1). Removal of the solvent and flash chromatography using hexane-EtOAc (6:1) as eluent afforded the following fractions: (i) 51 mg (0.35 mmol, 4%) of starting olefin; and (ii) 1.52 g (6.7 mmol, 87% yield) of methyl (2*RS*,3*RS*,3a*RS*)-3-acetyl-2-methylhexahydropyrrolo[1,2-*b*]isoxazole-2-carboxylate, **18C**, as a colorless oil. **18C**: IR (film) 2956, 2875, 1733, 1713 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.14 (td, $J_{3a,3}$ = $J_{3a,4}$ = 7.1 Hz, $J_{3a,4}$ = 3.6 Hz, 1 H, H-3a), 3.80 (s, 3 H, OMe), 3.67 (d, $J_{3,3a}$ = 7.1 Hz, 1 H, H-3), 3.20 (dt, $J_{6,6}$ = 12.5 Hz, $J_{6,5}$ = $J_{6,5}$ = 7.1 Hz, 1 H, H-6), 3.01 (dt, $J_{6,6}$ = 12.5 Hz, $J_{6,5}$ = $J_{6,5}$ = 7.4 Hz, 1 H, H-6), 2.20 (s, 3 H, MeCO), 2.05-1.88 (m, 2 H, H-4, H-5), 1.73 (m, 1 H, H-5), 1.63 (m, 1 H, H-4), 1.38 (s, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 203.3 (C=O), 171.9 (C=O), 83.9 (C-2), 66.8 (C-3), 66.4 (C-3a), 55.7 (C-6), 52.4 (OMe), 30.6 (CH_3CO), 29.1 (C-4), 22.4 (C-5), 19.4 (Me); MS *m/z* 228 (M^++1, 100), 227 (37), 110 (29), 43 (92). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.11; H, 7.69; N, 6.15.

Reaction between nitrone **1** *and olefin* **10**

A solution of nitrone **1** (1.56 g, 18.4 mmol) and methyl (*E*)-3-methyl-4-oxo-2-pentenoate, **10**, (1.30 g, 9.2 mmol) in CH_2Cl_2 (43 mL) was stirred at rt for 14 d following its evolution by tlc (hexane-EtOAc 2:1).

Removal of the solvent and flash chromatography using hexane-EtOAc (6:1) as eluent afforded the following fractions: (i) 69 mg (0.48 mmol, 5%) of starting olefin; and (ii) 1.68 g (7.4 mmol, 86% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-acetyl-2-methylhexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **19A**, as a colorless oil. **19A**: IR (film) 2955, 2875, 1737, 1735 cm^{-1}; ^1H NMR (400 MHz) δ 4.13 (td, $J_{3a,3} = J_{3a,4} = 7.1$ Hz, $J_{3a,4} = 3.0$ Hz, 1 H, H-3a), 3.68 (s, 3 H, OMe), 3.35 (d, $J_{3,3a} = 7.1$ Hz, 1 H, H-3), 3.09 (ddd, $J_{6,6} = 13.0$ Hz, $J_{6,5} = 7.7$ Hz, $J_{6,5} = 5.3$ Hz, 1 H, H-6), 3.00 (ddd, $J_{6,6} = 13.0$ Hz, $J_{6,5} = 7.1$ Hz, $J_{6,5} = 6.5$ Hz, 1 H, H-6), 2.25 (s, 3 H, MeCO), 2.00-1.86 (m, 2 H, H-4, H-5), 1.78-1.62 (m, 2 H, H-5, H-4), 1.32 (s, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 206.1 (C=O), 170.1 (C=O), 88.7 (C-2), 68.0 (C-3a), 58.6 (C-3), 56.1 (C-6), 51.9 (OMe), 29.6 (C-4), 24.1 (CH_3CO), 22.9 (C-5), 18.6 (Me); MS *m/z* 228 (M^++1, 20), 227 (10), 110 (99), 43 (100). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.13; H, 7.44; N, 6.11.

Reaction between nitrone **2** *and olefin* **9**

To a solution of nitrone **2** (prepared from *N*-hydroxypiperidine (533 mg, 5.28 mmol) and yellow HgO (3.43 g, 15.8 mmol)) in CH_2Cl_2 (20 mL) was added a solution of methyl (*E*)-2-methyl-4-oxo-2-pentenoate, **9**, (500 mg, 3.52 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at rt for 18 h following its evolution by tlc (hexane-EtOAc 2:1). Flash chromatography of the crude material using hexane-EtOAc (2:1) as eluent afforded 771 mg (3.2 mmol, 91% yield) of methyl (2*RS*,3*RS*,3a*RS*)-3-acetyl-2-methylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate, **20C**, as a colorless oil. **20C**: ^1H NMR (400 MHz) δ 3.79 (s, 3 H, OMe), 3.58 (d, $J_{3,3a} = 10.5$ Hz, 1 H, H-3), 3.42 (m, 1 H, H-7eq), 2.66 (td, $J_{3a,3} = J_{3a,4ax} = 10.5$ Hz, $J_{3a,4eq} = 2.2$ Hz, 1 H, H-3a), 2.43 (ddd, $J_{7ax,6ax} = 12.1$ Hz, $J_{7ax,7eq} = 9.2$ Hz, $J_{7ax,6eq} = 3.1$ Hz, 1 H, H-7ax), 2.29 (s, 3 H, COMe), 1.80-1.65 (m, 2 H, H-4eq, H-6eq), 1.65-1.40 (m, 2 H, H-6ax, H-5eq), 1.30-1.15 (m, 2 H, H-4ax, H-5ax), 1.27 (s, 3 H, Me); ^{13}C NMR (100 MHz) δ 206.1 (C=O), 175.4 (C=O), 80.4 (C-2), 68.4 (C-3a), 64.0 (C-3), 55.1 (C-7), 53.3 (OMe), 31.9 ($COCH_3$), 27.8 (C-4), 24.0 (C-6), 22.9 (C-5), 20.4 (Me); MS *m/z* 242 (M^++1, 40), 241 (26), 198 (1), 124 (49), 99 (25), 43 (100). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.70; H, 7.98; N, 5.83.

Reaction between nitrone **2** *and olefin* **10**

To a solution of nitrone **2** (prepared from *N*-hydroxypiperidine (533 mg, 5.28 mmol) and yellow HgO (3.43 g, 15.8 mmol)) in CH_2Cl_2 (20 mL) was added a solution of methyl (*E*)-3-methyl-4-oxo-2-pentenoate, **10**, (500 mg, 3.52 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at rt for 18 h following its evolution by tlc (hexane-EtOAc 2:1). Flash chromatography of the crude material using hexane-EtOAc (2:1) as eluent afforded 766 mg (3.17 mmol, 90% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-acetyl-2-methylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **21A**, as a colorless oil. **21A**: ^1H NMR (400 MHz) δ 3.67 (s, 3 H, OMe), 3.39 (d, $J_{3,3a} = 9.6$ Hz, 1 H, H-3), 3.39 (m, 1 H, H-7eq), 2.67 (br t, $J \approx 9.9$ Hz, 1 H, H-3a), 2.48 (ddd, $J_{7ax,6ax} = 12.0$ Hz, $J_{7ax,7eq} = 9.1$ Hz, $J_{7ax,6eq} = 2.8$ Hz, 1 H, H-7ax), 2.23 (s, 3 H, COMe), 1.85 (m, 1 H), 1.73 (m, 1 H), 1.63 (m, 1 H), 1.54 (m, 1 H), 1.30-1.15 (m, 2 H), 1.19 (s, 3 H, Me); ^{13}C NMR (100 MHz) δ 212.5 (C=O), 171.4 (C=O), 86.4 (C-2), 70.0 (C-3a), 56.7 (C-3), 54.9 (C-7), 51.8 (OMe), 28.5 (C-4), 24.4 (C-6), 23.5 ($COCH_3$), 23.4 (C-5), 17.8 (Me); MS *m/z* 242 (M^++1, 39), 241 (13), 210 (1), 198 (10), 124 (66), 43 (100). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.71; H, 7.99; N, 5.80.

General procedure for the reduction of oxo cycloadducts with $NaBH_4$

To a solution of cycloadduct (1.0 mmol) in a mixture of CH_2Cl_2-MeOH (1:1) (5 mL) was added $NaBH_4$ (0.28 mmol), and the mixture was stirred for 30 min at rt. The reaction was quenched by adding saturated aqueous NH_4Cl solution and the solvents were removed under vacuum. To the crude residue were added CH_2Cl_2 and brine, and the organic solvent was dried and evaporated. Purification by flash chromatography provided the corresponding alcohols.

General procedure for the reduction of oxo cycloadducts with LTBA, L-Selectride®, or NB-Enantride®

To a cooled (-78 °C) solution of cycloadduct (1.0 mmol) in dry THF (7 mL) was added dropwise LTBA, or L-Selectride®, or NB-Enantride® (1.0 M in THF, 1.13 mmol) under argon. The mixture was stirred for 1 h at -78 °C and allowed to reach rt, then quenched by adding saturated aqueous NH_4Cl solution and the solvents were removed under vaccum. To the crude residue were added CH_2Cl_2 and brine, and the organic solvent was dried and evaporated. Purification by flash chromatography provided the corresponding alcohols.

Reduction of **11A** *with $NaBH_4$*

Purification by flash chromatography on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (1:2) as eluent afforded an inseparable mixture of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-1-hydroxyethyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **11Aa**, and its (2*RS*,3*RS*,3a*RS*,1'*RS*)- isomer, **11As**, as a colorless oil (88% yield) in a ratio 1:1.5. **11Aa** + **11As**: IR (film) 3383, 1736 cm^{-1}; MS *m/z* 216 (M^++1, 16), 215 (14), 86 (100), 85 (38). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.52; H, 8.09; N, 6.76. **11Aa** (from the mixture): ^1H NMR (400 MHz) δ 4.11 (dd, $J_{2,3}$ = 8.0 Hz, $J_{2,1'}$ = 3.7 Hz, 1 H, H-2), 3.95 (m, 1 H, H-1'), 3.87 (m, 1 H, H-3a), 3.70 (s, 3 H, OMe), 3.33 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 7.3 Hz, $J_{6,5}$ = 2.9 Hz, 1 H, H-6), 3.10 (dd, $J_{3,2}$ = 8.0 Hz, $J_{3,3a}$ = 5.1 Hz, 1 H, H-3), 2.92 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 9.5 Hz, $J_{6,5}$ = 7.3 Hz, 1 H, H-6), 2.45 (br s, 1 H, OH), 2.07-1.87 (m, 2 H, H-4, H-5), 1.87-1.55 (m, 2 H, H-4, H-5), 1.14 (d, $J_{Me,1'}$ = 6.6 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 172.7 (C=O), 84.6 (C-2), 70.1/66.0 (C-3a/C-1'), 56.5 (C-6), 54.1 (C-3), 52.2 (OMe), 30.5 (C-4), 23.6 (C-5), 18.7 (Me). **11As** (from the mixture): ^1H NMR (400 MHz) δ 4.02 (dd, $J_{2,3}$ = 8.8 Hz, $J_{2,1'}$ = 4.4 Hz, 1 H, H-2), 3.92 (m, 1 H, H-3a), 3.85 (m, 1 H, H-1'), 3.72 (s, 3 H, OMe), 3.33 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 7.3 Hz, $J_{6,5}$ = 2.9 Hz, 1 H, H-6), 3.06 (dd, $J_{3,2}$ = 8.8 Hz, $J_{3,3a}$ = 5.1 Hz, 1 H, H-3), 2.92 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 9.5 Hz, $J_{6,5}$ = 7.3 Hz, 1 H, H-6), 2.30 (br s, 1 H, OH), 2.07-1.87 (m, 2 H, H-4, H-5), 1.87-1.55 (m, 2 H, H-4, H-5), 1.24 (d, $J_{Me,1'}$ = 6.6 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) δ 172.0 (C=O), 84.1 (C-2), 69.5/67.0 (C-3a/C-1'), 56.6 (C-6), 55.6 (C-3), 52.2 (OMe), 30.8 (C-4), 23.6 (C-5), 20.1 (Me).

Reduction of **11A** *with LTBA*

Products **11Aa** and **11As** were obtained in 83% yield in a ratio 1.5:1 by flash chromatography purification on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (1:2) as eluent.

Reduction of **11A** *with L-Selectride®*

Products **11Aa** and **11As** were obtained in 86% yield in a ratio 1:4 by flash chromatography purification on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (1:2) as eluent.

Reduction of **12A** *with* $NaBH_4$

Purification by flash chromatography on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (from 1:1 to 1:2) as eluent afforded the following fractions: (i) 45 mg (0.13 mmol, 36% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-3-(benzyloxy)-1-hydroxypropyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **12Aa**, as a colorlesss oil; and (ii) 67 mg (0.20 mmol, 54% yield) of its (2*RS*,3*RS*,3a*RS*,1'*RS*)- isomer, **12As**, as a colorless oil. **12Aa**: IR (film) 3458, 1737 cm^{-1}; ^1H NMR (250 MHz) δ 7.35-7.20 (m, 5 H, Ph), 4.49 (s, 2 H, CH_2Ph), 4.16 (dd, $J_{2,3}$ = 8.0 Hz, $J_{2,1}$ = 5.1 Hz, 1 H, H-2), 3.93 (m, 1 H, H-1'), 3.85 (m, 1 H, H-3a), 3.70 (s, 3 H, OMe), 3.78-3.57 (m, 2 H, H-3'), 3.32 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 7.3 Hz, $J_{6,5}$ = 2.9 Hz, 1 H, H-6), 3.11 (dd, $J_{3,2}$ = 8.0 Hz, $J_{3,3a}$ = 5.1 Hz, 1 H, H-3), 3.01 (br s, 1 H, OH), 2.92 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 8.9 Hz, $J_{6,5}$ = 7.1 Hz, 1 H, H-6), 2.10-1.60 (m, 6 H, H-2', H-4, H-5); ^{13}C NMR (62.5 MHz) δ 172.3 (C=O), 137.9/128.3/127.6 (Ph), 83.8 (C-2), 73.3 (CH_2-Ph), 70.4/70.2 (C-3a/C-1'), 68.4 (C-3'), 56.5 (C-6), 55.3 (C-3), 52.2 (OMe), 33.1 (C-2'), 30.5 (C-4), 23.6 (C-5); MS *m/z* 336 (M^++1, 2), 335 (3), 244 (6), 91 (100). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.41; H, 7.79; N, 4.20. **12As**: IR (film) 3444, 1735 cm^{-1}; ^1H NMR (250 MHz) δ 7.30-7.20 (m, 5 H, Ph), 4.49 (s, 2 H, CH_2Ph), 4.08 (dd, $J_{2,3}$ = 8.8 Hz, $J_{2,1}$ = 2.9 Hz, 1 H, H-2), 3.95-3.88 (m, 2 H, H-3a, H-1'), 3.69 (s, 3 H, OMe), 3.77-3.57 (m, 2 H, H-3'), 3.33 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 7.3 Hz, $J_{6,5}$ = 2.9 Hz, 1 H, H-6), 3.20 (dd, $J_{3,2}$ = 8.8 Hz, $J_{3,3a}$ = 5.1 Hz, 1 H, H-3), 2.91 (ddd, $J_{6,6}$ = 13.2 Hz, $J_{6,5}$ = 8.8 Hz, $J_{6,5}$ = 7.3 Hz, 1 H, H-6), 2.65 (br s, 1 H, OH), 2.10-1.55 (m, 6 H, H-2', H-4, H-5); ^{13}C NMR (62.5 MHz) δ 172.2 (C=O), 138.0/128.4/127.7 (Ph), 83.3 (C-2), 73.2 (CH_2Ph), 69.3/68.8 (C-3a/C-1'), 68.2 (C-3'), 56.6 (C-6), 55.0 (C-3), 52.1 (OMe), 33.9 (C-2'), 30.7 (C-4), 23.7 (C-5); MS *m/z* 336 (M^++1, 4), 335 (4), 304 (2), 244 (7), 91 (100). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.32; H, 7.72; N, 4.19.

Reduction of **12A** *with LTBA*

Purification by flash chromatography on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (from 1:1 to 1:2) as eluent afforded the following fractions: (i) 20 mg (0.06 mmol, 47% yield) of **12Aa**; and (ii) 17 mg (0.05 mmol, 39% yield) of **12As**.

Reduction of **12A** *with L-Selectride®*

Purification by flash chromatography on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (from 1:1 to 1:2) as eluent afforded the following fractions: (i) 6 mg (0.02 mmol, 10% yield) of **12Aa**; and (ii) 46 mg (0.14 mmol, 74% yield) of **12As**.

Reduction of **14A** *with* $NaBH_4$

Purification by flash chromatography on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (3:1) as eluent afforded the following fractions: (i) 81 mg (0.35 mmol, 40% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-1-hydroxyethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate,[8] **14Aa**, as a colorlesss oil; and (ii) 97 mg (0.42 mmol, 48% yield) of its (2*RS*,3*RS*,3a*RS*,1'*RS*)- isomer,[8] **14As**, as a colorless oil.

Reduction of **15A** *with* $NaBH_4$

Purification by flash chromatography using hexane-EtOAc (3:1) as eluent afforded the following fractions: (i) 78 mg (0.22 mmol, 39% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-3-(benzyloxy)-1-

hydroxypropyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate,[8] **15Aa**, as a colorlesss oil; and (ii) 94 mg (0.27 mmol, 47% yield) of its (2*RS*,3*RS*,3a*RS*,1'*RS*)- isomer,[8] **15As**, as a colorless oil.

Reduction of **15A** *with LTBA*

Purification by flash chromatography using hexane-EtOAc (3:1) as eluent afforded the following fractions: (i) 21 mg (0.06 mmol, 21% yield) of **15Aa**; and (ii) 64 mg (0.18 mmol, 63% yield) of **15As**.

Reduction of **15A** *with L-Selectride®*

Purification by flash chromatography using hexane-EtOAc (3:1) as eluent afforded the following fractions: (i) 9 mg (0.03 mmol, 14% yield) of **15Aa**; and (ii) 44 mg (0.13 mmol, 69% yield) of **15As**.

Reduction of **15A** *with NB-Enantride®*

Purification by flash chromatography using hexane-EtOAc (3:1) as eluent afforded the following fractions: (i) 7 mg (0.02 mmol, 10% yield) of **15Aa**; and (ii) 35 mg (0.10 mmol, 52% yield) of **15As**.

Reduction of **14C** *with* $NaBH_4$

Purification by flash chromatography on silica gel (J. T. Baker 30-60 μm) using hexane-EtOAc (1:1) as eluent afforded the following fractions: (i) 41 mg (0.27 mmol, 38% yield) of methyl (2*RS*,3*SR*,3a*RS*)-2-[(1*RS*)-1-hydroxyethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate, **22**, as a colorlesss oil; and (ii) 50 mg (0.22 mmol, 46% yield) of its (2*RS*,3*SR*,3a*RS*,1'*SR*)- isomer, **23**, as a colorless oil. **22**: IR (film) 3453, 2943, 1738 cm^{-1}; ^1H NMR (400 MHz, 250 K) (*ca.* 95% *trans*-invertomer) δ 4.24 (d, $J_{2,3}$ = 5.7 Hz, 1 H, H-2), 4.02 (m, 1 H, H-1'), 3.75 (s, 3 H, OMe), 3.52 (m, 1 H, H-7eq), 2.55-2.46 (m, 2 H, H-7ax, H-3), 2.17 (ddd, $J_{3a,4}$ = 11.3 Hz, $J_{3a,3}$ = 9.4 Hz, $J_{3a,4}$ = 2.2 Hz, 1 H, H-3a), 2.07 (m, 1 H, H-4), 1.90 (br s, 1 H, OH), 1.80-1.62 (m, 3 H, 2 H-6, H-5), 1.42 (m, 1 H, H-4), 1.28 (d $J_{Me,1'}$ = 6.5 Hz, 3 H, Me), 1.12 (m, 1 H, H-5); (*ca.* 5% *cis*-invertomer, observable signals) δ 4.43 (d, $J_{2,3}$ = 5.6 Hz, 1 H, H-2), 3.95 (m, 1 H, H-1'), 3.38 (m, 1 H, H-3a), 3.15 (m, 1 H, H-7), 3.02 (m, 1 H, H-7), 1.25 (d, $J_{Me,1'}$ = 6.3 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 172.3 (C=O), 75.6 (C-2), 69.8 (C-3a), 68.2 (C-1'), 58.5 (C-3), 55.4 (C-7), 52.5 (OMe), 29.7 (C-4), 24.4 (C-6), 23.5 (C-5), 21.9 (Me); MS *m/z* 229 (11), 99 (100). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.39; H, 8.19; N, 5.94. **23**: IR (film) 3453, 2943, 1741, 1439 cm^{-1}; ^1H NMR (400 MHz, 250 K) (*ca.* 95% *trans*-invertomer) δ 4.47 (d, $J_{2,3}$ = 5.6 Hz, 1 H, H-2), 3.88 (m, 1 H, H-1'), 3.79 (s, 3 H, OMe), 3.52 (m, 1 H, H-7eq), 2.48 (ddd, $J_{7ax,6ax}$ = 12.0 Hz, $J_{7ax,7eq}$ = 9.1 Hz, $J_{7ax,6eq}$ = 2.9 Hz, 1 H, H-7ax), 2.40 (ddd, $J_{3,3a}$ = 9.4 Hz, $J_{3,1'}$ = 6.5 Hz, $J_{3,2}$ = 5.6 Hz, 1 H, H-3), 3.50 (br d, J = 4.4 Hz, 1 H, OH), 2.05 (ddd, $J_{3a,4}$ = 11.2 Hz, $J_{3a,3}$ = 9.4 Hz, $J_{3a,4}$ = 2.1 Hz, 1 H, H-3a) 1.97 (m, 1 H, H-4), 1.80-1.60 (m, 3 H, 2 H-6, H-5), 1.38 (m, 1 H, H-4), 1.26 (d, $J_{Me,1'}$ = 6.6 Hz, 3 H, Me), 1.20 (m, 1 H, H-5); (*ca.* 5% *cis*-invertomer, observable signals) δ 4.65 (d, $J_{2,3}$ = 5.0 Hz, 1 H, H-2), 4.04 (m, 1 H, H-1'), 3.25 (m, 1 H, H-3a), 3.20 (m, 1 H, H-7), 3.02 (m, 1 H, H-7), 1.20 (d, $J_{Me,1'}$ = 6.5 Hz, 3 H, Me); ^{13}C NMR (62.5 MHz) (*trans*-invertomer) δ 172.3 (C=O), 76.0 (C-2), 69.0 (C-1'), 67.5 (C-3a), 59.1 (C-3), 55.2 (C-7), 52.5 (OMe), 28.6 (C-4), 24.2 (C-6), 23.4 (C-5), 22.7 (Me); MS *m/z* 229 (13), 99 (100). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.56; H, 8.40; N, 6.24.

Reduction of **14C** *with LTBA*

Purification by flash chromatography using hexane-EtOAc (1:1) as eluent afforded the following fractions: (i) 11 mg (0.05 mmol, 36% yield) of **22**; and (ii) 13 mg (0.06 mmol, 44% yield) of **23**.

Reduction of **14C** *with L-Selectride®*

Purification by flash chromatography using hexane-EtOAc (1:1) as eluent afforded the following fractions: (i) 8 mg (0.03 mmol, 23% yield) of **22**; and (ii) 19 mg (0.08 mmol, 54% yield) of **23**.

Reduction of **15C** *with* $NaBH_4$

Purification by chromatography using hexane-EtOAc (1:1) as eluent afforded the following fractions: (i) 35 mg (0.10 mmol, 40% yield) of methyl (2*RS*,3*SR*,3a*RS*)-2-[(1*RS*)-3-(benzyloxy)-1-hydroxypropyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate, **24**, as a colorless oil; and (ii) 34 mg (0.10 mmol, 40% yield) of its (2*RS*,3*SR*,3a*RS*,1'*SR*)- isomer, **25**, as a colorless oil. **24**: IR (film) 3499, 1734 cm^{-1}; ^1H NMR (400 MHz) δ 7.40-7.26 (m, 5 H, Ph), 4.50 (s, 2 H, CH_2Ph), 4.17 (d, $J_{2,3}$ = 5.3 Hz, 1 H, H-2), 3.99 (m, 1 H, H-1'), 3.75 (m, 1 H, H-3'), 3.75 (s, 3 H, OMe), 3.67 (m, 1 H, H-3'), 3.49 (m, 1 H, H-7), 3.44 (br s, 1 H, OH), 2.57-2.40 (m, 2 H, H-7, H-3), 2.27 (ddd, $J_{3a,4}$ = 11.7 Hz, $J_{3a,3}$ = 9.5 Hz, $J_{3a,4}$ = 2.1 Hz, 1 H, H-3a), 2.12 (m, 1 H, H-4), 1.92-1.81 (m, 2 H, H-2'), 1.78-1.53 (m, 3 H, 2 H-6, H-5), 1.40 (m, 1 H, H-4), 1.22 (m, 1 H, H-5); ^{13}C NMR (62.5 MHz) δ 173.3 (C=O), 137.4/128.4/127.7/127.6 (Ph), 75.7 (C-2), 73.4 (*C*H_2Ph), 72.9 (C-1'), 69.6 (C-3'), 69.5 (C-3a), 57.2 (C-3), 55.2 (C-7), 52.2 (OMe), 34.8 (C-2'), 29.8 (C-4), 24.3 (C-6), 23.4 (C-5); MS *m/z* 350 (M^++1, 7), 349 (5), 258 (77), 91 (100). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.39; H, 7.80; N, 4.01. Found: C, 65.38; H, 7.97; N, 4.02. **25**: IR (film) 3496, 2940, 1735 cm^{-1}; ^1H NMR (400 MHz, 250 K) (*ca.* 95% *trans*-invertomer) δ 7.40-7.26 (m, 5 H, Ph), 4.58 (d, $J_{2,3}$ = 5.3 Hz, 1 H, H-2), 4.52 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.49 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.03 (m, 1 H, H-1'), 3.94 (s, 1 H, OH), 3.81 (m, 1 H, H-3'), 3.78 (s, 3 H, OMe), 3.71 (td, $J_{3',3'}$ = $J_{3',2'}$ = 9.2 Hz, $J_{3',2'}$ = 3.3 Hz, 1 H, H-3'), 3.51 (m, 1 H, H-7), 2.52-2.43 (m, 2 H, H-7, H-3), 2.24 (ddd, $J_{3a,4}$ = 11.7 Hz, $J_{3a,3}$ = 9.5 Hz, $J_{3a,4}$ = 2.1 Hz, 1 H, H-3a), 1.98-1.92 (m, 2 H, H-4, H-2'), 1.75-1.65 (m, 4 H, H-2', 2 H-6, H-5), 1.35 (m, 1 H, H-4), 1.18 (m, 1 H, H-5); ^{13}C NMR (62.5 MHz) δ 173.3 (C=O), 137.5/128.4/127.8/127.7 (Ph), 74.5 (C-2), 73.5 (*C*H_2Ph), 69.7 (C-1'), 69.5 (C-3'), 68.3 (C-3a), 57.5 (C-3), 55.2 (C-7), 52.4 (OMe), 35.5 (C-2'), 28.4 (C-4), 24.4 (C-6), 23.4 (C-5); MS *m/z* 349 (22), 258 (67), 99 (100). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.39; H, 7.80; N, 4.01. Found: C, 65.48; H, 7.96; N, 4.01.

Reduction of **15C** *with LTBA*

Purification by flash chromatography using hexane-EtOAc (1:1) as eluent afforded the following fractions: (i) 13 mg (0.04 mmol, 36% yield) of **24**; and (ii) 18 mg (0.05 mmol, 46% yield) of **25**.

Reduction of **15C** *with L-Selectride®*

Purification by flash chromatography using hexane-EtOAc (1:1) as eluent afforded the following fractions: (i) 17 mg (0.05 mmol, 21% yield) of **24**; and (ii) 51 mg (0.15 mmol, 64% yield) of **25**.

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25. The *endo/exo* denomination refers always to the relative configuration of centers C-3/C-3a, independently of the substituent, ester or acyl, at C-3, that defines the regiochemistry. This denomination assists the discussion of the results.
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27. NOE experiments performed with the corresponding benzoates confirm the conformational preference and the assigned stereochemistries.