Asymmetric Induction in the Cycloaddition of a Masked *p*-Benzoquinone to Cyclic Nitrones†

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1,3-Dipolar cycloadditions of cyclic nitrones to achiral and chiral *p*-benzoquinone monoketals have shown poor chemo- and stereoselectivity. To overcome these problems, a highly efficient strategy has been set up on the basis of the temporary conjugate addition of thiophenol to the dipolarophile. The phenylthio derivative **10b**, available in both enantiopure forms, has demonstrated to be effective as a masked chiral synthetic equivalent of *p*-benzoquinone in the model reaction.

Introduction

p-Benzoquinone derivatives are interesting molecules not only due to their participation in important bioorganic redox processes but also because they have proved to be very useful in synthetic organic chemistry.[1] The reactivity of *p*-benzoquinones toward different classes of 1,3-dipoles has been investigated to some extent, and examples of cycloadditions to nitrile ylides,[2] nitrile oxides,[3] diazoalkanes,[4] phenyl azide,[5] azomethine ylides,[6] and nitrile sulfides[7] have already been reported, although the regio- and stereoselectivity of these reactions still remain uncertain.

Nitrones are among the most synthetically useful 1,3-dipoles, since their additions to olefins generate isoxazolidines, which are versatile intermediates for the preparation of interesting bioorganic molecules.[8] Generally, in the cycloaddition of a nitrone to an olefin there are two possible regioisomeric orientations. With 1,2-disubstituted electron poor olefins, a high degree of regioselectivity is usually achieved, in such way that the preferred regioadduct has the oxygen atom of the starting nitrone linked to the electronically more deficient carbon atom of the olefin,[9] although steric factors may also play an equally important role. *p*-Benzoquinone itself and its symmetric derivatives contain two double bonds that are identical initially, but once a single cycloaddition has taken place, the remaining double bond in the cycloadduct is expected to be more reactive toward the nucleophilic nitrone and therefore chemoselectivity has also to be considered. On the other hand, depending on the substitution of the starting nitrone and quinone, the resulting primary isoxazolidine may contain up to three new stereogenic centers from which various diastereoisomers originate. The reactivity of several *p*-benzoquinones toward nitrones was reported earlier and the expected cycloadducts were obtained only in very low yield, the suggested reason being the occurrence of complicated redox processes between reactants and products.[10] Moreover, depending on the substitution of the starting quinone, the aromatization of the primary adducts can easily take place, obscuring the stereochemical information of the process.

Quite often, the use of mono- and bisketals of quinones has been shown to be effective to overcome reactivity and/or selectivity problems presented by the corresponding unprotected quinones.[1] In particular, quinone monoketals have been successfully employed as key intermediates for the preparation of many bioactive molecules.[11] Recently, we have conveniently prepared two optically pure *p*-benzoquinone monoketals, (+)-**1c** and (+)-**1d**, derived from (2*R*,3*R*)-butane-2,3-diol and (2*R*,3*R*)-1,2-diphenyl-

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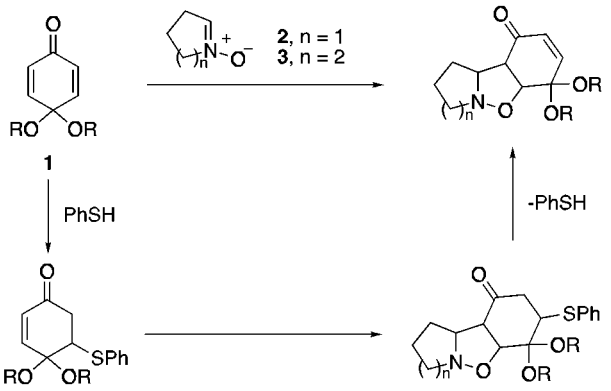
S0022-3263(97)01035-9 CCC: $14.00

Scheme 1



ethylene glycol, respectively (Scheme 2).[12] We thought that these compounds could be used as a source of chirality for developing enantioselective nitrone cycloadditions.[13] We therefore decided to investigate the reactivity of *p*-benzoquinone monoketals toward cyclic nitrones **2**[14] and **3**[15] (Scheme 1) as part of a more general study in which other 1,2-disubstituted electron-deficient olefins were also included,[9d−g,16] and our results are presented in this paper. As will be shown, we have developed a strategy consisting of masking one of each pair of the functional groups of *p*-benzoquinone, the carbonyl and the double bond, through ketalization followed by transient conjugate addition of thiophenol (Scheme 1). In this way a chiral synthetic equivalent of *p*-benzoquinone has been prepared and its efficiency has been tested in nitrone cycloaddition chemistry.

Results and Discussion

Cycloaddition of Nitrone 3 to *p*-Benzoquinone. For comparison, we first carried out the reaction between the more reactive nitrone 2,3,4,5-tetrahydropyridine 1-oxide (**3**) and an excess of unprotected *p*-benzoquinone in $CHCl_3$ at room temperature. The starting nitrone was completely consumed after 4 days, according to TLC analysis, but the ^{1}H-NMR spectrum of the crude product did not show any identifiable compound, as expected on the basis of the literature precedents.[10]

Cycloadditions of Nitrones 2 and 3 to Monoketals 1a−c. The results of the cycloadditions of nitrones **2** and **3** to *p*-benzoquinone monoketals **1a−c** (Scheme 2) are collected in Table 1. Ketal **1a**[17] was prepared *in situ* through oxidation of *p*-methoxyphenol with diacetoxyiodobenzene diacetate in methanol solution,[17a] and therefore the cycloadditions to **1a** run at room temperature or below were performed in methanol (entries 1 and 4−7). For the other ketals, the cycloadditions were done in chloroform or toluene solutions, depending on the reaction temperature. In all the cases an excess of ketal was used, in order to favor the formation of 1:1 cycloadducts, and the reactions were stopped when TLC analysis indicated that the nitrone was totally consumed. The reaction between nitrone **2** and ketal **1a** (entries 1 and 2) gave a low yield of 1:1 cycloadducts, along with a large quantity of unidentifiable products. In the ^{1}H-NMR spectra of the isolated isomers, the chemical shift of the hydrogen atoms at the α (H_{9a}) and β (H_{5a}) positions with respect to the carbonyl group (δ 3.04 and 4.54 for **4a** and δ 3.33 and 4.41 for **5a**, respectively) are in agreement with the expected regiochemistry. The *endo* or *exo* stereochemistry was established according to the value of the coupling constant $J_{9a,9b}$, that is 1.2 Hz for the *exo* adduct **4a** (H_{9a} and H_{9b} are in *trans*) and 9.6 Hz for the *endo* adduct **5a** (H_{9a} and H_{9b} are in *cis*). Diagnostic for the stereochemical elucidation are also the higher chemical shifts observed for the carbon atoms C_1, C_3, C_{9a}, and C_{9b} in the *exo* adduct **4a** (δ 31.2, 58.3, 58.3, and 70.0, respectively) in relation to the *endo* adduct **5a** (δ 27.5, 56.2, 54.4, and 69.5, respectively), due to the greater steric compression of these carbon atoms in the latter cycloadduct.[18] From the reaction between nitrone **2** and the ethylene ketal **1b**[19] (entry 3), the *exo* 1:1 cycloadduct **4b** ($J_{9a,9b}$ = 2.6 Hz) was obtained in 18% yield.[20] Despite the excess of starting ketal used in this reaction, a substantial quantity of a 2:1 cycloadduct (**6b**) was also isolated. The number of signals observed in the ^{13}C-NMR spectrum of this last compound reveals a highly symmetrical structure. In particular, the single absorption presented by the ethylenic carbon atoms of the dioxolane ring (δ 67.0) indicates C_2 symmetry and the value of $J_{11a,11b} = J_{12a,12b}$ = 2.9 Hz is in agreement with a doubly *exo* stereochemistry.[21]

The cycloadditions of nitrone **3** to the monoketals **1a** and **1b** (entries 4−10) gave better yields of identifiable products. With this nitrone the *exo* selectivity appears to be high for both ketals, although the relative quantities of 2:1 cycloadducts (**9a** and **9b**) also increased, even when larger excesses of the ketal were employed (entries 7 and

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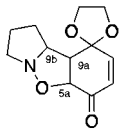
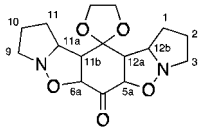
(20) Another 1:1 cycloadduct was also obtained from this reaction in 16% yield. This compound happened to be unstable and therefore could not be fully characterized. Nevertheless, its ^{1}H-NMR spectrum matches with a regioisomeric adduct **A**. The α carbonyl proton H_{5a} appears as a doublet with $J_{5a,9a}$ = 7.3 Hz at δ 4.35, while the β carbonyl proton H_{9a} resonates at δ 2.75 as a td with $J_{9a,5a} = J_{9a,9b}$ = 7.3 Hz and a long distance coupling $J_{9a,8}$ = 2.2 Hz, which is also observed in the ethylenic proton H_8 at δ 6.60 and only compatible with the regiochemistry depicted in **A**.



A

(21) The spectroscopic data do not allow us, however, to exclude the other possible regiochemistry (**B**), and although the regioisomer **6b** would be the one expected on the basis of the FMO theory and of most precedents, the isolation of the 1:1 cycloadduct **A** in the same reaction makes the structure assigned to **6b** only tentative.



B

Scheme 2

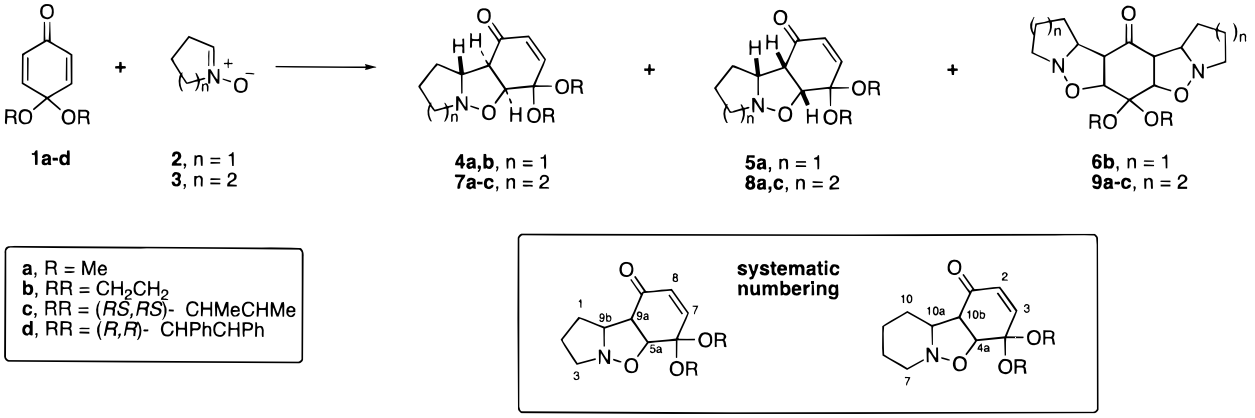


Table 1. 1,3-Dipolar Cycloaddition of Nitrones 2 and 3 to Quinone Monoketals 1a−c

entry	nitrone	ketal	[ketal]/[nitrone]	conditions	*exo*-adduct (%)	*endo*-adduct (%)	*2:1*-adduct (%)
1	**2**	**1a**	1.2	CH_3OH, rt, 3 months	**4a** (7)	**5a** (5)	
2	**2**	**1a**	2.0	$PhCH_3$, 110 °C, 8 h	**4a** (21)	**5a** (12)	
3[a]	**2**	**1b**	1.7	$PhCH_3$, 110 °C, 4.5 h	**4b** (18)		**6b** (24)
4	**3**	**1a**	1.1	CH_3OH, −18 °C, 6.5 months	**7a** (38)		**9a** (21)
5	**3**	**1a**	1.1	CH_3OH, 4 °C, 17 d	**7a** (39)		**9a** (33)
6	**3**	**1a**	1.1	CH_3OH, rt, 7 d	**7a** (41)	**8a** (0.6)	**9a** (40)
7	**3**	**1a**	1.8	CH_3OH, rt, 5 d	**7a** (51)	**8a** (1.3)	**9a** (30)
8	**3**	**1b**	1.2	$CHCl_3$, 4 °C, 16 d	**7b** (9)		**9b** (72)
9	**3**	**1b**	1.2	$CHCl_3$, rt, 7 d	**7b** (16)		**9b** (70)
10	**3**	**1b**	4.0	$CHCl_3$, rt, 7 d	**7b** (24)		**9b** (39)
11	**3**	(±)-**1c**	1.4	$CHCl_3$, rt, 6 d	**7c** (11)[b]		**9c** (80)
12	**3**	(±)-**1c**	4.5	$PhCH_3$, 110 °C, 1 h	**7c** (33)[b]		**9c** (62)
13	**3**	(±)-**1c**	12.2	$PhCH_3$, 110 °C, 1.5 h	**7c** (51)[b]	**8c** (<11)[c]	**9c** (30)
14	**3**	(±)-**1c**	23.0	110 °C, 10 min	**7c** (83)[b]		

[a] A regioisomeric 1:1 cycloadduct was also isolated in 16% yield. [b] Product **7c** was a mixture of the two possible *exo* cycloadducts. [c] The isolated sample of **8c** contained some unidentifiable impurities.

10). The assignment of the *exo* or *endo* stereochemistry to the 1:1 cycloadducts **7** and **8** was not always trivial because of the complicated conformational behavior of some of these compounds, due to the slow inversion of the nitrogen lone pair. Nevertheless, comparison of their ^{1}H- and ^{13}C-NMR spectra with those of related compounds previously prepared and carefully studied by our group[9d] allowed us to establish their stereochemistry. The conformational complexity is still amplified in the 2:1 cycloadducts (**9**) and we have not made efforts to elucidate their precise structural features. At room temperature, the major primary adduct **7a** derived from **1a** and **3** shows broad absorptions in its ^{1}H-NMR spectrum, while at 250 K two sets of signals can be observed with a relative intensity of 2:1 corresponding respectively to the *trans*- and *cis*-fused invertomers of the azabicyclic system. For the minor cycloadduct **8a**, only the *trans* invertomer is observed at any temperature, as was the case for other closely related cycloadducts with *endo* stereochemistry.[9d] The larger value of the coupling constant $J_{10a,10b}$ (9.2 *vs* 6.1 Hz) and the higher chemical shifts presented by C_{10}, C_{10a}, and C_{10b} for the *trans* invertomer of the *exo* adduct **7a** in relation to the *endo* **8a** are particularly useful for the stereochemical assignment. From the reactions between the ethylene ketal **1b** and nitrone **3**, only the *exo* primary adduct **7b** was isolated, its spectroscopical data being similar to those of **7a**.

We also wanted to evaluate how the introduction of a chiral auxiliary in the acetal moiety of the dipolarophile may influence the steric course of the cycloaddition process. To that end, we performed the 1,3-dipolar cycloaddition between racemic monoketal (±)-**1c**[22] and nitrone **3** (entries 11−14). After several trials under various conditions, the reaction was best carried out by addition of a solution of nitrone **3** in $CHCl_3$ to a large excess of preheated monoketal **1c** without solvent. In this way, a 83% yield of 1:1 cycloadducts was obtained, as a *ca.* 1:1 mixture of two diastereoisomers, **7c**, and most unreacted monoketal was recovered unchanged. We were not able to separate the two diastereoisomers **7c** and they were therefore characterized as a mixture. By analogy to the similar cycloadducts previously prepared, we assigned the *exo* stereochemistry to both. That means that the chiral auxiliary had not been able to induce facial selectivity during the cycloaddition reaction.

The results obtained so far indicated that the primary 1:1 cycloadducts are at least as good dipolarophiles as the starting ketals and only under very extreme conditions (entry 14) can one obtain high chemoselectivity in this kind of cycloaddition reaction. Therefore, the convenience of protecting one of the double bonds of the starting ketal becomes apparent.

Conjugate Addition of Thiophenol to Ketals 1a−d. We decided therefore to investigate the conjugate addition of thiols to *p*-benzoquinone monoketals. The resulting monoaddition products could be considered as masked *p*-benzoquinone equivalents, since the thioether functional group allows regeneration of the conjugated double bond and the hydrolysis of the ketal, the regeneration of the carbonyl group. We also hoped that the presence of the phenylthio group in the dipolarophile could somehow influence the stereochemical course of the cycloaddition.

The addition of thiophenol to monoketals **1a**, **1b**, (±)-**1c**, and (+)-**1d** delivered the phenyl thioketals **10a−d**

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Scheme 3

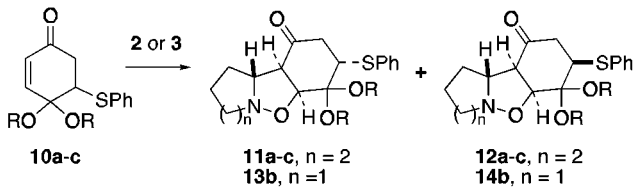


Table 2. 1,3-Dipolar Cycloaddition of Phenylthio Derivatives 10a−c and Consecutive Thiophenol Elimination

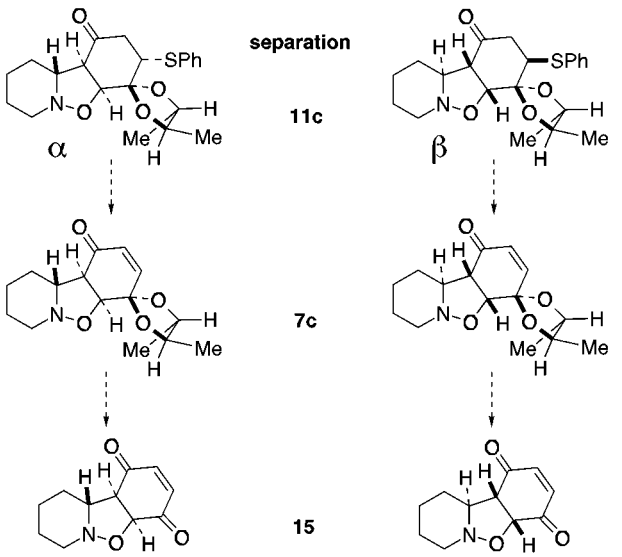
nitrone	dipolarophile	cycloaddition product (%)	*anti*/*syn*	elimination product (%)
3	**10a**	**11a** (39) **12a** (42)	0.9	**7a** (73)
3	**10b**	**11b** (98) **12b** (2)	49	**7b** (77)
3	**10c**	**11c** (94) **12c** (5)	17	**7c**[a] (77)
2	**10b**	**13b** (54) **14b** (9)	5	**4b** (33)

[a] Product **7c** was a mixture of the two possible diastereoisomers.

in good yields (Scheme 3).[23] Unfortunately, both **10c** and **10d** were obtained as *ca.* 1:1 mixtures of the two possible diastereoisomers that we were not able to separate. Although the addition of other thiols to (+)-**1d** was exhaustively studied, we never succeeded in obtaining a single diastereoisomer of the conjugate addition product. Since these reactions were performed under thermodynamically controlled conditions, the lack of diastereofacial differentiation indicates that the chiral auxiliary in the ketal moiety does not sensibly affect the relative stabilities of the thio derivatives.

Cycloadditions to Phenylthio Derivatives 10a−c. Nitrone **3** was used to study the 1,3-dipolar cycloaddition to the phenylthio derivatives. The reactions were carried out in chloroform always using an excess of nitrone, and the results are collected in Table 2. The cycloaddition between **3** and the dimethyl ketal **10a** gave a *ca.* 1:1 mixture of two cycloadducts, **11a** and **12a**, in 81% overall yield. The *exo*−*anti* stereochemistry of **11a** was evidenced by a positive NOE effect between H_3 (δ 4.07) and H_{10a} (δ 2.09 and 3.40 for the *trans*- and the *cis*-invertomers, respectively). For **12a** the *syn* stereochemistry could also be established by the observed NOE between H_{4a} (δ 4.27/4.63, *trans*/*cis*) and H_3 (δ 3.60/3.71, *trans*/*cis*), but the *exo* stereochemistry could only be later assured by chemical correlation (*vide infra*). In contrast, the addition of **3** to **10b** proceeded quantitatively to give mainly the *exo*−*anti* cycloadduct **11b** (98%) and a small percentage of another isomer tentatively assigned as *exo*−*syn*, **12b**. The ^{1}H-NMR data of the major compound were not enough to establish its stereochemistry, since it shows very complex spectra due to the existence of almost equimolar amounts of each possible invertomer. We prepared the *N*-benzyl quaternary bromide of **11b**,[24] but this derivative did not allow us to solve the problem either. Finally, the stereochemistry of **11b** could be secured as *exo*−*anti* by an X-ray diffraction analysis.[25] The great difference in the diastereoselectivity of the cycloaddition of nitrone **3** to each ketal **10a** and **10b** seems to indicate that the dioxolane ring plays an important role in the facial differentiation that is probably related to the major rigidity of the spiranic system.[26]

Scheme 4



Although **10c** was a mixture of diastereoisomers epimeric at the stereogenic center bearing the sulfur substituent, we considered that it was worthy to try its cycloaddition to nitrone **3**. Provided that the phenylthio group caused the anticipated diastereofacial selectivity, two major cycloadducts should be expected, both coming from *exo*−*anti* approaches of the reactants in the transition state (Scheme 4). If it was possible to separate the isomers α and β of **11c**, then, through elimination of thiophenol, we could obtain each diastereoisomer of **7c**. On the other hand, starting the sequence with the enantiopure ketal (+)-**1c**, the subsequent hydrolysis of the ketal function in **7** would give an independent access to every enantiomer of a cycloadduct **15** formally coming from *p*-benzoquinone. Our expectations were accomplished only in part. **10c** reacted with nitrone **3** giving the corresponding cycloadducts **11c** and **12c** in 99% overall yield, with a very high *anti*/*syn* selectivity of 17:1, but we were unable to separate each diastereoisomer from the mixture **11c**.

The cycloaddition of the dioxolane derivative **10b** to nitrone **2** was also studied. From this reaction the corresponding cycloadducts **13b** and **14b** were isolated with poorer yield (63%) and facial selectivity (*anti*/*syn* = 5), in agreement with the lower reactivity and minor sterical demand of nitrone **2** compared to **3**.[9d,e]

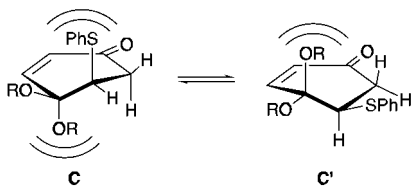
Elimination of Thiophenol. The major adducts obtained in these last cycloadditions were correlated with

(23) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Medrano, J. *An. Quim. Int. Ed.* **1997**, *93*, 81.

(24) In related compounds we have observed that *N*-benzylation yields *cis*-fused isoxazolidinium salts, independent of the preferred invertomer of the starting azabicyclic system. Sometimes this fact can help to elucidate the stereochemistry of these compounds. Although the benzylation of **11b** gave as expected a unique *cis*-fused salt, its spectroscopic data were not enough to unequivocally assign its stereochemistry.

(25) The authors have deposited atomic coordinates for **11b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(26) Compound **10a** presents values of the coupling constants between H_5 and the protons at C_6 of 3.7 and 2.2 Hz,[23] which indicate its preference for a conformer like **C**, where the phenylthio and the *trans*-alkoxy groups are axially located, each one of these groups hindering opposite faces of the double bond. On the contrary, the values of $J_{5,6}$ measured for **10b** are 9.5 and 6.6 Hz, in better agreement with a preference for the conformer **C′**, in which only the *cis*-alkoxy group is axial, therefore making its face more sterically demanding.



those previously prepared from the *p*-benzoquinone monoketals **1a**−**c** (Table 2). The base-promoted elimination of thiophenol proceeded in better yields than the alternative pyrolytic elimination of the corresponding sulfoxides. The conversion of **11a**/**12a** into **7a**, **11b** into **7b**, **11c** into **7c**, and **13b**/**14b** into **4b** confirmed the *exo* relative stereochemistry of all these compounds.

Cycloaddition of Nitrone 3 to (+)-10b. With the results so far obtained, we concluded that an enantiopure dipolarophile equivalent to *p*-benzoquinone should fulfill the following structural features: (i) a dioxolane spiranic system in order to achieve a good diastereofacial selectivity and (ii) the carbon atom bearing the phenylthio group as the only source of chirality. It was also desirable to have access to both enantiomers. Therefore, we attempted the direct resolution of racemic derivative **10b**. This resolution could be effected by liquid chromatography using cellulose triacetate as chiral stationary phase.[23]

Compound (+)-**10b** was then treated with an excess of nitrone **3** and it afforded a single adduct (+)-**11b** with $[\alpha]^{20}_D = +13.2$ ($c = 2.35$, $CHCl_3$). Then the base-promoted elimination of thiophenol under the standard conditions gave (−)-**7b** with $[\alpha]^{20}_D = -27.7$ ($c = 0.65$, $CHCl_3$).[27]

Conclusion

In summary, we have developed a methodology for masking one of each pair of functional groups of *p*-benzoquinone, the carbonyl and the double bond, through monoketalization and transient conjugate addition of thiophenol, respectively. By direct resolution of **10b**, both antipodes of an enantiopure equivalent of *p*-benzoquinone have been obtained. To show the efficiency of our strategy, the 1,3-dipolar cycloaddition to a cyclic nitrone has been studied as a model reaction and a very high degree of both regio- and stereoselectivity has been achieved. We are now extending that methodology to other processes.

Experimental Section

General. See ref 9d. The NMR spectra were recorded by Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona. HRMS were performed by Servei de Masses, Departament d'Ecotecnologies, CSIC. The following compounds were prepared according to previously described methods: **1a**,[17a] **1b**,[19] (±)-**1c**,[22] (+)-**1c**,[12] (+)-**1d**,[12] **2**,[14] **3**,[15] and **10a**−**c**.[23] The NMR spectra of several cycloadducts are too complex to be described and they have been supplied as Supporting Information.

Reaction between Nitrone 2 and Monoketal 1a. Nitrone **2** (300 mg, 3.5 mmol) was added to a solution of **1a** in 16 mL of anhydrous toluene (prepared from 875 mg, 7.1 mmol, of *p*-methoxyphenol and 2.3 g, 7.2 mmol, of diacetoxyiodobenzene in MeOH through evaporation and solvent exchange) and the mixture was stirred at reflux under argon for 8 h. Removal of the solvent *in vacuo* gave 2.9 g of crude material. Flash column chromatography through silica gel using EtOAc/ether 3:2 as eluent afforded the following fractions: (i) 1.4 g of iodobenzene; (ii) 733 mg of **1a**; (iii) 177 mg (21% yield) of (5a*RS*,9a*SR*,9b*SR*)-1,2,3,5a,6,9,9a,9b-octahydro-6,6-dimethoxypyrrolo[1,2-*b*][1,2]benzisoxazol-9-one, **4a**; (iv) 98 mg (12% yield) of its (5a*RS*,9a*SR*,9b*RS*)-isomer, **5a**; and (v) 380 mg of unidentified material. **4a**: IR (film) 1688, 1131, 1061 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 6.76 (dd, $J = 10.4$, 2.4 Hz, 1H), 6.04 (d, $J = 10.4$ Hz, 1H), 4.54 (dd, $J = 4.9$, 2.4 Hz, 1H), 3.90 (br t, $J = 7.3$ Hz, 1H), 3.35 (s, 3H), 3.25 (s, 3H), 3.15 (dt, $J = 11.5$, 6.6 Hz, 1H), 3.04 (dd, $J = 4.9$, 1.2 Hz, 1H), 3.01 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.68 (m, 2H); ^{13}C-NMR (62.5 MHz, acetone-d_6) δ 196.5, 147.5, 130.2, 96.5, 75.5, 70.0, 58.3, 49.1, 48.7, 31.2, 25.2; MS *m*/*z* 239 (7), 128 (100), 123 (85). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.22; H, 7.17; N, 5.86. Found: C, 60.40; H, 7.12; N, 5.73. **5a**: mp 30−32 °C (EtOAc/hexane); IR (film) 2924, 1680, 1117, 1054 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 6.73 (dd, $J = 10.4$, 2.4 Hz, 1H), 6.11 (d, $J = 10.4$ Hz, 1H), 4.41 (dd, $J = 6.1$, 2.4 Hz, 1H), 3.96 (dt, $J = 9.6$, 7.3 Hz, 1H), 3.33 (dd, $J = 9.6$, 6.1 Hz, 1H), 3.33 (s, 3H), 3.20 (m, 1H), 3.18 (s, 3H), 2.90 (dt, $J = 13.4$, 7.3 Hz, 1H), 1.69 (m, 1H), 1.62 (m, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 196.4, 147.6, 131.1, 96.3, 77.4, 69.5, 56.2, 54.4, 48.59, 48.54, 27.5, 24.8; MS *m*/*z* 239 (27), 154 (85), 123 (100), 86 (88). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.22; H, 7.17; N, 5.86. Found: C, 60.31; H, 7.20; N, 5.83.

The same reaction run at rt in MeOH for 3 months with a molar ratio **1a**/**2** = 1.2 yielded 7% of **4a** and 5% of **5a**.

Reaction between Nitrone 2 and Monoketal 1b. Nitrone **2** (200 mg, 2.4 mmol) was added to a solution of **1b** (629 mg, 4.1 mmol) in anhydrous toluene (12 mL) and the mixture was stirred at reflux under argon for 4.5 h. Removal of the solvent *in vacuo* gave 810 mg of crude material. Flash column chromatography through silica gel using EtOAc/ether 3:2 as eluent afforded the following fractions: (i) 440 mg of **1b**; (ii) 91 mg (16% yield) of (5a*RS*,9a*SR*,9b*RS*)-9,9-(ethylenedioxy)-1,2,3,5a,6,9,9a,9b-octahydropyrrolo[1,2-*b*][1,2]benzisoxazol-6-one, **A**; (iii) 102 mg (18% yield) of (5a*RS*,9a*SR*,9b*SR*)-6,6-(ethylenedioxy)-1,2,3,5a,6,9,9a,9b-octahydropyrrolo[1,2-*b*]-[1,2]benzisoxazol-9-one, **4b**; and (iv) 94 mg (24% yield) of a 2:1 cycloadduct, **6b**. **A**: IR (film) 2958, 1688, 1010, 943 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.60 (dd, $J = 10.2$, 2.2 Hz, 1H), 6.12 (d, $J = 10.2$ Hz, 1H), 4.35 (d, $J = 7.3$ Hz, 1H), 4.00 (m, 4H), 3.65 (td, $J = 7.3$, 2.9 Hz, 1H), 3.30 (dd, $J = 13.4$, 6.1 Hz, 1H), 2.75 (m, 1H), 2.75 (td, $J = 7.3$, 2.2 Hz, 1H), 1.75 (m, 4H). **4b**: mp 103−106 °C (CH_2Cl_2/hexane); IR (KBr) 1680, 1138, 1012, 991 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 6.67 (dd, $J = 10.2$, 2.0 Hz, 1H), 6.02 (d, $J = 10.2$ Hz, 1H), 4.40 (dd, $J = 5.2$, 2.0 Hz, 1H), 4.10 (m, 4H), 3.94 (ddd, $J = 8.2$, 5.6, 2.6 Hz, 1H), 3.15 (dd, $J = 5.2$, 2.6 Hz, 1H), 3.15 (m, 1H), 2.97 (dt, $J = 12.5$, 7.0 Hz, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.70 (m, 2H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 196.4, 146.5, 131.1, 103.3, 78.3, 69.7, 66.8, 66.1, 58.5, 58.3, 30.5, 24.9; MS *m*/*z* 237 (6), 126 (100). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.73; H, 6.38; N, 5.91. Found: C, 60.66; H, 6.42; N, 5.89. **6b**: mp 169−171 °C (CH_2Cl_2/hexane); IR (KBr) 2966, 1715, 1152, 1082, 1054 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.62 (d, $J = 8.8$ Hz, 2H), 4.05 (m, 4H), 3.70 (m, 2H), 3.37 (dd, $J = 8.8$, 2.9 Hz, 2H), 3.20 (m, 2H), 3.00 (m, 2H), 2.00 (m, 4H), 1.70 (m, 4H); ^{13}C-NMR (62.5 MHz, acetone-d_6) δ 79.3, 69.1, 67.0, 61.9, 56.7, 23.6; MS *m*/*z* 322 (7), 321 (31), 237 (15), 192 (69), 152 (85), 136 (79), 126 (100), 98 (75), 86 (87).

Reaction between Nitrone 3 and Monoketal 1a. A methanol solution of nitrone **3** (prepared from 168 mg, 1.7 mmol, of *N*-hydroxypiperidine and 992 mg, 4.6 mmol, of yellow HgO) was added to a solution of **1a** in 25 mL of MeOH (prepared from 222 mg, 1.8 mmol, of *p*-methoxyphenol and 585 mg, 1.8 mmol, of diacetoxyiodobenzene). The mixture was stirred at rt under argon for 7 d. Removal of the solvent *in vacuo* gave 858 mg of crude material. Flash column chromatography through silica gel using CH_2Cl_2/ether 10:1 as eluent afforded the following fractions: (i) 196 mg of iodobenzene; (ii) 87 mg of **1a**; (iii) 3 mg (0.6% yield) of (4a*RS*,10a*RS*,10b*SR*)-4,4a,7,8,9,10,10a,10b-octahydro-4,4-dimethoxy-1*H*-pyrido[1,2-*b*][1,2]-benzisoxazol-1-one, **8a**; (iv) 177 mg (41% yield) of its (4a*RS*,10a*SR*,10b*SR*)-isomer, **7a**; and (v) 120 mg (40% yield) of 2:1 a cycloadduct, **9a**. **8a**: IR (film) 2938, 1687, 1131, 1061 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 6.72 (dd, $J = 9.8$, 2.4 Hz, 1H), 6.09 (d, $J = 9.8$ Hz, 1H), 4.59 (dd, $J = 6.1$, 2.4 Hz, 1H), 3.30 (s, 3H), 3.27 (m, 1H), 3.17 (t, $J = 6.1$ Hz, 1H), 3.15 (s, 3H), 2.65 (ddd, $J = 11.0$, 6.1, 2.4 Hz, 1H), 2.34 (ddd, $J = 12.2$, 8.6, 2.4 Hz, 1H), 1.92 (m, 1H), 1.65 (m, 2H), 1.48 (m, 1H), 1.15 (m, 2H); ^{13}C-NMR (62.5 MHz, acetone-d_6) δ 195.9, 148.2, 133.1, 97.4, 75.8, 70.8, 56.8, 55.2, 48.9, 48.8, 28.0, 25.3, 24.1;

(27) The absolute configuration of (+)-**10b** has been determined to be *S* by chemical correlation: we have used compounds (+)- and (-)-**10b** as starting materials for the asymmetric syntheses of (*S*)- and (*R*)-4-hydroxycyclohexenone respectively,[28] which will be published in due course. Accordingly, the absolute configuration of (+)-**11b** is (3*S*,4a*S*,10a*R*,10b*R*) and that of (−)-**7**, (4a*S*,10a*R*,10b*R*).

(28) Gebauer, O.; Brückner, R. *Liebigs Ann.* **1996**, 1559.

MS *m*/*z* 253 (19), 154 (20), 123 (100), 100 (83), 99 (57). **7a**: IR (film) 2938, 1687, 1131, 1117, 1061 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6, 250 K) *trans*-invertomer (67%): δ 6.76 (dd, J = 10.4, 2.5 Hz, 1H), 6.15 (d, J = 10.4 Hz, 1H), 4.36 (dd, J = 7.3, 2.4 Hz, 1H), 3.32 (s, 3H), 3.30 (m, 1H), 3.14 (s, 3H), 2.90 (dd, J = 9.2, 7.3 Hz, 1H), 2.36 (ddd, J = 12.2, 9.1, 3.1 Hz, 1H), 1.97 (ddd, J = 11.6, 9.2, 2.4 Hz, 1H), 1.82 (m, 1H), 1.70 (m, 2H), 1.50 (m, 2H), 1.16 (m, 1H); *cis*-invertomer (33%), observable signals: δ 6.77 (dd, J = 10.4, 2.4 Hz, 1H), 6.14 (d, J = 10.4 Hz, 1H), 4.80 (dd, J = 7.7, 2.4 Hz, 1H), 3.31 (s, 3H), 3.27 (m, 1H), 3.19 (br t, J = 7.7, 1H), 3.15 (s, 3H), 2.90 (m, 2H); ^{13}C-NMR (100 MHz, acetone-d_6, 250 K) *trans*-invertomer: δ 196.0, 149.2, 131.0, 96.5 or 96.0, 76.3, 72.0, 57.1, 55.3, 49.0, 48.7 or 48.6, 29.2, 24.9, 24.0; *cis*-invertomer, observable signals: δ 196.8, 148.7, 131.2, 96.5 or 96.0, 75.8, 66.3, 54.8, 50.4, 49.0, 48.7 or 48.6, 25.1, 19.8; MS *m*/*z* 253 (33), 222 (18), 128 (100), 123 (92), 100 (79), 99 (52). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.54; H, 7.55; N, 5.34. **9a**: mp 154−157 °C ($CHCl_3$/pentane); IR (KBr) 2944, 2923, 2845, 1710, 1150, 1057 cm^{-1}; ^{1}H-NMR: see Supporting Information; MS *m*/*z* 352 (17), 253 (21), 221 (31), 154 (39), 100 (100). Anal. Calcd for $C_{18}H_{28}N_2O_5$: C, 61.35; H, 8.01; N, 7.95. Found: C, 61.22; H, 8.07; N, 7.96.

The same reaction performed at 4 °C for 17 d yielded 39% of **7a** and 33% of **9a**; at −18 °C for 6.5 months, 38% of **7a** and 21% of **9a**; and at rt for 5 d with a molar ratio **1a**/**3** = 1.8, 51% of **7a**, 1.3% of **8a**, and 30% of **9a**.

Reaction between Nitrone 3 and Monoketal 1b. A chloroform solution of nitrone **3** (prepared from 249 mg, 2.5 mmol, of *N*-hydroxypiperidine and 1.53 g, 7.1 mmol, of yellow HgO) was added to a solution of **1b** (443 mg, 2.9 mmol) in $CHCl_3$ (25 mL) and the mixture was stirred at rt under argon for 7 d. Removal of the solvent *in vacuo* gave 696 mg of crude material. Flash column chromatography through silica gel using EtOAc/ether 2:1 as eluent afforded the following fractions: (i) 152 mg of **1b**; (ii) 103 mg (16% yield) of (4a*RS*,10a*SR*,10b*SR*)-4,4-(ethylenedioxy)-4,4a,7,8,9,10,10a,10b-octahydro-1*H*-pyrido[1,2-*b*]-[1,2]benzisoxazol-1-one, **7b**; and (iii) 304 mg (70% yield) of a 2:1 cycloadduct, **9b**. **7b**: IR (film) 2941, 1681, 1149, 1014 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6, 250 K) *trans*-invertomer (53%): δ 6.77 (dd, J = 10.2, 1.0 Hz, 1H), 6.13 (d, J = 10.2 Hz, 1H), 4.31 (dd, J = 8.5, 1.0 Hz, 1H), 4.00 (m, 4H), 3.33 (dt, J = 8.9, 3.5 Hz, 1H), 3.00 (dd, J = 10.0, 8.5 Hz, 1H), 2.42 (ddd, J = 12.1, 8.9, 2.9 Hz, 1H), 2.20 (ddd, J = 11.8, 10.0, 2.4 Hz, 1H), 2.03 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 1.50 (m, 1H), 1.35 (m, 1H), 1.15 (m, 1H); *cis*-invertomer (47%), observable signals: δ 6.78 (dd, J = 10.1, 1.0 Hz, 1H), 6.11 (d, J = 10.1 Hz, 1H), 4.69 (br d, J = 8.1 Hz, 1H), 3.46 (dt, J = 8.7, 4.5 Hz, 1H), 3.39 (m, 1H), 2.95 (m 1H), 2.75 (m, 1H); ^{13}C-NMR (100 MHz, acetone-d_6, 250 K) *trans*-invertomer: δ 195.8, 147.3, 132.3, 102.7, 77.0, 69.8, 66.9, 65.9 or 65.7, 55.8, 55.4, 29.3, 25.0, 23.7; *cis*-invertomer, observable signals: δ 196.9, 103.3, 78.3, 65.9 or 65.7, 63.9, 55.1, 51.6, 19.4; MS *m*/*z* 251 (30), 152 (9), 126 (100), 99 (41), 98 (52). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.18; H, 6.83; N, 5.48. **9b**: mp 164−166 °C (CH_2Cl_2/hexane); IR (KBr) 2947, 2923, 2855, 2824, 1706, 1198, 1159, 1034, 1006 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.0−1.0 (broad absorptions); MS *m*/*z* 350 (12), 251 (23), 152 (14), 126 (67), 100 (57), 99 (43), 55 (72), 41 (100). Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.69; H ,7.48; N, 7.99. Found: C, 61.60; H, 7.46; N, 7.87.

The same reaction performed at 4 °C for 16 d yielded 9% of **7b** and 72% of **9b**, and at rt for 7 d with a molar ratio **1b**/**3** = 4, it gave 24% of **7b** and 39% of **9b**.

Reaction between Nitrone 3 and Monoketal (±)-1c. A chloroform solution of nitrone **3** (prepared from 105 mg, 1.0 mmol, of *N*-hydroxypiperidine and 614 mg, 2.8 mmol, of yellow HgO) was added to a refluxing solution of (±)-**1c** (2.20 g, 12.2 mmol) in toluene (9.5 mL) and the mixture was heated at reflux for 1.5 h. Removal of the solvent *in vacuo* gave 2.20 g of crude material. Flash column chromatography through silica gel using CH_2Cl_2/ether 4:1 as eluent afforded the following fractions: (i) 1.87 g of (±)-**1c**; (ii) 31 mg of a mixture of (4a*RS*,10a*RS*,10b*SR*)-4,4-[(1*RS*,2*RS*)- and (4a*RS*,10a*RS*,-10b*SR*)-4,4-[(1*SR*,2*SR*)-(1,2-dimethylethylene)dioxy]-4,4a,7,8,9,10,10a,10b-octahydro-1*H*-pyrido[1,2-*b*][1,2]-benzisoxazol-1-one, **8c**, along with some impurities; (iii) 142 mg (51% yield) of a mixture of (4a*RS*,10a*SR*,10b*SR*)-4,4-[(1*RS*,2*RS*)- and (4a*RS*,10a*SR*,10b*SR*)-4,4-[(1*SR*,2*SR*)-isomers, **7c**; and (iv) 57 mg (30%) of a mixture of 2:1 cycloadducts, **9c**. **8c**: IR (film) 2924, 1673, 1638 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) significant signals: δ 6.83 (dd, J = 10.2, 2.2 Hz) + 6.75 (dd, J = 10.2, 2.5 Hz) (H_3), 6.17 (d, J = 10.2 Hz) + 6.13 (d, J = 10.2 Hz) (H_2), 4.38 (dd, J = 5.8, 2.2 Hz) + 4.30 (dd, J = 5.9, 2.2 Hz) (H_{4a}), 3.47 (m, H_{7eq}), 3.21 (t, J = 5.5 Hz, H_{10b}), 2.63 (m, H_{10a}), 2.41 (m, H_{7ax}); MS *m*/*z* 279 (8), 180 (42), 154 (54), 126 (62), 110 (91), 99 (44), 82 (57), 64 (57), 55 (100), 43 (80), 41 (68). **7c**: IR (film) 2938, 2861, 1680, 1145, 1103, 1082 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6, 250 K) δ 6.78 (H_3), 6.05 (H_2), 4.72 (d, J = 8.5 Hz, *cis*-invertomer) + 4.57 (dd, J = 7.5, 1.5 Hz, *trans*-invertomer) + 4.36 (d, J = 9.2 Hz, *cis*-invertomer) + 4.20 (dd, J = 8.3, 1.4 Hz, *trans*-invertomer) (H_{4a}), see also Supporting Information; ^{13}C-NMR: see Supporting Information; MS *m*/*z* 279 (25), 180, (11), 154 (100), 126 (59), 99 (34), 55 (47). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.46; H, 7.65; N, 4.97. **9c**: mp 61−71 °C (CH_2Cl_2/hexane); IR (KBr) 2938, 1708, 1082 cm^{-1}; ^{1}H-NMR: see Supporting Information; MS *m*/*z* 378 (27), 279 (23), 180 (46), 154 (70), 100 (100), 55 (91), 41 (61). Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.46; H, 7.99; N, 7.40. Found: C, 63.53; H, 7.97; N, 7.31.

When the reaction was run for 10 min with a molar ratio (±)-**1c**/**3** = 23, 83% of **7c** was isolated as the only product, and when it was run for 1 h with a molar ratio (±)-**1c**/**3** = 4.5, the yield was 33% of **7c** and 62% of **9c**. The same reaction performed in $CHCl_3$ at rt for 6 d with a molar ratio (±)-**1c**/**3** = 1.4 yielded 11% of **7c** and 80% of **9c**.

Reaction between Nitrone 3 and Phenylthio Derivative 10a (General Procedure). Compound **10a** (1.47 g, 5.6 mmol) was added to a stirred solution of nitrone **3** (prepared from 844 mg, 8.4 mmol, of *N*-hydroxypiperidine and 5.13 g, 23.6 mmol, of yellow HgO) in $CHCl_3$ (19 mL) and the mixture was heated at reflux for 24 h. Removal of the solvent *in vacuo* gave 3.12 g of crude material. Flash column chromatography through silica gel using CH_2Cl_2/ether 4:1 as eluent afforded 788 mg (39% yield) of (3*RS*,4a*RS*,10a*SR*,10b*SR*)-decahydro-4,4-dimethoxy-3-(phenylthio)-1*H*-pyrido[1,2-*b*][1,2]benzisoxazol-1-one, **11a**, and 850 mg (42% yield) of its (3*RS*,4a*SR*,10a*RS*,-10b*RS*)-isomer, **12a**.

11a: mp 101−103 °C (CH_2Cl_2/pentane); IR (film) 2938, 1708, 1138, 1061 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), *trans*/*cis* = 1.8: δ 7.36 (m, 2H), 7.23 (m, 3H), 4.72 (d, J = 9.5 Hz, 1H *cis*), 4.41 (d, J = 9.5 Hz, 1H *trans*), 4.07 (m, 1H), 3.40 (m, 1H *trans* + 1H *cis*), 3.34 (s) + 3.33 (s) (6H), 3.20 (t, J = 9.5 Hz, 1H *cis*), 3.05 (m, 1H *cis*), 3.00 (t, J = 9.5 Hz, 1H *trans*), 2.70 (m, 1H), 2.55 (m, 1H *cis*), 2.46 (m, 2H *trans* + 1H *cis*), 2.09 (t, J = 10.4 Hz, 1H *trans*), 1.95 (m, 1H *trans*), 1.80−1.20 (complex absorption, 4H *trans* + 6H *cis*), 1.10 (m, 1H *trans*); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 206.1, 205.6, 135.3, 133.3, 131.6, 131.5, 129.0, 127.2, 99.3, 99.0, 77.3, 76.4, 69.2, 63.6, 59.6, 55.5, 55.3, 51.0, 50.7, 49.6, 46.3, 42.8, 28.9, 24.5, 24.3, 23.4, 23.3, 18.6; MS *m*/*z* 363 (2), 331 (8), 232 (80), 128 (100), 100 (81). Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.78; H, 6.94; N, 3.86; S, 8.80. Found: C, 62.82; H, 6.90; N, 3.85; S, 8.77.

12a: mp 71−73 °C (EtOAc/pentane); IR (film) 2938, 1708, 1117, 1061 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *trans*-invertomer (79%): δ 7.29 (m, 2H), 7.15 (m, 3H), 4.27 (d, J = 8.6 Hz, 1H), 3.60 (m, 1H), 3.45 (m, 1H), 3.44 (s, 3H), 3.16 (s, 3H), 2.85 (t, J = 9.2 Hz, 1H), 2.75 (m, 1H), 2.68 (dd, J = 18.3, 6.1 Hz, 1H), 2.67 (m, 1H), 2.60 (dd, J = 18.3, 3.0 Hz, 1H), 2.05 (m, 1H), 1.90−1.10 (complex absorption, 5H); *cis*-invertomer (21%), observable signals: δ 4.63 (m, 1H), 4.07 (m, 1H), 3.71 (m, 1H), 3.05 (m, 1H), 2.48 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) *trans*-invertomer: δ 206.6, 131.9, 129.1, 127.3, 98.6, 69.1, 58.0, 55.0, 49.8, 48.2, 46.8, 43.3, 29.5, 24.6, 23.5; MS *m*/*z* 363 (14), 232 (14), 128 (100), 110 (59), 100 (57). Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.78; H, 6.94; N, 3.86; S, 8.80. Found: C, 62.78; H, 7.02; N, 3.81; S, 8.88.

Reaction between Nitrone 3 and Phenylthio Derivative 10b. Following the general procedure, from 2.50 g (9.6 mmol) of **10b**, after 5.5 h of reaction, 5.66 g of crude material was obtained. Flash column chromatography through silica gel using CH_2Cl_2/ether 9:1 as eluent afforded 3.39 g (98% yield) of (3*RS*,4a*RS*,10a*SR*,10b*SR*)-4,4-(ethylenedioxy)decahydro-3-

(phenylthio)-1*H*-pyrido[1,2-*b*][1,2]benzisoxazol-1-one, **11b**, and 69 mg (2% yield) of its (3*RS*,4a*SR*,10a*RS*,10b*RS*)-isomer, **12b**.

11b: mp 83−86 °C (EtOAc/hexane); IR (KBr) 2945, 1708, 1159 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6, 250 K), *cis*/*trans* = 1.5: δ 7.50−7.20 (complex absorption, 5H), 4.61 (d, J = 9.0 Hz, 1H *cis*), 4.40 (dd, J = 11.4, 8.1 Hz, 1H *trans*), 4.30 (dd, J = 11.0, 7.6 Hz, 1H *cis*), 4.18 (d, J = 9.0 Hz, 1H *trans*), 4.18−4.00 (complex absorption, 4H), 3.69 (m, 1H *cis*), 3.37 (m, 1H *cis* + 1H *trans*), 3.18 (m, 1H *trans*), 3.12 (m, 1H *cis*), 2.95 (m, 1H *cis* + 1H *trans*), 2.64 (m, 1H *cis*), 2.50 (m, 1H *cis* + 3H *trans*), 1.90−1.10 (complex absorption, 6H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 206.0, 205.4, 134.8, 134.6, 131.1, 128.9, 126.9, 107.8, 107.1, 78.3, 69.9, 67.0, 66.2, 66.1, 64.3, 60.0, 56.6, 55.2, 50.6, 46.5, 43.7, 43.5, 28.6, 24.3, 24.2, 23.2, 22.6, 19.0; MS *m*/*z* 361 (7), 262 (64), 126 (100), 100 (53), 99 (53). Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.42; N, 3.88; S, 8.85. Found: C, 63.10; H, 6.53; N, 3.90; S, 8.72.

(3*S*,4a*S*,10a*R*,10b*R*)-11b. This compound was obtained in 79% yield starting from (*S*)-**10b.** (3*S*,4a*S*,10a*R*,10b*R*)-**11b**: mp 84−88 °C (EtOAc/hexane); $[\alpha]^{20}_D$ = +13.2° (c = 2.35 in $CHCl_3$).

12b: IR (film) 2938, 1708, 1209, 1075 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40−7.10 (complex absorption, 5H), 4.57 (d, J = 9.8 Hz) + 4.29 (d, J = 10.4 Hz) (1H), 4.20−1.10 (complex absorption), see also Supporting Information; ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 205.6, 134.7, 131.8, 128.9, 127.2, 107.7, 79.9, 78.6, 67.9, 67.6, 67.2, 67.1, 67.0, 62.3, 58.8, 55.1, 53.1, 51.6, 49.4, 49.0, 44.8, 29.3, 24.6, 24.3, 24.0, 23.1, 18.2; MS *m*/*z* 361 (20), 126 (53), 99 (71), 55 (100); HRMS (EI) (M^+) calcd for $C_{19}H_{23}NO_4S$ 361.1348, found 361.1343.

***N*-Benzylation of 11b.** Benzyl bromide (18 μL, 0.15 mmol) was added to a solution of **11b** (50 mg, 0.14 mmol) in anhydrous THF (7 mL) and the mixture was let at rt for 4 d. Removal of the solvent *in vacuo* gave 74 mg (100% yield) of a white solid identified as (3*RS*,4a*RS*,6*RS*,10a*SR*,10b*SR*)-*N*-benzyl-4,4-(ethylenedioxy)decahydro-1-oxo-3-(phenylthio)-1*H*-pyrido[1,2-*b*][1,2]benzisoxazolium bromide: mp 156−158 °C; IR (KBr) 2945, 1715 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 10H), 5.72 (d, J = 8.6 Hz, 1H), 5.36 (d, J = 14.0 Hz, 1H), 5.03 (d, J = 14.0 Hz, 1H), 4.49 (m, 1H), 4.22 (m, 3H), 4.12 (m, 2H), 3.97 (m, 1H), 3.72 (t, J = 7.3 Hz, 1H), 3.54 (br d, J = 12.0 Hz, 1H), 2.98 (dd, J = 17.4, 6.4 Hz, 1H), 2.71 (dd, J = 17.4, 8.3 Hz, 1H), 2.62 (m, 1H), 2.37 (m, 1H), 2.17 (m, 1H), 2.00 (m, 2H), 1.75 (m, 1H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 200.6, 133.2, 132.7, 132.4, 130.8, 129.1, 129.0, 127.8, 106.5, 80.3, 72.0, 66.8, 66.1, 58.9, 53.1, 47.1, 43.4, 23.3, 21.2, 15.3.

Reaction between Nitrone 3 and Phenylthio Derivative 10c. Following the general procedure, from 214 mg (0.74 mmol) of **10c**, after 9 h of reaction, 408 mg of crude material was obtained. Flash column chromatography through silica gel using CH_2Cl_2/ether 9:1 as eluent afforded 272 mg (94% yield) of a mixture of (3*RS*,4a*RS*,10a*SR*,10b*SR*)-4,4-[(1*RS*,2*RS*)- and (3*RS*,4a*RS*,10a*SR*,10b*SR*)-4,4-[(1*SR*,2*SR*)-(1,2-dimethylethylene)dioxy]decahydro-3-(phenylthio)-1*H*-pyrido[1,2-*b*][1,2]benzisoxazol-1-one, **11c**, and 16 mg (5% yield) of a mixture of their (3*RS*,4a*SR*,10a*RS*,10b*RS*)-isomers, **12c**.

11c: mp 44−46 °C (pentane); IR (KBr) 2938, 1708, 1082 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.15 (m, 3H), 4.53 (d, J = 8.6 Hz) + 4.42 (d, J = 8.6 Hz) + 4.25 (d, J = 7.9 Hz) + 4.13 (d, J = 9.8 Hz) (1H), 4.10−1.10 (complex absorption), see also Supporting Information; ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 202.8, 202.1, 132.1, 127.8, 127.4, 127.1, 125.5, 125.4, 124.8, 123.4, 123.3, 123.1, 103.6, 102.9, 77.2, 76.9, 76.0, 75.6, 75.1, 74.4, 74.2, 73.7, 73.2, 66.8, 66.6, 61.3, 60.9, 57.1, 56.3, 54.0, 52.9, 52.0, 47.4, 47.1, 43.4, 43.2, 43.0, 40.5, 40.3, 40.1, 26.2, 25.4, 21.1, 20.9, 19.9, 19.3, 19.1, 15.9, 13.5, 13.3, 12.4, 12.3; MS *m*/*z* 389 (18), 290 (49), 154 (100), 126 (50), 55 (82). Anal. Calcd for $C_{21}H_{27}NO_4S$: C, 64.75; H 6.99; N, 3.60; S, 8.22. Found: C, 64.74; H, 7.05; N, 3.54; S, 8.11.

12c: IR (film) 2931, 1708, 1082 cm^{-1}; ^{1}H-NMR: see Supporting Information; MS *m*/*z* 389 (9), 290 (12), 154 (19), 126 (19), 55 (100); HRMS (EI) (M^+) calcd for $C_{21}H_{27}NO_4S$ 389.1661, found 389.1663.

Reaction between Nitrone 2 and Phenylthio Derivative 10b. Nitrone **2** (100 mg, 1.2 mmol) was added to a solution of **1b** (145 mg, 0.55 mmol) in anhydrous toluene (2 mL) and the mixture was heated at reflux for 6 h. Removal of the solvent *in vacuo* gave 230 mg of crude material. Flash column chromatography through silica gel using CH_2Cl_2/ether 4:1 as eluent afforded 107 mg (54% yield) of (5a*RS*,7*RS*,9a*SR*,9b*SR*)-6,6-(ethylenedioxy)decahydro-7-(phenylthio)pyrrolo[1,2-*b*][1,2]benzisoxazol-9-one, **13b**, and 17 mg (9% yield) of its (5a*RS*,7*SR*,9a*SR*,9b*SR*)-isomer, **14b**.

13b: mp 126−130 °C (CH_2Cl_2/pentane); IR (KBr) 1715, 1159, 1047 cm^{-1}; ^{1}H-NMR (250 MHz, acetone-d_6) δ 7.34 (d, J = 6.9 Hz, 2H), 7.12 (m, 3H), 4.21 (d, J = 5.9 Hz, 1H), 4.03 (m, 4H), 3.85 (m, 2H), 2.99 (dd, J = 5.9, 1.5 Hz, 1H), 2.88 (m, 2H), 2.63 (m, 2H), 1.95 (m, 1H), 1.70 (m, 1H), 1.58 (m 2H); ^{13}C-NMR (62.5 MHz, acetone-d_6) δ 206.1, 131.7, 129.7, 127.5, 108.6, 78.3, 67.9, 67.2, 61.5, 57.9, 49.3, 46.3, 30.1, 24.8; MS *m*/*z* 347 (3), 262 (21), 126 (100), 110 (38), 99 (41), 98 (62), 55 (49). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.10; N, 4.03; S, 9.21. Found: C, 62.56; H, 5.94; N, 3.78; S, 8.89.

14b: IR (film) 1708, 1068, 1047 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.26 (m, 3H), 4.48(d, J = 8.8 Hz, 1H), 4.25 (m, 4H), 4.00 (td, J = 6.9, 3.3 Hz, 1H), 3.47 (dd, J = 10.6, 6.9 Hz, 1H), 3.12 (m, 1H), 2.98 (t, J = 6.9 Hz, 1H), 2.96 (m, 1H), 2.80 (m, 2H), 1.90 (m 4H); ^{13}C-NMR (62.5 MHz, acetone-d_6) δ 203.4, 136.8, 131.6, 129.6, 127.4, 109.1, 82.4, 67.9, 67.8, 67.6, 61.4, 56.7, 49.0, 44.8, 22.9; MS *m*/*z* 347 (5), 262 (45), 126 (100), 110 (25), 99 (66), 98 (68); HRMS (EI) (M^+) calcd for $C_{18}H_{21}NO_4S$ 347.1191, found 347.1187.

Chemical Correlation between 11a/12a and 7a. A stirred solution of a 1:1 mixture of **11a** and **12a** (150 mg, 0.41 mmol) in pyridine (5 mL) and Ac_2O (5 mL) was heated at 70 °C under nitrogen for 22 h. Removal of the solvent *in vacuo*, followed by flash column chromatography through silica gel using EtOAc/ether 3:2 as eluent, afforded 77 mg (73% yield) of **7a**.

Chemical Correlation between 11b and 7b. A stirred solution of **11b** (305 mg, 0.84 mmol) in pyridine (10 mL) and Ac_2O (10 mL) was heated at 70 °C under nitrogen for 21 h. Removal of the solvent *in vacuo*, followed by flash column chromatography through silica gel using EtOAc/ether 3:2 as eluent, afforded 163 mg (77% yield) of **7b**.

(10a*R*,10b*R*)-7b. This compound was obtained in 77% yield starting from (3*S*,4a*S*,10a*R*,10b*R*)-**11b**. (10a*R*,10b*R*)-**7b**: $[\alpha]^{20}_D$ = −27.7° (c = 0.65 in $CHCl_3$).

Chemical Correlation between 11c and 7c. A stirred solution of **11c** (84 mg, 0.22 mmol) in pyridine (2.5 mL) and Ac_2O (2.5 mL) was heated at 70 °C under nitrogen for 21 h. Removal of the solvent *in vacuo*, followed by flash column chromatography through silica gel using CH_2Cl_2/ether 9:1 as eluent afforded 47 mg (77% yield) of **7c**.

Chemical Correlation between 13b/14b and 4b. A stirred solution of a 2.5:1 mixture of **13b** and **14b** (32 mg, 0.09 mmol) in pyridine (1 mL) and Ac_2O (1 mL) was heated at 75 °C under nitrogen for 15 h. Removal of the solvent *in vacuo*, followed by flash column chromatography through silica gel using EtOAc/ether 3:2 as eluent afforded 6 mg (33% yield) of **4b**.

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Supporting Information Available: Full assignment of ^{1}H- and ^{13}C-NMR peaks of compounds **4a**,**b**, **7a**,**b**, **11a**,**b** and **12a**, copies of the ^{1}H-NMR spectra of **7c**, **9a**,**c**, **11c** and **12b**,**c** and ^{13}C-NMR spectrum of **7c**, and ORTEP drawing and details for the X-ray data acquisition for **11b** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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