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1,3-Dipolar cycloadditions of cyclic nitrones to γ-bromo α,β-unsaturated esters and lactones

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Abstract

The 1,3-dipolar cycloaddition of cyclic nitrones to several γ-bromo α,β-unsaturated esters and lactones has been studied. All the reactions have shown high stereoselectivity, with a predominance of the *endo* or *exo* transition state for the *trans* or *cis* dipolarophiles, respectively.

Keywords: nitrones; olefins; cycloaddition; stereoselection

1. Introduction

Substituted isoxazolidines are versatile intermediates for the synthesis of polyfunctionalized compounds [1-3]. An effective way to prepare them is through the 1,3-dipolar cycloaddition of nitrones to olefins, which is often a highly regio- and stereoselective process. In particular, electron-deficient 1,2-disubstituted olefins lead to isoxazolidine adducts with the electron-withdrawing group attached to position 4, in agreement with the FMO theory [1,3-15]. The stereoselectivity depends on the electronic and steric factors influencing the relative energy of the competitive *endo* and *exo* transition states.

As part of a program on alkaloid synthesis, we have been interested in the reaction between five and six-membered cyclic nitrones and α,β-unsaturated esters and lactones with different degrees of functionality [7-15]. In some cases, a good leaving group at the allylic position was required for our synthetic purposes and therefore we examined the cycloadditions of 2,3,4,5-tetrahydropyridine 1-oxide, **1**, and 3,4-dihydro-2*H*-pyrrole 1-oxide, **2**, (Figure 1) to several γ-oxy and γ-thio dipolarophiles [10,12,14]. These reactions showed very high stereoselectivity, *E* olefins leading mainly to *endo* adducts and *Z* olefins to *exo* adducts. In the search for a good nucleofuge activity of the dipolarophile substituent, we had also performed the cycloadditions of nitrone **1** to methyl 6-bromosorbate, **3**, and to γ-bromo-α,β-hexenolide, **4**. The reaction with the lactone followed the expected general trend and an *exo* cycloadduct, **9**, (Figure 2) was obtained in 70% yield [10], but we were unable to isolate any cycloaddition product of the reaction with the bromo ester [16]. These previous observations let us to investigate the cycloadditions of nitrones **1** [17,18] and **2** [19] to other γ-bromo α,β-unsaturated esters and lactones. The results are described herein.

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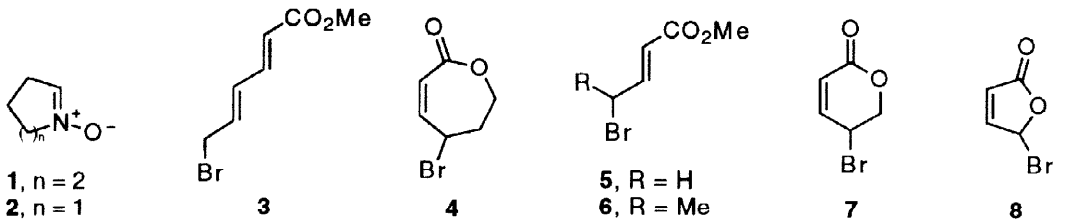

Figure 1

2. Results and discussion

Methyl (*E*)-4-bromo-2-butenoate, **5**, and methyl (*E*)-4-bromo-2-pentenoate, **6**, [20] were selected as *trans* dipolarophiles, 5-bromo-5,6-dihydro-2*H*-pyran-2-one, **7**, [21] and 5-bromo-2(5*H*)-furanone, **8**, [22] as *cis*. Table 1 shows the results of the cycloadditions of the allylic bromides **3-8** to the cyclic nitrones **1** and **2**. Nitrone **1** is more reactive than **2**, therefore when the dipolarophile was sufficiently active, the reactions of **1** were run under milder conditions. All the cycloadducts isolated in these reactions showed the expected regiochemistry. From the cycloaddition of nitrone **1** to the ester **5**, we obtained two isoxazolidines in 59% overall yield. The stereochemistry of the products was established considering the value of the coupling constant $J_{3,3a}$, which is 8.0 Hz for the major *endo* cycloadduct **10** and 9.9 Hz for the minor *exo* cycloadduct **11**, according with the *cis* or *trans* relationship between H_3 and H_{3a} respectively [11,12]. The *endo* transition state was hence favoured over the *exo*, as in many related precedents. This result indicates that the presence of a bromine atom in a terminal allylic position is not incompatible with the dipolar process or the reaction conditions. The cause for the negative results obtained in the attempted reaction of nitrone **1** with the bromosorbate **3** is probably related to a lack of chemoselectivity, leading to complex mixtures of 1:1 and 1:2 cycloadducts.

Table 1.
Cycloadditions of nitrones **1** and **2** to allylic bromo olefins **3-8**.

Nitrone	Olefin	Conditions	*endo* (yield)	*exo* (yield)	
1	**3**	$CHCl_3$, 60 °C, 18 h	-	-	[16]
1	**4**	toluene, 100 °C, 5 h	-	**9** (70%)	[10]
1	**5**	$CHCl_3$, 60 °C, 13 h	**10** (51%)	**11** (8%)	
1	**6**	$CHCl_3$, 60 °C, 19 h	**12** (57%), **13** (16%)	**14/15** (4%/5%)	
1	**7**	$CHCl_3$, 60 °C, 17 h	-	**16** (87%)	
1	**8**	CH_2Cl_2, rt, 7 d	**17** (27%)	**18** (17%)	
2	**5**	toluene, 100 °C, 14 h	**19** (54%)	**20** (10%)	
2	**6**	toluene, 100 °C, 24 h	**21** (51%), **22** (14%)	**23** (11%)	
2	**7**	toluene, 100 °C, 22 h	-	**24** (50%), **25** (6%)	

When nitrone **1** was reacted with the chiral ester **6**, we isolated four cycloadducts, **12-15**, in 82% total yield. Their *endo/exo* stereochemistry was determined as above according to the observed $J_{3,3a}$ value and again a clear preference for the *endo* transition states was encountered. Now, the presence of the allylic stereocenter in the dipolarophile accounts for

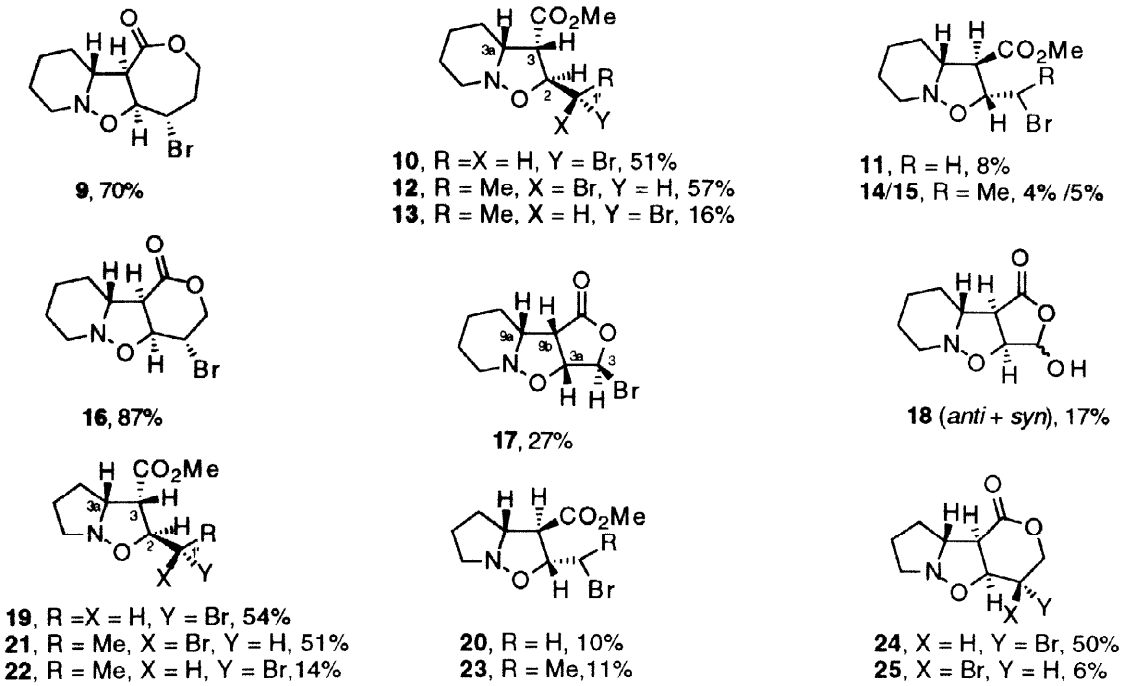

Figure 2

two possible geometries, *anti* or *syn*, for either the *endo* or *exo* approach of the reactants in the transition state. Unfortunately, the free rotation around the C_2-$C_{1'}$ bond prevents the assignment of the relative configuration of these two centers on the basis of the NMR data of each cycloadduct. We assume that the major *endo* diastereoisomer should come from an approach in which either the methyl group or the bromine atom are positioned *anti* to the incoming dipole. Then we can consider four different scenarios: **A** and **B**, leading to the *anti* cycloadduct, and **C** and **D**, leading to the *syn* cycloadduct (Figure 3). In **A** the methyl group is *anti*, while the bromine occupies the *inside* region, avoiding repulsive electrostatic interactions with the oxygen atom of the nitrone [23]. In **B** the bromine is *anti* and the methyl group is in the *outside* region, where the steric interactions are obviously smaller. The alternative approaches **C** and **D** would be less favored for electronic (**C**) or steric (**D**) reasons. We consequently assigned the *anti* configuration to the major product **12**.

The reaction of nitrone **1** with pentenolide **7** gave exclusively a product, **16**, in 87% yield. Due to the slow nitrogen inversion, its ^{1}H NMR spectrum presents two sets of signals in a ratio close to 3:2, corresponding to the *trans* and *cis* fused conformers of the perhydroisoxazole[2,3-*a*]pyridine system respectively [8], but, with the help of 2D experiments, the absorptions could be fully assigned. The *exo-anti* stereochemistry of **16** was determined through a NOESY experiment and is in agreement with previous results obtained with the hexenolide **4** [10].

In the reaction between nitrone **1** and butenolide **8**, we isolated a product (27% yield), whose NMR data match with the *endo-anti* cycloadduct **17**, when compared to other compounds with the same skeleton [7,8]. Diagnostic data for the *endo* stereochemistry are the clear predominance of the *trans* invertomer (>90%) in solution and the ^{13}C chemical shifts of the piperidine carbon atoms. The *anti* geometry of **17** is deduced from the value of $J_{3,3a}$ = 0 Hz, which denotes a *trans* relationship between H_3 and H_{3a}. From this reaction, we were

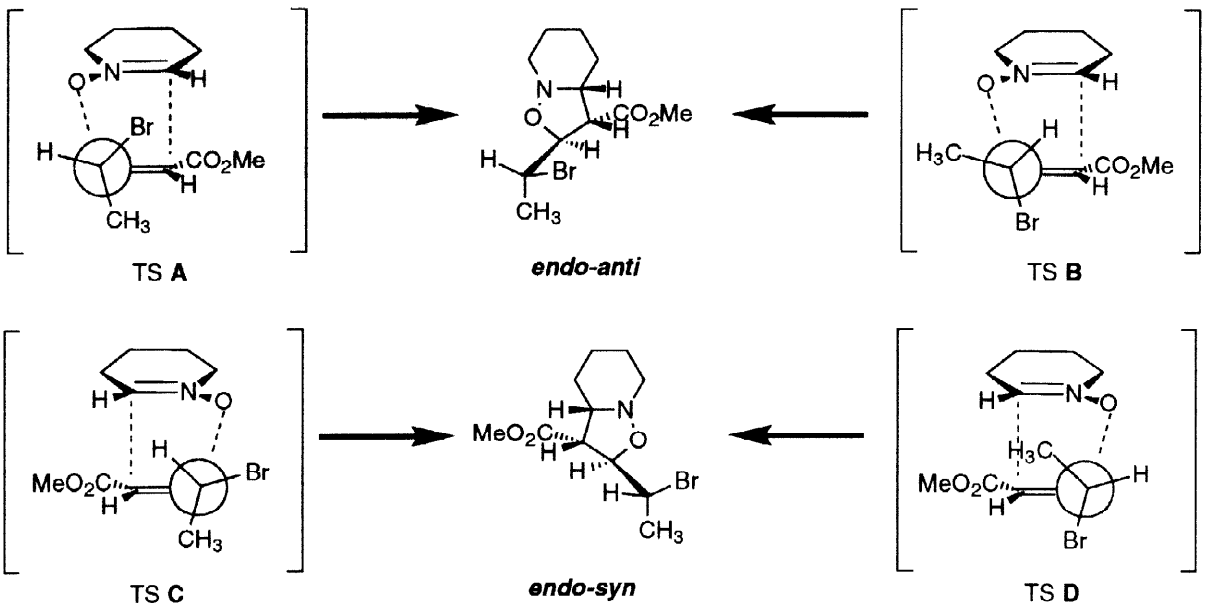

Figure 3

unable to isolate any bromo cycloadduct with *exo* stereochemistry. This result was surprising since in former cycloadditions of cyclic nitrones to butenolides the *exo* cycloadducts were always predominant over the *endo*. Nevertheless, in chromatographic fractions of higher polarity we detected a mixture of two diastereoisomeric products, to which we assigned the structure **18**. This assignment was based on the strong hydroxylic absorption observed in the IR spectrum and the presence of two signals at *ca* δ 100 in the ^{13}C NMR spectrum, corresponding to the pseudoacid carbon atom C_3, that is downfield shifted in around 15 ppm in relation to the corresponding carbon atom in the bromo adduct **17**. The *exo* stereochemistry of both compounds **18** (*anti* + *syn*) was evidenced by the predominance of the *cis* invertomer along with the chemical shift values shown by the carbon atoms of the piperidine ring [8]. We were not able to separate and purify each component of this mixture. The isolation of **17** as the unique bromo cycloadduct could be due to the easier hydrolysis of the *exo* bromo cycloadducts.

Next we performed the cycloadditions of the less reactive nitrone **2** with those bromo olefins that had rendered better results with nitrone **1** and we obtained very similar results. From the *trans* dipolarophiles, **5** and **6**, the *endo* cycloadducts, **19** and **21-22**, were clearly predominant over the *exo*, **20** and **23**, respectively. NOE experiments or the value of $J_{3,3a}$ (around 8 Hz for **19**, **21** and **22** and around 5 Hz for **20** and **23**) were used to asses the *endo* or *exo* stereochemistry. From the *cis* dipolarophile **7** only the *exo* derivatives were obtained, with a prevalence of the *anti* isomer, **24**, over the *syn*, **25**. In spite of its lower reactivity, nitrone **2** has showed a lower facial differentiation toward the chiral pentenolide **7** than nitrone **1**, this is probably due to the higher planarity of the former nitrone.

In conclusion, the allylic bromo dipolarophiles have proved as liable partners for the cycloaddition reaction to nitrones, with the exception of the labile γ-bromobutenolide **8**. The stereoselectivity observed with these olefins follows the same trend as with the related γ-oxy derivatives, namely a clear preference is evidenced for the *endo* or *exo* transition state depending on the *E* or *Z* configuration of the dipolarophile, respectively.

3. Experimental

The following products were prepared according to previously described methods: **1** [17,18], **2** [19], **6** [20], **7** [21], **8** [22]. Compound **5** is commercially available. 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. 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.

*Cycloaddition of nitrone **1** to olefin **5***

To a solution of *N*-hydroxypiperidine (435 mg, 4.3 mmol) in $CHCl_3$ (12 ml) at 0 °C, yellow HgO (2.07 g, 9.6 mmol) was added in one portion. After five minutes the ice bath was removed and the mixture was stirred at room temperature for 2 h. Then, additional HgO (0.5 g, 2.3 mmol) was added, and after 2 h, the mixture was filtered through washed *celite*. The filtrate was transferred to a 50 ml round-bottomed flask fitted with a reflux condenser and olefin **5** (786 mg, 4.39 mmol) was added in one portion. The mixture was stirred at 60 °C for 13 h, cooled down to room temperature and the solvent was evaporated. The residue was purified by flash chromatography using hexane-AcOEt 4:1 as eluent, yielding the following fractions: (i) 92 mg (0.33 mmol, 8%) of methyl (2*RS*,3*RS*,3a*RS*)-2-bromomethylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **11**; (ii) 608 mg (2.2 mmol, 51%) of its (2*RS*,3*RS*,3a*SR*)-isomer, **10**, both as colorless oils. **10**: IR (film): 2948, 1739, 1438 cm^{-1}; ^{1}H NMR (250 MHz): δ 4.48 (q, $J_{2,1'}\approx J_{2,3}\approx 5.1$ Hz, 1H: H_2), 3.58 (s, 3H: OCH_3), 3.34 (m, 3H: $2H_{1'}$ and H_{7eq}), 3.03 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=4.4$ Hz, 1H: H_3), 2.32 (m, 2H: H_{3a} and H_{7ax}), 1.81 (br d, J=7.3 Hz, 1H: H_{4eq}), 1.60-1.06 (m, 5H: H_{4ax}, $2H_5$, and $2H_6$); ^{13}C NMR (62.5 MHz): δ 170.8 (CO_2CH_3), 76.7 (C_2), 68.8 (C_{3a}), 55.0/54.4 (C_3/C_7), 51.5 (OCH_3), 32.4 ($C_{1'}$), 26.3 (C_4), 23.8 (C_6), 23.0 (C_5); MS (CI, NH_3) (*m/z*) 280-278 (M^++1, 100-100). Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; N, 5.04. Found: C, 43.30; H, 5.70; N, 4.99. **11**: IR (film): 2947, 1740, 1437 cm^{-1}; ^{1}H NMR (250 MHz): δ 4.45 (q, $J_{2,1'}\approx J_{2,3}\approx 5.8$ Hz, 1H: H_2), 3.69 (s, 3H: OCH_3), 3.54 (dd, $J_{gem}=10.2$ Hz, $J_{1',2}\approx 6.6$ Hz, 1H: $H_{1'}$), 3.34 (m, 2H: H_{7eq} and $H_{1'}$), 2.80 (dd, $J_{3,3a}=9.9$ Hz, $J_{3,2}=5.5$ Hz, 1H: H_3), 2.40 (m, 2H: H_{3a} and H_{7ax}), 2.03 (br d, J=13.1 Hz, 1H: H_{4eq}), 1.78-1.10 (m, 5H: H_{4ax}, $2H_5$, and $2H_6$); ^{13}C NMR (62.5 MHz): δ 171.3 (CO_2CH_3), 77.9 (C_2), 70.9 (C_{3a}), 57.9 (C_7), 54.9 (C_3), 52.2 (OCH_3), 34.4 ($C_{1'}$), 28.6 (C_4), 24.3 (C_6), 23.1 (C_5); MS (CI, NH_3) (*m/z*) 280-278 (M^++1, 100-98). Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; N, 5.04. Found: C, 43.07; H, 5.78; N, 4.93.

*Cycloaddition of nitrone **1** to olefin **6***

Olefin **6** (628 mg, 3.25 mmol) was added to a solution of nitrone **1** prepared from 642 mg (6.36 mmol) of *N*-hydroxypiperidine and 3.43 g of HgO in $CHCl_3$ (20 ml). The mixture was heated at 60 °C for 19 h, cooled down to room temperature and the solvent was

evaporated. The residue was purified by flash chromatography using hexane-AcOEt 4:1 as eluent, yielding the following fractions: (i) 38 mg (0.13 mmol, 4%) of methyl (2*RS*,3*RS*,3a*RS*,1'*RS*)/(2*RS*,3*RS*,3a*RS*,1'*SR*)-2-(1-bromoethyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, **14/15**; (ii) 45 mg (0.15 mmol, 5%) of **15/14**; (iii) 540 mg (1.9 mmol, 57%) of the (2*RS*,3*RS*,3a*SR*,1'*SR*)-isomer, **12**; (iv) 156 mg (0.53 mmol, 16%) of the (2*RS*,3*RS*,3a*SR*,1'*RS*)-isomer, **13**, all of them as colorless oils. **12**: IR (film): 2948, 1741, 1439 cm^{-1}; ^1H NMR (250 MHz) (major *trans*-invertomer): δ 4.32 (t, $J_{2,1'}\approx J_{2,3}\approx 5.8$ Hz, 1H: H_2), 4.01 (qn, $J_{1',2}\approx J_{1',2'}\approx 6.6$ Hz, 1H: $H_{1'}$), 3.63 (s, 3H: OCH_3), 3.36 (m, 1H: H_{7eq}), 3.12 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=5.1$ Hz, 1H: H_3), 2.36 (m, 2H: H_{3a} and H_{7ax}), 1.84 (m, 1H: H_{4eq}), 1.61 (d, $J_{2',1'}=6.6$ Hz, 3H: $3H_{2'}$), 1.60 (m, 3H), 1.12 (m, 2H); ^{13}C NMR (62.5 MHz): δ 171.4 (CO_2CH_3), 82.0 (C_2), 69.1 (C_{3a}), 55.3/54.4 (C_3/C_7), 51.7 (OCH_3), 49.2 ($C_{1'}$), 26.5 (C_4), 24.0 (C_6), 23.3 (C_5), 22.4 ($C_{2'}$); MS (CI, NH_3) (*m/z*) 294-292 (M^++1, 100-97). Anal. Calcd for $C_{11}H_{18}BrNO_3$: C, 45.22; H, 6.21; N, 4.79. Found: C, 45.39; H, 5.96; N, 4.69. **13**: IR (film): 2952, 1736, 1439 cm^{-1}; ^1H NMR (250 MHz): δ 4.49 (t, $J_{2,1'}\approx J_{2,3}\approx 4.4$ Hz, 1H: H_2), 4.16 (dd, $J_{1',2'}=6.6$ Hz, $J_{1',2}=4.4$ Hz, 1H: $H_{1'}$), 3.70 (s, 3H: OCH_3), 3.47 (m, 1H: H_{7eq}), 3.17 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=5.1$ Hz, 1H: H_3), 2.45 (m, 2H: H_{3a} and H_{7ax}), 1.92 (m, 1H: H_{4eq}), 1.61 (d, $J_{2',1'}=6.6$ Hz, 3H: $3H_{2'}$), 1.70 (m, 3H), 1.20 (m, 2H); ^{13}C NMR (62.5 MHz): δ 171.6 (CO_2CH_3), 81.2 (C_2), 69.4 (C_{3a}), 55.3/54.1 (C_3/C_7), 51.9 (OCH_3), 48.6 ($C_{1'}$), 26.7 (C_4), 24.2 (C_6), 23.5 (C_5), 21.7 ($C_{2'}$); MS (CI, NH_3) (*m/z*) 294-292 (M^++1, 100-98). Anal. Calcd for $C_{11}H_{18}BrNO_3$: C, 45.22; H, 6.21; N, 4.79. Found: C, 45.55; H, 5.74; N, 4.77. **14/15** (first eluted): IR (film): 2948, 1742, 1438 cm^{-1}; ^1H NMR (250 MHz): δ 4.30 (dd, $J_{2,1'}=10.2$ Hz, $J_{2,3}=5.1$ Hz, 1H: H_2), 4.03 (dq, $J_{1',2}=10.2$ Hz, $J_{1',2'}=6.6$ Hz, 1H: $H_{1'}$), 3.72 (s, 3H: OCH_3), 3.34 (m, 1H: H_{7eq}), 2.98 (dd, $J_{3,3a}=10.2$ Hz, $J_{3,2}=5.1$ Hz, 1H: H_3), 2.37 (m, 2H: H_{3a} and H_{7ax}), 2.02 (br d, J=12.4 Hz, 1H: H_{4eq}), 1.75 (d, $J_{2',1'}=6.6$ Hz, 3H: $3H_{2'}$), 1.80-1.13 (m, 5H: H_{4ax}, $2H_5$, $2H_6$); ^{13}C NMR (62.5 MHz): δ 171.9 (CO_2CH_3), 82.9 (C_2), 71.9 (C_{3a}), 59.2 (C_3), 55.1 (C_7), 52.3/51.9 ($OCH_3/C_{1'}$), 28.7 (C_4), 24.4 (C_6), 23.4/23.2 ($C_5/C_{2'}$); MS (CI, NH_3) (*m/z*) 294-292 (M^++1, 100-96). Anal. Calcd for $C_{11}H_{18}BrNO_3$: C, 45.22; H, 6.21; N, 4.79. Found: C, 45.34; H, 5.64; N, 4.56. **15/14** (second eluted): IR (film): 2945, 1736, 1438 cm^{-1}; ^1H NMR (250 MHz): δ 4.24 (m, 2H: H_2 and $H_{1'}$), 3.66 (s, 3H: OCH_3), 3.38 (m, 1H: H_{7eq}), 3.09 (t, $J_{3,3a}\approx J_{3,2}\approx 9.1$ Hz, 1H: H_3), 2.44 (m, 2H: H_{3a} and H_{7ax}), 1.87 (br d, J=12.4 Hz, 1H: H_{4eq}), 1.68 (d, J=5.8 Hz, 3H: $3H_{2'}$), 1.80-1.10 (m, 5H: H_{4ax}, $2H_5$, $2H_6$); ^{13}C NMR (62.5 MHz): δ 171.7 (CO_2CH_3), 81.7 (C_2), 71.8 (C_{3a}), 55.2/55.1 (C_3/C_7), 52.1 (OCH_3), 45.9 ($C_{1'}$), 28.5 (C_4), 24.4 (C_6), 23.3/22.9 ($C_5/C_{2'}$); MS (CI, NH_3) (*m/z*) 294-292 (M^++1, 99-100). Anal. Calcd for $C_{11}H_{18}BrNO_3$: C, 45.22; H, 6.21; N, 4.79. Found: C, 44.95; H, 6.11; N, 4.77.

*Cycloaddition of nitrone **1** to olefin **7***

Olefin **7** (882 mg, 4.98 mmol) was added to a solution of nitrone **1** prepared from 618 mg (6.12 mmol) of *N*-hydroxypiperidine and 3.21 g of HgO in $CHCl_3$ (20 ml). The mixture was heated at 60 °C for 17 h, cooled down to room temperature and the solvent was evaporated. The residue was purified by flash chromatography using hexane-AcOEt 1:1 as eluent, yielding 1.12 g (4.33 mmol, 87%) of (4*RS*,4a*RS*,10a*SR*,10b*SR*)-4-bromooctahydro-1*H*,3*H*-pyrano[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **16**, as a colorless oil: ^1H NMR (250 MHz) (*trans*-invertomer, 60%): δ 4.70 (d, $J_{gem}=12.2$ Hz, 1H: H_3), 4.48 (br d, $J_{4a,10b}=9.3$ Hz, 1H: H_{4a}), 4.32 (m, 1H: H_3), 4.10 (m, 1H: H_4), 3.48 (m, 1H: H_{7eq}), 3.20 (t,

$J_{10b,4a}\approx J_{10b,10a}\approx 9.3$ Hz, 1H: H_{10b}), 2.48 (m, 1H: H_{7ax}), 2.25 (m, 2H: H_{10a} and H_{10}), 2.00-1.45 (m, 4H: $2H_8$, H_9 and H_{10}), 1.25 (m, 1H: H_9); (*cis*-invertomer, 40%): δ 4.80 (m, 2H: H_3 and H_{4a}), 4.36 (m, 1H: H_4), 4.20 (m, 1H: H_3), 3.60 (m, 1H: H_{10a}), 3.45 (t, $J_{10b,4a}\approx J_{10b,10a}\approx 8.8$ Hz, 1H: H_{10b}), 3.10 (m, 1H: H_7), 2.73 (m, 1H: H_7), 2.00-1.45 (m, 6H: $2H_8$, $2H_9$ and $2H_{10}$); ^{13}C NMR (62.5 MHz): δ 168.0 (C_1), 78.4 ($^{trans}C_{4a}$), 77.5 ($^{cis}C_{4a}$), 70.1 ($^{trans}C_{10a}$), 67.6 (C_3), 65.3 ($^{cis}C_{10a}$), 55.1 ($^{trans}C_7$), 51.0/50.4 ($^{cis}C_7/^{trans}C_{10b}$), 48.1 ($^{cis}C_{10b}$), 43.1/41.7 ($^{cis}C_4/^{trans}C_4$), 28.9 ($^{trans}C_{10}$), 24.5/24.4/23.2/22.4 ($^{cis}C_8/^{trans}C_8/^{trans}C_9/^{cis}C_{10}$), 19.1 ($^{cis}C_9$); MS (CI, NH_3) (*m/z*) 278-276 (M^++1, 100-96). Anal. Calcd for $C_{10}H_{14}BrNO_3$: C, 43.50; H, 5.11; N, 5.07. Found: C, 42.98; H, 4.88; N, 4.77.

Cycloaddition of nitrone 1 to olefin 8

Olefin **8** (246 mg, 1.51 mmol) was added to a solution of nitrone **1** prepared from 354 mg (3.51 mmol) of *N*-hydroxypiperidine and 2.06 g of HgO in CH_2Cl_2 (15 ml). The mixture was stirred at room temperature for 7 days. The solvent was evaporated and the residue was purified by flash chromatography using hexane-AcOEt 2:1 as eluent, yielding the following fractions: (i) 107 mg (0.41 mmol, 27%) of (3*RS*,3a*SR*,9a*SR*,9b*RS*)-3-bromo-octahydro-1*H*-furo[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **17**, as a colorless oil; (ii) 52 mg (0.26 mmol, 17%) of a mixture of two diastereoisomeric pseudoacids, **18**. **17**: IR (film): 2946, 1808 cm^{-1}; ^{1}H NMR (250 MHz): δ 6.36 (s, 1H: H_3), 5.04 (d, $J_{3a,9b}$=6.6 Hz, 1H: H_{3a}), 3.49 (t, $J_{9b,3a}\approx J_{9b,9a}\approx 6.6$ Hz, 1H: H_{9b}), 3.44 (m, 1H: H_{6eq}), 2.45 (ddd, $J_{9a,9ax}$=11.9 Hz, $J_{9a,9b}$=6.6 Hz, $J_{9a,9eq}$=3.6 Hz, 1H: H_{9a}), 2.39 (ddd, $J_{6ax,7ax}$=12.2 Hz, J_{gem}=9.4 Hz, $J_{6ax,7eq}$=2.8 Hz, 1H: H_{6ax}) 2.07 (m, 1H: H_{9eq}), 1.80-1.20 (m, 5H: $2H_7$, $2H_8$, H_9); ^{13}C NMR (62.5 MHz): δ 171.9 (C_1), 84.4/84.2 (C_3/C_{3a}), 68.5 (C_{9a}), 55.2 (C_6), 49.1 (C_{9b}), 25.6 (C_9), 24.2 (C_7), 23.0 (C_8); MS (CI, NH_3) (*m/z*) 264-262 (M^++1, 91-100). Anal. Calcd for $C_9H_{12}BrNO_3$: C, 41.24; H, 4.61; N, 5.34. Found: C, 41.50; H, 4.48; N, 5.00. **18**: IR (film): 3376 (br), 2943, 1769 cm^{-1}; ^{13}C NMR (62.5 MHz): δ 176.4 and 174.8 (C_1), 103.3 and 99.2 (C_3), 81.4 and 74.7 (C_{3a}), 63.7 and 62.9 (C_{9a}), 54.9 and 53.8 (C_6), 50.1 (C_{9b}), 25.7 and 25.2 (C_9), 22.4 and 21.6 (C_7), 19.5 and 18.7 (C_8).

Cycloaddition of nitrone 2 to olefin 5

Olefin **5** (268 mg, 1.50 mmol) was added to a solution of nitrone **2** (318 mg, 3.74 mmol) in toluene (30 ml) and the mixture was stirred at 100 °C for 14 h. Then, it was cooled down to room temperature and the solvent was evaporated. The residue was purified by flash chromatography using hexane-AcOEt 1:1 as eluent, yielding the following fractions: (i) 214 mg (0.81 mmol, 54%) of (2*RS*,3*RS*,3a*SR*)-2-methylhexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **19**; (ii) 41 mg (0.16 mmol, 10%) of its (2*RS*,3*RS*,3a*RS*)-isomer, **20**, both as colorless oils. **19**: IR (film): 2954, 1738, 1438 cm^{-1}; ^{1}H NMR (250 MHz): δ 4.55 (q, $J_{2,1'}\approx J_{2,3}\approx 6.0$ Hz, 1H: H_2), 3.87 (q, $J_{3a,3}\approx J_{3a,4}\approx 7.8$ Hz, 1H: H_{3a}), 3.71 (s, 3H: OCH_3), 3.59 (t, $J_{3,3a}\approx J_{3,2}\approx 7.3$ Hz, 1H: H_3), 3.50 (d, $J_{1',2}$=5.8 Hz, 2H: $2H_{1'}$), 3.31 (ddd, J_{gem}=13.9 Hz, $J_{6,5}$=8.0 Hz, $J_{6,5}$=4.4 Hz, 1H: H_6), 3.06 (dt, J_{gem}=13.9 Hz, $J_{5,6}$=7.3 Hz, 1H: H_6), 2.01-1.52 (m, 4H: $2H_4$, $2H_5$); ^{13}C NMR (62.5 MHz): δ 170.4 (CO_2CH_3), 76.7 (C_2), 68.2 (C_{3a}), 56.6 (C_6), 55.8 (C_3), 52.1 (OCH_3), 33.5 ($C_{1'}$), 26.9 (C_4), 24.1 (C_5); MS (CI, NH_3) (*m/z*) 266-264 (M^++1, 100-90). Anal. Calcd for $C_9H_{14}BrNO_3$: C, 40.93; H, 5.34; N, 5.30. Found: C, 41.05; H, 5.48; N, 5.05. **20**: IR (film): 2955, 1740, 1438 cm^{-1}; ^{1}H NMR (250 MHz): δ 4.27 (dt,

$J_{2,3}$= 8.0 Hz, $J_{2,1'}$=3.7 Hz, 1H: H_2), 3.99 (dt, $J_{3a,4}$=8.0 Hz, $J_{3a,3}$=$J_{3a,4}$=5.1 Hz, 1H: H_{3a}), 3.72 (s, 3H: OCH_3), 3.70 (dd, J_{gem}=11.0 Hz, $J_{2,1'}$=3.7 Hz, 1H: $H_{1'}$), 3.57 (dd, J_{gem}=11.0 Hz, $J_{2,1'}$=3.7 Hz, 1H: $H_{1'}$), 3.38 (m, 1H: H_6), 3.05 (dd, $J_{3,2}$=8.7 Hz, $J_{3,3a}$=5.1 Hz, 1H: H_3), 2.87 (ddd, J_{gem}=13.9 Hz, $J_{6,5}$=9.5 Hz, $J_{6,5}$=7.3 Hz, 1H: H_6), 2.15-1.65 (m, 4H: $2H_4$, $2H_5$); ^{13}C NMR (62.5 MHz): δ 171.2 (CO_2CH_3), 78.3 (C_2), 69.2 (C_{3a}), 57.7/56.9 (C_3/C_6), 52.3 (OCH_3), 32.0/31.3 ($C_{1'}$/C_4), 23.9 (C_5); MS (CI, NH_3) (*m/z*) 266-264 (M^++1, 100-97).

Cycloaddition of nitrone 2 to olefin 6

Olefin **6** (501 mg, 2.60 mmol) was added to a solution of nitrone **2** (530 mg, 6.31 mmol) in toluene (50 ml) and the mixture was stirred at 100 °C for 24 h. Then, it was cooled down to room temperature and the solvent was evaporated. The residue was purified by flash chromatography using hexane-EtAcO 1:1 as eluent, yielding the following fractions: (i) 316 mg (1.32 mmol, 51%) of (2*RS*,3*RS*,3a*SR*,1'*RS*)-2-(1-bromoethyl)hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate, **21**; (ii) 100 mg (0.36 mmol, 14%) of the (2*RS*,3*RS*,3a*SR*,1'*SR*)-isomer, **22**; (iii) 82 mg (0.30 mmol, 11%) of a (2*RS*,3*RS*,3a*RS*)-isomer, **23**, all of them as colorless oils. **21**: IR (film): 2953, 1742, 1438 cm^{-1}; ^1H NMR (400 MHz): δ 4.38 (dd, $J_{2,1'}$= 8.9 Hz, $J_{2,3}$=5.5 Hz, 1H: H_2), 4.04 (dq, $J_{1',2}$=8.9 Hz, $J_{1',2'}$=6.7 Hz, 1H: $H_{1'}$), 3.80 (q, $J_{3a,3}$=$J_{3a,4}$=7.7 Hz, 1H: H_{3a}), 3.71 (s, 3H: OCH_3), 3.68 (dd, $J_{3,3a}$=7.7 Hz, $J_{3,2}$=5.5 Hz, 1H: H_3), 3.32 (m, 1H: H_6), 3.00 (m, 1H: H_6), 2.04 (m, 1H: H_5), 1.72 (d, $J_{2',1'}$=6.7 Hz, 3H: $3H_{2'}$), 1.80-1.60 (m, 3H: $2H_4$, H_5); ^{13}C NMR (62.5 MHz): δ 171.0 (CO_2CH_3), 82.3 (C_2), 68.9 (C_{3a}), 56.8 (C_3), 56.0 (C_6), 52.1 (OCH_3), 51.0 ($C_{1'}$), 26.2 (C_4), 24.0 (C_5), 22.8 ($C_{2'}$); MS (CI, NH_3) (*m/z*) 280-278 (M^++1, 100-96). Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; N, 5.04. Found: C, 42.72; H, 5.44; N, 4.86. **22**: IR (film): 2953, 2874, 1739, 1438 cm^{-1}; ^1H NMR (400 MHz): δ 4.38 (dd, $J_{2,3}$=8.4 Hz, $J_{2,1'}$=4.5 Hz, 1H: H_2), 4.20 (qd, $J_{1',2'}$=7.1 Hz, $J_{1',2}$=4.5 Hz, 1H: $H_{1'}$), 3.88 (q, $J_{3a,3}$=$J_{3a,4}$=8.1 Hz, 1H: H_{3a}), 3.71 (s, 3H: OCH_3), 3.68 (t, $J_{3,2}$≈$J_{3,3a}$≈8.0 Hz, 1H: H_3), 3.32 (m, 1H: H_6), 3.04 (dt, J_{gem}=13.1 Hz, $J_{6,5}$=7.3 Hz, 1H: H_6), 1.98 (m, 1H: H_5), 1.69 (d, $J_{2',1'}$=7.1 Hz, 3H: $3H_{2'}$), 1.85-1.52 (m, 3H: $2H_4$, H_5); ^{13}C NMR (62.5 MHz): δ 170.7 (CO_2CH_3), 80.7 (C_2), 68.4 (C_{3a}), 56.8 (C_3), 54.7 (C_6), 52.1 (OCH_3), 50.0 ($C_{1'}$), 26.9 (C_4), 24.1 (C_5), 22.0 ($C_{2'}$); MS (CI, NH_3) (*m/z*) 280-278 (M^++1, 100-95). Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; N, 5.04. Found: C, 42.58; H, 5.54; N, 5.18. **23**: IR (film): 2954, 1739 cm^{-1}; ^1H NMR (400 MHz): δ 4.28 (dd, $J_{2,3}$=7.7 Hz, $J_{2,1'}$=5.5 Hz, 1H: H_2), 4.22 (qd, $J_{1',2'}$=6.7 Hz, $J_{1',2}$=5.5 Hz, 1H: $H_{1'}$), 3.85 (m, 1H: H_{3a}), 3.66 (s, 3H: OCH_3), 3.35 (m, 1H: H_6), 3.08 (dd, $J_{3,2}$=7.7 Hz, $J_{3,3a}$=4.3 Hz, 1H: H_3), 2.91 (m, 1H: H_6), 2.02 (m, 2H: H_4, H_5), 1.86 (m, 1H: H_4), 1.75 (m, 1H: H_5), 1.67 (d, $J_{2',1'}$=6.7 Hz, 3H: $3H_{2'}$); ^{13}C NMR (62.5 MHz): δ 172.2 (CO_2CH_3), 84.0 (C_2), 70.6 (C_{3a}), 57.6 (C_3), 56.8 (C_6), 52.3 (OCH_3), 48.5 ($C_{1'}$), 30.7 (C_4), 23.8 (C_5), 22.5 ($C_{2'}$); MS (CI, NH_3) (*m/z*) 280-278 (M^++1, 100-97). Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; N, 5.04. Found: C, 43.01; H, 5.41; N, 5.09.

Cycloaddition of nitrone 2 to olefin 7

Olefin **7** (199 mg, 1.12 mmol) was added to a solution of nitrone **2** (240 mg, 2.86 mmol) in toluene (15 ml) and the mixture was stirred at 100 °C for 22 h. Then, it was cooled down to room temperature and the solvent was evaporated. The residue was purified by flash chromatography using hexane-AcOEt 1:1 as eluent, yielding the following fractions: (i) 146

mg (0.56 mmol, 50%) of (4*RS*,4a*RS*,9a*SR*,9b*SR*)-4-bromooctahydro-1*H*-pyrano[3,4-*d*]-pyrrolo[1,2-*b*]isoxazol-1-one, **24**; (ii) 18 mg (0.07 mmol, 6%) of the (4*RS*,4a*RS*,9a*SR*, 9b*RS*)-isomer, **25**, both as colorless oils. **24**: ^{1}H NMR (250 MHz): δ 4.85 (dd, J_{gem}=11.7 Hz, $J_{3,4}$=2.2 Hz, 1H: H_3), 4.62 (dd, $J_{4a,9b}$=8.0 Hz, $J_{4a,4}$=4.0 Hz, 1H: H_{4a}), 4.31 (dd, J_{gem}=11.7 Hz, $J_{3,4}$=3.6 Hz, 1H: H_3), 4.19 (m, 1H: H_4), 3.80 (td, $J_{9a,9}$=7.0 Hz, $J_{9a,9b}$=2.5 Hz, 1H: H_{9a}), 3.47 (dd, $J_{9b,4a}$=8.0 Hz, $J_{9b,9a}$=2.5 Hz, 1H: H_{9b}), 3.23 (ddd, J_{gem}=13.1 Hz, $J_{7,8}$=8.1 Hz, $J_{7,8}$=4.4 Hz, 1H: H_7), 2.97 (dt, J_{gem}=13.1 Hz, $J_{7,8}$=7.7 Hz, 1H: H_7), 2.13 (m, 1H: H_9), 1.99 (m, 1H: H_8), 1.73 (m, 2H: H_8, H_9); ^{13}C NMR (62.5 MHz): δ 168.8 (C_1), 77.9 (C_{4a}), 71.5 (C_{9a}), 68.0 (C_3), 56.1 (C_7), 52.6 (C_{9b}), 43.2 (C_4), 29.8 (C_9), 23.3 (C_8); MS (CI, NH_3) (*m/z*) 264-262 (M^++1, 99-100). Anal. Calcd for $C_9H_{12}BrNO_3$: C, 41.24; H, 4.61; N, 5.34. Found: C, 41.48; H, 4.46; N, 5.16. **25**: ^{1}H NMR (250 MHz): δ 4.81 (t, J_{gem}=$J_{3,4}$=10.2 Hz, 1H: H_3), 4.63 (m, 1H: H_{4a}), 4.30 (m, 2H: H_3, H_4), 3.96 (td, $J_{9a,9}$=7.0 Hz, $J_{9a,9b}$=2.2 Hz, 1H: H_{9a}), 3.42 (dd, $J_{9b,4a}$=7.3 Hz, $J_{9b,9a}$=2.2 Hz, 1H: H_{9b}), 3.31 (ddd, J_{gem}=13.1 Hz, $J_{7,8}$=8.0 Hz, $J_{7,8}$=5.1 Hz, 1H: H_7), 3.09 (dt, J_{gem}=13.1 Hz, $J_{7,8}$=7.3 Hz, 1H: H_7), 2.15 (m, 2H: H_8, H_9), 1.75 (m, 2H: H_8, H_9); ^{13}C NMR (62.5 MHz): δ 168.5 (C_1), 74.5 (C_{4a}), 72.3 (C_{9a}), 67.2 (C_3), 56.5 (C_7), 54.6 (C_{9b}), 42.5 (C_4), 29.9 (C_9), 23.5 (C_8); MS (CI, NH_3) (*m/z*) 264-262 (M^++1, 98-100).

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