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The Role of the Sulfinyl Group on the Course of the Reactions of 3-*p*-Tolylsulfinylfuran-2(5*H*)-ones with Nitrones. Synthetic Uses of Cycloreversion Processes

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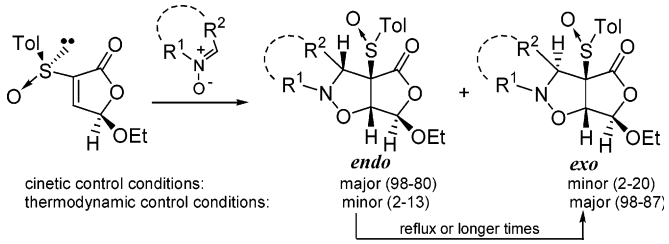

The reaction of enantiopure 3-*p*-tolylsulfinylfuran-2(5*H*)-ones (**2a** and **2b**) with cyclic (**4**) and acyclic (**6**) nitrones afforded furoisoxazolidines (**5** and **7**) in high yields under mild conditions. The reactivity of the dipolarophile was dramatically enhanced by the sulfinyl group, which modulated the π-facial selectivity (it was complete for reactions from **2b**, yielding only the *anti* adducts) and was the main controller of the *endo*/*exo* selectivity. Cycloreversion processes from the resulting sulfinyl furoisoxazolidines proceeded readily and were to be considered to account for an improvement in the selectivity (facial and *endo*/*exo*) and even for an inversion of it when the composition of the reaction mixtures obtained under kinetic and thermodynamic conditions were quite different.

Introduction

The asymmetric 1,3-dipolar cycloaddition of nitrones to homochiral olefins is one of the most efficient methods for obtaining isoxazolidines.[1] In this context, the use of furan-2(5*H*)-ones (butenolides) and their 5-alkoxy derivatives as dipolarophiles has been widely investigated due to the interest in the resulting furoisoxazolidines.[2] Vinyl sulfoxides have been only occasionally used as dipolarophiles in these reactions,[3] despite the good results obtained from them in Diels–Alder reactions.[4] Several years ago, we initiated a program to explore the usefulness of vinyl sulfoxides in asymmetric 1,3-dipolar reactions. The behavior of arylsulfinylfuran-2(5*H*)-ones in their reactions with diazoalkanes,[5] and nitrile oxides[6] demonstrated the strong influence of the sulfinyl group in the course of these reactions, as it dramatically enhanced the features of butenolides as chiral dipolarophiles. Similar good results were observed in reactions of vinyl sulfoxides with azomethine ylides,[7] where the final elimination of the sulfinyl group from the adducts was used for synthesizing interesting dihydropyrroles. More recently, we reported the synthesis of pyrroloazepines from the isoxazoloazepines[2b] obtained by reac-

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SCHEME 1

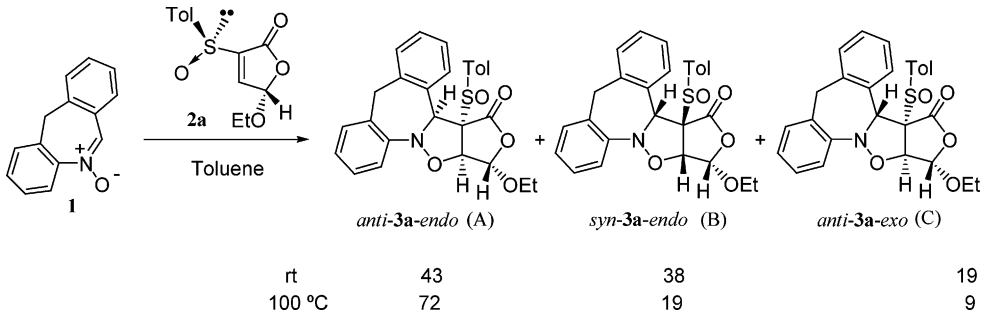
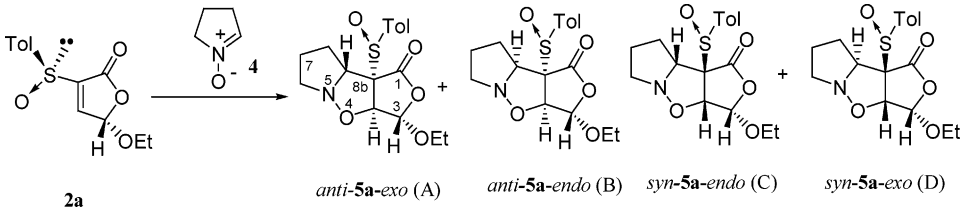


TABLE 1. Results Obtained in Reactions of 2a with 4



entry	solvent	*T* (°C)	time (h)	A/B/C/D	*anti*/*syn*	*anti* *endo*/*exo*	*syn* *endo*/*exo*
1	$CHCl_3$	−40	336	23:39:38:0	62:38	63:37	100:0
2	$CHCl_3$	0	14	28:39:32:1	67:33	58:42	97:3
3[a]	$CHCl_3$	rt	1	24:46:29:1	70:30	66:34	97:3
4	$CHCl_3$	rt	24	29:40:27:4	69:31	58:42	87:13
5	$CHCl_3$	rt	96	35:42:19:4	77:23	55:45	83:17
6	$CHCl_3$	60	0.3	31:40:28:1	71:29	56:44	97:3
7	Toluene	0	2	33:36:30:1	69:31	52:48	97:3
8	Toluene	rt	0.25	36:38:24:2	74:26	51:49	92:8
9	Toluene	rt	648	43:46:7:4	89:11	52:48	64:36
10	Toluene	110	0.1	50:40:5:5	90:10	44:56	50:50
11	CH_3CN	0	15.5	41:45:14:0	86:14	52:48	100:0
12	CH_3CN	rt	24	41:45:14:0	86:14	52:48	100:0
13	CH_3CN	80	0.25	44:43:11:2	87:13	49:51	85:15

[a] 86% combined yield.

tion of morphantridine *N*-oxide **1** with the two epimers at C_5 of 5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-one (**2**). The stereoselectivity of these reactions suggested that the sulfinyl group played a significant role, but their most intriguing point was related to the readiness of the cycloreversion, which determined their use with synthetic purposes. Thus, reaction of **1** with **2a** yielded a mixture of three adducts (Scheme 1), the major one, *anti*-**3a**-*endo,* having been obtained with low diastereomeric ratio in the reactions at rt. However, its relative proportion increased significantly when the reaction was conducted at 100 °C and finally it was obtained in 76% isolated yield after crystallization from the reaction crude.

Initially, we thought that this interesting behavior associated to the cycloreversion should be related to the stability of the nitrone **1**, but the publication of another paper on the easy cycloreversion of isoxazolines derived from alkylidene malonates[8] suggested us the possibility that the easy cycloreversion could be a general property of isoxazolidines derived from olefines bearing two electron-withdrawing groups in the *gem*-position. If this was the case, sulfinylbutenolides **2a** and **2b** would exhibit a higher potential as chiral dipolarophiles because the stereoselectivity could be substantially modified with the reaction conditions (kinetic versus thermodynamic control). To clarify this point, we have studied the reactions of **2a** and **2b** with other cyclic and acyclic nitrones (**4** and **6**), with the aim of better understanding the role of sulfinyl group on the stereoselectivity of these cycloadditions. These results would also provide further evidences to rationalize the cycloreversion involving nitrones, which to our knowledge had not been so far systematically considered in the literature.

Sulfinylfuranones **2a** and **2b** were prepared according to previously reported procedures.[9] Reaction of furanone **2a** with 3,4-dihydro-2*H*-pyrrole 1-oxide (**4**) in chloroform at rt for 1 h (entry 3, Table 1) afforded a mixture of four stereoisomeric adducts **5a** (Table 1).[10] All of them, except the minor one, *syn*-**5a**-*exo*, were isolated as pure compounds by column chromatography. The high stability of the adducts in the solid state (they remain unaltered for several months without special precautions) contrasts with the instability of some of them in polar solvents, since they evolved in solution at rt into a mixture of adducts and the starting furanone. This was the first evidence proving that cycloreversion was very easy from

(8) The easy cycloreversion of isoxazolidines derived from alkylidene malonates was reported during the preparation of this manuscript (Huang, Z.-Z., Kang, Y.-B., Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, *6*, 1677).

(9) Carretero, J. C.; García Ruano, J. L.; Lorente, A.; Yuste, F. *Tetrahedron: Asymmetry* **1993**, *4*, 177−180.

these adducts. The same conclusion could be reached from the reaction crudes obtained when the reactions of **2a** and **4** were performed at different times or under different conditions (see Table 1). The reaction was completely regioselective in all conditions, exclusively yielding compounds with the oxygen at the nitrone bonded to C_4 at the furanone. The π-facial selectivity (*anti*/*syn* ratio) was moderate in toluene or $CHCl_3$ at low temperatures (presumably kinetic control conditions), ranging between ~2:1 and ~3:1 (entries 1−4, 7, and 8). It increased when the reaction times were longer (entries 5 and 9) or when the temperature raised (entries 6 and 10), which presumably are thermodynamic control conditions. The best stereoselectivity was observed in refluxing toluene (*anti*/*syn* = 90:10, entry 10). The use of acetonitrile as the solvent increased significantly the *anti*/*syn* ratio, which was almost identical at 0 °C (86:14, entry 11) and 80 °C (87:13, entry 13) and similar to that of entry 10 (presumably thermodynamic control conditions).

Concerning the *endo*/*exo* selectivity, the *anti* approach was moderately *endo* selective, whereas the *syn* approach was almost completely *endo* selective when the reactions were conducted under kinetic control conditions. By contrast, under thermodynamic control conditions, the *anti* approach afforded almost equimolecular mixtures of *endo* and *exo* adducts regardless the solvent, whereas the *syn* approach gave mixtures where the *endo*/*exo* ratio was very small in toluene (entry 10) but it remained significant in more polar solvents (entries 5 and 12).

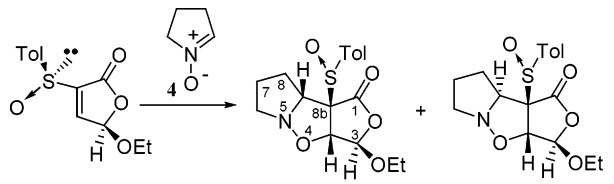
An additional result demonstrating that cycloreversion was very easy was the formation of a 60:40 mixture of *anti*-**5a**-*endo* and *anti*-**5a**-*exo* by refluxing in toluene diastereomerically pure samples of *anti*-**5a**-*endo* or *anti*-**5**-*exo*.

Reactions of **2b** with **4** were faster than those of **2a** and afforded only *anti* adducts (Table 2), which were easily separated by chromathography. Under kinetic control conditions (low temperature and short reaction time), compound *anti*-**5b**-*endo* was obtained as the major one. However, under thermodynamic control conditions (longer reaction times and mainly higher temperatures), the *anti*-**5b**-*exo* adduct became the major one.

As an unequivocal proof that cycloreversion was also very easy in these reactions, compound *anti*-**5b**-*endo* evolved into a 90:10 mixture of *anti*-**5b**-*exo* and *anti*-**5b**-*endo* by refluxing in toluene for 1 h.

The results of the reactions of *N*-methyl-α-phenylnitrone **6** with sulfinylfuranones **2a** and **2b** are shown in Tables 3 and 4, respectively. The reactivity of the acyclic nitrone **6** was lower than that of the cyclic one **4**, as it can be deduced from the reaction times required to reach completion (compare Tables 1 and 3 or 2 and 4). The π-facial selectivity was very high for **2a** and became complete for **2b** (the *anti* adducts were always favored)

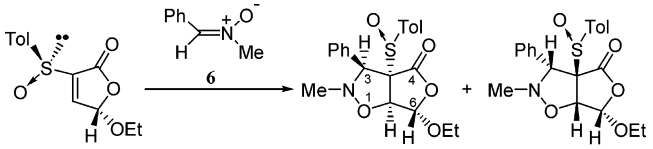
TABLE 2. Reactions of 2b with Nitrone 4



2b *anti*-**5b**-*endo* *anti*-**5b**-*exo*

					isolated yield (%)	
entry	solvent	*T* (°C)	time	*endo*/*exo*	*endo*	*exo*
1	CH_3CN	−40	48 h	80:20	65	15
2	CH_3CN	rt	10 min	72:28		
3	CH_3CN	rt	4 days	59:41		
4	$CHCl_3$	−40	48 h	80:20	71	18
5	$CHCl_3$	−22	4 h	75:25		
6	$CHCl_3$	0	1 h	69:31		
7	$CHCl_3$	rt	10 min	67:33	58	29
8	$CHCl_3$	rt	1 day	62:38		
9	$CHCl_3$	rt	4 days	54:46		
10	toluene	−40	22 h	68:32		
11	toluene	0	10 min	58:42		
12	toluene	rt	5 min	59:41		
13	toluene	rt	1 day	53:47		
14	toluene	rt	4 days	47:53		
15	toluene	110	5 min	18:82		
16	toluene	110	1 h	13:87	11	71

TABLE 3. Cycloadditions of *N*-Methyl-α-phenylnitrone (6) to Sulfinylfuranone 2a



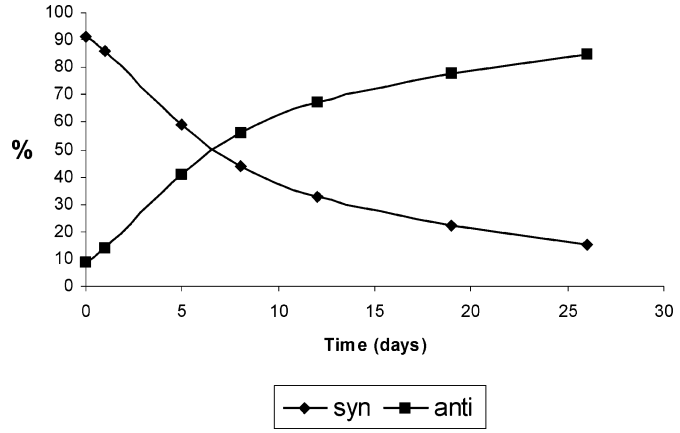
2a *anti*-**7a**-*endo* *syn*-**7a**-*endo*

					isolated yield (%)	
entry	solvent	*T* (°C)	time (h)	*anti*/*syn*	*anti*	*syn*
1	CH_3CN	0	48	93:7	90	6
2	CH_3CN	rt	8[a]	92:8	90	7
3	$CHCl_3$	rt	18	70:30[a]	68	27
4	$CHCl_3$	rt	96	74:26		
5	$CHCl_3$	60	2.5	71:29		
6	toluene	rt	7.5	82:18		
7	toluene	rt	24	81:19		
8	toluene	rt	96	84:16		
9	toluene	110	3.5	89:11	73	9

[a] The same results were obtained after 24 h.

under both kinetic and thermodynamic control conditions. The best de's were those obtained in acetonitrile at low temperatures (entries 1 and 2 in Table 3 and entry 1 in Table 4). It indicates that the *anti* adducts are both the most easily formed as well as the most stable ones. However, the observed *endo* selectivity was complete for **2a** and high, but not complete, for **2b**. Under conditions of entries 3, 13, and 14 (Table 4), the *endo* selectivity was very high. Therefore, the differences in the behavior of **2b** and **2a** when they reacted with **6** were similar to those observed in their reactions with **4**. However, both the π-facial (with **2a**) and the *endo* selectivity substantially improved for acyclic nitrone **6** as compared with the cyclic one **4**.

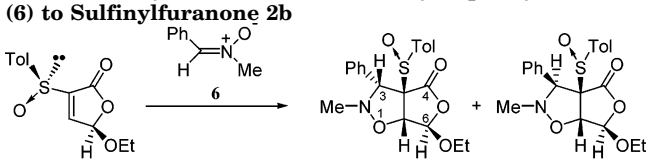
(10) The *syn* or *anti* character of the adducts, which indicates the *cis* or *trans* relationship between H_3 and H_{3a} (Table 1), is related to the face of the dipolarophile attacked by the dipole, using as a reference the spatial arrangement of the ethoxy group. Thus, the *syn* adducts result from the approach of the dipole to the face bearing the OEt group, whereas the *anti* adducts are obtained by the approach to the opposite face. The *endo* or *exo* terms indicate, respectively, the *cis* or *trans* arrangement adopted by the furanone and pyrrolidine (or phenyl) moieties at the isoxazolidine ring formed in the reactions from nitrone **4** (or **6**). They are related to the *endo* and *exo* addition modes of the dipole, using the ester group at the furanone ring as a reference.



Time (days)	*syn*	*anti*	(*endo* + *exo*)
0	91	9	3 + 6
1	86	14	6 + 8
5	59	41	19 + 22
8	44	56	27 + 29
12	33	67	32 + 35
19	22	78	33 + 45
26	15	85	35 + 50

FIGURE 1. Evolution of a 91:9 mixture of *syn*-**5a**-*endo* and *anti*-**5a** in acetonitrile at rt.

TABLE 4. Cycloadditions of *N*-Methyl-α-phenylnitrone (6) to Sulfinylfuranone 2b



2b *anti*-**7b**-*endo* *anti*-**7b**-*exo*

					isolated yield (%)	
entry	solvent	*T* (°C)	time	*endo*/*exo*	*endo*	*exo*
1	CH_3CN	−20	72 h	86:14	72	13
2	CH_3CN	rt	2.5 h	84:16		
3	CH_3CN	rt	24 h	>98:<2		
4	$CHCl_3$	0	10 h	90:10		
5	$CHCl_3$	rt	2.5 h	80:20	67	19
6	$CHCl_3$	rt	1 day	89:11		
7	$CHCl_3$	rt	4 days	89:11		
8	$CHCl_3$	60	15 min	79:21		
9	toluene	0	5.5 h	82:18		
10	toluene	rt	1 h	67:33	59	29
11	toluene	rt	1 day	70:30		
12	toluene	rt	4 days	76:24		
13	toluene	110	5 min	>98:<2	86	
14	toluene	110	1 h	>98:<2	82	

One interesting point deduced from the results collected in Tables 3 and 4 is the fact that they indicate that cycloreversion also took place from adducts **7**, and it affected the *endo*/*exo* and the *anti*/*syn* equilibria. As compounds *anti*-**7a**-*endo* and *anti*-**7b**-*endo* are favored under both kinetic and thermodynamic conditions, they were the major isomers obtained under all conditions. In turn, the minor components, *syn*-**7a**-*endo* and *anti*-**7b**-*exo*, can only be obtained in low yields under specific conditions (entry 3, Table 3, and entry 10, Table 4). The completely stereoselective conversion of **2b** into *anti*-**7b**-*endo* under thermodynamic conditions (entries 3, 13, and 14 in Table 4) was also remarkable. From Tables 3 and 4, it seems that thermodynamic equilibria were reached more quickly as the solvent polarity increased, the shorter times having been observed in acetonitrile. The same conclusion could be reached from the results collected in Tables 1 and 2. Finally, the composition of the reaction mixtures obtained under thermodynamic conditions was dependent on the relative stability of the species in equilibrium, which in turn were related to the solvent polarity.

Several experiences have been performed in order to get a more direct information about the cycloreversion processes. Thus, starting from a 91:9 (6 + 3) mixture of *syn*-**5a**-*endo* and *anti*-**5a** (*exo* + *endo*) solved in acetonitrile at rt, when recording the ^1H NMR spectra at different times, we obtained the results depicted in Figure 1. As we see, the original mixture evolved into a mixture of three compounds with a similar composition to that indicated in entry 12 of Table 1, which clearly evidences that both equilibria (*endo*/*exo* and *syn*/*anti*) were taking place.

Clearer results were obtained in cases where only one of the above-mentioned equilibria were reached. Thus, reaction of **2b** with the cyclic nitrone **4** allowed us to follow the *endo*/*exo* equilibration in acetonitrile or toluene at 60 °C (Figure 2). We can see that it was slower in toluene but the proportion of the major adduct was the highest.

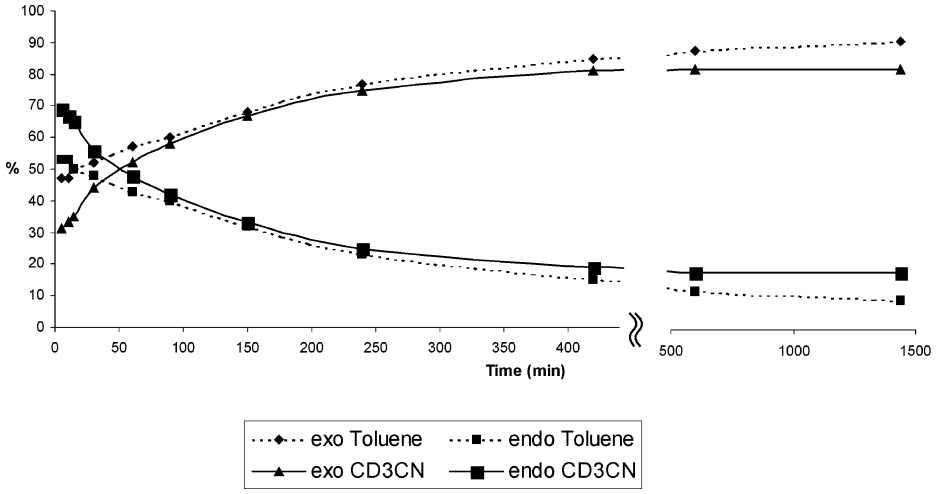
Finally, a similar study was performed with the reaction of **2a** with the acyclic nitrone **6** in order to obtain evidence about the *syn*/*anti* equilibration. The obtained results were almost identical, the equilibration being slower in toluene, which was also the solvent where the observed de's were the highest.

The elucidation of the structures of all the obtained adducts (**5** and **7**) was performed from their NMR parameters and those of their corresponding desulfinilated compound (**5′** and **7′**) shown in Scheme 2.[11] All of the obtained adducts exhibit the same regiochemistry, which was inferred from the $\Delta\delta$ values ($\delta C_{3a} - \delta C_{6a}$) observed for different compounds, all smaller than 6 ppm.[12] The *syn* or *anti* stereochemistry was easily deduced from the value of the vicinal coupling constant $J_{3,3a}$. It was lower than 2.2 Hz for protons in a *trans* relationship (*anti* adducts) but higher than 4.3 Hz for protons in a *cis* arrangement (*syn* adducts).[5b,13] As an additional confirmation, all of the *anti* adducts exhibited higher chemical shifts for the acetalic proton than those of their corresponding *syn* adducts, presumably due to

(11) To simplify the discussion of structural elucidation of adducts, all adducts are numbered as indicated in Scheme 2, despite the fact that it is not correct for compounds **7**.

(12) The regioisomer with a sulfur and an oxygen bonded to the same carbon would display a higher $\Delta\delta$ value because of the additive influence of the two electronegative atoms.

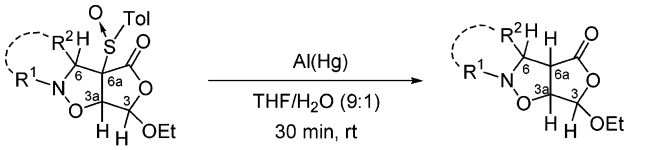
(13) Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607−624.



Time	Toluene		CD3CN	
(min)	endo	exo	endo	exo
5	47	53	31	69
10	47	53	33	67
15	50	50	35	65
30	52	48	44	56
60	57	43	52	48
90	60	40	58	42
150	68	32	67	33
240	77	23	75	25
420	85	15	81	19
600	88	12	82	18
1440	91	9	82	18

FIGURE 2. Evolution of adducts *anti*-**5b** at 60 °C in acetonitrile or toluene.

SCHEME 2[11]



5: $R^1 \cdots R^2 = (CH_2)_3$
7: R^1 = Me; R^2 = Ph

5′: $R^1 \cdots R^2 = (CH_2)_3$
7′: R^1 = Me; R^2 = Ph

the shielding effect of the *p*-tolyl group in the latter ones. The relative configuration of C_6 and C_{6a}, indicative of the *endo* or *exo* character of the adducts, could not be unequivocally established from the NMR parameters of compounds **5**−**7**. This problem was solved by desulfinylation of these adducts with aluminum amalgam in THF/H_2O (9:1), which afforded compounds **5′**−**7′** with a hydrogen atom at the position initially occupied by the sulfur function. The rigid cyclic structure of the adducts precludes epimerization at C_{6a}, and therefore, H_{6a} and H_{3a} are in a *cis* relationship. The *endo* or *exo* stereochemistry of compounds **5′**−**7′** was unequivocally deduced from their $J_{6,6a}$ values, which were higher than 7 Hz for compounds exhibiting a *cis* relationship between the involved protons and lower than 4.5 Hz for those with a *trans* relationship.[2b,13,14]

The structures and absolute configurations for compounds *syn*-**5a**-*endo* and *anti*-**5b**-*endo* were unequivocally established by X-ray diffraction studies.[15] In Figure 3, the relative position of the *p*-tolyl group with respect to H_3 in adduct *syn*-**5a**-*endo* can be seen, which would explain the shielding observed for such a proton in compounds of identical stereochemistry.

We have also confirmed the absolute configuration of compound *anti*-**5b**-*exo* by chemical correlation with the adduct **8**, obtained by Feringa in the reaction of 5-menthyloxyfuran-2(5*H*)-one with nitrone **4**.[13] Both compounds were transformed into (−)-**9** by following the sequence indicated in Scheme 3. This correlation confirms that **8** and *anti*-**5b′**-*exo* exhibit the same absolute configurations at C_6, C_{6a}, and C_{3a}.

To determine the role of the sulfinyl group on the course of the 1,3-dipolar cycloadditions, it was necessary to compare the results of Tables 1−4 with those obtained in reactions of **4** and **6** with 5-alkoxyfuran-2(5*H*)-ones bearing no sulfinyl group. These reactions were studied by Feringa from 5-methoxy- and (5*R*)-menthyloxyfuran-2(5*H*)-ones[13,16] and by Hegedus from 5-alkyl-5-alkoxyfuran-2(5*H*)-ones and cyclic nitrones.[17] The reactions of 5-monosubstituted furanones with **4** and **6** required 16 and 12 h, respectively (in refluxing toluene), and gave only the *anti-exo* and *anti-endo* adducts (*exo*/*endo* = 88:12 from **4** and 69:31 from **6** and menthyloxyfuranone). Reactions of 5-disubstituted furanones with **4** (in refluxing toluene for 3−4 h at rt) afforded *anti-exo* as the only adduct. Steric[13,16] and electrostatic repulsions between the oxygen at nitrone and the 5-alkoxy moiety[17] were invoked to account for the complete control of the π-facial selectivity. Comparison of these results with those collected in Tables 1−4 allowed us to reach some conclusions. Concerning the reactivity, the influence of the sulfinyl group seemed very high, mainly in the case of the epimer **2b** (which was more reactive than **2a**, vide infra), whose reactions in refluxing toluene were complete in 5 min with both nitrones (Tables 2 and 4). This dramatic enhancement of the dipolarophilic reactivity toward nitrones induced by the sulfinyl group at C_3 of furan-2(5*H*)-ones had also been found in their reactions with diazoalkanes[5] but significantly contrasts with the rather moderate influence the sulfinyl group on the dienophilic reactivity of the furanones.[18] This different behavior suggests an important role of the electrostatic interactions in the stability of the transition states of 1,3-dipolar cycloadditions, which is not significant in Diels−

(14) Alonso-Perarnau, D.; de March, P.; Figueredo, M.; Font, J.; Soria, A. *Tetrahedron* **1993**, *49*, 4267−4274.

(15) Crystallographic data (excluding structure factors) for *syn*-**5a**-*endo* and *anti*-**5b**-*endo* have been deposited with the Cambridge Crystallographic Data Centre as suplementary publication number CCDC 274908 and 274907, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44(0)-1223-366033 or e-mail: deposit@ccdc.cam.ac.uk].

(16) Keller, E.; de Lange, B.; Rispens, M. T.; Feringa, B. L. *Tetrahedron* **1993**, *49*, 8899−8910.

(17) Reed, A. D.; Hegedus, L. S. *J. Org. Chem.* **1995**, *60*, 3787−3794.

(18) The reactivity at room temperature of the sulfinylfuranone **2** with cyclopentadiene (see ref 9) was less than 20 times higher than that of the desulfinylated furanone (García Ruano, J. L.; Bercial, F.; Fraile, A.; Martín Castro, A. M.; Martín, M. R. *Tetrahedron: Asymmetry* **2000**, *11*, 4737−4752).

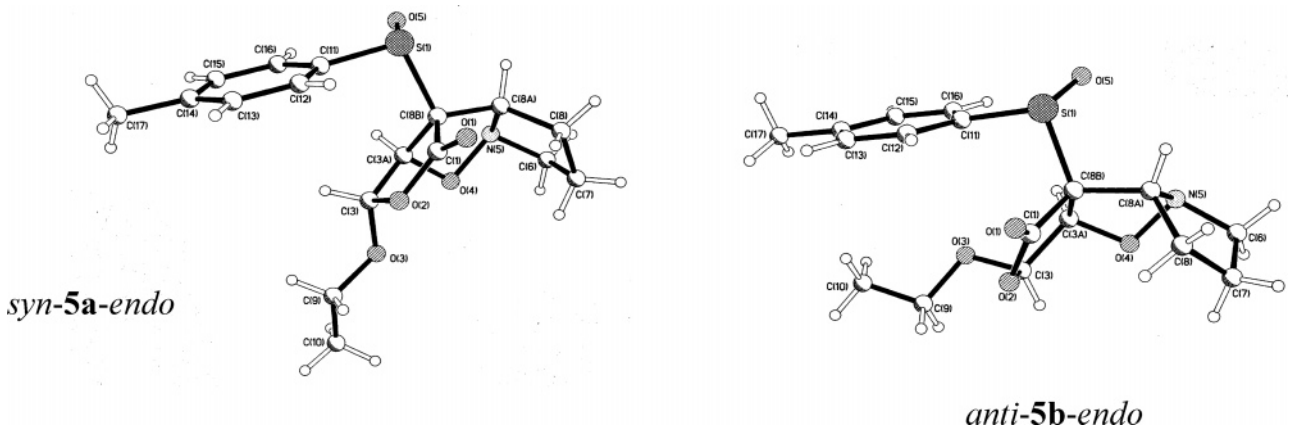
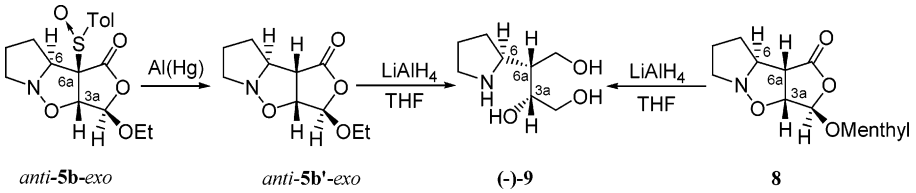


FIGURE 3. X-ray structures for *syn*-**5a**-*endo* and *anti*-**5b**-*endo*.

SCHEME 3



Alder reactions. In this sense, the reactions of **2** and nitrones are faster in toluene, the less polar solvent out of all those used.

The regioselectivity of the reactions of **2a** and **2b** with **4** and **6** was complete, only affording isoxazolidines with the nitrone oxygen bonded to C_4 at furanone. As this is the same regioisomer that it was obtained in reactions of these nitrones with 5-alkoxyfuran-2-(5*H*)-one, we can conclude that the regioselectivity was not modified by the sulfinyl group.

The π-facial selectivity observed in reactions from **2b** was identical to that of desulfinylated furanones, with the exclusive formation of the *anti* adducts (Tables 2 and 4). It can be easily explained by assuming that the *anti* approach was strongly favored by the 5-alkoxy group due to its steric and electrostatic repulsions with the oxygen at the nitrone,[17] as well as the steric grounds of the sulfoxide adopting the *s-cis* arrangement of its sulfinyl oxygen (Figure 4) to minimize repulsions with the carbonyl oxygen. Therefore, the *anti* approach to **2b** must be favored by both 5-alkoxy and 3-*p*-tolylsulfinyl groups (Figure 4). In the case of the epimer **2a**, the preferred conformation around the C−S bond arranges the *p*-tolyl group at the opposite face to that bearing the ethoxy group, which would explain the incomplete π-facial selectivity observed in these reactions (Tables 1 and 3) as a consequence of the competence between both directing groups (Figure 4). As the *anti* adducts also were predominant in reactions from **2a** (Tables 1 and 3), a conformational equilibrium between **A** and **B** rotamers (Figure 4) can be assumed and the *anti* adducts were obtained by *anti* approach to **B** conformer. We can conclude that the orientating character of the alkoxy group was rather higher than that of the sulfinyl one. The same model would allow us to explain the lower reactivity exhibited by the epimer **2a**.

The presence of the sulfinyl group sharply increased the proportion of the *endo* isomers in all the cases (with cyclic or acyclic nitrone, *anti* or *syn* approach). The cycloadditions reported in this paper, under kinetic control conditions, were almost completely *endo* selective (Tables 1−4), except for the addition of nitrone **4** to **2a** in the *anti* approach (see Table 1), where the *endo*/*exo* ratios ranged between 63/37 and 52/48. The sulfinyl group must be the main responsible for this behavior as it can be inferred from the comparison of our results with those obtained in reactions of 5-alkoxyfuran-2(5*H*)-ones

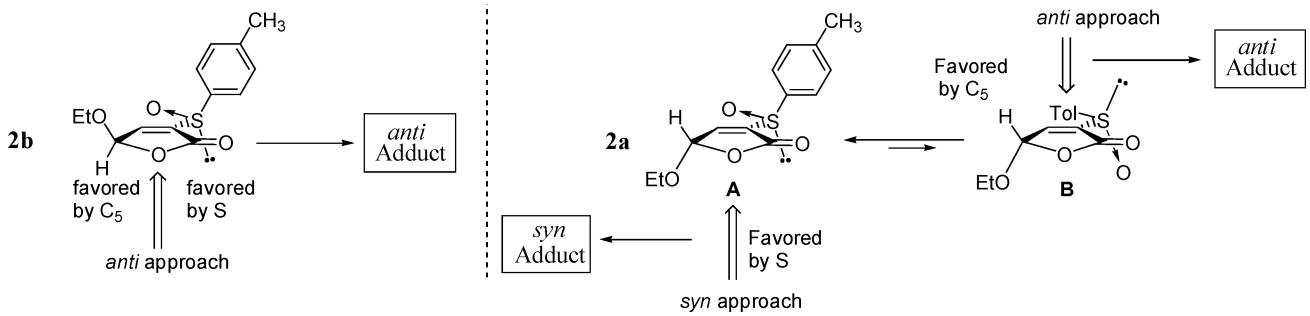


FIGURE 4. π-Facial selectivity of additions of nitrones to 3-sulfinylfuranones **2**.

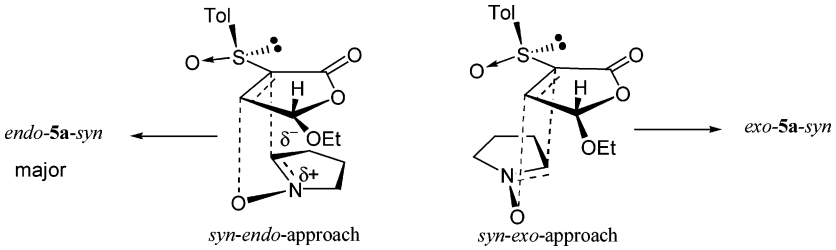


FIGURE 5. Transition states for the *syn*-approach of nitrone **4** to furanone **2a**.

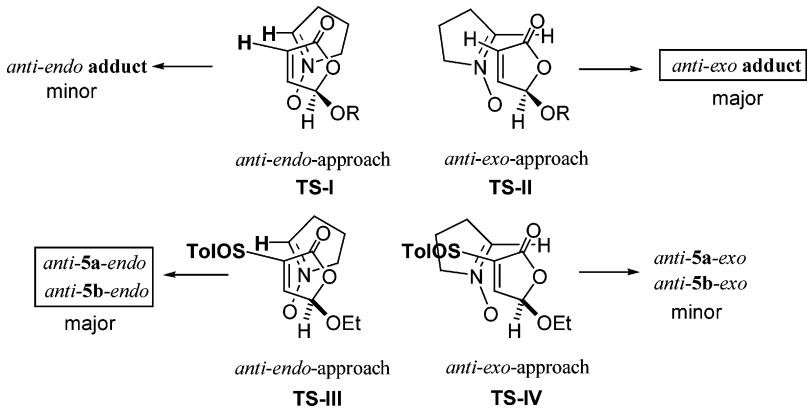


FIGURE 6. Stereochemical course of the reactions of 5-alkoxyfuranones with nitrone **4**.

with **4** and **6**, which afforded the *exo* isomers as the only or major product.

In Figure 5 are depicted the TSs for the *endo-syn* and *exo-syn* approaches of nitrone **4** to **2a**. The *endo*-orienting character of the ester group and the electrostatic attraction between the negative charge at the acetalic oxygen and the positive charge at the nitrogen could account for the almost exclusive formation of the *endo*-**5a**-*syn* adduct under kinetic control conditions.[19]

In the case of the *anti* approaches, where the above-mentioned electrostatic attraction was not significant, steric interactions must be predominant. **TS-I** and **TS-II** (Figure 6) are the two possible transition states for the reactions of **4** with 5-alkoxyfuran-2(5*H*)-ones. The formation of the *anti-exo* adduct as the major[13,16] or only[17] product can be explained by assuming that steric interactions at **TS-I** are larger than at **TS-II**. The introduction of the sulfinyl group at C_3 of dipolarophile increases the proportion of the *endo* isomers under kinetic control conditions (Tables 1 and 2) and scarcely modifies the stability of the transition state corresponding to the *endo-anti* approach (**TS-III** and **TS-I** only differ in the H/SOTol interaction) whereas strongly destabilizes the *exo-anti* approach (**TS-IV** much less stable than **TS-II** due to the ring/SOTol interactions), which could become the least stable one for reactions of sulfinylbutenolides with **4**.

The results obtained in reactions of the acyclic nitrone **6** are much more difficult to be explained because of the configurational instability of the nitrone. At low temperature, this compound adopts the *Z* configuration but the *Z*−*E* equilibration is very easy, and on many occasions the formation of the resulting cycloadducts has been explained by evolution via the *E*-isomer, which is usually much more reactive, despite the fact that it exists as the minor isomer in the equilibrium.[20] The fact that the same product was obtained through an *anti-endo* approach of the *Z*-nitrone or an *anti-exo* approach of the *E*-isomer, as it is illustrated in Figure 7 for the formation of *anti*-**7a,b**-*endo* and *anti*-**7a,b**-*exo*, makes difficult any explanation. However, in Figure 7 it can be seen that the approaches **I** and **II** to yield *anti*-**7a,b**-*endo* are more stabilized than **III** and **IV**, which afford their corresponding *exo* isomers, due to the steric interaction Ph/SOTol in the later ones. This interactions must be more destabilizing for **2a** than for **2b** (compare the approaches **III,IV-a** with **III,IV-b**). This justifies the low or none proportion of the *anti*-**7b**-*exo* and *anti*-**7a**-*exo* in their respective reactions.

The last point to be discussed concerns the cycloreversion processes, which determined significant changes in the composition of the reaction mixtures depending on the reaction conditions and can be used for synthetic purposes. Under thermodynamic control conditions (high temperatures and long reaction times) the formation of the presumably more stable *anti* adducts was always favored (see Tables 1 and 3) but the *endo*/*exo* ratio was markedly dependent on the stereochemistry of the sulfinylfuranone and the structure of the nitrone. The predominance of the *endo* adducts was very high or even exclusive in reactions from the acyclic nitrone **6** (Tables 3 and 4), but it was almost inexistent or even the *exo* adduct was predominant in reactions from cyclic nitrone **4** (Tables 1 and 2). The different polarity of the adducts must be responsible for the different composition of the equilibria in the studied solvent.

(19) One of the reviewers has suggested that the *endo*/*exo* selectivity in polar cycloadditions could be explained by favorable coulombic interactions between the nitrone, positively charged, and the furanone, negatively charged, at the corresponding *endo* zwitterionic TS.

(20) Cristina, D.; De Micheli, C.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2891−2895 and references therein.

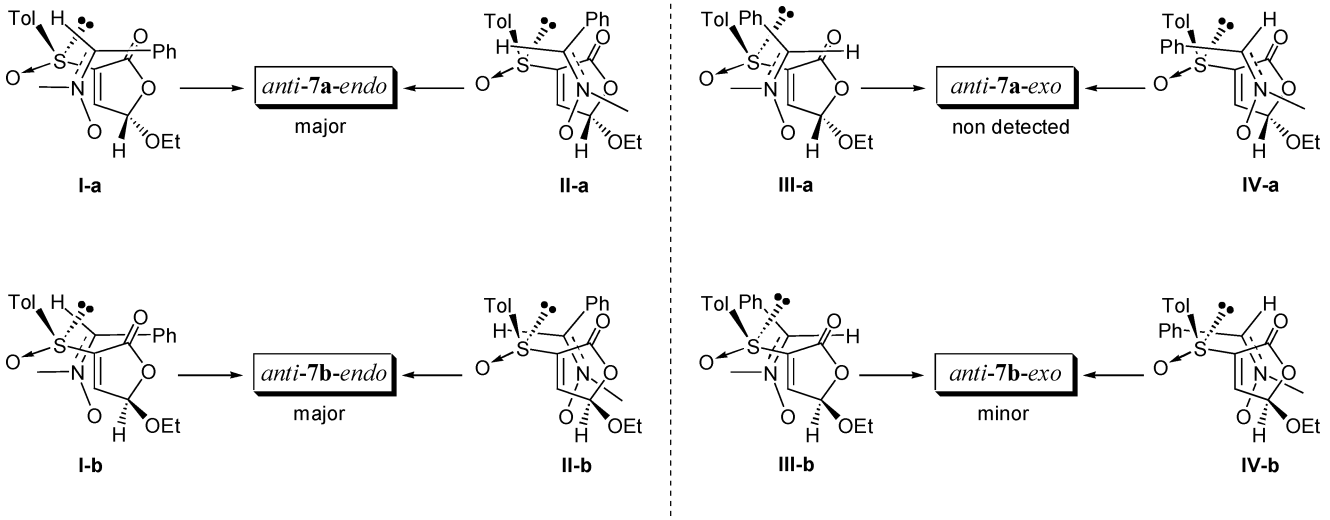
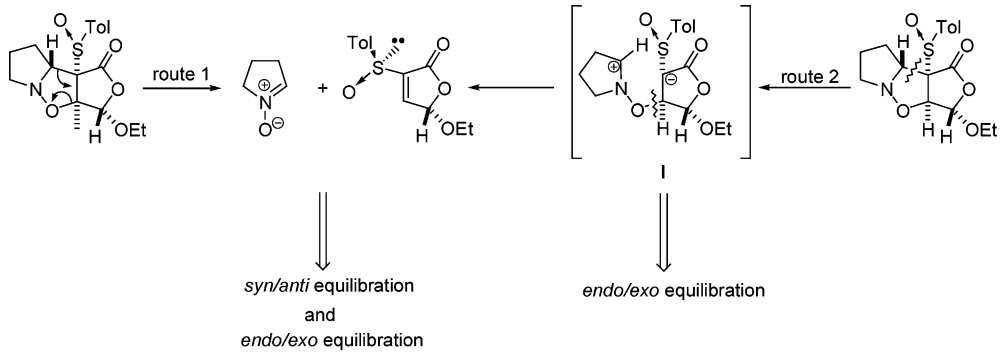
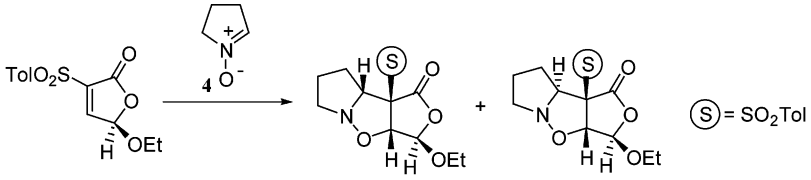


FIGURE 7. Stereochemical course of the reactions of sulfinylfuranones **2** with nitrone **6**.

SCHEME 4



SCHEME 5



Toluene (rt, 5 min)	20	80
Acetonitrile (rt, 5 min)	34	66
Acetonitrile (rt, 18 h)	28	72

Cycloreversion could take place either according to concerted or by step mechanisms (route 1 and route 2, respectively, Scheme 4). The influence of the solvent polarity on the cycloreversion rate (it was faster in the most polar solvent, see Figures 1 and 2) does not allow differentiation because the ring-opening products are more polar in any case. However, from the available data it seemed that the *endo/exo* equilibration required shorter reaction times than the *syn/anti* equilibration (see Tables 1−4). It supports route 2 (Scheme 4) involving the cleavage of the C−C in the first step because the resulting intermediates **I** are able to give the *endo/exo* conversion but not the *syn/anti* conversion, which would require the cleavage of the O−C bond.

If route 2 was operative, the readiness of the cycloreversion would depend on the stabilization of the carbanion generated in the first step. Then, the cycloreversion would be faster from sulfonylisoxazolidines than from the corresponding sulfinyl derivatives, whereas it would be slower from isoxazolidines bearing only one electron-withdrawing group. Thus, cycloreversion from sulfonylisoxazolidines **11**, obtained by reaction of 5-ethoxy-3-*p*-tolylsulfonylfuran-2(5*H*)-one (**10**)[21] with nitrone **4** (Scheme 5), was faster than that from the corresponding sulfinyl derivatives **5**. In turn, when starting from (+)-*anti*-**5′**-*endo*, with no sulfur function, the cycloreversion was scarcely detected (after 16 h in refluxing toluene only 15% of the presumably most stable (−)-*anti*-**5′**-*exo* was obtained). It suggests that the ready cycloreversion took

(21) García Ruano, J. L.; Fajardo, C.; Fraile, A.; Martín, M. R. *J. Org. Chem.* **2005**, *70*, 4300−4306.

place only when two electron-withdrawing groups were bonded to C_{8b}.

Conclusion

We have studied the reactions of sulfinyl furanones **2a** and **2b** with cyclic and acyclic nitrones (**4** and **6**). The sulfinyl group significantly enhances the dipolarophilic reactivity of the furanones, it is the main responsible for the *endo*/*exo* selectivity, and modulates the facial selectivity imposed by the 5-alkoxy substituent. The adducts suffer an easy cycloreversion, which determines significant changes in the composition of the equilibria depending on the experimental conditions. As these changes increase or invert the stereoselectivity, they can be used with synthetic purposes. Finally, we have established that cycloreversion must be expected for those isoxazolidines bearing two electron withdrawing groups at C_4.

Experimental Section

Cycloadditions of Nitrones. General Procedure. A solution of furanone **2a** or **2b** (1.21 mmol) and nitrone **4** (1.82 mmol in 15 mL) or **6** (4.84 mmol in 16 mL) in the solvent indicated in Tables 1−4 was stirred under argon at the temperature and for the time indicated in Tables 1−4. The reaction was monitored by TLC and ^{1}H NMR. After completion, the solvent was removed at reduced pressure. The adducts were isolated by column chromatography with the eluent indicated in each case.

(*S*$_3$,*S*$_S$)-3-Ethoxy-8b-[(4-methylphenyl)sulfinyl]-3a,6,7,8,8a,8b-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-ones (5a). Compound **5a** was obtained from (*S*$_5$,*S*$_S$)-5-ethoxy-3-[(4-methylphenyl)sulfinyl]furan-2(5*H*)-one (**2a**) and nitrone **4** (see Table 1) after 1 h of reaction time in chloroform at room temperature in 86% combined yield. The stereoisomers were separated by column chromatography (hexane/ethyl acetate, 3:2).

(*S*$_3$,*R*$_{3a}$,*R*$_{8a}$,*S*$_{8b}$,*S*$_S$)-*anti*-5a-*exo*. White solid. Mp: 86−87 °C. $[\alpha]^{20}_D = +219.7$ (*c* 1.0, $CHCl_3$). IR (Nujol): 1770, 1595, 1460, 1090, 1070. ^{1}H NMR (200 MHz) δ: 7.60 and 7.25 (AA′BB′ system, 4H), 5.18 (s, 1H), 4.25 (s, 1H), 3.84 (dd, 1H, J = 7.6 and 9.1), 3.34 (m, 1H), 3.31 (q, 2H, J = 7.1), 2.95 (m, 1H), 2.40−2.07 (m, 3H), 2.34 (s, 3H), 1.95−1.83 (m, 1H), 0.88 (t, 3H, J = 7.1). ^{13}C NMR (50.3 MHz) δ: 170.0 (C), 143.2 (C), 135.4 (C), 129.7 (CH), 126.2 (CH), 106.5 (CH), 81.2 (CH), 79.6 (C), 73.9 (CH), 65.4 (CH_2), 55.2 (CH_2), 24.8 (CH_2), 24.3 (CH_2), 21.4 (CH_3), 14.4 (CH_3). Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; S, 9.12. Found: C, 57.78; H, 5.66; N, 4.01; S, 8.82.

(*S*$_3$,*R*$_{3a}$,*S*$_{8a}$,*S*$_{8b}$,*S*$_S$)-*anti*-5a-*endo*. White solid. Mp: 74−75 °C. $[\alpha]^{20}_D = +56.8$ (*c* 1.0, $CHCl_3$). IR (Nujol): 1775, 1595, 1460, 1082, 1057. ^{1}H NMR (200 MHz) δ: 7.64 and 7.36 (AA′BB′ system, 4H), 5.36 (s, 1H), 4.72 (s, 1H), 4.27 (m, 1H), 3.74 (m, 1H), 3.61 (m, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.45 (s, 3H), 1.90−1.65 (m, 4H), 1.17 (t, 3H, J = 7.0). ^{13}C NMR (50.3 MHz) δ: 169.1 (C), 143.1 (C), 135.0 (C), 129.4 (CH), 126.0 (CH), 102.6 (CH), 84.4 (CH), 78.9 (C), 68.4 (CH), 65.6 (CH_2), 55.9 (CH_2), 25.6 (CH_2), 23.6 (CH_2), 21.4 (CH_3), 14.4 (CH_3). Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; S, 9.12. Found: C, 58.08; H, 5.71; N, 3.80; S, 9.56.

(*S*$_3$,*S*$_{3a}$,*R*$_{8a}$,*R*$_{8b}$,*S*$_S$)-*syn*-5a-*endo*. White solid. Mp: 89−90 °C. $[\alpha]^{20}_D = +256.6$ (*c* 1.0, $CHCl_3$). IR (Nujol): 1760, 1595, 1460, 1080, 1055. ^{1}H NMR (200 MHz) δ: 7.55 and 7.35 (AA′BB′ system, 4H), 5.00 (d, 1H, J = 4.3), 4.68 (d, 1H, J = 4.3), 4.09 (m, 1H), 3.78 (m, 1H), 3.59 (m, 1H), 3.32 (m, 1H), 3.05 (m, 1H), 2.43 (s, 3H), 2.11−1.68 (m, 4H), 1.19 (t, 3H, J = 7.1). ^{13}C NMR (50.3 MHz) δ: 167.5 (C), 143.6 (C), 135.0 (C), 130.0 (CH), 125.1 (CH), 101.9 (CH), 83.6 (C), 80.1 (CH), 71.1 (CH), 67.9 (CH_2), 55.6 (CH_2), 25.2 (CH_2), 23.6 (CH_2), 21.5 (CH_3), 14.6 (CH_3). Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; S, 9.12. Found: C, 58.13; H, 5.91; N, 4.15; S, 9.43.

(*R*$_3$,*S*$_S$)-3-Ethoxy-8b-[(4-methylphenyl)sulfinyl-3a,6,7,8,8a,8b-hexahydrofuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-ones (5b). Compound **5b** was obtained as a mixture of *anti*-**5b**-*exo* and *anti*-**5b**-*endo* from (*R*$_5$,*S*$_S$)-5-ethoxy-3-[(4-methylphenyl)sulfinylfuran-2(5*H*)-one (**2b**) and **4**. The experimental conditions, the stereoisomer ratio, and the obtained yields are shown in Table 2. The products were separated by column chromatography (hexane/ethyl acetate, 3:1).

(*R*$_3$,*S*$_{3a}$,*S*$_{8a}$,*R*$_{8b}$,*S*$_S$)-*anti*-5b-*exo*. Colorless oil. $[\alpha]^{20}_D = -52.8$ (*c* 1.4, $CHCl_3$). IR ($CHCl_3$): 1765, 1597, 1352, 1083, 1057. ^{1}H NMR (200 MHz) δ: 7.58 and 7.28 (AA′BB′ system, 4H), 5.35 (s, 1H), 4.83 (s, 1H), 4.06 (dd, 1H, J = 8.1 and 8.9), 3.40 (m, 3H), 3.02 (m, 1H), 2.58 (m, 1H); 2.40 (s, 3H), 2.22 (m, 1H), 2.06 (m, 1H), 1.89 (m, 1H), 0.99 (t, 3H, J = 7.0). ^{13}C NMR (50.3 MHz) δ: 171.2 (C), 143.0 (C), 135.4 (C), 129.4 (CH), 126.4 (CH), 108.1 (CH), 83.0 (C), 78.3 (CH), 74.2 (CH), 65.6 (CH_2), 55.0 (CH_2), 24.7 (CH_2), 24.1 (CH_2), 21.4 (CH_3), 14.5 (CH_3). Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; S, 9.12. Found: C, 57.45; H, 6.12; N, 4.13; S, 8.65.

(*R*$_3$,*S*$_{3a}$,*R*$_{8a}$,*R*$_{8b}$,*S*$_S$)-*anti*-5b-*endo*. White solid. Mp: 103−104 °C. $[\alpha]^{20}_D = +81.2$ (*c* 1.0, $CHCl_3$). IR (KBr): 1765, 1595, 1361, 1086, 1063. ^{1}H NMR (200 MHz) δ: 7.55 and 7.31 (AA′BB′ system, 4H), 5.21 (s, 1H), 4.66 (s, 1H), 4.31 (m, 1H), 3.37−3.06 (m, 4H), 2.41 (s, 3H), 2.22−1.79 (m, 4H), 0.84 (t, 3H, J = 7.0). ^{13}C NMR (50.3 MHz) δ: 170.3 (C), 142.8 (C), 135.1 (C), 129.7 (CH), 125.6 (CH), 105.1 (CH), 83.7 (C), 82.3 (CH), 72.6 (CH), 65.6 (CH_2), 55.6 (CH_2), 26.1 (CH_2), 23.6 (CH_2), 21.4 (CH_3), 14.2 (CH_3). Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; S, 9.12. Found: C, 58.15; H, 5.70; N, 3.74; S, 8.86.

(*S*$_6$,*S*$_S$)-6-Ethoxy-2-methyl-3a-[(4-methylphenyl)sulfinyl]-3-phenyl-3,3a,6,6a-tetrahydrofuro[3,4-*d*]isoxazol-4(2*H*)-ones (7a). Compound **7a** was obtained as a mixture of *anti*-**7a**-*endo* and *syn*-**7a**-*endo* from (*S*$_5$,*S*$_S$)-5-ethoxy-3-[(4-methylphenyl)sulfinyl]furan-2(5*H*)-one (**2a**) and nitrone **6**, following the general procedure. The stereoisomer ratio and the obtained yields are indicated in Table 3. The products were isolated by column chromatography (hexane/ethyl acetate, 3:1).

(*S*$_3$,*S*$_{3a}$,*S*$_6$,*R*$_{6a}$,*S*$_S$)-*anti*-7a-*endo*. White solid. Mp: 56−58 °C. $[\alpha]^{20}_D = +188.0$ (*c* 0.5, $CHCl_3$). IR (KBr): 1778, 1595, 1083, 1051. ^{1}H NMR (300 MHz) δ: 7.75 and 7.34 (AA′BB′ system, 4H), 7.22 (m, 3H), 6.89 (m, 2H), 5.64 (d, 1H, J = 2.2), 4.98 (d, 1H, J = 2.2), 3.88 (m, 1H), 3.73 (s, 1H), 3.70 (m, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 1.25 (t, 3H, J = 7.1). ^{13}C NMR (75.5 MHz) δ: 168.2 (C), 143.2 (C), 135.2 (C), 132.1 (C), 129.7 (CH), 129.0 (CH), 128.3 (CH), 126.5 (CH), 106.5 (CH), 83.2 (CH), 81.3 (C), 76.8 (CH), 66.3 (CH_2), 42.1 (CH_3), 21.4 (CH_3), 14.7 (CH_3). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.49; S, 7.99. Found: C, 62.90; H, 5.78; N, 3.44; S, 8.33.

(*R*$_3$,*R*$_{3a}$,*S*$_6$,*S*$_{6a}$,*S*$_S$)-*syn*-7a-*endo*. White solid. Mp: 122−124 °C. $[\alpha]^{20}_D = -41.6$ (*c* 0.25, $CHCl_3$). IR (KBr): 1773, 1595, 1495, 1073, 1053. ^{1}H NMR (300 MHz) δ: 7.50 and 7.34 (AA′BB′ system, 4H), 7.46 (m, 5H), 4.87 (d, 1H, J = 5.1), 4.28 (s, 1H), 4.25 (d, 1H, J = 5.1), 3.82 (m, 1H), 3.57 (m, 1H), 2.69 (s, 3H), 2.42 (s, 3H), 1.23 (t, 3H, J = 7.1). ^{13}C NMR (75.5 MHz) δ: 166.9 (C), 143.4 (C), 134.9 (C), 131.4 (C), 130.3 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 124.6 (CH), 103.1 (CH), 84.4 (C), 76.5 (CH), 74.0 (CH), 67.3 (CH_2), 43.1 (CH_3), 21.4 (CH_3), 14.6 (CH_3). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.49; S, 7.99. Found: C, 62.60; H, 5.42; N, 3.48; S, 7.60.

(*R*$_6$,*S*$_S$)-6-Ethoxy-2-methyl-3a-[(4-methylphenyl)sulfinyl]-3-phenyl-3,3a,6,6a-tetrahydrofuro[3,4-*d*]isoxazol-4(2*H*)-ones (7b). Compound **7b** was obtained following the general procedure from (*R*$_5$,*S*$_S$)-5-ethoxy-3-[(4-methylphenyl)sulfinyl]-furan-2(5*H*)-one (**2b**) and **6** as mixtures of *anti*-**7b**-*endo* and *anti*-**7b**-*exo* in the ratio and yields indicated in Table 4. The adducts were purified by column chromatography (hexane/ethyl acetate, 7:1).

(*R*$_3$,*R*$_{3a}$,*R*$_6$,*S*$_{6a}$,*S*$_S$)-*anti*-7b-*endo*. White solid. Mp: 142−143 °C. $[\alpha]^{20}_D = -144.0$ (*c* 0.5, $CHCl_3$). IR (KBr): 1773, 1594, 1493, 1082, 1051. ^{1}H NMR (300 MHz) δ: 7.49 and 7.29 (AA′BB′

system, 4H), 7.42 (s, 5H), 5.38 (d, 1H, J = 1.4), 4.65 (d, 1H, J = 1.4), 4.31 (s, 1H), 3.38 (m, 2H), 2.65 (s, 3H), 2.39 (s, 3H), 0.87 (t, 3H, J = 7.1). ^{13}C NMR (75.5 MHz) δ: 168.5 (C), 142.8 (C), 135.0 (C), 131.6 (C), 129.9 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 125.5 (CH), 107.5 (CH), 84.4 (C), 80.0 (CH), 76.9 (CH), 65.3 (CH_2), 42.6 (CH_3), 21.4 (CH_3), 14.5 (CH_3). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.49; S, 7.99. Found: C, 62.98; H, 5.71; N, 3.49; S, 8.35.

(S_3,R_{3a},R_6,S_{6a},S_S)-*anti*-7b-*exo*. White solid. Mp: 100−102 °C. $[\alpha]^{20}_D$ = +62.8 (c 0.25, $CHCl_3$). IR (KBr): 1771, 1494, 1374, 1085, 1062, 1032. ^{1}H NMR (55 °C, 300 MHz) δ: 7.65 (m, 2H), 7.46 (m, 5H), 7.22 (d, 2H, J = 7.9), 5.32 (s, 1H), 4.99 (s, 1H), 4.16 (broad s, 1H), 3.36 (m, 2H), 2.64 (s, 3H), 2.37 (s, 3H), 0.94 (t, 3H, J = 7.1). ^{13}C NMR (55 °C, 75.5 MHz) δ: 170.8 (C), 142.4 (C), 134.9 (C), 131.2 (C), 129.8 (CH), 129.4 (CH), 129.4 (CH), 128.6 (CH), 126.4 (CH), 105.1 (CH), 84.1 (C), 80.3 (CH), 79.5 (CH), 65.7 (CH_2), 43.0 (CH_3), 21.4 (CH_3), 14.4 (CH_3). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.49; S, 7.99. Found: C, 62.78; H, 5.82; N, 3.44; S, 8.00.

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Supporting Information Available: Experimental procedures and characterization data of compounds [(+)-*anti*-**5′a**-*exo*], [(−)-*anti*-**5′a**-*endo*], [(−)-*anti*-**5′b**-*exo*], [(+)-*anti*-**5′b**-*endo*], [(+)-*anti*-**7′a**-*endo*], [(−)-*syn*-**7′a**-*endo*], [(−)-*anti*-**7′b**-*endo*], [(−)-*anti*-**7′b**-*exo*], [(−)-**9**], and adducts **11**, as well as the crystallographic data for compounds *syn*-**5a**-*endo* and *anti*-**5b**-*endo* (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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