Influence of the Sulfinyl Group on the Chemoselectivity and π-Facial Selectivity of Diels−Alder Reactions of *(S)*-2-(*p*-Tolylsulfinyl)-1,4-benzoquinone

M. Carmen Carreño,* José L. García Ruano,* Miguel A. Toledo, and Antonio Urbano

Departamento de Química Orgánica (C-I), Universidad Autónoma, Cantoblanco, 28049 Madrid, Spain

Cynthia Z. Remor and Valter Stefani

Instituto de Química/UFRGS, Porto Alegre (RS), Brazil

Jean Fischer

Laboratoire de Cristallochimie, UA 424, Université Louis Pasteur, 67070 Strasbourg, France

Received August 3, 1995[⊗]

Diels−Alder reactions of *(S)*-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **(1a)** with cyclic (cyclopentadiene and cyclohexadiene) and acyclic dienes (1-[(trimethylsilyl)oxy]-1,3-butadiene and *trans*-piperylene) under different thermal and Lewis acid conditions are reported. Chemoselectivity (reactions on C_2-C_3 versus C_5-C_6 double bonds) is mainly related to the cyclic (on C_5-C_6) or acyclic (on C_2-C_3) structure of the diene. The high π-facial selectivity observed could be controlled by choosing adequate experimental conditions.

Introduction

In a previous paper,[1] we reported the preliminary results obtained in the study of the Diels−Alder cycloadditions of *(S)*-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **(1a)** (Figure 1), mainly focused on reactions with cyclopentadiene. Unexpectedly, the cycloadditions took place on the unsubstituted C_5-C_6 double bond in a high π-facial diastereoselective manner (up to 82% of de). Diels−Alder reactions of (*S*)-3-chloro- **(1b)** and (*S*)-3-ethyl-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **(1c)** (Figure 1) with cyclopentadiene and 2,3-dimethylbutadiene in the presence of $ZnBr_2$ took place on the C_5-C_6 bond with diastereoisomeric excesses ranging from 40 to 72%.[2] With the goal of using sulfinylquinones as chiral starting materials in the synthesis of optically enriched polycyclic systems, we later studied the behavior of several sulfinylnaphthoquinones **2a−c** (Figure 1) in asymmetric Diels−Alder cycloadditions.[3] This study revealed that the sulfinyl group was able to control both regiochemistry and π-facial diastereoselectivity of cycloadditions on the dienophilic double bond. This result was not unexpected, taking into account the close disposition of the sulfinyl group and the reactive double bond in these substrates. Recent studies concerning Diels−Alder reactions of naphthazarin thio derivatives[4] evidenced a strong influence of the sulfur substituent on the ring selectivity of cycloadditions with several dienes. Moreover, in the case of sulfinylnaphthazarin **3** (Figure 1), cycloaddition with cyclopentadiene in the presence of $BF_3{\cdot}OEt_2$ on the unsubstituted dienophilic double bond of tautomer **3B** proceeded with a significant (70:30) π-facial diastereoselectivity despite the remoteness of the chiral sulfur with respect to the reactive double bond.

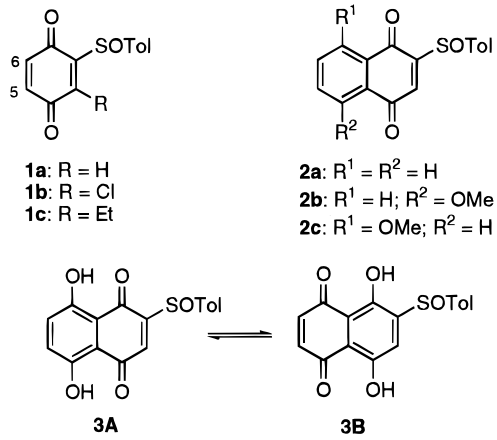

Figure 1.

All these facts, as well as our interest in synthetic aplications of sulfinylquinones,[5] suggested the convenience of undertaking a complete study of the behavior of benzoquinone **1a** as dienophile in order to know the influence of the sulfinyl group on the reactivity and diastereoselectivity of the two dienophilic double bonds present in the quinonic structure. In this paper, we report the results obtained in the Diels−Alder reactions of **1a** with cyclic and acyclic dienes carried out in different solvents and temperatures and in the presence of several Lewis acids.

Results and Discussion

Enantiomerically pure *(S)*-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **(1a)** was synthesized as previously described.[6] The reaction of **1a** with cyclopentadiene under thermal conditions afforded a mixture of only two adducts **4a** and **4b** ($n = 1$ in Scheme 1), out of the eight possible diastereoisomers. Both adducts resulted from the *endo* approach of the diene on the two diastereotopic faces of

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

(1) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Tetrahedron Lett.* **1989**, *30*, 4003.

(2) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1994**, *35*, 9759.

(3) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *J. Org. Chem.* **1992**, *57*, 6870.

(4) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Tetrahedron Lett.* **1994**, *35*, 3789.

(5) For a review on synthetic aplications of sulfoxides see: Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.

(6) (a) Carreño, M. C.; García Ruano, J. L.; Mata, J. M.; Urbano, A. *Tetrahedron* **1991**, *47*, 605. (b) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Synthesis* **1992**, 651.

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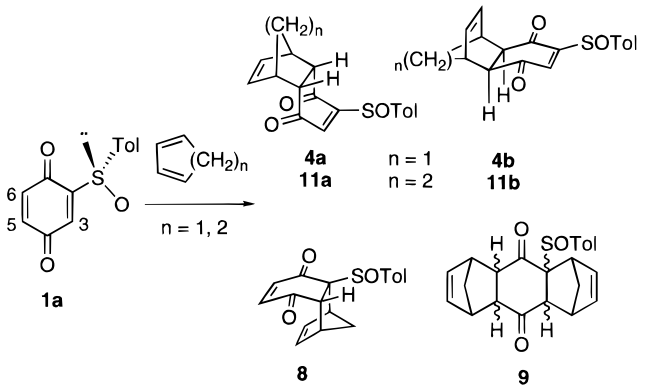
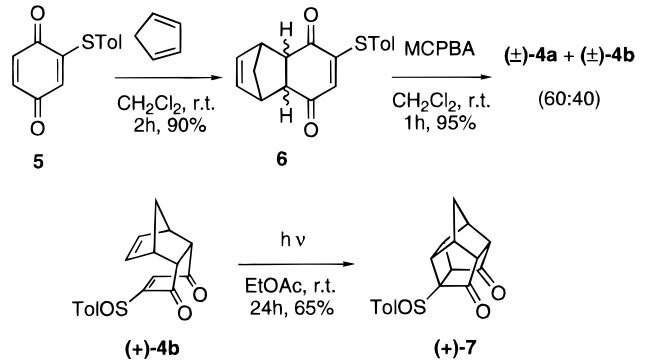
Scheme 1



Scheme 2



the unsubstituted C_5-C_6 double bond of **1a** and could be readily separated diastereoisomerically pure after flash chromatography.

The *endo* configuration of **4a** and **4b** was confirmed as depicted in Scheme 2. The reaction of 2-(*p*-tolylthio)-1,4-benzoquinone **(5)**[7] with cyclopentadiene yielded adduct **6**,[8] whose controlled oxidation with m-CPBA afforded a 60:40 diastereoisomeric mixture of the corresponding racemic sulfoxides **(±)-4a** and **(±)-4b**, their ^{1}H-NMR spectra being identical to those obtained for optically pure compounds **4a** and **4b**. Therefore, both sulfoxides must exhibit the same *endo* or *exo* configuration because they derive from the same thioether. The *endo* configuration of these compounds could be unequivocally established by irradiation of **4b** to yield **7** showing a cage structure. This evolution is only possible for *endo*-adducts.[9]

The relative configuration of **4a** and **4b** was initially established on the basis of their ^{1}H-NMR parameters (see Figure 2 and Table 1), taking into account the favored *s-cis* conformation between the S−O and C_2-C_3 bonds[10] and the known anisotropic effect of the *p*-tolyl group[3,11] on the protons under its influence. So, the main difference between adducts **4a** and **4b** is the chemical shifts of H_6 and H_7 olefinic protons which appear at 6.13 ppm

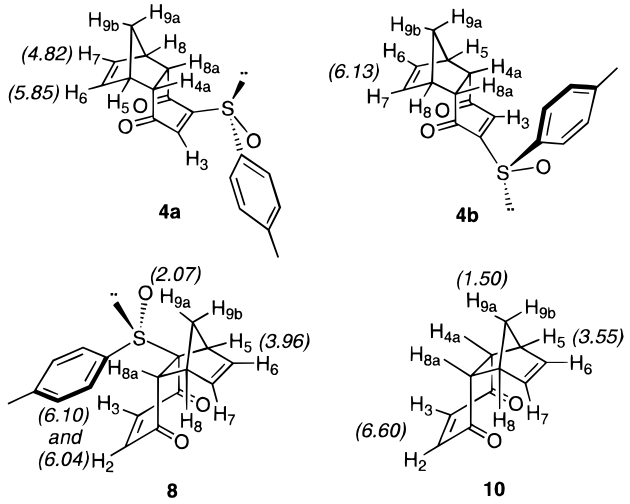


Figure 2.

in **4b** and at 5.85 and 4.82 ppm in **4a**. The high shielding observed for H_7 ($\Delta\delta$ = 1.31 ppm) in **4a** is probably produced by the aromatic ring of the *p*-tolyl group and is only possible if the stereochemistry of adduct **4a** is that shown in Scheme 1 and Figure 2. Similar shielding effects of remote aromatic rings have been already described for one of the two adducts obtained in the reaction of (α-hydroxybenzyl)-1,4-benzoquinone with cyclopentadiene.[11]

On the basis of the stereochemistry assigned to **4a** and **4b**, we tried to rationalize the stereochemical course of the cycloadditions. Nevertheless, some problems related to the stereochemical models (see later) suggested the convenience of confirming this configurational assignment. This was achieved by X-ray diffraction of **4b**,[12] whose solid state disposition (see the supporting information) revealed the same relative stereochemistry to that suggested by the ^{1}H-NMR parameters as well as the *s-cis* disposition of the sulfinylic oxygen and the C_2-C_3 double bond as shown in Figure 2. Thus, the absolute configuration [4a*R*,5*R*,8*S*,8a*R*,(S)*S*] could be unequivocally assigned to the adduct *endo*-**4b** and the [4a*S*,5*S*,8*R*,8a*S*,(S)*S*] one to the diastereoisomer *endo*-**4a**.

The results obtained in the Diels−Alder reactions of **1a** with cyclopentadiene under different thermal conditions are collected in Table 2. In all cases, clean mixtures of **4a** and **4b** were formed. As can be deduced from these data, the stereoselectivity increased (always in favor of **4a**) and the reactivity decreased (longer reaction times) when the temperature became lower. The polarity of the solvents also had a significant effect on both reactivity and diastereoselectivity of the reaction. We observed a gradual decrease of the reaction times with the increasing polarity of solvents.[13] At −20 °C the highest reactivity was observed in H_2O/EtOH mixtures (entries 15 and 16), while at rt the lowest reaction times corresponded to the use of H_2O (entry 17). The diastereoselectivity also increased (again in favor of **4a**) with the polarity of the solvent. Thus, the best diastereoisomeric excess (72%) was obtained in EtOH at −20 °C (entry 14). Under these conditions, the addition of H_2O, even in little amount (entries 15 and 16) increased the reactivity but decreased

(7) Ukai, S.; Hirose, K. *Bull. Soc. Chem. Pharm.* **1968**, *16*, 195.
(8) Wilgus, H. S., III; Frauenglass, E.; Chiesa, P. P.; Nawn, G. H.; Evans, F. J.; Gates, J. W., Jr. *Can. J. Chem.* **1966**, *44*, 603.
(9) (a) Bruce, J. M. In *Rodd's Chemistry of Carbon Compounds;* Coffey, S., Ed.; Elsevier: Amsterdam, 1974; Vol. IIIB, p 8. (b) Filipescu, N.; Menter, J. M. *J. Chem. Soc. B* **1969**, 616. (c) Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062. (d) Linz, G. S.; Zektzer, A. S. S.; Martin, G. E. *J. Org. Chem.* **1988**, *53*, 2647.
(10) (a) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1986**, *27*, 6041. (b) Koizumi, T.; Arai, Y.; Takayama, H. *Tetrahedron Lett.* **1987**, *28*, 3689. (c) Solladié, G.; Carreño, M. C. In *Organic Sulfur Chemistry. Synthetic Aspects*; Page, P., Ed.; Academic Press: London, 1995; pp 1−47.
(11) Al-Hamdany, R.; Bruce, J. M.; Heatley, F.; Khalafy, J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1395.
(12) The authors have deposited atomic coordinates for **4b** 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.
(13) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

Table 1. ^{1}H-NMR Data for Compounds 4a,b, 8, 10, and 11a,b

	δ (ppm), multiplicity, J (in Hz)					
proton	**4a**	**4b**	**8**	**10**	**11a**	**11b**
H_2 and/or H_3	7.17, s	7.23, s	6.10, 6.04, AB system, 10.3	6.60, s	7.24, s	7.30, s
H_5	3.48, m	3.54, m	3.96, m	3.55, m	3.08, m	3.24, m
H_8	3.26, m	3.54, m	3.65, m	3.55, m	2.71, m	3.24, m
H_6	5.85, dd, 2.9, 5.6	6.13, t, 2.0	6.16, m	6.10, m	6.02, ddd, 1.4, 6.5, 7.6	6.25, m
H_7	4.82, m	6.13, t, 2.0	6.16, m	6.10, m	5.21, ddd, 1.4, 6.6, 8.1	6.25, m
H_{4a} and/or H_{8a}	3.26, m	3.23, 3.12, 2dd, 3.9, 8.5	3.20, d, 3.8	3.25, m	3.01, m	2.98, 2.85, 2dd, 2.4, 9.3
H_{9a}	1.39, m	1.40, dt, 8.9, 2.0	2.07, m	1.50, m		
H_{9b}	1.39, m	1.57, dt, 8.9, 2.0	1.67, m	1.60, m		
H_9 and H_{10}					1.64, 1.24, 2m	1.66, 1.36, 2m
CH_3	2.41, s	2.38, s	2.37, s		2.41	2.38
AA′BB′tolylsystem	7.55, 7.29	7.62, 7.28	7.42, 7.25		7.55, 7.29	7.61, 7.27

Table 2. Thermal Diels−Alder Reactions of Sulfinylbenzoquinone 1a with Cyclic Dienes

entry	diene[a]	solvent	T (°C)	time (h)	yield (%)	**4a:4b**	**11a:11b**	de
1	cyclopentadiene	benzene	80	0.5	76	50:50		0
2	cyclopentadiene	benzene	rt	2	81	57:43		14
3	cyclopentadiene	benzene	5	2	85	60:40		20
4	cyclopentadiene	THF	67	0.5	80	60:40		20
5	cyclopentadiene	THF	rt	5	82	67:33		34
6	cyclopentadiene	THF	−20	24	86	69:31		38
7	cyclopentadiene	CH_2Cl_2	rt	1	90	69:31		38
8	cyclopentadiene	CH_2Cl_2	−20	16	95	71:29		42
9	cyclopentadiene	DMSO	−20	12	92	74:26		48
10	cyclopentadiene	DMF	−20	10	91	75:25		50
11	cyclopentadiene	acetone	−20	10	92	75:25		50
12	cyclopentadiene	CH_3CN	−20	10	92	75:25		50
13	cyclopentadiene	EtOH	0	1	91	80:20		60
14	cyclopentadiene	EtOH	−20	6	95	86:14		72
15	cyclopentadiene	EtOH/H_2O(19:1)	−20	1	90	81:19		62
16	cyclopentadiene	EtOH/H_2O (9:1)	−20	1	92	78:22		56
17	cyclopentadiene	H_2O	rt	0.5	91	70:30		40
18	cyclohexadiene	CH_2Cl_2	rt	24	91		78:22	56
19	cyclohexadiene	CH_2Cl_2	−20	480	94		83:17	66
20	cyclohexadiene	EtOH	−20	360	96		89:11	78
21	cyclohexadiene	EtOH/H_2O (9:1)	−20	336	92		84:16	68
22	cyclohexadiene	H_2O	rt	2	94		80:20	60

[a] One equiv of cyclopentadiene and 5 equiv of cyclohexadiene.

Table 3. Lewis Acid Reactions of Sulfinylbenzoquinone 1a in CH_2Cl_2 with Cyclic Dienes

entry	diene[a]	Lewis acid (equiv)	T (°C)	time (h)	**4a:4b**	**8**	**9**	**11a:11b**	yield (%)	de
1	cyclopentadiene		−20	16	71:29				95	42
2	cyclopentadiene	$BF_3{\cdot}OEt_2$ (5)	rt	0.1	13:87				80	74
3	cyclopentadiene	$BF_3{\cdot}OEt_2$ (5)	−20	0.5	10:90				90	80
4	cyclopentadiene	$Eu(fod)_3$ (2)	rt	0.1	75:25				75	50
5	cyclopentadiene	$Eu(fod)_3$ (2)	−20	0.5	89:11				80	78
6	cyclopentadiene	$ZnBr_2$ (2)	40	0.05		60	40		80	
7	cyclopentadiene	$ZnBr_2$ (2)	rt	0.05	20:20	60			83	
8	cyclopentadiene	$ZnBr_2$ (2)	0	0.05	30:30	40			85	
9	cyclopentadiene	$ZnBr_2$ (2)	−20	1	26:38	36			89	
10	cyclopentadiene	$ZnBr_2$ (2)	−78	3	41:56	3			83	
11	cyclohexadiene		−20	480				83:17	94	66
12	cyclohexadiene	$BF_3{\cdot}OEt_2$ (5)	−20	2				9 :91	95	82
13	cyclohexadiene	$Eu(fod)_3$ (2)	−20	24				90:10	81	80
14	cyclohexadiene	$ZnBr_2$ (2)	40	0.2				42:58	85	16
15	cyclohexadiene	$ZnBr_2$ (2)	rt	1				43:57	92	14
16	cyclohexadiene	$ZnBr_2$ (2)	0	6				44:56	91	12
17	cyclohexadiene	$ZnBr_2$ (2)	−20	24				46:54	95	8

[a] One equiv of cyclopentadiene and 5 equiv of cyclohexadiene.

the diastereoselectivity of the cycloaddition. These facts demonstrated once again that Diels−Alder reactions are not insensitive to solvent effects.[14] Although the origin of the phenomenon is not well understood, the strong influence of the solvent on both rate and stereoselectivity of cycloadditions is generally observed.[15]

The influence of several Lewis acids on these cycloadditions has also been evaluated. The results are summarized in Scheme 1 and Table 3. As expected, Lewis acid reactions were always faster than their thermal analogues. In the presence of $Eu(fod)_3$, cycloaddition took place only on C_5-C_6 and the π-facial selectivity increased with respect to that observed in the absence of Lewis acid, the diastereoisomeric excess becoming up to 78% at −20 °C (compare entries 1 and 5 in Table 3). Compound **4a**

(14) Blokzijl, W.; Engberts, N. *J. Am. Chem. Soc.* **1992**, *114*, 5440 and references cited therein.

(15) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.

was the major adduct under these conditions. The use of $BF_3{\cdot}OEt_2$ did not modify the chemoselectivity but determined the total inversion of the π-facial selectivity in favor of **4b** (de 80%, entry 3).

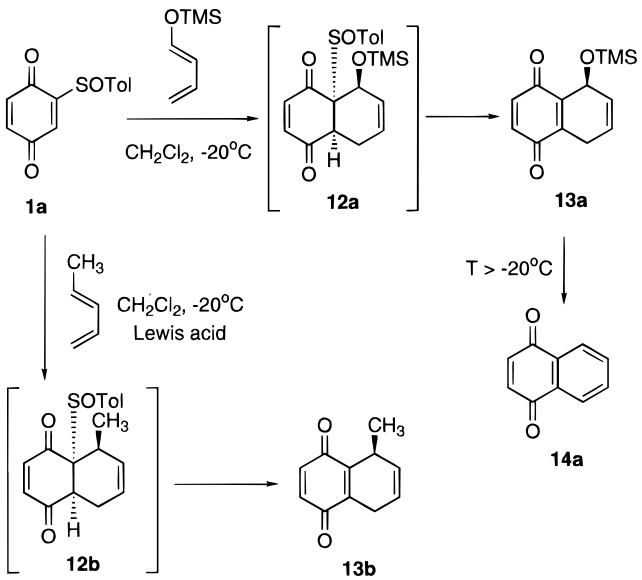
When $ZnBr_2$ was present in the reaction medium, the results were highly temperature dependent. At 40 °C (Table 3, entry 6), a mixture of a new adduct **8** and different double adducts **9** was formed (Scheme 1). Compound **8**, obtained as the major product, was isolated by flash chromatography and was characterized as the adduct resulting in the *endo* approach of cyclopentadiene on the substituted C_2-C_3 double bond. This result revealed a dramatic change in the chemoselectivity of the cycloaddition in the presence of $ZnBr_2$. Moreover, this approach yielded only one diastereoisomer. Compounds **9** were a mixture of the possible double adducts resulting in a second Diels−Alder reaction of cyclopentadiene on **4a** and **4b**.[16] At rt (entry 7), a 20:20:60 mixture of **4a**, **4b**, and **8** was obtained when the reaction was quenched inmediately with H_2O (longer reaction times determined the evolution of **4a** and **4b** into bis-adducts **9**). The increasing amount of $ZnBr_2$ did not modify these results. At lower temperatures (entries 8−10), the ratio of adducts **4a** and **4b** increased whereas that of **8** decreased, being almost none at −78 °C (entry 10). When compounds **4a** and **4b** were formed in the presence of $ZnBr_2$, low diastereoisomeric excesses were observed (entries 7−10).

A comparative study of the ^{1}H-NMR parameters of compound **8** and the *endo*-adduct **10** obtained in the reaction between cyclopentadiene and 1,4-benzoquinone (δ values are collected in Table 1) allowed the configurational assignment of **8** depicted in Figure 2. The first remarkable observation was the strong shielding shown by protons H_2 and H_3 in **8** with respect to that of **10** ($\Delta\delta$ = 0.50−0.56). This effect is probably due to the rigid disposition of the sulfinyl group where the aromatic *p*-tolyl ring must be oriented parallel to the C_2-C_3 double bond of the tetrahydronaphthoquinone moiety, resulting in the shielding of H_2 and H_3 protons in **8**. This disposition must be the most stable due to π-stacking[3,17] interactions between the aromatic ring and the double bond. In such a conformation, the sulfinylic oxygen is located close to H_5 and H_{9a} protons if adduct **8** has the *endo* configuration. The deshielding observed for both protons in **8** if compared with **10** ($\Delta\delta$ = 0.41 for H_5 and $\Delta\delta$ = 0.57 for H_{9a}) confirmed the proposed geometry, the well-known anisotropic effect associated to the sulfinylic oxygen[18] being responsible for this variation.

Adduct **8** was not able to react as dienophile in a second cycloaddition with cyclopentadiene even in refluxing CH_2Cl_2 and in the presence of $ZnBr_2$. This unreactivity must be a consequence of the blocking of both dienophilic faces of the C_2-C_3 double bond of **8** by the *p*-tolyl group (the upper face) and by the rigid structure of the norbornenyl moiety (the bottom face), as evidenced by inspection of the system shown in Figure 2.

The results obtained in the reactions of **1a** with cyclohexadiene are summarized in Tables 2 and 3. As

Scheme 3



Lewis acid	t(h)	13b: $[\alpha]_D^{20}$
---------	48	+102 (*c* 0.5, $CHCl_3$) (e.e.>97%)
$BF_3\,OEt_2$	0.25	+101 (*c* 0.46, $CHCl_3$)
$ZnBr_2$	0.1	+100 (*c* 0.5, $CHCl_3$)
$Eu(fod)_3$	1	+91 (*c* 0.18, $CHCl_3$)

can be seen, mixtures of adducts **11a** and **11b** (n = 2 in Scheme 1), both resulting in the *endo* attack of the diene on the unsubstituted quinonic C_5-C_6 double bond, were formed under thermal and Lewis acid conditions. The similarity of the ^{1}H-NMR parameters (see Figure 2 and Table 1) of adducts **4** and **11** allowed us to establish the configurational assignment of **11a** and **11b**.

The main differences between the behavior of both cyclic dienes were those derived from the known lower reactivity of cyclohexadiene which required larger reaction times. As a consequence, the observed π-facial selectivities were slightly higher than those of cyclopentadiene under similar conditions. On the other hand, the double adducts and that resulting from reaction of cyclohexadiene on the sulfinyl-substituted C_2-C_3 double bond were not detected, even in the presence of $ZnBr_2$ under reflux of CH_2Cl_2. As in the case of reactions with cyclopentadiene, a low π-facial diastereoselectivity resulted when the reaction of cyclohexadiene ocurred on C_5-C_6 in the presence of $ZnBr_2$, in contrast to those obtained under thermal or other Lewis acid conditions (see Tables 2 and 3).

Finally, we studied the reactions of sulfinylquinone **1a** with acyclic dienes such as 1-[(trimethylsilyl)oxy]-1,3-butadiene and *trans*-piperylene. The results are shown in Scheme 3. With this kind of acyclic dienes, compound **1a** underwent cycloaddition on the sulfinyl-substituted C_2-C_3 double bond exclusively. The initially formed adducts **12a**,**b** could not be detected even when reactions were conducted at low temperatures due to the pyrolytic elimination of the sulfinyl group which took place spontaneously giving rise to quinonic compounds **13a**,**b**. In the case of the reaction with 1-[(trimethylsilyl)oxy]-1,3-butadiene, compound **13a** was stable enough to be detected by ^{1}H-NMR only at −20 °C but inmediately underwent aromatisation into 1,4-naphthoquinone **(14a)** when the temperature increased.

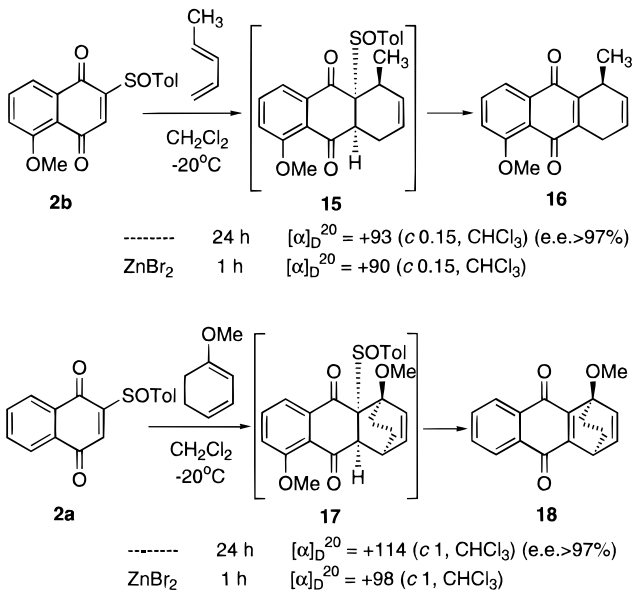
In the case of reactions with *trans*-piperylene under thermal conditions, dihydronaphthoquinone **13b** could be

(16) The composition of these mixtures, as well as the stereochemical assignment of the bis-adducts and the study of the cycloadditions of monoadducts **4a** and **4b** with cyclopentadiene in different conditions, are currently being studied.

(17) Jones, G. D.; Chapman, B. J. *Synthesis* **1995**, 475.

(18) (a) Foster, A. B.; Inch, T. D.; Qadir, M. H.; Weber, J. M. *J. Chem. Soc., Chem. Commun.* **1968**, 1086. (b) Cook, M. J. *Kemia-Kemi* **1976**, *3*, 16.

Scheme 4



isolated optically pure (ee > 97%) as was determined in the presence of the chiral shift reagent Pr(hfc)$_3$. The same enantiomer of **13b** was formed by using BF_3·OEt_2, $ZnBr_2$, and Eu(fod)$_3$ as Lewis acids. The reaction times decreased in their presence, but the influence on the π-facial diastereoselectivity was scarce as can be deduced from the value and sign of the specific rotation of the isolated samples shown in Scheme 3. On the other hand, cycloadditions between sulfinylnaphthoquinones **2a**−**c** (see Figure 1) and cyclopentadiene had given the opposite π-facial diastereoselection under thermal conditions and in the presence of $ZnBr_2$.[3] In order to ascertain whether these results were due to the different nature (cyclic or acyclic) of the dienes or if the formation of the same enantiomer with *trans*-piperylene in both conditions was a consequence of the simultaneous inversion of the π-facial selectivity and the regiochemistry of the process taking place on the sulfinyl-substituted double bond in the presence of $ZnBr_2$, we carried out the reaction of *(S)*-5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **(2b)** with *trans*-piperylene under thermal and $ZnBr_2$-catalyzed conditions (Scheme 4).

As we can see, the results obtained from sulfinylnaphthoquinone **2b** were identical to those resulting from sulfinylbenzoquinone **1a**. A sole regioisomer **16** resulting from the pyrolysis of the initially formed *ortho*-adduct **15** was obtained in the reaction of **2b** with *trans*-piperylene under thermal conditions and in the presence of $ZnBr_2$. The enantiomeric purity of **16** could be determined to be as high as 97% in the presence of the chiral shift reagent Pr(hfc)$_3$. From the specific rotations shown in Scheme 4, we could state that the absolute configuration of **16** formed in both conditions was the same. As a consequence, the behavior of *trans*-piperylene is different from that observed with cyclopentadiene which had given the opposite π-face selectivity under both conditions in the reaction with **2b**.[3]

The different chemoselectivity observed in the cycloadditions of **1a** with cyclic and acyclic dienes is surprising if we consider the activation of the C_2-C_3 double bond exerted by the sulfinyl group. A similar situation was found in the Diels−Alder reactions of sulfinylnaphthazarin **3** (Figure 1).[4] This absence of cycloaddition on the sulfinylic-substituted double bond with cyclic dienes could

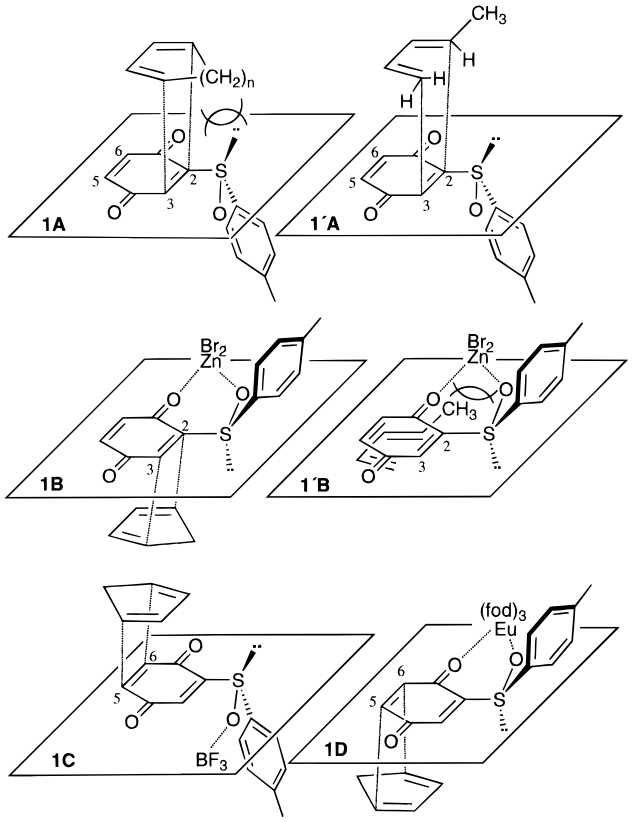


Figure 3. Favored approaches of cyclic and acylic dienes in Diels−Alder reactions of (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone.

be explained by assuming that the activating effect of the SOTol group on C_2-C_3 is overridden by steric interactions between the $(CH_2)_n$ bridge of cyclic dienes and the sulfinyl group, which develop in the transition state giving rise to *endo*-adducts when sulfinylquinone **1a** reacts from the expectedly more reactive *s-cis* conformation (**1A** in Figure 3). This interaction must be more severe when n = 2 and does not exist with acyclic dienes (**1′A** in Figure 3).

The only exception to this behavior corresponded to the reactions of cyclopentadiene in the presence of $ZnBr_2$ which mainly afforded adduct **8** upon reaction of the C_2-C_3 bond (Scheme 1 and Table 3). Assuming the formation of the chelated species **1B** from **1a** and $ZnBr_2$ shown in Figure 3, an increased reactivity of the substituted C_2-C_3 double bond should be expected. Moreover, the possible steric interactions between the methylene bridge of cyclopentadiene and the sulfur function in the bottom face approach of the diene must be lower in this conformation due to the planarity of the chelate and the disposition of the sulfur atom now included in a half-chair. The effect of the temperature on the chemoselectivity of these reactions (the ratio of **8** decreased with the temperature) is not easy to rationalize, but we could suggest that the formation of the chelate between **1a** and $ZnBr_2$ is more difficult at low temperatures.

The origin of the high π-facial diastereoselectivity observed in these cycloadditions is intriguing. The model based on steric approach control already proposed to rationalize the π-face diastereoselectivity of cycloadditions on differently substituted vinyl sulfoxides[3,10b,c] could explain our results when cycloaddition of dienes took place on the sulfinylic substituted double bond C_2-C_3. Thus, assuming the formation of the chelated species **1B**

in the presence of $ZnBr_2$ (Figure 3), cyclopentadiene approach must be favored from the less hindered bottom face where the lone pair at sulfur is located to yield exclusively diastereoisomer **8**. The same π-facial diastereoselectivity observed in cycloadditions of *trans*-piperylene with both sulfinylquinones **1a** and **2b** in thermal and Lewis acid conditions suggested the existence of a similar reactive conformation of the sulfinyl quinonic system in all the cases. A detailed examination of the possible situations allowed us to propose that, in thermal conditions, **1′A** (Figure 3) could be the reactive conformation responsible for the favored approach of acyclic dienes from the less hindered top face of **1a** to afford, after pyrolytic elimination of the sulfoxide, dihydroquinones **13b** and **16** with the *(S)* absolute configuration at the new stereogenic center. This model agrees with those proposed in the literature to explain the cycloadditions of activated vinyl sulfoxides in thermal conditions[10] but implies a contradiction with the accepted model when $ZnBr_2$, able to form chelated species, is present. In our case, if we analyze the interactions resulting in the less hindered approach of *trans*-piperylene to a chelated conformation such as **1′B** (Figure 3) the close disposition between the quinonic and sulfinylic oxygens and the methyl group of the diene could determine a high energy content of the resulting transition state. In such situation, a shift toward conformation **1′A** with the zinc atom attached to the sulfinylic oxygen in the *s-cis* disposition could occur. The approach of the diene from the less hindered top face of **1′A** avoids the above-mentioned destabilizing interactions, giving rise again to the same enantiomer of **13b**. Moreover, the results obtained by us[3] in the reaction of *(S)*-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **(2a)** with 1-methoxy-1,3-cyclohexadiene support this explanation. Under thermal conditions, the reaction afforded, after pyrolysis of the initially formed adduct **17**, compound **18**, whose optical rotation had the same sign as that resulting in the reaction in the presence of $ZnBr_2$ (Scheme 4).[19] Since under similar conditions cyclohexadiene had given adducts of opposite π-facial selectivity,[3] the behavior observed in the case of 1-methoxy-1,3-cyclohexadiene (as well as *trans*-piperylene) should be a consequence of the destabilization of the transition state **1′B** due to the presence of the substituent at C-1 of the diene.

When cycloadditions with cyclic dienes took place on the unsubstituted C_5-C_6 double bond of **1a**, a similar steric approach control had been invoked by us to explain the results obtained.[1] Nevertheless, the high π-facial diastereoselectivity observed in these reactions is difficult to understand only on steric grounds considering the distance existent between the sulfinyl group and the reactive dienophilic double bond. Moreover, the diastereoselectivity (70:30) which resulted in the reaction of the **3B** tautomer of sulfinylnaphthazarin **3** (Figure 1) and cyclopentadiene[4] in the presence of $BF_3{\cdot}OEt_2$ is not possible to explain invoking steric factors.[20] Thus, taking into account the delocalized nature of the π-orbitals in the quinonic system which are involved in the [4 + 2]-cycloadditions, we propose a desymmetrization of the π-cloud due to the presence of the stereogenic sulfur as the responsible for the observed π-facial diastereoselection. Considering the electronic repulsion between the lone electron pair at sulfur and the π-cloud of the quinonic system, a desymmetrization of the latter by increasing the electron density of the face opposite to that containing the lone electron pair could exist. In such situation, the favored approach of the electron rich cyclic diene from the electron poor face containing the lone pair (Figure 3, **1C** in the presence of $BF_3{\cdot}OEt_2$ to afford adducts **4b** and **11b** as majors, and **1D** in the presence of $Eu(fod)_3$ to give mainly adducts **4a** and **11a**) could be responsible for the high π-facial diastereoselectivity observed. This desymmetrization is probably also associated to the frontier orbitals which control these concerted reactions as well as other processes.[21]

Conclusions

We have shown the efficiency of the sulfinyl group to control the π-facial diastereoselectivity of Diels–Alder reactions on sulfinylquinones by choosing the adequate experimental conditions. A high asymmetric induction is noticed even in remote control when the sulfoxide is not directly joined to the reactive double bond. To our knowledge these are the first sulfinyl dienophiles where the chiral auxiliary is acting from a remote point. The chemoselectivity of reactions with ambident dienophile **1a** is mainly dependent on the cyclic or acyclic nature of dienes.

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. IR spectra are given in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 200.1 and 50.3 MHz, respectively. ^1H-NMR data of compounds **4a**, **4b**, **8**, **11a**, and **11b** are collected in Table 1. Diastereoisomeric adducts ratios were established by integration of well-separated signals of the diastereoisomers in the crude reaction mixtures and are listed in Tables 2 and 3. All reactions were monitored by thin layer chromatography that was performed on precoated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230–400 mesh) of Macherey-Nagel. Eluting solvents are indicated in the text. Apparatuses for inert atmosphere experiments were dried by flaming in a stream of dry argon. Cyclopentadiene was used freshly distilled. Dry THF was distilled from sodium/benzophenone ketyl. CH_2Cl_2 was dried over P_2O_5. $ZnBr_2$ was flamed in the reaction flask, in a stream of dry argon before using. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2, and solvent dryness with Na_2SO_4.

General Procedure for Diels–Alder Reactions. Method A. To a solution of *(S)*-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **(1a)**[6] (100 mg, 0.4 mmol) in 5 mL of the dry solvent was added the corresponding diene under argon (see Table 2 for reaction conditions). After the consumption of all the quinone and evaporation of the solvent, the resulting material was purified by flash chromatography (CH_2Cl_2/acetone 40/1). Yields and diastereoisomeric ratios of adducts are detailed in Table 2.

General Procedure for Lewis Acid Diels–Alder Reactions. Method B. A solution of **1a**[6] (100 mg, 0.4 mmol) in 3 mL of dry CH_2Cl_2 was added to the appropiate Lewis acid in 2 mL of CH_2Cl_2 under argon (see Table 3 for reaction

(19) In this reaction, carried out in the presence of $ZnBr_2$, a mixture of compound **16** and that resulting from the 1,4-addition of the diene to the activated double bond was formed. After flash chromatography, **16** could be isolated and characterized (see ref 3 for physical and spectral data of **16**).

(20) The major adduct resulting in the reaction of the **3B** tautomer of sulfinylnaphthazarin **3** (see Figure 1) with cyclopentadiene in the presence of $BF_3{\cdot}OEt_2$ had the same configuration in its stereogenic centers that adduct **4b**, as was demonstrated by X-ray diffraction: unpublished results.

(21) (a) Liotta, C. L. *Tetrahedron Lett.* **1975**, *16*, 519. (b) Klein, J. *Tetrahedron Lett.* **1973**, *14*, 4307. (c) Frenking, G.; Kohler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146. (d) Fujita, M.; Ishida, M.; Manako, K.; Sato, K.; Ogura, K. *Tetrahedron Lett.* **1993**, *34*, 645.

conditions). The reaction was stirred for 1 h at rt, and then the diene was added at the desired temperature. After the time required and workup, the resulting material was purified by flash chromatography (CH_2Cl_2/acetone 40/1). Yields and diastereoisomeric ratios of adducts are detailed in Table 3.

***endo*-[4a*R*,5*S*,8*R*,8a*S*,(S)*S*]-5,8-Methano-2-(*p*-tolylsulfinyl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4a).** Compound **4a** was obtained as a yellow oil from **1a** and cyclopentadiene following methods A or B: $[\alpha]^{20}_D = +276$ (*c* 1, $CHCl_3$); ^{13}C-NMR δ 196.5, 196.0, 161.0, 142.6, 138.1, 136.4, 135.2, 134.0, 129.8, 125.9, 50.0, 49.7, 49.5, 49.4, 49.2, 21.4; IR (NaCl) 1660, 1590, 1310, 1265, 1160, 1070, 810. Anal. Calcd for $C_{18}H_{16}SO_3$: C, 69.23; H, 5.13; S, 10.26. Found: C, 69.50; H, 5.47; S, 9.89.

***endo*-[4a*S*,5*R*,8*S*,8a*R*,(S)*S*]-5,8-Methano-2-(*p*-tolylsulfinyl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4b).** Compound **4b** was obtained from **1a** and cyclopentadiene following methods A or B as a yellow solid: mp 162−163 °C (hexane); $[\alpha]^{20}_D = +472$ (*c* 1, $CHCl_3$); ^{13}C-NMR δ 196.6, 195.7, 160.7, 142.5, 138.4, 137.0, 135.6, 135.2, 130.0, 125.7, 50.2, 49.4, 48.8, 48.6, 48.5, 21.3; IR (KBr) 1670, 1600, 1310, 1250, 1180, 1080, 1060, 810. Anal. Calcd for $C_{18}H_{16}SO_3$: C, 69.23; H, 5.13; S, 10.26. Found: C, 69.25; H, 5.48; S, 10.02.

***endo*-5,8-Methano-2-(*p*-tolylthio)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (6).** A solution of 2-(*p*-tolylthio)-1,4-benzoquinone **(5)**[7] (100 mg, 0.34 mmol) and cyclopentadiene (100 μL, 1.5 mmol) in 5 mL of CH_2Cl_2 was stirred at rt for 2 h. The solvent was evaporated in vacuo and the residue purified by crystallization in hexane to afford compound **6** (90% yield) as a yellow solid: mp 150−152 °C (lit.[8] 144−154 °C); ^{1}H-NMR δ 7.30 and 7.23 (4H, AA'BB' system), 6.13 and 6.06 (2H, 2dd, J = 2.9 and 5.4 Hz), 5.81 (1H, s), 3.59 and 3.49 (2H, 2m), 3.34 and 3.16 (2H, 2dd, J = 4.1 and 8.5 Hz), 2.39 (3H, s), 1.55 and 1.44 (2H, 2dt, J = 8.8 and 1.8 Hz); ^{13}C-NMR δ 195.9, 195.7, 160.4, 140.8, 135.7, 135.4, 134.7, 132.4, 131.0, 124.1, 49.2, 48.9, 48.7, 48.6, 48.5, 21.3.

***endo*-[4a*R**,5*S**,8*R**,8a*S**,(S)*S**]-5,8-Methano-2-(*p*-tolylsulfinyl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4a) and *endo*-[4a*S**,5*R**,8*S**,8a*R**,(S)*S**]-5,8-methano-2-(*p*-tolylsulfinyl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (4b).** To a solution of **6** (15 mg, 0.05 mmol) in 1 mL of CH_2Cl_2 was added *m*-CPBA (10 mg, 0.05 mmol) in 1 mL of CH_2Cl_2. After 1 h at rt, the mixture was treated with a saturated solution of $NaHCO_3$. Workup afforded a 60:40 diastereoisomeric mixture of **(±)-4a** and **(±)-4b**. The ^{1}H-NMR spectroscopic data of these racemic adducts were identical with the optically actives **4a** and **4b**.

(+)-1-(*p*-Tolylsulfinyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione (7). A solution of **4b** (100 mg, 0.32 mmol) in 50 mL of dry ethyl acetate was irradiated under argon with an OSRAM HQL-125 W lamp. After 24 h, the solvent was evaporated and the residue purified by flash chromatography (EtOAc) to afford compound **7** as an oil (65% yield): $[\alpha]^{20}_D = +30$ (*c* 1, $CHCl_3$); ^{1}H-NMR δ 7.65 and 7.34 (4H, AA'BB' system), 3.72 (1H, m), 3.08 (1H, m), 2.93 (3H, m), 2.71 (2H, m), 2.42 (3H, s), 2.09 (1H, dt, J = 11.5 and 1.5 Hz), 1.97 (1H, dt, J = 11.5 and 1.3 Hz); ^{13}C-NMR δ 209.3, 205.4, 142.4, 136.0, 129.9, 125.4, 68.3, 56.0, 54.9, 44.3, 44.0, 43.9, 40.8, 37.5, 21.5; IR (NaCl) 1590, 1540, 1440, 1230, 1190. Anal. Calcd for $C_{18}H_{16}SO_3$: C, 69.23; H, 5.13; S, 10.26. Found: C, 69.40; H, 4.99; S, 9.91.

***endo*-[4a*S*,5*S*,8*R*,8a*R*,(S)*S*]-5,8-Methano-4a-(*p*-tolylsulfinyl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (8).** Compound **8** was obtained from **1a** and cyclopentadiene following method B as a yellow oil which decomposes on standing: $[\alpha]^{20}_D = -148$ (*c* 0.6, $CHCl_3$); ^{13}C-NMR δ 196.2, 190.9, 142.8, 141.4, 138.7, 137.7, 137.0, 135.5, 130.0, 124.7, 75.5, 50.4, 48.4 (2 C), 44.4, 21.2; IR (NaCl): 2990, 2390, 1660, 1590, 1280, 1180, 1080, 910.

***endo*-[4a*R*,5*S*,8*R*,8a*S*,(S)*S*]-5,8-Ethano-2-(*p*-tolylsulfinyl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (11a).** Compound **11a** was obtained from **1a** and cyclohexadiene following methods A or B as a yellow solid: mp 145−6 °C (methanol); $[\alpha]^{20}_D = +319$ (*c* 1, $CHCl_3$); ^{13}C-NMR δ 197.0, 196.4, 161.3, 142.6, 138.0, 136.5, 133.4, 132.4, 129.9, 126.1, 50.5, 50.3, 36.3, 36.2, 24.7, 24.6, 21.5; IR (KBr) 1670, 1250, 1160, 1080, 1050. Anal. Calcd for $C_{19}H_{18}SO_3$: C, 69.94; H, 5.52; S, 9.82. Found: C, 70.11; H, 5.37; S, 9.70.

***endo*-[4a*S*,5*R*,8*S*,8a*R*,(S)*S*]-5,8-Ethano-2-(*p*-tolylsulfinyl)-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (11b).** Compound **11b** was obtained from **1a** and cyclohexadiene following methods A or B as a yellow solid: mp 161−2 °C (hexane); $[\alpha]^{20}_D = +367$ (*c* 1, $CHCl_3$); ^{13}C-NMR δ 197.1, 195.8, 161.3, 142.7, 138.3, 137.0, 133.8, 133.3, 130.1, 125.8, 50.9, 50.1, 35.2, 34.9, 24.7, 24.3, 21.5; IR (KBr) 1660, 1250, 1170, 1080, 1050. Anal. Calcd for $C_{19}H_{18}SO_3$: C, 69.94; H, 5.52; S, 9.82. Found: C, 69.92; H, 5.68; S, 9.71.

5-[(Trimethylsilyl)oxy]-5,8-dihydro-1,4-naphthoquinone (13a). To a solution of **1a**[6] (100 mg, 0.4 mmol) in 4 mL of dry CH_2Cl_2 cooled at −20 °C was added 1-[(trimethylsilyl)-oxy]-1,3-butadiene (90 μL, 0.5 mmol) under argon. After 8 h, the solvent was evaporated at −20 °C at reduced pressure and the resulting material was analyzed directly by ^{1}H-NMR to avoid the easy aromatization of **13a** to 1,4-naphthoquinone **(14a)** at temperatures above −20 °C: ^{1}H-NMR δ 6.73 (2H, s), 6.02 (1H, dt, J = 10.1 and 3.1 Hz), 5.91 (1H, ddt, J = 3.8, 10.1, and 1.9 Hz), 5.23 (1H, q, J = 3.8 Hz), 3.07 (2H, m), 0.39 (9H, s).

(5*S*)-5,8-Dihydro-5-methyl-1,4-naphthoquinone (13b). To a solution of **1a**[6] (125 mg, 0.5 mmol) in 5 mL of dry CH_2Cl_2 was added *trans*-piperylene (200 μL, 2 mmol). After 48 h at −20 °C, the solvent was evaporated and the resulting material was purified by flash chromatography (CH_2Cl_2) to afford compound **13b** as a yellow solid (71% yield): mp 85−86 °C (hexane); $[\alpha]^{20}_D = +102$ (*c* 0.5, $CHCl_3$); ^{1}H-NMR δ 6.72 (2H, s), 5.79 (2H, m), 3.41 (1H, m), 3.25−2.85 (2H, m), 1.18 (3H, d, J = 7.0 Hz); ^{13}C-NMR δ 187.2, 186.7, 144.1, 139.4, 136.7, 136.0, 129.9, 121.2, 28.8, 24.0, 21.8; IR (KBr) 1695, 1640, 1350, 1295. Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.86; H, 5.75. Found: C, 75.74; H, 5.89.

(5*S*)-5,8-Dihydro-1-methoxy-5-methyl-9,10-anthraquinone (16). To a solution of (*S*)-5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone **(2b)**[6] (33 mg, 0.1 mmol) in 2 mL of dry CH_2Cl_2 was added *trans*-piperylene (30 μL, 0.3 mmol, 3 equiv). After 16 h at rt, the solvent was evaporated and the resulting material was purified by flash chromatography (CH_2Cl_2) to afford compound **16** as a yellow solid (78% yield): mp 138−40 °C (hexane); $[\alpha]^{20}_D = +93$ (*c* 0.15, $CHCl_3$); ^{1}H-NMR δ 7.72 (1H, dd, J = 1.4 and 8.0 Hz), 7.65 (1H, t, J = 8.0 Hz), 7.27 (1H, dd, J = 1.4 and 8.0 Hz), 5.82 (2H, m), 4.01 (3H, s), 3.57 (1H, m), 3.43−2.97 (2H, m), 1.23 (3H, d, J = 7.0 Hz); ^{13}C-NMR δ 184.1, 183.9, 159.3, 144.1, 143.2, 136.9, 134.8, 134.4, 129.7, 121.4, 119.0, 117.3, 56.3, 29.0, 24.6, 21.7; IR (KBr) 1651, 1585, 1472, 1290, 1057. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.72; H, 5.48.

Acknowledgment. We thank Dirección General de Investigación Científica y Técnica (Grants PB92-0161 and PB92-0162) and Ministerio de Educación y Ciencia: Programa de Cooperación con Iberoamérica for financial support.

Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **8** and **13a** and an ORTEP drawing and X-ray experimental data for **4b** (2 pages). This material is contained in libraries on microfiche, inmediately 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.

JO951438Y