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1,3-Dipolar Cycloadditions of 3,4,5,6-Tetrahydropyridine 1-Oxide to α,β-Unsaturated Lactones: Stereochemical Assignment and Conformational Analysis of the Products

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Abstract: We have investigated the 1,3-dipolar cycloaddition of nitrone **1** to seven, six, and five membered α,β-unsaturated lactones (**2**, **3**, and **4-6**) and 2,5-dihydrofuran, **18**. In all these reactions, *exo* adducts are obtained as major or exclusive products. To elucidate the stereochemistry of the obtained heterocyclic compounds, an accurate conformational analysis has been performed. Important differences in their conformational behavior in solution have been found as a function of the lactone ring size and the presence or absence of a carbonyl group. This study points out the existence of an attractive interaction between the nitrogen lone electron pair and a carbonyl group at a fitting distance, which induces the preference for the *cis* fusion of type **E** in the furanonic *exo* adducts (**10**, **12**, **13**, **15**, and **16**). In all the other cases, where this distance is too long (**7**, **8**,**9**, **11**, **14**) or no carbonyl group is present in the molecule (**20**), the *trans* invertomers predominate.

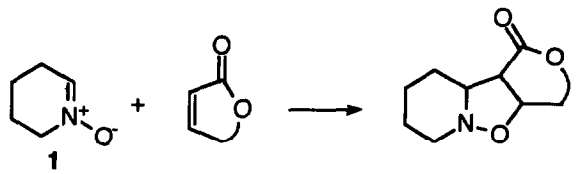
INTRODUCTION

The 1,3-dipolar cycloaddition reaction of nitrones to alkenes has found wide synthetic application in the preparation of nitrogen containing target molecules, mainly alkaloids.[1] One of the main advantages of employing such a type of concerted process is its ability to generate up to three new adjacent chiral centers in a stereospecific manner. The isoxazolidine cycloadducts formed in those reactions can be further elaborated to provide polyfunctionalized cyclic or acyclic chiral compounds with complete control of the relative stereochemistry.

Electron-deficient unsymmetrically 1,2-disubstituted olefins add regiospecifically to nitrones affording only isoxazolidines with the electron-withdrawing group attached to the 4-position.[1-9] In such cases, the interaction HOMO (nitrone)-LUMO (dipolarophile) dominates in the transition state, since the difference in steric demand between the two extremes of the double bond is negligible. There is only a very recent publication,[10] where the formation of regioisomeric cycloadducts is reported in some reactions, albeit in very low yields.

The stereochemical outcome of nitrone cycloadditions, *i.e.* the *endo*/*exo* selectivity, has been a matter of investigation for several groups.[3-11] For years, it has been generally accepted that secondary orbital interactions favor the *endo* mode of approach in the transition state and the formation of *exo* adducts has been explained on the basis of a predominance of steric factors over orbital interactions. However, in a recent communication, Gandolfi and col.,[11] based on semiempirical MO C-INDO calculations, state that "for cycloadditions involving nitrones and electron poor 1,2-disubstituted Z-dipolarophiles the *endo* form is destabilized by secondary

orbital overlaps involving the nitrogen atom in *ca.* 0.5 kcal mol^{-1} with respect to the *exo* orientation, whereas electrostatic effects appear to favor *endo* orientation". These stereochemical studies present two main problems: the *E/Z* isomerization of the starting nitrone and the difficulties associated to unambiguous assignment of the stereochemistry of the adducts. The use of cyclic nitrones, incapable of *E/Z* isomerization, allows one to relate directly the stereochemistry of the products to the *endo/exo* selectivity of the cycloadducts, if the reaction is conducted under kinetic control conditions.



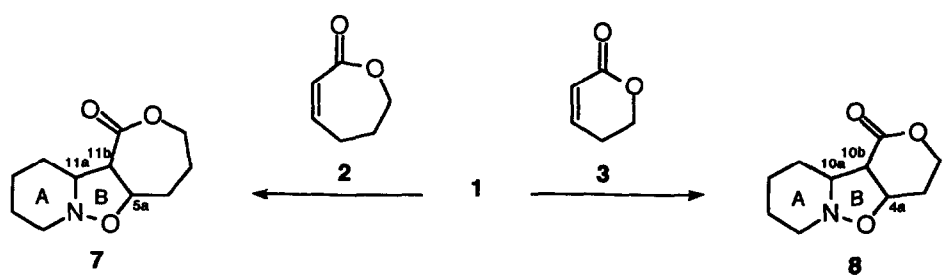
1

Equation 1

Our synthetic plans in the field of alkaloids required that we had some knowledge of the stereochemical course of the cycloaddition of 3,4,5,6-tetrahydropyridine 1-oxide, **1**, to some α,β-unsaturated lactones (Equation 1). To the best of our knowledge, at the begining of our work, only one example of 1,3-dipolar cycloaddition of a nitrone to an α,β-unsaturated lactone was published[12] and the stereochemistry of the cycloadduct was not indicated. Recently, a few other examples have appeared including our own research.[2,5,6,8,9,13] Coupling constant values have been usually considered as definitive to decide the relative stereochemistry of the cycloadducts, but the omission of a careful conformational analysis has often resulted in erroneous assignments.[8,14] For these reasons we undertook a systematic study of the reaction of nitrone **1** with five, six, and seven membered α,β-unsaturated lactones. The detailed investigation of the conformational behavior of the heterocyclic systems obtained in these cycloadditions, based on high field nmr techniques, has allowed us to unequivocally establish their stereochemistry and therefore to deduce the *endo/exo* selectivity of these reactions. When γ-substituted lactones were used as dipolarophiles, the diastereofacial (*i.e. syn/anti*) selectivity has been also determined. In this paper we report our full results in this field.

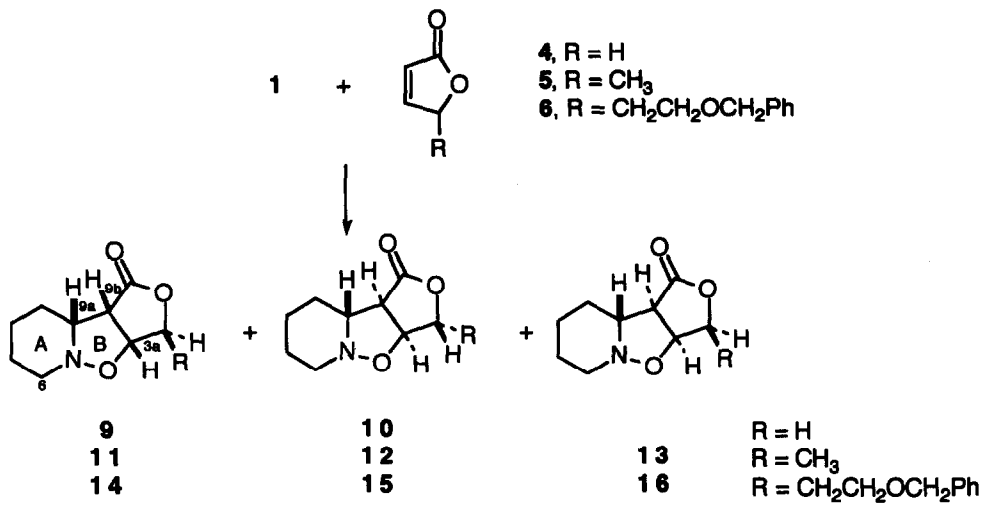
RESULTS AND DISCUSSION

For our purposes we have investigated the 1,3-dipolar cycloaddition of nitrone **1** to the following lactones: 6,7-dihydro-2(5*H*)-oxepinone, **2**, 5,6-dihydro-2-pyranone, **3**, 2(5*H*)-furanone, **4**, 5-methyl-2(5*H*)-furanone, **5**, and 5-(2-benzyloxy)ethyl-2(5*H*)-furanone, **6**, (Schemes 1 and 2). A first set of reactions were performed under mild temperature conditions to ensure a kinetic control with a good degree of diastereoselectivity. Then, the cycloadditions were repeated at higher temperatures in order to permit isolation of the minor adducts. Reaction conditions and yields are given in Table 1.



7 2 1 3 8

Scheme 1



Scheme 2

Cycloadditions to lactones **2** *and* **3**

The cycloaddition of nitrone **1**[15] to hexenolide **2**[16] at different temperatures (Table 1, entries 1-3) yielded in all cases a product, **7**, whose ^1H and ^{13}C nmr spectra in deuterochloroform at room temperature presented two sets of signals in a ratio 93:7.[6] Since warming the sample up to 322 K caused a collapse of most signals, each set was attributed to different conformers of a unique compound.

Table 1. Cycloadditions of Nitrone **1** to α,β -Unsaturated Lactones

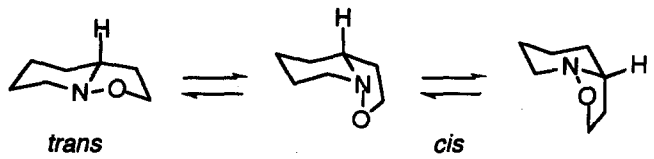
entry	lactone	solvent	T (°C)	time	yield (%)	*exo/endo*	*anti/syn*
1	**2**	$CHCl_3$	20	24d	31(59)[a]	b	-
2	**2**	$CHCl_3$	60	38h	46(91)[a]	b	-
3[6]	**2**	toluene	100	9h	59(79)[a]	b	-
4	**3**	CH_2Cl_2	20	13d	86	b	-
5	**3**	toluene	110	15h	85	b	-
6	**4**	$CHCl_3$	4	30d	90	31	-
7	**4**	toluene	110	15h	79	6	-
8[5]	**5**	$CHCl_3$	40	17h	73	21	8
9[5]	**5**	toluene	110	15h	84	7	2
10	**6**	$CHCl_3$	25	18d	70	c	10
11	**6**	toluene	110	9h	79	14	6

[a] yield considering recovered lactone
[b] only exo adduct was isolated
[c] only traces of endo adduct were detected

When pentenolide **3**[17] was used as dipolarophile (Table 1, entries 4 and 5) a sole product was isolated, **8**, which is the first example of an octahydro-1*H*,3*H*-pyrano[3',4':4,5]isoxazolo[2,3-*a*]pyridine system. The 400 MHz ^1H nmr spectrum of this compound in hexadeuteroacetone at room temperature showed broad

signals and no information could be derived from it. At 250 K the signals resolved in two separate sets in a ratio 2:1 and each set of data could be analysed separately.

The cycloadducts formed in these reactions contain in their structure the perhydroisoxazolo[2,3-*a*]pyridine system which may exist in solution as a mixture of a rigid *trans* and two flexible *cis* conformers, due to both nitrogen and six membered ring inversion processes (Equation 2).[18] This equilibrium is reflected in their nmr spectra. A detailed nmr study using 2D sequences (COSY and $^1H/^{13}C$ correlation) and nOe experiments was undertaken in order to assign the stereochemistry and obtain conformational information on compounds **7** and **8**; the most meaningful signals of the spectra could be associated to the corresponding nuclei.



Equation 2

For both, **7** and **8**, the absence of a doublet at $\delta \approx 5$ discards possible regioisomeric structures.[19] Tables 2 and 3 summarize the representative ^1H nmr data for each invertomer of adducts **7** and **8** respectively. The assignment of the signals corresponding to the major *trans* invertomer of **7** in $CDCl_3$ was already discussed in a preceeding paper.[6] For better comparison, the spectrum has now been repeated in d_6-acetone, which is a more appropriate solvent for low temperature measurements; in this solvent the *trans* invertomer predominates fivefold over the *cis*.

Table 2. Significant ^1H nmr Data (d_6-acetone, 298 K, 400 MHz) for Adduct **7**

	δH_3	δH_{5a}	δH_{8ax}	δH_{8eq}	δH_{11a}	δH_{11b}	$J_{11a,11b}$ (Hz)	% conf.
trans	4.17/4.31	4.12	2.37	3.27	2.49	3.46	9.5	83
cis	≈4.20/4.41	4.66	2.74/2.95		3.72	3.88	9.2	17

Table 3. Significant ^1H nmr Data (d_6-acetone, 250 K, 400 MHz) for Adduct **8**

	δH_3	δH_{4a}	δH_{7ax}	δH_{7eq}	δH_{10a}	δH_{10b}	$J_{10a,10b}$ (Hz)	% conf.
trans	4.25/4.40	4.35	2.43	3.32	2.22	3.03	10.3	66
cis	4.25/4.40	4.82	2.63/2.96		3.50	3.45	10.1	33

For the major invertomer of compound **8**, the expected double doublet corresponding to the α-carbonylic hydrogen H_{10b} is clearly observed at δ 3.03. In the COSY spectrum this signal correlates with absorptions at δ 4.35 and 2.22, which were consequently assigned to H_{4a} and H_{10a} respectively (see Table 3). The diastereotopic protons at C_3 resonate at δ 4.25 and 4.40, and those at C_7 at δ 2.43 and 3.32. All these assignments were corroborated by the $^1H/^{13}C$ correlation spectrum. In a similar way, the δ values of the minor invertomer were deduced starting from the double doublet at δ 3.45 due to H_{10b}. The chemical shift difference of *ca.* 1 ppm between the two protons at C_7 in the major invertomer indicates a rigid *trans* fusion for rings A and B, with the nitrogen lone pair *anti* to the axial H_7. In the *cis* invertomer, where these protons are not locked in a unique conformation, the chemical shift difference is much smaller.[20]

Cycloadditions to butenolides

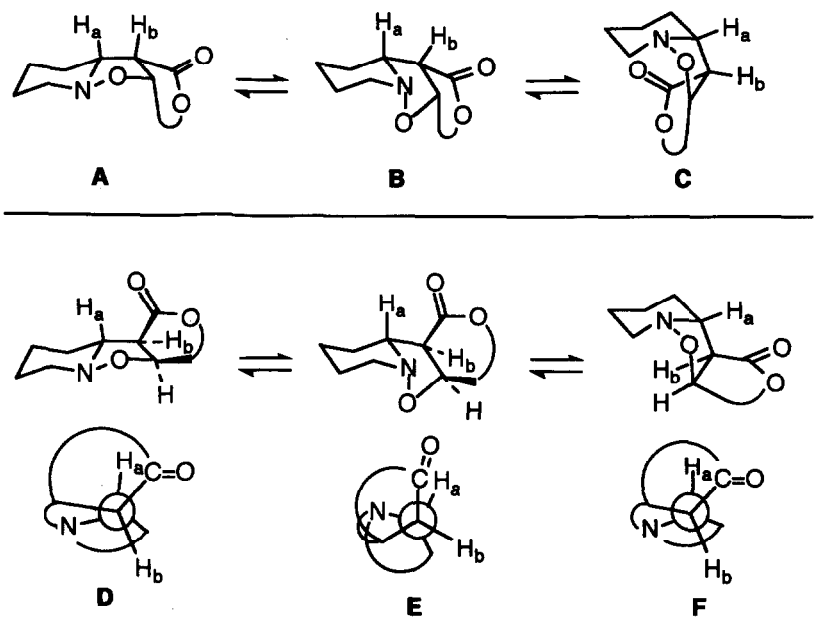
Lactones **4**[21] and **5**[22] were prepared according to literature procedures and butenolide **6** was synthesized from phenylselenoacetic acid and (2-benzyloxy)ethyloxirane[23] following our previously described method[24] in a 65% overall yield. This highly functionalized C_6 synthon has recently received much attention as a useful intermediate in organic synthesis.[25]

The cycloadditions of nitrone **1** to butenolides **4**, **5**, and **6** (Scheme 2) afforded in all cases, after flash column chromatography, two different fractions of diastereoisomeric cycloadducts.[5,9] The less polar fraction was always the minor one and it contained a unique isomer (**9**, **11**, and **14**; *vide infra* for their stereochemical assignment). For the reaction with **5**, repeated column chromatography of the more polar fraction, allowed the isolation of two isomeric cycloadducts, **12** and **13**, whereas for **6** only the major of the two isomers present in the more polar fraction, **15**, could be obtained in 95% purity.

Most nmr spectra of these fractions at room temperature show broad absorptions. By lowering the temperature, two separate sets of well resolved signals can be observed for the *trans* and *cis* invertomers. The conformational equilibrium position, along with significant chemical shift and coupling constant values for compounds **9**-**16** obtained on those cycloaddition reactions are given in Table 4. For the less polar compounds **9**, **11**, and **14** just the *trans* invertomer can be observed and in compounds **10**, **12**, **13**, **15**, and **16** the *cis* invertomer clearly predominates, as can be deduced from the chemical shift differences between the methylenic protons attached to C_6.

Stereochemical assignment

Once the *cis* or *trans* fusion was established for all the cycloadducts **7**, **8**, and **9**-**16**, the problem of assigning the *endo* or *exo* stereochemistry could be considered. The conformational analysis of these systems demonstrates that the value of the vicinal coupling constant J_{ab} between the α-nitrogen methynic proton H_a and the α-carbonylic proton H_b is definitive for the stereochemical assignment only in a few cases.



Equation 3

Table 4. Significant ^{1}H nmr Data (d_6-acetone, 400 MHz) for Adducts **9-16**

Comp.	T	A/B fusion	δ H_3	δ H_{3a}	δ H_{6ax}	δ H_{6eq}	δ H_{9a}	δ H_{9b}	$J_{9a,9b}$ (Hz)	$J_{3,3a}$ (Hz)	% conf
9	250	*trans*	4.18/4.56	4.95	2.37	3.36	2.37	3.47	6.7	6.6 and 2.2	>98
10	250	*trans*	4.29/4.51	4.79	2.49	3.36	2.17	3.32	8.4	5.5 and 1.1	25
		cis	4.24/4.54	5.02	3.00/3.25		3.42	3.31	**1.9**	5.9 and 1.6	75
11	253	*trans*	4.45	4.47	2.35	3.33	2.35	3.53	7.2	2.0	>98
12	253	*trans*	4.57	4.37	2.45	3.32	2.16	≈3.40	8.3	1.2	20
		cis	4.50	4.53	2.96/3.20		3.40	≈3.40	-	1.6	80
13	253	*trans*	-	4.63	2.48	-	2.15	-	8.0	5.2	15
		cis	4.70	4.77	2.92/-		-	3.36	-	5.4	85
14	250	*trans*	4.57	4.67	2.38	3.37	2.35	3.50	7.0	2.3	>98
15	270	*trans*	4.67	4.56	2.50	-	2.20	3.35	8.3	1.2	25
		cis	4.61	4.74	3.00/3.25		3.43	3.34	**2.0**	1.7	75
16	270	*cis*	4.79	4.87	2.96/-	-	3.42	-	-	5.0	-

Table 6. Significant ^{1}H nmr Data (d_6-acetone, 250 K, 400 MHz) for Adduct **20**

	δ H_1	δ $H_{1'}$	δ H_3	δ $H_{3'}$	δ H_{3a}	δ H_{6ax}	δ H_{6eq}	δ H_{9a}	δ H_{9b}	$J_{9a,9b}$ (Hz)	$J_{1,9b}$ (Hz)	$J_{1',9b}$ (Hz)	$J_{3,3a}$ (Hz)	$J_{3',3a}$ (Hz)	% conf
trans	3.82	3.36	3.78	3.29	4.48	2.32	3.23	1.81	2.70	9.0	0	5.5	0	4.0	68
cis	3.71	3.48	3.75	3.42	4.92	2.66/2.90		3.02	3.10	[a]	0	5.3	0	4.2	32

[a] J = 9.0 Hz, J' = 4.9 Hz, J'' = 2.4 Hz.

Thus, with the help of molecular models one can observe that in any of the three possible conformers (**A**, **B**, and **C**) of the *endo* adducts protons H_a and H_b are almost eclipsed. In conformers **D** and **F** of the *exo* adducts, these protons present a nearly antiperiplanar arrangement (Equation 3). Therefore, in all these five cases a large value of J_{ab} would be expected. By contrast, in conformation **E** of the *exo* adducts, the mentioned protons are almost orthogonal, implying a small coupling constant value. Consequently, only in the case that a J_{ab} in the range 0-2 Hz is observed in the spectrum of the *cis* invertomer, one can be certain that the stereochemistry is *exo* with a predominance of the **E** conformer over the **F**. Adducts **7** and **8** present for both *cis* and *trans* invertomers coupling constant values J_{ab} in the range 9-10 Hz (Tables 2 and 3) and therefore no information can be deduced from them. Decisive for the final stereochemical assignment of **7** as *exo* were the following observations:[6] i) presaturation of H_{11b} causes *ca.* 2% nOe effect on H_{11ax}; ii) the absence of nOe effect on H_{11b} from H_{11a}; iii) there is a 9% hetero-nOe effect on C_1 from H_{11a} (Figure 1). For compound **8** in the nOe difference spectrum there was a strong through-space polarization of H_{10b} (7.7%) and H_{4a} (7.7%) on irradiation of H_7 at δ 2.63. This result is only consistent with an *exo* adduct through the *cis* fused conformer **F**, occupying the presaturated proton the axial position (Figure 1).

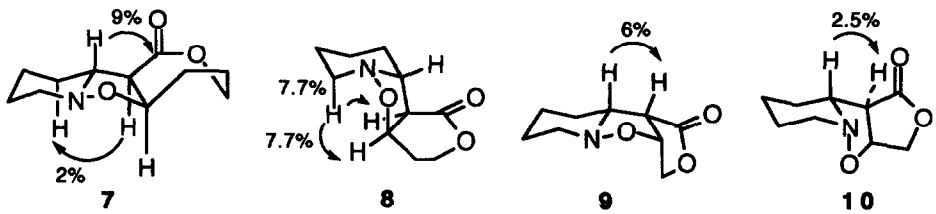


Figure 1. Observed nOe's in Cycloadducts **7**, **8**, **9**, and **10**.

In the ^1H nmr spectrum of compound **10**, the major invertomer presents a coupling constant $J_{9a,9b}$ = 1.9 Hz, and therefore its stereochemistry could be directly assigned as *exo*, conformer **E** being the most populated. Thus, the minor product **9** has to be the *endo* adduct. These assignments were reinforced by nOe experiments: presaturation of the signals corresponding to H_{9a} (δ 2.17 for **10**) caused a nOe effect on H_{9b} of 6 and 2.5% for compounds **9** and **10** respectively (Figure 1). The small nOe effect observed in adduct **10** can be explained through conformer **E** where H_a and H_b are nearly orthogonal.

For the rest of cycloadducts **11-16** with the same heterocyclic skeleton, only in the case of **15**, a small value of $J_{9a,9b}$ = 2.0 Hz was measurable, which demonstrates the *exo* stereochemistry of this adduct. The perfect matching observed for δH_{9a}, δH_{9b}, and $J_{9a,9b}$ in the series **9**, **11**, and **14**, and **10**, **12**, **13**, **15**, and **16** for both *cis* and *trans* invertomers (Table 4), indicates that the former have *endo* and the latter *exo* stereochemistry.

Other representative data can be obtained from the ^{13}C nmr spectra (Table 5): in *trans* conformers, C_9, C_{9a}, and C_{9b} are upfield shifted in *endo* with respect to *exo* adducts, due to their position relative to the pseudoaxial carbonyl group.[26]

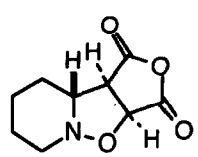
Compounds **11-16** present an additional stereochemical feature, namely the *cis-trans* relationship between protons H_3 and H_{3a}, which is a consequence of diastereofacial *syn* and *anti* approaches in the transition state respectively. This geometrical relationship can be directly deduced from $J_{3,3a}$: when these two protons are *trans* to each other a small value < 2.5 Hz is observed (compounds **11**, **12**, **14**, and **15**), while larger values are presented by the *cis* isomers (compounds **13** and **16**).[27]

Table 5. Significant ^{13}C nmr Data (100 MHz, δ) for Compounds **9-15** in their *trans* A/B Fusions

Comp.	Temp.	Solvent	C_9	C_{9a}	C_{9b}
9	298 K	d_6-acetone	26.5	68.9	50.5
10	260 K	d_6-acetone	29.5	71.9	53.7
11[5]	298 K	$CDCl_3$	25.9	68.6	51.0
12[5]	270 K	$CDCl_3$	28.5	70.4	53.1
13[5]	270 K	$CDCl_3$	28.9	71.2	-
14	298 K	d_6-acetone	26.8	69.1	51.4
15	250 K	d_6-acetone	29.5	71.7	54.0

Comparative conformational behavior

The nmr data of the tricyclic systems studied in this work reveal their distinct conformational behavior. In *endo* adducts only the *trans* invertomers are observed. That seems reasonable since both conformers of the *cis* invertomers are clearly more sterically hindered (see molecular models). Interestingly, in *exo* adducts the preference for the *trans* fused invertomer increases with the size of the lactone ring, as shown in Tables 2, 3, and 4. Moreover, of the two possible chair conformers of the *cis* invertomer, compounds **7** and **8** prefer the one depicted in **F**, as can be deduced from the large value of the coupling constant J_{ab} in their *cis* invertomers, while *exo* compounds with the five membered lactone show a clear predominance of the chair conformer **E**. In compounds **10** and **15** this is evidenced by the small $J_{9a,9b}$ value, and in **12**, **13**, and **16** by the previously discussed chemical shift correspondence with the former that denotes identical conformational biases. Now, a careful observation of molecular models shows that: i) the *trans* conformer **D** is more flattened, *i.e.* less sterically hindered than both *cis* conformers; ii) in *cis* conformers of type **E** the carbonyl group is closer to the lone electron pair at nitrogen than in conformers of type **F**. This proximity is especially relevant in the case of the five membered lactones, where the distance could be appropriate for the existence of an attractive interaction between the lone electron pair at nitrogen and the carbonyl group. We reasoned that, if this assumption was correct, an analogous heterocyclic system without the carbonyl group would probably behave similarly as the tricyclic systems **7** and **8**. On the other hand, the *exo* cycloadduct **17**, derived from nitrone **1** and maleic anhydride, having two carbonyl groups at suitable distances to interact with the nitrogen lone pair, should show still more preference for the *cis* conformer **E**, than the furanonic cycloadducts.

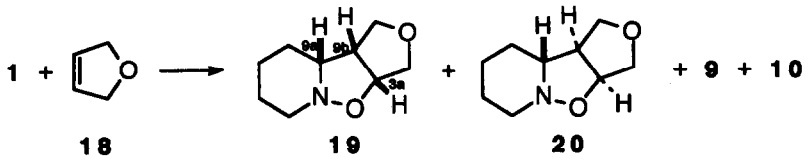


17

Compound **17** has been previously prepared by Ali and col.[28] Although the authors do not refer to the conformational behavior of this compound, according to the reported $J_{9a,9b}$ value of zero, one can deduce the exclusive existence of a *cis* invertomer of type **E**, in agreement with our prediction.

To further test our hypothesis we performed the cycloaddition of nitrone **1** with 2,5-dihydrofuran, **18** (Scheme 3). The reaction in chloroform at 20 °C for 7 days with a large excess of **18**, afforded a 44% yield of adduct **20**, identified as *exo* (*vide infra*) and a 2% of another compound, which at room temperature quickly isomerizes to **20**, and therefore was tentatively assigned as the *endo* diastereoisomer **19**. As byproducts, compounds **9** (2%) and **10** (13%) could also be isolated. Their formation may be explained by the *in situ*

oxidation of the starting dihydrofuran to the lactone **4**, by the yellow mercury(II) oxide used to prepare the nitrone, and its subsequent 1,3-dipolar cycloaddition, which is much faster than that of **18**. In a control experiment, **18** was oxidized to butenolide **4** by yellow mercury(II) oxide.



Scheme 3

Table 6 summarizes the meaningful ^1H nmr data of compound **20**. The zero values of the coupling constants $J_{1,9b}$ and $J_{3,3a}$ indicate that protons H_1 and H_3 are those *trans* to H_{9b} and H_{3a}, respectively. Presaturation of H_1 at δ 3.82 (*trans* invertomer) causes a 2.5% nOe effect on H_{9a} and the signal at δ 2.70, corresponding to H_{9b}, does not experience any enhancement (Figure 2). These results are only compatible with the *exo* stereochemistry. As expected, compound **20** shows a remarkable preference for the *trans* invertomer over the *cis*, as it was the case for the cycloadducts derived from the seven and six membered lactones. Since we could not decide which of the three *J* values observed for H_{9a} (9.0, 4.9, and 2.4 Hz) corresponded to $J_{9a,9b}$, the preference for the **E** or **F** conformer of the minor *cis* invertomer had to be determined on the basis of other data. We realized that in the previously studied cycloadducts with a predominance of the **E** conformer (**10**, **12**, **13**, **15**, and **16**) the α-nitrogen methylenic protons present chemical shifts of δ *ca.* 3.0 and 3.2, while in those adducts where conformer **F** was preferred (**7** and **8**) the corresponding protons resonate at δ *ca.* 2.70 and 2.95. On the other hand, for the former group a difference of *ca.* 0.2 ppm is observed in the chemical shift of the α-oxygen methynic proton (H_{3a}) between their *cis* and *trans* invertomers and in the latter group this Δδ value is around 0.5 ppm (H_{5a} and H_{4a} for **7** and **8**, respectively). In compound **20** the observed chemical shifts for protons at C_6 in the *cis* invertomer are δ 2.6 and 2.9, and the Δδ (*cis*/*trans*) for H_{3a} is 0.44 ppm. These facts clearly indicate that the *cis* invertomer of **20** is preferently in a conformer of type **F** and most probably the value of $J_{9a,9b}$ is that of 9.0 Hz.

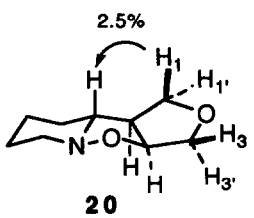


Figure 2. Observed nOe in Cycloadduct **20**.

Table 7. Calculated $\Delta G^{\neq}$ for Adducts **7**, **8**, **10**, and **20**

Compound	Reference proton	T_c (K)[a]	$\Delta G^{\neq}$ (kcal/mol)
7	H_{5a}	330	15.4
8	H_{4a}	345	16.2
10	H_{3a}	325	15.7
20	H_{3a}	350	16.4

[a] T_c = coalescence temperature.

Finally, the $\Delta G^{\neq}$ barriers for interconversion of the *trans* and *cis* conformers of the *exo* cycloadducts **7**, **8**, **10**, and **20**, representative of each skeleton prepared in this work have been calculated and are given in Table 7, along with the observed coalescence temperature for the reference proton.

In summary, in all the nitrone cycloadditions studied employing α,β-unsaturated lactones as dipolarophiles, *exo* adducts are obtained as major or exclusive products under kinetic control conditions. These results using *Z*-1,2-disubstituted olefins with only one electron-withdrawing group reinforce those obtained by Gandolfi[11] in the sense that the *endo* rule does not hold for nitrone cycloadditions with *cis* disubstituted alkenes. The reaction with 2,5-dihydrofuran affords exclusively the *exo* adduct, although in this case it can be due also to a thermodynamic equilibration. To elucidate the stereochemistry of the obtained heterocyclic compounds, **8** being the first example of its skeleton, an accurate conformational analysis has been performed. Important differences in their conformational behavior in solution have been found as a function of the lactone ring size and the presence or absence of a carbonyl group. This study points out the existence of an attractive interaction between the nitrogen lone electron pair and a carbonyl group at a fitting distance, which induces the preference for the *cis* fusion of type **E** in the furanonic *exo* adducts. In all the other cases, where this distance is too long or no carbonyl group is present in the molecule, the *trans* invertomers predominate.

EXPERIMENTAL SECTION

Commercial grade solvents were used without further purification except as indicated below. Commercial *N*-ethylpiperidine and 2,5-dihydrofuran, **18**, were used. The following compounds were prepared according to previously described methods: **1**,[15] **2**,[16] **3**,[17] **4**,[21] and **5**.[22] Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15-20 Torr. Column chromatographies were performed by using silica gel (230-400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H nmr were recorded at 400 MHz and ^{13}C nmr spectra at 100 MHz on Bruker AM-400-WB or AC-400 NB instruments. Mass spectra were performed on a Hewlett-Packard 5985B instrument at 70 eV. High resolution mass spectra were performed on a VG spectrometer model Autospect-q.

5-(2-Benzyloxy)ethyl-2(5H)-furanone, **6**

To a solution of LDA, prepared from 1.2 mL of diisopropylamine and 5.3 mL of 1.6 M *n*-BuLi in hexane, at 0 °C under argon atmosphere, a solution of 864 mg (4 mmol) of phenylselenoacetic acid in 4 mL of anhydrous THF was added. The mixture was stirred for several minutes until a white solid appeared. Then, a solution of 712 mg (4 mmol) of (2-benzyloxy)ethyloxirane[23] in 4 mL anhydrous THF was added and the reaction mixture let to stand at room temperature for 4 h. The mixture was acidified with glacial acetic acid and heated at reflux overnight. After neutralization with $NaHCO_3$ saturated solution, extraction with ether (3 x 15 mL), and evaporation of the solvent, 1.6 g of crude material was obtained. Purification of the crude by flash chromatography (hexane-ethyl acetate 3:1) gave 1.05 g (70%) of a pale yellow oil, identified as a 1:1 mixture of the two diastereoisomers of 5-(2-benzyloxy)ethyl-3-phenylseleno-2-oxolanone: ir (neat) 2925, 2864, 1770, 1183, 1101 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.67-7.61 (m, 2 H), 7.37-7.25 (m, 8 H), 4.64-4.40 (m, 3 H), 4.00 (t, J = 9 Hz) and 3.92 (dd, J = 6.3 and 4.6 Hz) (1 H), 3.58-3.47 (m, 2 H), 2.75-2.31 (m, 2 H), 2.00-1.74 (m, 2 H); ^{13}C cmr ($CDCl_3$) δ 175.5, 137.9, 135.6, 135.4, 129.3, 129.2, 128.9, 128.7, 128.3, 127.6, 127.50, 127.49, 127.0, 126.8, 76.8, 76.5, 73.1, 73.0, 65.94, 65.86, 37.3, 36.9, 35.9, 35.6, 35.3; MS *m/z* 378-376-374-373-372 (M^+, 0.8, 3.4, 2.2, 0.9, 0.8), 285 (M-CH_2Ph, 0.9), 219 (M-PhSe, 3.2), 157 (14), 91 (100). Anal. Calcd. for $C_{19}H_{20}O_3Se$: C, 60.80; H, 5.37. Found: C, 60.98; H, 5.19.

To a solution of 0.5 g (1.3 mmol) of the phenylselenooxolanone in 4 mL of THF at 0 °C, 3 drops of glacial acetic acid were added. The solution was careful treated with 1 mL (8.8 mmol) of 30% H_2O_2 and stirred at 0 °C for 30 min. Then, the mixture was neutralized with $NaHCO_3$ saturated solution and extracted with CH_2Cl_2 (3 x 5 mL). Removal of the solvent gave a crude which was purified by distillation affording 268 mg

(93%) of butenolide **6**: bp 156-7 °C/0.6 Torr; ir (neat) 3089, 3064, 3031, 2928, 2868, 1754, 1164, 1099 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.51 (dd, J = 6.0 and 0.9 Hz, 1 H, H_4), 7.40-7.25 (m, 5 H, Ph), 6.08 (dd, J = 6.0 and 2.2 Hz, 1 H, H_3), 5.23 (m, 1 H, H_5), 4.54, 4.51, 4.50, 4.47 (AB system, 2 H, OCH_2Ph), 3.73-3.63 (m, 1 H, $H_{2'}$), 3.63-3.56 (m, 1 H, $H_{2'}$), 2.11-2.02 (m, 1 H, $H_{1'}$), 1.97-1.81 (m, 1 H, $H_{1'}$); ^{13}C nmr ($CDCl_3$) δ 172.8 (C_2), 156.8 (C_4), 137.8/128.3/127.6/127.5 (Ph), 120.7 (C_3), 80.9 (C_5), 73.0 (OCH_2Ph), 65.6 ($C_{2'}$), 33.5 ($C_{1'}$); MS *m/z* 218 (M^+, 2.1), 112 (16), 97 (M-CH_2OCH_2Ph, 11), 91 (100), 84 (49), 83 (17). Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.52; H, 6.44.

Cycloaddition of nitrone **1** *to lactone* **2**

A solution of **1** (prepared from 270 mg, 2.7 mmol, of *N*-hydroxypiperidine and 1.31 g, 6.05 mmol, of yellow HgO) in 9 mL of chloroform was treated with a solution of 300 mg (2.7 mmol) of **2** in 4 mL of chloroform at room temperature for 24 d. Removal of the solvent afforded 757 mg of crude product. Purification by flash chromatography (ether-ethyl acetate 3:1) gave 142 mg (47%) of the starting lactone and 177 mg (31%) of (5a*R**,11a*R**,11b*R**)-decahydro-1*H*-oxepino[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **7**.[6]

The same reaction was repeated at 60 °C for 38 h yielding 146 mg (49%) of **2** and 264 mg (46%) of **7**. Cycloaddition of **1** to **2** in toluene at 100°C and some analytical data for **7** are described in reference 6.

Cycloaddition of nitrone **1** *to lactone* **3**

To a solution of **1** (prepared from 309 mg, 3.1 mmol, of *N*-hydroxypiperidine and 1.99 g, 9.2 mmol, of yellow HgO) in 25 mL of CH_2Cl_2, 231 mg (2.4 mmol) of lactone **3** were added and the mixture was kept at room temperature for 13 d. Removal of the solvent gave 526 mg of crude product. Purification by flash chromatography (CH_2Cl_2-ether 3:1) yielded 407 mg (86 %) of (4a*R**,10a*R**,10b*R**)-octahydro-1*H*,3*H*-pyrano[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **8**: mp 73-4 °C (hexane); ir (KBr) 2945, 2861, 2833, 1722, 1265, 1061 cm^{-1}; ^1H nmr (d_6-acetone, 250 K) [*trans*-invertomer] δ 4.40 (m, 1 H, H_3), 4.35 (m, 1 H, H_{4a}), 4.25 (m, 1 H, H_3), 3.32 (m, 1 H, H_{7eq}), 3.03 (dd, J = 10.3 and 8.7 Hz, 1 H, H_{10b}), 2.43 (ddd, J = 12.2, 9.1, and 3.0 Hz, 1 H, H_{7ax}), 2.22 (ddd, $J \approx$ 10.5 (x 2) and 2.5 Hz, 1 H, H_{10a}), 2.10 (m, 1 H, H_4), 2.02 (m, 1 H, H_{10eq}), 1.82-1.32 (m, 5 H, H_4, H_{8eq}, H_{8ax}, H_{9eq}, H_{10ax}), 1.25 (qt, J = 12.9 (x 3) and 4.0 (x 2) Hz, 1 H, H_{9ax}), [*cis*-invertomer] δ 4.82 (m, 1 H, H_{4a}), 4.40 (m, 1 H, H_3), 4.25 (m, 1 H, H_3), 3.50 (ddd, J = 10.1, 4.7, and 2.0 Hz, 1 H, H_{10a}), 3.45 (dd, J = 10.1 and 8.4 Hz, 1 H, H_{10b}), 2.96 (m, 1 H, H_7), 2.63 (m, 1 H, H_7), 2.10 (m, 1 H, H_4), 2.0-1.32 (m, 7 H, H_4, 2 x H_8, 2 x H_9, 2 x H_{10}); ^{13}C nmr ($CDCl_3$, 298 K) [*trans*-invertomer] δ 169.9 (C_1), 71.8 (C_{4a}), 70.4 (C_{10a}), 64.5 (C_3), 54.9 (C_7), 51.9 (C_{10b}), 29.0 (C_{10}), 27.4 (C_4), 24.4 (C_8), 23.3 (C_9), [*cis*-invertomer] δ 170.1 (C_1), 72.5 (C_{4a}), 65.1 (C_{10a}), 64.4 (C_3), 50.0 (C_7), 47.7 (C_{10b}), 27.8 (C_4), 24.3 (C_{10}), 23.9 (C_8), 18.0 (C_9); MS *m/z* 198 (M+1, 2), 100 (100), 83 (12), 55 (26), 41 (15). Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.98; H, 7.62; N, 7.10.

The same reaction was performed in toluene at 110 °C for 15 h yielding 85% of **8**.

Cycloaddition of nitrone **1** *to lactone* **4**

From 410 mg (4 mmol) of *N*-hydroxypiperidine, 2.53 g (11.7 mmol) of yellow HgO, and 283 mg (3.4 mmol) of lactone **4** in 20 mL of $CHCl_3$ at 4 °C for 30 d, after flash chromatography (ethyl acetate-hexane 7:3), 17 mg (2.7 %) of **9** and 540 mg (87%) of **10** were obtained.

(3a*R**,9a*R**,9b*S**)-Octahydro-1*H*-furo[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **9**: mp 94-5 °C (CH_2Cl_2-hexane); ir (KBr) 2953, 2931, 2843, 1764, 1187 cm^{-1}; ^1H nmr (d_6-acetone, 250 K) δ 4.95 (ddd, J = 7.7, 6.6, and 2.2 Hz, 1 H, H_{3a}), 4.56 (dd, J = 10.2 and 6.6 Hz, 1 H, H_3), 4.18 (dd, J = 10.2 and 2.2 Hz, 1 H, H_3), 3.47 (dd, J = 7.7 and 6.7 Hz, 1 H, H_{9b}), 3.36 (m, 1 H, H_{6eq}), 2.37 (m, 2 H, H_{6ax} and H_{9a}), 2.02 (m, 1 H, H_{9eq}), 1.75 (m, 2 H, H_{7eq} and H_{8eq}), 1.49 (m, 1 H, H_{7ax}), 1.42 (m, 1 H, H_{9ax}), 1.22 (m, 1 H, H_{8ax}); ^{13}C nmr (d_6-acetone, 298 K) δ 175.7 (C_1), 76.0 (C_{3a}), 75.6 (C_3), 68.9 (C_{9a}), 55.5 (C_6), 50.5 (C_{9b}),

26.5 (C_9), 24.8 (C_7), 23.7 (C_8); MS *m/z* 183 (M^+, 20), 182 (9), 99 (C_5H_9NO, 100), 82 (10), 69 (40), 55 (16), 41 (47). Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.07; H, 7.16; N, 7.65. Found: C, 59.12; H, 7.34; N, 7.70. (3a*R**,9a*S**,9b*S**)-Octahydro-1*H*-furo[3',4':4,5]isoxazolo[2,3-*a*]pyridin-1-one, **10**: mp 111-2 °C (CH_2Cl_2-hexane); ir (KBr) 2950, 2869, 1753, 1182 cm^{-1}; ^1H nmr (d_6-acetone, 250 K) [*cis*-invertomer] δ 5.02 (ddd, *J* = 7.6, 5.9, and 1.6 Hz, 1 H, H_{3a}), 4.54 (dd, *J* = 10.4 and 5.9 Hz, 1 H, H_3), 4.24 (dd, *J* = 10.4 and 1.6 Hz, 1 H, H_3), 3.42 (ddd, *J* = 8.4, 6.8, and 1.9 Hz, 1 H, H_{9a}) , 3.31 (dd, *J* = 7.6 and 1.9 Hz, 1 H, H_{9b}), 3.25 (m, 1 H, H_6), 3.00 (dddd, *J* = 14.7, 11.3, 3.7, and 0.8 Hz, 1 H, H_6), 1.80-1.20 (m, 6 H, 2 x H_7, 2 x H_8, 2 x H_9), [*trans*-invertomer] δ 4.79 (ddd, *J* = 7.5, 5.5, and 1.1 Hz, 1 H, H_{3a}), 4.51 (dd, *J* = 10.9 and 5.5 Hz, 1 H, H_3), 4.29 (dd, *J* = 10.9 and 1.1 Hz, 1 H, H_3), 3.36 (m, 1 H, H_{6eq}), 3.32 (dd, *J* = 8.4 and 7.5 Hz, 1 H, H_{9b}), 2.49 (ddd, *J* = 12.1, 8.9, and 3.1 Hz, 1 H, H_{6ax}), 2.17 (ddd, *J* = 12.9, 8.4, and 2.5 Hz, 1 H, H_{9a}), 2.11 (m, 1 H, H_{9eq}), 1.80-1.20 (m, 5 H, 2 x H_7, 2 x H_8, H_{9ax}); ^{13}C nmr (d_6-acetone, 260 K) [*cis*-invertomer] δ 177.9 (C_1), 76.0 (C_{3a}), 75.5 (C_3), 64.0 (C_{9a}), 54.0 (C_{9b}), 50.0 (C_6), 25.5 (C_9), 22.4 (C_7), 19.8 (C_8), [*trans*-invertomer] δ 177.0 (C_1), 78.0 (C_{3a}), 71.9 (C_{9a}), 71.2 (C_3), 55.0 (C_6), 53.7 (C_{9b}), 29.5 (C_9), 24.7 (C_7), 23.9 (C_8); MS *m/z* 183 (M^+, 24), 182 (7), 99 (C_5H_9NO, 100), 84 (13), 82 (13), 69 (42), 55 (22), 41 (52). Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.07; H, 7.16; N, 7.65. Found: C, 59.00; H, 7.15; N, 7.67.

The same reaction was performed in toluene at 110 °C for 15 h yielding 11% of **9** and 68% of **10**.

Cycloaddition of nitrone **1** *to lactone* **5**

Experimetal details and analytical data for cycloadducts **11**, **12**, and **13** were previously reported.[5]

Cycloaddition of nitrone **1** *to lactone* **6**

From 139 mg (1.4 mmol) of *N*-hydroxypiperidine, 652 mg (3 mmol) of yellow HgO, and 300 mg (1.4 mmol) of lactone **6** in 14 mL of chloroform at 25 °C for 18 d, after flash chromatography (CH_2Cl_2-hexane 19:1), the following fractions were obtained: 36 mg (12%) of the starting lactone **6** impurified by cycloadduct **14**, and 310 mg (70%) of a 10:1 mixture of **15** and **16**. The same reaction was performed in toluene at reflux for 9 h affording 5% of adduct **14** and 74% of a 6:1 mixture of **15** and **16**.

(3*R**,3a*S**,9a*S**,9b*R**)-Octahydro-3-(2-benzyloxy)ethyl-1*H*-furo[3',4':4,5]isoxazolo[2,3-*a*]-pyridin-1-one, **14**: ^1H nmr (d_6-acetone, 250 K) δ 7.40-7.25 (m, 5 H, Ph), 4.67 (dd, *J* = 7.8 and 2.3 Hz, 1 H, H_{3a}), 4.57 (ddd, *J* = 7.0, 5.4, and 2.3 Hz, 1 H, H_3), 4.54 (s, 2 H, CH_2Ph), 3.61 (m, 2 H, CH_2O), 3.50 (dd, *J* = 7.7 and 7.0 Hz, 1 H, H_{9b}), 3.37 (dt, *J* = 9.1, 3.2, and 3.2 Hz, 1 H, H_{6eq}), 2.38 (ddd, *J* = 12.2, 9.2, and 2.9 Hz, 1 H, H_{6ax}), 2.35 (ddd, *J* = 11.0, 7.0, and 2.5 Hz, 1 H, H_{9a}), 2.05 (m, 3 H, CH_2CH_2O and H_{9eq}), 1.75 (m, 2 H, H_{7eq} and H_{8eq}), 1.50 (qt, *J* = 13.0 (x 3) and 4.0 (x 2) Hz, 1 H, H_{7ax}), 1.41 (m, 1 H, H_{9ax}), 1.21 (qt, *J* = 13.0 (x 3) and 4.3 (x 2) Hz, 1 H, H_{8ax}); ^{13}C nmr (d_6-acetone, 298 K) δ 174.9 (C_1), 139.6/129.0/128.4/128.2 (Ph), 85.0 (C_3), 81.0 (C_{3a}), 73.5 (CH_2Ph), 69.1 (C_{9a}), 66.6 (CH_2O), 55.8 (C_6), 51.4 (C_{9b}), 34.9 (CH_2CH_2O), 26.8 (C_9), 25.0 (C_7), 23.8 (C_8).

Repeated flash chromatography afforded an analytical sample of **15** in a 95% purity: ^1H nmr (d_6-acetone, 270 K) [*cis*-invertomer] δ 7.44-7.29 (m, 5 H, Ph), 4.74 (br d, *J* = 7.6 Hz, 1 H, H_{3a}), 4.61 (ddd, *J* = 7.9, 5.8, and 1.7 Hz, 1 H, H_3), 4.54 (m, 2 H, CH_2Ph), 3.62 (m, 2 H, CH_2O), 3.43 (m, 1 H, H_{9a}), 3.34 (dd, *J* = 7.6 and 2.0 Hz, 1 H, H_{9b}), 3.25 (m, 1 H, H_6), 3.00 (ddd, *J* = 14.6, 11.3, and 3.5 Hz, 1 H, H_6), 2.0 (m, 2 H, CH_2CH_2O), 1.80-1.20 (m, 6 H, 2 x H_7, 2 x H_8, and 2 x H_9), [*trans*-invertomer] observed absorptions δ 4.67 (ddd, *J* = 7.6, 5.8, and 1.2 Hz, 1 H, H_3), 4.56 (dd, *J* = 7.5 and 1.2 Hz, 1 H, H_{3a}), 3.35 (dd, *J* = 8.3 and 7.5 Hz, 1 H, H_{9b}), 2.50 (ddd, *J* = 12.0, 9.1, and 3.5 Hz, 1 H, H_{6ax}), 2.20 (ddd, *J* = 11.2, 8.3, and 2.5 Hz, 1 H, H_{9a}); ^{13}C nmr (d_6-acetone, 250 K) [*cis*-invertomer] δ 177.1 (C_1), 139.3/128.9/128.1/128.0 (Ph), 84.7 (C_3), 80.6 (C_{3a}), 73.1 (CH_2Ph), 66.2 (CH_2O), 64.2 (C_{9a}), 54.4 (C_{9b}), 50.2 (C_6), 34.4 (CH_2CH_2O), 25.7 (C_9), 22.4 (C_7), 20.1 (C_8), [*trans*-invertomer] δ 176.4 (C_1), 139.2/128.9/128.1/128.0 (Ph), 82.2/80.7 (C_3/C_{3a}), 73.1 (CH_2Ph), 71.7 (C_{9a}), 65.9 (CH_2O), 55.1 (C_6), 54.0 (C_{9b}), 34.4 (CH_2CH_2O), 29.5 (C_9), 24.8 (C_7), 23.9 (C_8).

Mixture 6:1 of **15** and **16**: ir (neat) 2940, 1770, 1185, and 1096 cm^{-1}; MS *m/z* 317 (M^+, 5), 226 (M-CH_2Ph, 6), 100 ($C_5H_{10}NO$, 22), 99 (C_5H_9NO, 21), 91 (100), 84 (36), 55 (30), 41 (37). Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.12; H, 7.25; N, 4.33.

16: ^1H nmr (d_6-acetone, 270 K) [*cis*-invertomer] observed absorptions δ 4.87 (dd, J = 7.0 and 5.0 Hz, 1 H, H_{3a}), 4.79 (m, 1 H, H_3), 3.42 (m, 1 H, H_{9a}), 2.96 (m, 1 H, H_6); ^{13}C nmr (d_6-acetone, 270 K) [*cis*-invertomer] observed absorptions δ 78.8/76.6 (C_3/C_{3a}), 72.9 (CH_2Ph), 67.0 (CH_2O), 63.6 (C_{9a}), 55.6 (C_{9b}), 50.1 (C_6), 34.4 (CH_2CH_2O), 25.5 (C_9), 22.6 (C_7), 19.3 (C_8).

Cycloaddition of nitrone **1** *to dihydrofuran* **18**

From 200 mg (1.9 mmol) of *N*-hydroxypiperidine, 1.23 g (5.7 mmol) of yellow HgO, and 1.38 g (19 mmol) of **18** in 10 mL of chloroform at 20 °C for 7 d, after flash chromatography (ethyl acetate-hexane 1:1), the following fractions were obtained: 8 mg (2%) of **9**, 6 mg (2%) of **19**, 45 mg (13%) of **10**, and 140 mg (44%) of (3a*R**,9a*S**,9b*R**)-octahydro-1*H*-furo[3',4':4,5]isoxazolo[2,3-*a*]pyridine, **20**: bp 82-3 °C/0.4 Torr; ir (neat) 2931, 2852, 1732, 1076 cm^{-1}; ^1H nmr (d_6-acetone, 250 K) [*trans*-invertomer] δ 4.48 (dd, J = 7.5 and 4.0 Hz, 1 H, H_{3a}), 3.82 (d, J = 9.3 Hz, 1 H, H_1), 3.78 (d, J = 10.6 Hz, 1 H, H_3), 3.36 (dd, J = 9.3 and 5.5 Hz, 1 H, $H_{1'}$) , 3.29 (dd, J = 10.6 and 4.0 Hz, 1 H, $H_{3'}$), 3.23 (m, 1 H, H_{6eq}), 2.70 (td, $J \approx 8.3$ (x 2) and 5.5 Hz, 1 H, H_{9b}), 2.32 (ddd, J = 12.1, 9.0, and 2.8 Hz, 1 H, H_{6ax}), 1.98 (m, 1 H, H_{9eq}), 1.81 (ddd, J = 11.4, 9.0, and 2.5 Hz, 1 H, H_{9a}), 1.72 (m, 1 H, H_{8eq}), 1.63 (m, 1 H, H_{7eq}), 1.48 (m, 1 H, H_{7ax}), 1.33 (m, 1 H, H_{9ax}), 1.17 (m, 1 H, H_{8ax}), [*cis*-invertomer] δ 4.92 (dd, J = 8.1 and 4.2 Hz, 1 H, H_{3a}), 3.76 (d, J = 10.4, 1 H, H_3), 3.71 (d, J = 9.1 Hz, 1 H, H_1), 3.48 (dd, J = 9.1 and 5.3 Hz, 1 H, $H_{1'}$), 3.42 (dd, J = 10.4 and 4.2 Hz, 1 H, $H_{3'}$), 3.10 (m, 1 H, H_{9b}), 3.02 (ddd, J = 9.0, 4.9, and 2.4 Hz, 1 H, H_{9a}), 2.90 (m, 1 H, $H_{6'}$), 2.66 (m, 1 H, H_6), 1.10-1.90 (m, 6 H, 2 x H_7, 2 x H_8, 2 x H_9); ^{13}C nmr (d_6-acetone, 250 K) [*trans*-invertomer] δ 82.2 (C_{3a}), 72.6 (C_{9a}), 72.0 (C_3), 70.0 (C_1), 55.2 (C_6), 54.6 (C_{9b}), 29.1 (C_9), 24.9 (C_7), 24.2 (C_8), [*cis*-invertomer] δ 83.5 (C_{3a}), 73.2 (C_3), 71.2 (C_1), 66.5 (C_{9a}), 50.1 (C_6), 50.0 (C_{9b}), 30.1 (C_9), 25.3 (C_7), 19.0 (C_8); HRMS *m/z* calcd for $C_9H_{15}NO_2$ 169.1104, found 169.1103.

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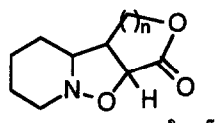
REFERENCES AND NOTES

1. Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley and Sons, Inc.: New York, 1984; Vol. 2. Chapt. 9; Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Verlagsgesellschaft: Weinheim, 1988.
2. de Lange, B.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 5317-5320.
3. Blake, A. J.; Forsyth, A. C.; Paton, R. M. *J. Chem. Soc., Chem. Commun.* **1988**, 440-442.
4. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119* , 253-269.
5. Figueredo, M.; Font, J.; de March, P. *Chem. Ber.* **1989**, *122*, 1701-1704; *ibid.* **1990**, *123*, 1595.
6. Cid, P.; Figueredo, M.; Font, J.; Jaime, C.; de March, P.; Virgili, A. *Magn. Reson. Chem.* **1990**, *28*, 947-951.
7. Olsson, T.; Stern, K.; Westman, G. *Tetrahedron* **1990**, *46*, 2473-2482.
8. Panfil, I.; Belzecki, C.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **1991**, *47*, 10087-10094.
9. Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milán, S. *Tetrahedron Lett.* **1992**, *33*, 667-670.
10. Ali, Sk. A.; Perzanowski, H. P. *J. Chem. Res., Synop.* **1992**, 146-147.
11. Burdisso, M.; Gandolfi, R.; Grünanger, P.; Rastelli, A. *J. Org. Chem.* **1990**, *55*, 3427-3429.
12. Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866-3869.

13. Banerji, A.; Basu, S. *Tetrahedron* **1992**, *48*, 3335-3344.
14. Burdisso, M.; Gamba, A.; Gandolfi, R.; Oberti, R. *Tetrahedron* **1988**, *44*, 3735-3748.
15. Thesing, J.; Sirrenberg, W. *Chem. Ber.* **1959**, *92*, 1748-1755; Sabel, W. *Chem. Ind. (London)* **1966**, 1216-1217.
16. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447; Chow, H.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815-1819.
17. Nakagawa, M.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T. *Synthesis* **1974**, 510-511.
18. Gössinger, E. *Monatsh. Chem.* **1981**, *112*, 1017-1043; Carruthers, W.; Moses, R. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2251-2253; Crabb, T.; Jackson, D.; Patel, A. V. *Adv. Heterocycl. Chem.* **1990**, *49*, 193-269.
19. The ^{1}H nmr spectrum of regioisomeric cycloadducts of type **I** would present a doublet at $\delta \approx 5$.



$\delta \approx 5$

I

n = 1,2, 3

20. Banting, L.; Crabb, T. A. *Magn. Reson. Chem.* **1987**, *25*, 696-706; Livant, P. D.; Beutler, J. A. *Tetrahedron* **1987**, *43*, 2915-2924.
21. Price, C. C.; Judge, J. M. *Organic Synthesis*; John Wiley and Sons: New York. 1973; Coll. Vol. 5, pp. 255-258.
22. Ortuño, R. M.; Cardellach, J.; Font, J. *J. Heterocycl. Chem.* **1987**, *24*, 79-84.
23. Mühlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1988**, *53*, 1026-1030.
24. Figueredo, M.; Font, J.; Virgili, A. *Tetrahedron* **1987**, *43*, 1881-1886.
25. Suemune, H.; Hizuka, M.; Kamashita, T.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 1379-1381; Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204-2210; Herradon, B. *Tetrahedron: Asymmetry* **1991**, *2*, 191-194; Burgess, K.; Henderson, I. *Tetrahedron* **1991**, *47*, 6601-6616.
26. Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden*; Springer Verlag: Berlin, 1976.
27. Fariña, F.; Martín, M. V.; Sánchez, F. *Heterocycles* **1986**, *24*, 2587-2592; Jaime, C.; Ortuño, R. M.; Font, J. *J. Org. Chem.* **1986**, *51*, 3946-3951; *ibid.* **1987**, *52*, 5600.
28. Ali, Sk. A.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 597-605.