# Asymmetric Diels–Alder Reactions of (S)-2-(p-Tolylsulfinyl)-1,4-naphthoquinones

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The asymmetric Diels–Alder reactions of (*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinones **1a–c** with cyclic dienes have been explored. The high $\pi$ facial diastereoselectivity observed can be reversed in the presence of $ZnBr_2$. Evidence is presented to show that the regiochemical outcome of these reactions is controlled only by the sulfinyl group. The in situ cycloaddition/pyrolytic sulfoxide elimination starting from chiral **1a–c** offers a convenient new route for the construction of enantiomerically pure 1,4-dihydro-9,10-anthraquinones (+)-**10** and (+)-**12a–c**.

## Introduction

The Diels–Alder reaction of quinones as dienophiles has been widely used as a key step in the synthesis of natural products.[1] The presence of a substituent in the starting quinone is often necessary to control the regiochemistry of the cycloaddition and to regenerate the quinone moiety in further steps of the synthesis. Haloquinones[2] and sulfinylquinones[3] have been successfully used with this aim in the synthesis of certain anthracyclinones,[2a] pyranoquinone antibiotics,[2c] and differently substituted anthraquinones.[3] The quinone sulfoxide methodology presents the advantage that the sulfinyl group can be regioselectively introduced in the quinone system in such a way that, with quinones such as juglone, the 2- or 3-sulfinyl-substituted framework is available.[4]

The possibility of applying this methodology in asymmetric synthesis remained unexploited by the lack of a method to obtain enantiomerically pure sulfinylquinones.[5] Recently, we have described a general and efficient method, based on Andersen's synthesis, giving access to either sulfinylbenzo-[6,7] or naphthoquinone derivatives[6] starting from 1,4-dimethoxyaromatic derivatives.

Our preliminary studies on asymmetric Diels–Alder reactions of (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone with cyclic dienes[7] showed that the sulfinyl group was able to control the $\pi$ facial selectivity when cycloaddition took place on the unsubstituted dienophilic double bond $C_5$–$C_6$. Nevertheless, the ability of the sulfoxide to control the stereochemical course of sulfinylquinone cycloadditions on the substituted double bond $C_2$–$C_3$ remained unknown. According to preceding work on chiral dienophiles such as 2-sulfinyl-substituted acrylates,[8] cycloalkenones,[9] maleates,[10] and maleimides,[11] the sulfinyl group was an efficient director on the diene approach in Diels–Alder reactions. These results indicated that the absolute configuration of the new chiral centers produced in the reaction could be controlled by choosing the experimental conditions. In light of the above information, we reasoned that the situation must be very similar in the sulfinylquinone family of dienophiles. With the aim of testing this assumption we undertook a study of Diels–Alder reactions of enantiomerically pure (*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinones with cyclic dienes.

## Results and Discussion

The reactions of naphthoquinones **1a–c** with cyclopentadiene (Scheme I and Table I) afforded mixtures of two endo adducts **2** and **3**. Best results were obtained at −20 °C in $CH_2Cl_2$.[12] Under these conditions, diastereomers **2** were the major components of the reaction mixtures (de ranged between 80 and 90% depending on the dienophile). In the presence of $ZnBr_2$ the cycloadditions required shorter times and the facial diastereoselectivity of the process was reversed, **3** now being predominant or exclusive in the resulting mixtures. The de's were excellent (>97%) with dienophiles **1a** and **1b** and only moderate (20%) with **1c**.

The separation of the adducts **2** and **3** from the mixtures was not possible because they are thermally unstable and are converted, even at room temperature, into the products resulting from pyrolytic elimination of the sulfinyl group (Scheme I). As can be seen, **4** is obtained from **2a** and **3a**, (−)-**5** would result from **2c** and **3b**, and (+)-**5** from **2b** and **3c**. From the de data in Table I, it can be deduced that (−)-**5** was obtained enantiomerically pure and that the enantiomeric purity of (+)-**5** was 80% ee.

The endo configuration of the chiral cycloadducts **2a** and **3a** (and presumably for all **2** and **3** cycloadducts) was demonstrated by chemical correlation with the sulfoxides resulting from the *m*-CPBA oxidation of the endo adduct **6** (Scheme II), obtained in the reaction of cyclopentadiene with 2-(*p*-tolylthio)-1,4-naphthoquinone (**7**).[13] This oxi-

(1) Desimoni, G. *Natural Products Synthesis*; ACS Monograph No. 180; American Chemical Society: Washington DC, 1983.

(2) (a) Echavarren, A.; Prados, P.; Fariña, F. *Tetrahedron* **1984**, *40*, 4561. (b) Bauman, J. G.; Hawley, R. C.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1569. (c) Kraus, A. G.; Shi, J. *J. Org. Chem.* **1990**, *55*, 1105 and references cited therein.

(3) Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1986**, *51*, 114.

(4) (a) Thompson, R. *J. Org. Chem.* **1951**, *16*, 1082. (b) Boeckman, R. K., Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.

(5) Greunberg, H.; Gogoll, A.; Bäckwall, J. E. *J. Org. Chem.* **1991**, *56*, 5808.

(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.

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

(8) (a) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Tetrahedron Lett.* **1985**, *26*, 6205. (b) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, *25*, 1727.

(9) Alonso, I.; Carretero, J. C.; García Ruano, J. L. *Tetrahedron Lett.* **1989**, *30*, 3853.

(10) (a) Arai, Y.; Hayashi, K.; Koizumi, T.; Shiro, M.; Kuriyama, K. *Tetrahedron Lett.* **1988**, *29*, 6143. (b) Alonso, I.; Carretero, J. C.; García Ruano, J. L. *Tetrahedron Lett.* **1991**, *32*, 947. (c) Alonso, I.; Cid, M. B.; Carretero, J. C.; García *Ruano*, J. L.; Hoyos, M. A. *Tetrahedron Asymmetry* **1991**, *2*, 1193.

(11) Arai, Y.; Matsui, M.; Koizumi, T.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 1983.

(12) The reactions of **1a–c** have been carried out in different polar solvents and reaction temperatures. Nevertheless, these changes did not increase the diastereoselectivity shown in Table I.

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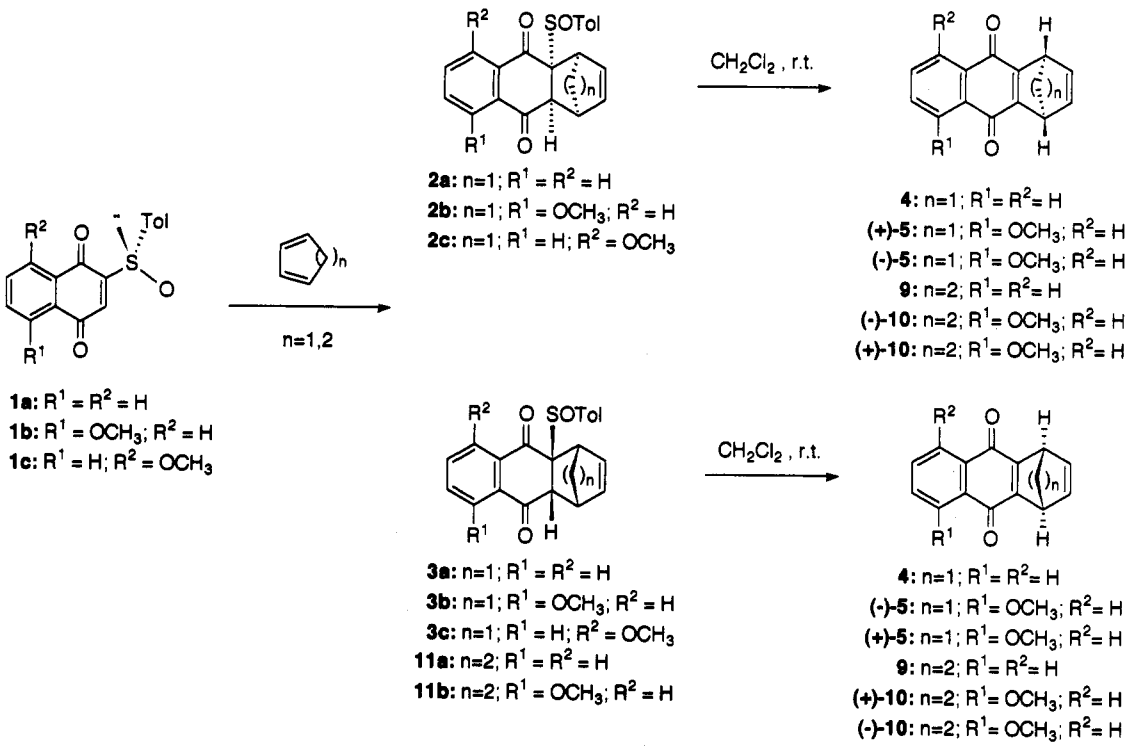
**Table I. Diels–Alder Cycloadditions of (*S*)-2-(*p*-Tolylsulfinyl)-1,4-naphthoquinones 1a–c**

| entry | dienophile | diene | solvent | *T* (°C) | cat. | time (h) | adducts (ratio) | de (%) | elim prod. | ee (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | cyclopentadiene | $CH_2Cl_2$ | −20 | | 24 | **2a:3a** (94:6) | 88 | **4** | |
| 2 | **1b** | cyclopentadiene | $CH_2Cl_2$ | −20 | | 24 | **2b:3b** (90:10) | 80 | **(+)-5** | |
| 3 | **1c** | cyclopentadiene | $CH_2Cl_2$ | −20 | | 24 | **2c:3c** (95:5) | 90 | **(−)-5** | |
| 4 | **1a** | cyclopentadiene | $CH_2Cl_2$ | −20 | $ZnBr_2$ | 1 | **3a** (>97) | >97 | **4** | |
| 5 | **1b** | cyclopentadiene | $CH_2Cl_2$ | −20 | $ZnBr_2$ | 1 | **3b** (>97) | >97 | **(−)-5** | |
| 6 | **1c** | cyclopentadiene | $CH_2Cl_2$ | −20 | $ZnBr_2$ | 1 | **2c:3c** (40:60) | 20 | **(+)-5** | 20[a] |
| 7 | **1a** | cyclohexadiene | $CHCl_3$ | 60 | | 72 | | | **9** | |
| 8 | **1b** | cyclohexadiene | $CHCl_3$ | 60 | | 72 | | | **(−)-10** | 20[a] |
| 9 | **1c** | cyclohexadiene | $CHCl_3$ | 60 | | 72 | | | **(+)-10** | 25[a] |
| 10 | **1a** | cyclohexadiene | $CH_2Cl_2$ | −20 | $ZnBr_2$ | 48 | **11a** (>97) | >97 | **9** | |
| 11 | **1b** | cyclohexadiene | $CH_2Cl_2$ | −20 | $ZnBr_2$ | 48 | **11b** (>97) | >97 | **(+)-10** | >97[a] |
| 12 | **1c** | cyclohexadiene | $CH_2Cl_2$ | 20 | $ZnBr_2$ | 48 | | | **(−)-10** | 40[a] |

[a] Determined by $^1$H-NMR in the presence of $Pr(tfc)_3$.

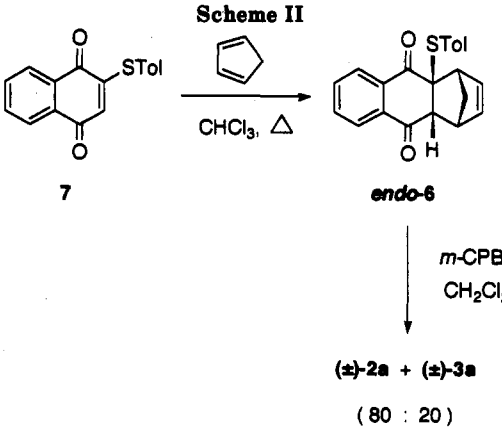
**Scheme I**




dation afforded a 80:20 mixture of two racemic diastereomeric sulfoxides (±)-**2a** and (±)-**3a**. The $^1$H-NMR parameters of these racemic derivatives are identical with those of the chiral cycloadducts **2a** and **3a** resulting from sulfinylquinone **1a**.

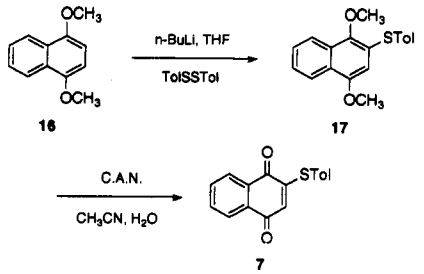
These configurational assignments were confirmed from the $^1$H-NMR chemical shifts of the different adducts **2** and **3** and by comparison with those of the endo adduct **8**,[15]

**Scheme II**




obtained in the reaction between cyclopentadiene and 1,4-naphthoquinone, used as reference (δ values are collected in Table II). The first remarkable observation was the low δ values showed by the AA′BB′ tolyl system of sulfoxides **2a–c** and **3a–c** (7.35–7.24 and 6.97–6.88 ppm)

(13) Compound **7** was synthesized by us in two steps starting from 1,4-dimethoxynaphthalene (**16**). Its direct metalation with *n*-BuLi and further reaction with di-*p*-tolyl disulfide yielded 2-(*p*-tolylsulfenyl)-1,4-dimethoxynaphthalene (**17**), whose oxidation with ceric ammonium nitrate (CAN) afforded quinone **7** in 96% yield without further oxidation on sulfur.[14]




(14) Ho, T. L.; Wong, C. M. *Synthesis* **1972**, 561.

(15) Adduct **8** was already described[16] but its $^1$H-NMR parameters were not well detailed.

(16) Filipescu, N.; Menter, J. M. *J. Chem. Soc. B* **1969**, *6*, 616.

Table II. $^1$H NMR Data for Compounds 2a–c, 3a–c, and 8

| proton | δ (ppm), multiplicity, J (in Hz) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2a | 2b | 2c | 3a | 3b | 3c | 8 |
| $H_1$ | 3.65, m | 3.67, m | 3.65, m | 3.81, m | 3.78, m | 3.76, m | 3.65, m |
| $H_2$ | 6.17, dd, 2.8, 5.4 | 6.22, dd, 2.8, 5.6 | 6.20, t, 1.6 | 6.18, m | 6.26, dd, 2.7, 5.6 | 6.21, m | 5.96, t, 1.8 |
| $H_3$ | 6.15, dd, 3.0, 5.2 | 6.14, dd, 2.9, 5.4 | 6.20, t, 1.6 | 6.18, m | 6.18, dd, 3.1, 5.6 | 6.21, m | 5.96, t, 1.8 |
| $H_4$ | 3.97, m | 3.84, m | 3.89, m | 4.08, m | 3.99, m | 4.01, m | 3.65, m |
| $H_5$ and $H_8$ | 7.77–7.66, m | 7.06, dd, 1.2, 7.8 | 7.34, m | 7.73–7.60, m | 7.16, dd, 1.1, 7.7 | 7.30, m | 8.01, m |
| $H_6$ and $H_7$ | 7.56–7.43, m | 7.39, t, 8.0 | 6.95, m | 7.46, m | 7.34, t, 7.9 | 6.90, m | 7.68, m |
| | | 7.17, dd, 1.2, 7.8 | 7.44, m | | 6.98, dd, 1.1, 7.7 | 7.40, m | |
| $H_{9a}$ | 3.98, d, 3.8 | 3.98, d, 3.8 | 3.98, d, 3.9 | 3.48, d, 3.8 | 3.48, d, 3.8 | 3.45, d, 3.8 | 3.44, m |
| $H_{11a}$ | 2.35, dt, 1.6, 9.1 | 2.29, dt, 1.6, 9.1 | 2.29, m | 2.17, dt, 1.4, 9.7 | 2.16, m | 2.17, m | 1.54, m |
| $H_{11b}$ | 1.50, dt, 1.7, 9.1 | 1.51, dt, 1.6, 9.2 | 1.49, dt, 1.6, 9.1 | 1.70, dt, 1.4, 9.7 | 1.68, dt, 1.7, 9.7 | 1.67, dt, 1.5, 9.5 | 1.54, m |
| $CH_3$ | 2.09, s | 2.20, s | 2.16, s | 2.11, s | 2.18, s | 2.18, s | |
| $CH_3O$ | | 3.86, s | 3.83, s | | 3.84, s | 3.84, s | |
| AA'BB'tolyl system | 7.24, 6.88 | 7.27, 6.97 | 7.30, 6.90 | 7.33, 6.90 | 7.32, 6.93 | 7.35, 6.92 | |

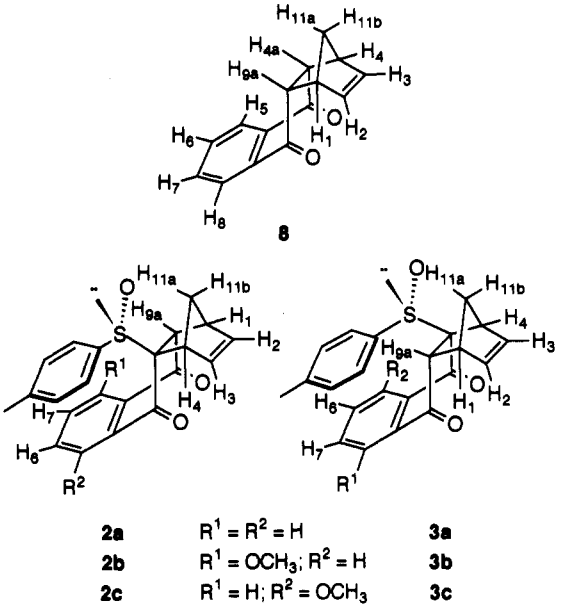



Figure 1.

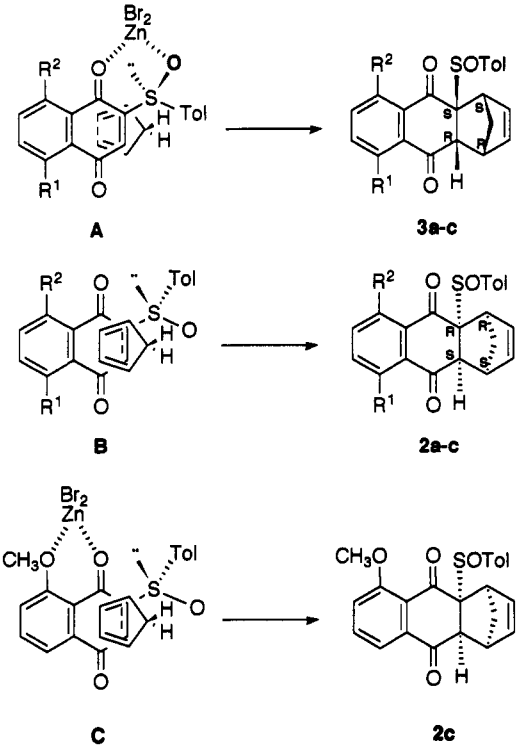



Figure 2. Favored approaches of cyclopentadiene in Diels–Alder reactions of (S)-2-(p-tolylsulfinyl)-1,4-naphthoquinones.

if compared with the corresponding absorptions in other p-tolyl sulfoxides[17] (ca. 7.6 and 7.3 ppm). This effect is probably due to the rigid disposition of the sulfinyl group in the Diels–Alder adducts showed in Figure 1, where the aromatic tolyl ring must be oriented paralell spelling to the aromatic ring of the tetrahydroanthraquinone moiety, resulting in the shielding of the ortho and meta protons to the sulfinyl group, and reciprocally those on $C_5$ and $C_8$ (less pronounced on $C_6$ and $C_7$) of **2a** and **3a** if compared with the corresponding δ values in **8** (the higher shielding observed for these protons in **2b,c** and **3b,c** is a consequence of the presence of the OMe substituent in the aromatic framework). This disposition must be the most stable due to π-stacking interactions between both aromatic rings.

In such conformations the sulfinylic oxygen is located very close to $H_{11a}$ if adducts **2** and **3** have the endo configuration. The deshielding observed for this proton confirmed the proposed geometry, the well-known anisotropic effect associated to the sulfinylic oxygen[18] being responsible for this variation.

The main difference between adducts **2a–c** and **3a–c** is the chemical shift of the $H_{9a}$ hydrogen (Table II), which appears ca. 0.5 ppm more deshielded in compounds **2**. Considering the configurational assignment shown in Figure 1, the difference observed in $H_{9a}$ chemical shift could also be attributed to the orientation of the sulfinylic oxygen in both adducts, which shifts only $H_{9a}$ downfield in compounds **2a–c**. Therefore, the anisotropic effect of the sulfinylic oxygen simultaneously affects $H_{9a}$ and $H_{11a}$ in adducts **2a–c**, but only $H_{11a}$ in the case of **3a–c**. According to this assignment, and taking into account the (*S*) configuration at the sulfinyl sulfur of the dienophile, which remains unaltered in these reactions, the absolute configuration for adducts **2** must be [1*S*,4*R*,4a*R*,9a*S*,(S)*S*] and that for **3** [1*R*,4*S*,4a*S*,9a*R*,(S)*S*].

This assignment is consistent with the expected stereochemical course for these asymmetric Diels–Alder reactions controlled on steric grounds.[19] The favored endo approach of the diene must take place from the less hindered face of the reactive conformation of dienophiles **1a–c**, which bears the lone electron pair at sulfur.

(17) Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1958.

(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.

(19) (a) Koizumi, T.; Hakamada, I.; Yoshii, E. *Tetrahedron Lett.* **1984**, *25*, 87. (b) Koizumi, T.; Arai, Y.; Takayama, H. *Tetrahedron Lett.* **1987**, *28*, 3689.

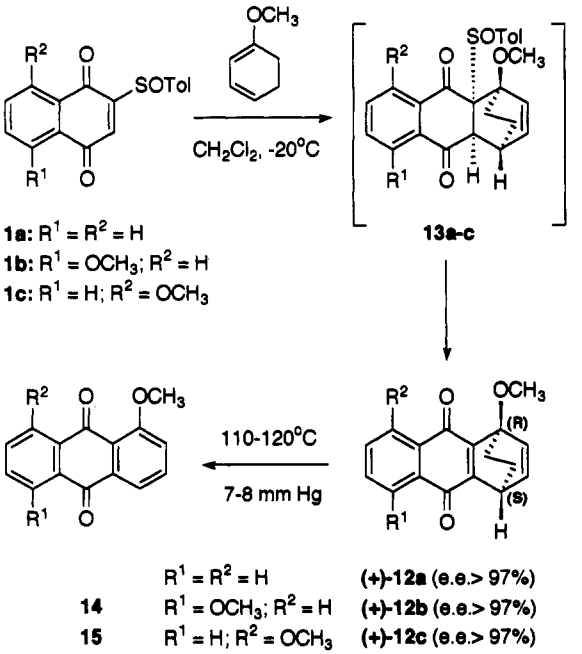
Assuming that these compounds form the chelate A depicted in Figure 2 in the presence of $ZnBr_2$,[20] the major adducts 3 (see Table I) obtained in these conditions must be those resulting from the approach of the diene from the bottom face of A. The inversion of the stereoselectivity observed in the absence of $ZnBr_2$ (adducts 2 are now the major, see Table I) suggested that, in this case, the most reactive conformation was the one with the sulfinyl and carbonyl oxygens in an antiperiplanar arrangement (B in Figure 2), where the electrostatic repulsion between both polar groups is minimized. The low de obtained in the reaction of 1c in the presence of $ZnBr_2$ (20%, see Table I) can be explained by assuming the competitive formation of the chelate C (Figure 2), with the zinc atom positioned between the methoxy and carbonyl groups, which leads to adduct 2c.

The results obtained in the reactions of sulfinylquinones 1a–c with cyclohexadiene are also depicted in Scheme I and Table I. The lower reactivity of this diene compared to cyclopentadiene resulted in a slower reaction in the absence of catalyst. In refluxing $CHCl_3$ the initial Diels–Alder adducts could not be detected, and the products resulting from the pyrolytic elimination of the sulfinyl group were formed.

Dienophile 1a yielded the dihydroanthraquinone 9, while 1b and 1c gave into the mixtures of both enantiomers of 10. As can be seen in Table I, the ee values[21] are low in both cases as a consequence of the low diastereofacial selectivity of the cycloadditions. This suggests the existence of several reactive conformations on the rotamer populations around the C–S bond of the dienophile as can be expected considering the high temperature necessary for the reaction.

The $ZnBr_2$-catalyzed cycloadditions, carried out in $CH_2Cl_2$ at −20 °C for sulfinylquinones 1a and 1b and at room temperature for 1c, were completed in 2 days (Table I). In these conditions the adducts 11a and 11b could be detected by $^1$H-NMR spectroscopy. Starting from 1a and 1b the cycloaddition was highly diastereoselective, and only one diastereomer 11 was detected in each case by $^1$H-NMR analysis of the crude reaction mixture. The reaction of 1c yielded a mixture of diastereomers that could not be determined directly. In this case the relative ratio was determined indirectly from the ee of the elimination product. As can be seen in Table I, the facial selectivity of the $ZnBr_2$-catalyzed reaction of sulfinylquinones 1a and 1b is excellent (>97%), allowing us to obtain the enantiomer

**Scheme III**




| | | |
|---|---|---|
| | $R^1 = R^2 = H$ | (+)-12a (e.e.> 97%) |
| 14 | $R^1 = OCH_3$; $R^2 = H$ | (+)-12b (e.e.> 97%) |
| 15 | $R^1 = H$; $R^2 = OCH_3$ | (+)-12c (e.e.> 97%) |

(+)-10 optically pure. The low selectivity observed in the reaction of 1c with cyclohexadiene (ee = 40%) must be again a consequence of the competitive formation of the chelate C depicted in Figure 2.

In order to study the regioselectivity of these processes, we carried out the cycloadditions of dienophiles 1a–c with 1-methoxy-1,3-cyclohexadiene. In the absence of catalysts,[22] all these reactions required 1 day to be completed at −20 °C in $CH_2Cl_2$ as solvent. As can be seen in Scheme III, a single compound (+)-12a–c, resulting from the elimination of the sulfinyl group on the corresponding Diels–Alder adducts 13a–c, was isolated in each reaction. The initially formed adducts could not be detected due to their low stability even at −20 °C.

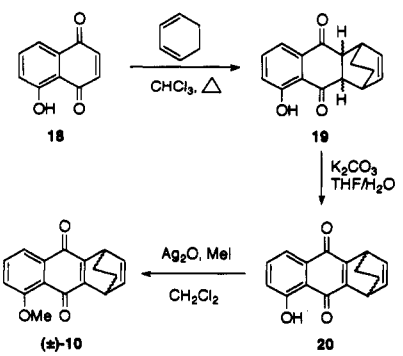
The optical purity of compounds 12a–c was shown to be higher than 97% by $^1$H-NMR analysis using $Pr(tfc)_3$ as chiral lantanide shift reagent.[23] This fact indicated that the facial diastereoselectivity of the 1-methoxy-1,3-cyclohexadiene cycloadditions in all cases had been excellent, giving rise to a unique regioisomer.

The substitution pattern of compounds 12b and 12c could not be unequivocally established from their spectroscopic data. The transformation of these compounds by aromatization into the known derivatives 14 and 15 was necessary to clarify this point. Thus, vacuum pyrolysis at 110–120 °C and 7–8 mmHg afforded 1,5-dimethoxyanthraquinone (14)[24] from 12b and 1,8-dimethoxyanthraquinone (15)[25] from 12c (Scheme III). The differences in their $^{13}$C-NMR spectra (15 exhibits two different signals for its two carbonyl groups, whereas 14 shows only one due to its symmetry) confirmed this assignment.

The results shown in Scheme III provide evidence that the regiochemical course of the cycloadditions between sulfinylnaphthoquinones 1a–c and 1-methoxy-1,3-cyclohexadiene was directed by the sulfinyl group, yielding

(20) This kind of chelation has been suggested for β-keto sulfoxides and structurally similar compounds: Carreño, M. C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120.

(21) The optical purity of compounds obtained on thermal and catalytic reactions was studied by $^1$H-NMR spectroscopy using $Eu(tfc)_3$ as chiral lantanide shift reagent. Racemic compound (±)-10, necessary for such a determination, was synthesized from juglone (18) in three steps as follows:




(22) When these reactions were carried out in the presence of $ZnBr_2$ as catalyst, the corresponding addition products of the diene to the activated double bond were obtained. Their study is now in progress in our laboratory.

(23) The racemic compounds (±)-12a–c necessary for such a evaluation were also obtained by Diels–Alder reaction starting from racemic quinones (±)-1a–c (see ref 5b).

(24) Wiles, L. A. *J. Chem. Soc.* **1952**, 1358.

(25) Brockmann, H.; Neeff, R.; Mühlmann, E. *Chem. Ber.* **1950**, *83*, 467.

exclusively the ortho adducts. It is noteworthy that compound 1c, where the 5-methoxy substituent in the quinone framework is known to polarize the dienophilic double bond in the opposite sense to the sulfinyl group,[26] yielded only one regioisomer. Previous results of racemic sulfinylnaphthoquinone cycloadditions with isoprene showed a regioselectivity partially governed by the sulfinyl group, which improved in the presence of $BF_3{\cdot}Et_2O$.[4b]

Assuming that the facial diastereoselectivity is identical in the reactions of compounds 1a–c with 1-methoxy-1,3-cyclohexadiene and cyclopentadiene, we assign the (1*R*,4*S*) absolute configuration to 12a–c (Scheme III).

## Conclusions

(*S*)-2-(*p*-Tolylsulfinyl)-1,4-naphthoquinones 1a–c have been shown to exhibit a range of diastereoselectivities in their cycloadditions with various cyclic dienes. The stereochemical course seems to be mainly controlled by steric interactions at the transition state resulting from the approach of the diene on the s-cis (thermal reactions) or s-trans ($ZnBr_2$ catalysis) conformations of the sulfinyl group.

One-pot chiral synthesis of 5-methoxy-1,4-dihydro-9,10-anthraquinone derivatives has been achieved by pyrolytic elimination of the sulfoxide on the adducts initially formed from (*S*)-2- and 3-(*p*-tolylsulfinyl)-1,4-naphthoquinones. The regiochemistry of the reaction with 1-methoxy-1,3-cyclohexadiene was completely directed by the sulfinyl substituent. The reactions presented here give rise to new chirons of potential interest for approaches to natural anthraquinones.

## Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. The electron-impact mass spectra were recorded at 70 eV. IR spectra are given in $cm^{-1}$. $^1H$- and $^{13}C$-NMR spectra were recorded at 200.1 and 50.3 MHz in $CDCl_3$. Diastereomeric adducts ratios were established by integration of well-separated signals of both diastereomers in the crude reaction mixtures and are listed in Table I. When a mixture of diastereomers was obtained, the data indicated correspond to those of the major component. $^1H$ NMR data of compounds 2a–c, 3a–c, and 8 are collected in Table II. All reactions were monitored by TLC 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. The apparatus for inert atmosphere experiments was dried by flaming in a stream of dry argon. Cyclopentadiene was 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, under a stream of dry argon, before using. For routine workup, hydrolysis was carried out with water, extractions with $CH_2Cl_2$, and solvent drying with $Na_2SO_4$.

**General Procedures for Diels–Alder Reactions. Method A.** To a solution of sulfinylnaphthoquinones 1a–c (0.3 mmol) in 3 mL of dry $CH_2Cl_2$ at −20 °C was added cyclopentadiene (33 mg, 0.5 mmol) under argon. After 24 h, the solvent was evaporated at reduced pressure below 0 °C to avoid pyrolytic elimination of the sulfinyl group. The resulting adducts, isolated as an oil, were shown to be over 96% pure by $^1H$-NMR analysis.

**Method B.** A solution of sulfinylnaphthoquinones 1a–c (0.3 mmol) in 3 mL of dry $CH_2Cl_2$ was added to $ZnBr_2$ (135 mg, 0.6 mmol) and stirred for 1 h at rt. After the solution was cooled at −20 °C, cyclopentadiene (33 mg, 0.5 mmol) or cyclohexadiene (480 mg, 6 mmol) was added. After completion of the reaction (see Table I for reaction times) the mixture was quenched with ice–water. After workup, the solvent was evaporated at reduced pressure below 0 °C to avoid pyrolytic elimination of the sulfiny group. The resulting adducts, isolated as an oil, were shown to be over 96% pure by $^1H$-NMR analysis.

**Method C.** A solution of the sulfinylnaphthoquinones 1a–c (0.3 mmol) and cyclohexadiene (480 mg, 6 mmol) in 10 mL of $CHCl_3$ was refluxed for 3 days. After evaporation of the solvent, the residue was purified by flash chromatography (eluent $CH_2Cl_2$–hexane (1:1)).

**Method D.** To a solution of the sulfinylnaphthoquinones 1a–c (0.3 mmol) in 3 mL of dry $CH_2Cl_2$ at −20 °C was added 1-methoxy-1,3-cyclohexadiene (110 mg, 1 mmol) under argon. After 24 h, the solvent was evaporated and the residue purified by flash chromatography (eluent $CH_2Cl_2$).

**General Procedure for the Sulfinyl Group Elimination from the Diels–Alder Adducts. Method E.** The corresponding Diels–Alder adducts 2, 3, or 11 (0.2 mmol) obtained as above were stirred in 5 mL of $CH_2Cl_2$ at rt. After 24 h, the solvent was evaporated and the residue purified by flash chromatography (eluent $CH_2Cl_2$ for compounds 4, (−)-5, and (+)-5 and $CH_2Cl_2$–hexane (1:1) for 9 and (+)-10).

***endo*-[1*S*,4*R*,4a*R*,9a*S*,(S)*S*]-1,4-Methano-4a-(*p*-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (2a).** Compound 2a was obtained following method A from 1a (89 mg) as a 94:6 mixture of diastereomers 2a and 3a (100 mg, 92% yield): $[\alpha]^{20}_D$ −112° (*c* = 1, $CHCl_3$); IR (film) 2970, 1650, 1315, 1260, 1075 $cm^{-1}$.

***endo*-[1*S*,4*R*,4a*R*,9a*S*,(S)*S*]-1,4-Methano-8-methoxy-4a-(*p*-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (2b).** Compound 2b was obtained following method A from 1b (98 mg) as a 90:10 mixture of diastereomers 2b and 3b (106 mg, 90% yield): $[\alpha]^{20}_D$ −21° (*c* = 1, $CHCl_3$); IR (film) 2950, 1680, 1575, 1290, 1075 $cm^{-1}$.

***endo*-[1*S*,4*R*,4a*R*,9a*S*,(S)*S*]-1,4-Methano-5-methoxy-4a-(*p*-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (2c).** Compound 2c was obtained following method A from 1c (98 mg) as a 95:5 mixture of diastereomers 2c and 3c (110 mg, 94% yield: $[\alpha]^{20}_D$ −365° (*c* = 1, $CHCl_3$); IR (film) 2960, 1675, 1550, 1280, 1080 $cm^{-1}$.

***endo*-[1*R*,4*S*,4a*S*,9a*R*,(S)*S*]-1,4-Methano-4a-(*p*-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (3a).** Compound 3a was obtained following method B from 1a (89 mg) and cyclopentadiene diastereomerically pure (91 mg, 84% yield): $[\alpha]^{20}_D$ −45° (*c* = 1, $CHCl_3$); IR (film) 2980, 1660, 1590, 1270, 1060 $cm^{-1}$.

***endo*-[1*R*,4*S*,4a*S*,9a*R*,(S)*S*]-1,4-Methano-8-methoxy-4a-(*p*-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (3b).** Compound 3b was obtained following method B from 1b (98 mg) and cyclopentadiene diastereomerically pure (95 mg, 81% yield): $[\alpha]^{20}_D$ −57° (*c* = 1, $CHCl_3$); IR (film) 2960, 1665, 1580, 1280, 1080 $cm^{-1}$.

***endo*-[1*R*,4*S*,4a*S*,9a*R*,(S)*S*]-1,4-Methano-5-methoxy-4a-(*p*-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (3c).** Compound 3c was obtained following method B from 1c (98 mg) and cyclopentadiene as a 60:40 mixture of diastereomers 3c and 2c (94 mg, 80% yield): $[\alpha]^{20}_D$ −101° (*C* = 1, $CHCl_3$); IR (film) 2950, 1685, 1570, 1275, 1075 $cm^{-1}$.

**1,4-Methano-1,4-dihydro-9,10-anthraquinone (4).** Compound 4 was obtained following method E from 72 mg of a 94:6 mixture of 2a and 3a (36 mg 82% yield) or from 72 mg of 3a (38 mg, 84% yield): mp 155–156 °C (methanol) (lit.[27] mp 155 °C); MS *m*/*z* (relative intensity) 222 ($M^+$, 72), 194 (30), 165 (100), 139 (35); $^1H$-NMR δ 2.31 (2 H, m, $H_{11a}$ and $H_{11b}$), 4.17 (2 H, m, $H_1$ and $H_4$), 6.78 (2 H, m, $H_2$ and $H_3$), 7.51 (2 H, m, $H_6$ and $H_7$), 7.89 (2 H, m, $H_5$ and $H_8$); $^{13}C$-NMR 48.6, 73.3, 126.0, 132.6, 133.2, 142.4, 162.9, 181.5. Anal. Calcd for $C_{15}H_{10}O_2$: C, 81.08; H, 4.51. Found: C, 81.20; H, 4.42.

**(−)-(1*R*,4*S*)-1,4-Methano-5-methoxy-1,4-dihydro-9,10-anthraquinone (5).** Compound (−)-5 was obtained following method E from 78 mg of 3b (40 mg 81% yield; $[\alpha]^{20}_D$ −12° (*c* = 1, $CHCl_3$)) or from 78 mg of a 95:5 mixture of 2c and 3c (43 mg, 85% yield): mp 143–144 °C (methanol); $[\alpha]^{20}_D$ −10° (*c* = 1, $CHCl_3$); IR (KBr) 1640, 1580, 1270, 1055, 750 $cm^{-1}$; MS *m*/*z* (relative intensity) 252 ($M^+$, 100), 237 (40), 209 (41), 181 (34), 165 (69), 152 (57); $^1H$-NMR δ 2.20 (2 H, m, $H_{11a}$ and $H_{11b}$), 3.87 (3 H, s, $CH_3O$), 4.51 (2 H, m, $H_1$ and $H_4$), 6.77 (2 H, t, *J* = 1.9 Hz, $H_2$ and

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$H_3$), 7.14 (1 H, dd, $J$ = 1.3 and 8.1 Hz, $H_8$), 7.48 (1 H, dd, $J$ = 7.6 and 8.1 Hz, $H_7$), 7.57 (1 H, dd, $J$ = 1.5 and 7.6 Hz, $H_8$); $^{13}$C-NMR 48.2, 48.6, 56.2, 72.5, 117.6, 118.8, 119.8, 129.6, 134.1, 135.0, 142.2, 142.3, 159.4, 164.6, 181.1, 181.3. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.19; H, 4.76. Found: C, 75.92; H, 4.62.

**(+)-(1*S*,4*R*)-1,4-Methano-5-methoxy-1,4-dihydro-9,10-anthraquinone (5).** Compound (+)-5 was obtained following method E from 78 mg of a 90:10 mixture of **2b** and **3b** (40 mg, 79% yield) [mp 140–142 °C (methanol); $[\alpha]^{20}_D$ +9° ($c$ = 1, $CHCl_3$)] or from 78 mg of a 60:40 mixture of **3c** and **2c** (38 mg, 75% yield): mp 143–144 °C (methanol); $[\alpha]^{20}_D$ +3° ($c$ = 1, $CHCl_3$).

**1,4-Dimethoxy-2-(p-tolylthio)naphthalene (17).** A solution of 1,4-dimethoxynaphthalene (**16**) (1.86 g, 9.9 mmol) in 50 mL of dry THF was slowly added over a solution of *n*-BuLi 1.6 M (6.2 mL, 9.9 mmol) in 20 mL of dry THF at rt. The mixture was stirred 1 h and then added via cannula to a solution of di-*p*-tolyl disulfide (2.51 g, 10.2 mmol) in 50 mL of dry THF. After being stirred 1 h and workup, the residue was chromatographed on silica gel (eluent acetone:hexane = 1:8) to give compound **17** (2.03 g, 66% yield: mp 95–97 °C (methanol); IR (KBr) 1590, 1460, 1380, 1270, 1240, 1090 cm$^{-1}$; MS $m/z$ (relative intensity) 310 ($M^+$, 100), 295 (77), 149 (41), 113 (32); $^1$H-NMR $\delta$ 2.34 (3 H, s, $CH_3Ar$), 3.78 and 3.97 (6 H, 2s, $CH_3O$), 6.49 (1 H, s, $H_3$), 7.18 and 7.30 (4 H, AA'BB' system, tolyl group), 7.50 (2 H, m, $H_6$ and $H_7$), 8.17 and 8.06 (2 H, 2dd, $J$ = 1.9 and 7.9 Hz, $H_5$ and $H_8$); $^{13}$C-NMR $\delta$ 21.0, 55.3, 61.4, 105.9, 121.6, 122.3, 125.4, 125.7, 126.9, 128.5, 129.9, 130.5, 131.1, 131.4, 135.9, 137.0, 151.9. Anal. Calcd for $C_{19}H_{18}SO_2$: C, 73.55; H, 5.81. Found: C, 73.30; H, 5.92.

**2-(p-Tolylthio)-1,4-naphthoquinone (7).** A solution of ammonium cerium(IV) nitrate (CAN) (5.50 g, 10 mmol) in 50 mL of $H_2O$ was added to a solution of **17** (1.24 g, 4 mmol) in 50 mL of $CH_3CN$ at rt and stirred for 1 h. After $CH_3CN$ evaporation and workup, compound **7** (1.07 g, 96% yield) was obtained as a yellow solid: mp 120–122 °C (methanol) (lit.[28] mp 121–122 °C); MS $m/z$ (relative intensity) 280 ($M^+$, 100), 265 (34), 251 (33), 237 (28), 189 (38), 104 (42); $^1$H-NMR $\delta$ 2.43 (3 H, s, $CH_3Ar$), 7.30 and 7.42 (4 H, AA'BB' system, tolyl group), 7.72 (2 H, m, $H_6$ and $H_7$), 8.02 and 8.17 (2 H, 2m, $H_5$ and $H_8$); $^{13}$C-NMR $\delta$ 21.1, 123.4, 126.1, 126.4, 127.7, 130.9, 131.3, 131.8, 133.0, 134.0, 135.2, 140.6, 156.6, 181.5, 181.7. Anal. Calcd for $C_{17}H_{12}SO_2$: C, 72.86; H, 4.29. Found: C, 73.05; H, 4.34.

***endo*-1,4-Methano-4a-(p-tolylthio)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (6).** A solution of **7** (100 mg, 3.6 mmol) and cyclopentadiene (500 mg, 76 mmol) in 10 mL of $CHCl_3$ was refluxed for 2 days. The solvent was evaporated in vacuo and the residue purified by crystallization to afford compound **6** (106 mg, 85% yield): mp 118–120 °C (methanol); IR (KBr) 1670, 1590, 1265, 810, 710 cm$^{-1}$; MS $m/z$ (relative intensity) 346 ($M^+$, 2), 280 (100), 265 (27), 251 (25), 237 (21), 189 (25), 104 (29); $^1$H-NMR $\delta$ 1.72 (1 H, dt, $J$ = 9.0 and 1.8 Hz, $H_{11b}$), 2.33 (1 H, m, $H_{11a}$), 2.36 (3 H, s, $CH_3Ar$), 3.27 (1 H, d, $J$ = 3.8 Hz, $H_{9a}$), 3.38 (1 H, m, $H_4$), 3.69 (1 H, m, $H_1$), 6.01 and 6.12 (2 H, 2dd, $J$ = 2.9 and 5.6 Hz, $H_2$ and $H_3$), 7.15 and 7.28 (4 H, AA'BB' system, tolyl group), 7.69 (2 H, m, $H_6$ and $H_7$), 7.96 (2 H, m, $H_5$ and $H_8$); $^{13}$C-NMR $\delta$ 21.3, 45.5, 47.5, 49.3, 58.6, 63.9, 126.5, 127.0, 127.5, 129.7, 131.9, 133.3, 134.2, 135.9, 136.8, 137.3, 137.6, 140.3, 191.1, 196.0. Anal. Calcd for $C_{22}H_{18}SO_2$: C, 76.30; H, 5.20. Found: C, 76.09; H, 4.97.

***endo*-[1*S**,4*R**,4a*R**,9a*S**,(S)*S**]-1,4-Methano-4a-(p-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (2a) and *endo*-[1*R**,4*S**,4a*S**,9a*R**,(S)*S**]-1,4-Methano-4a-(p-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (3a).** *m*-CPBA (10 mg, 0.05 mmol) was added to a solution of **6** (18 mg, 0.05 mmol) in 0.4 mL of $CDCl_3$. The reaction, which was monitored by $^1$H-NMR, afforded almost instantaneously a 80:20 mixture of (±)-**2a** and (±)-**3a**. The $^1$H-NMR spectroscopic parameters of these racemic adducts were identical to the optically active **2a** and **3a**.

***endo*-[1*R*,4*S*,4a*S*,9a*R*,(S)*S*]-1,4-Ethano-4a-(p-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (11a).** Compound **11a** was obtained following method B from **1a** (89 mg) and cyclohexadiene (96 mg, 85% yield): $[\alpha]^{20}_D$ −27° ($c$ = 1, $CHCl_3$); IR (film) 2985, 1670, 1585, 1270, 1080 cm$^{-1}$; $^1$H-NMR $\delta$ 1.41–1.60 (2 H, m, $H_{11b}$ and $H_{12b}$), 2.00 and 2.40 (2 H, 2m, $H_{11a}$ and $H_{12a}$), 2.05 (3 H, s, $CH_3Ar$), 3.01 (1 H, d, $J$ = 1.9 Hz, $H_{9a}$), 3.42 (1 H, m, $H_1$), 3.99 (1 H, m, $H_4$), 6.21 and 6.39 (2 H, 2ddd, $J$ = 1.2, 6.3, and 7.5 Hz; $J$ = 1.3, 6.5, and 7.9 Hz, $H_2$ and $H_3$), 6.80 and 7.25 (4 H, AA'BB' system, tolyl group), 7.45 (2 H, m, $H_6$ and $H_7$), 7.65 (2 H, m, $H_5$ and $H_8$).

***endo*-[1*R*,4*S*,4a*S*,9a*R*,(S)*S*]-1,4-Ethano-8-methoxy-4a-(p-tolylsulfinyl)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (11b).** Compound **11b** was obtained following method B from **1b** (98 mg) and cyclohexadiene (100 mg, 82% yield): $[\alpha]^{20}_D$ −27° ($c$ = 0.5, $CHCl_3$); IR (film) 2980, 1655, 1595, 1275, 1060 cm$^{-1}$; $^1$H-NMR $\delta$ 1.30–1.70 (2 H, m, $H_{11b}$ and $H_{12b}$), 1.92 and 2.38 (2 H, 2m, $H_{11a}$ and $H_{12a}$), 2.12 (3 H, s), 2.95 (1 H, d, $J$ = 2.1 Hz, $H_{9a}$), 3.54 (1 H, m, $H_1$), 3.81 (3 H, s, $CH_3O$), 3.92 (1 H, m, $H_4$), 6.23 and 6.37 (2 H, 2ddd, $J$ = 1.1, 6.2, and 8.1 Hz; $J$ = 1.4, 6.5, and 7.9 Hz, $H_2$ and $H_3$), 6.95 (1 H, dd, $J$ = 2.0 and 7.5 Hz, $H_7$), 6.85 and 7.27 (4 H, AA'BB' system, tolyl group), 7.20–7.40 (2 H, m, $H_5$ and $H_6$).

**1,4-Ethano-1,4-dihydro-9,10-anthraquinone (9).** Compound **9** was obtained following method C from 89 mg of **1a** (53 mg, 75% yield) or following method E from 75 mg of **11a** (38 mg, 81% yield): mp 165–185 °C (gas evolution) (methanol) (lit.[27] mp 160–190 °C); IR (KBr) 1645, 1585, 1330, 1295, 1265, 720 cm$^{-1}$; MS $m/z$ (relative intensity) 236 ($M^+$, 19), 208 (100), 180 (85), 152 (72); $^1$H-NMR $\delta$ 1.40–1.60 (4 H, m, $H_{11a}$, $H_{11b}$, $H_{12a}$, and $H_{12b}$), 4.54 (2 H, m, $H_1$ and $H_4$), 6.44 (2 H, m, $H_2$ and $H_3$), 7.68 (2 H, m, $H_6$ and $H_7$), 8.06 (2 H, m, $H_5$ and $H_8$); $^{13}$C-NMR 24.6, 34.1, 126.2, 132.2, 133.3, 133.7, 150.5, 181.3. Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.36; H, 5.08. Found: C, 81.50; H, 4.87.

**(+)-(1*S*,4*R*)-1,4-Ethano-5-methoxy-1,4-dihydro-9,10-anthraquinone (10).** Compound (+)-**10** was obtained following method C from 98 mg of **1c** (59 mg, 74% yield, $[\alpha]^{20}_D$ +5° ($c$ = 1, $CHCl_3$)) or following method E from 81 mg of **11b** (44 mg, 84% yield: $[\alpha]^{20}_D$ +20° ($c$ = 1, $CHCl_3$)): mp 149–150 °C (methanol); IR (KBr) 1640, 1580, 1330, 1225, 1065, 955, 715 cm$^{-1}$; MS $m/z$ (relative intensity) 266 ($M^+$, 14), 238 (100), 209 (55), 180 (36), 152 (68), 139 (45), 113 (12), 76 (41); $^1$H-NMR $\delta$ 1.30–1.60 (4 H, m, $H_{11a}$, $H_{11b}$, $H_{12a}$, and $H_{12b}$), 3.99 (3 H, s, $CH_3O$), 4.51 (2 H, m, $H_1$ and $H_4$), 6.42 (2 H, m, $H_2$ and $H_3$), 7.25 (1 H, dd, $J$ = 1.2 and 8.2 Hz, $H_6$), 7.61 (1 H, dd, $J$ = 7.8 and 8.2 Hz, $H_7$), 7.74 (1 H, dd, $J$ = 1.2, and 7.8 Hz, $H_8$); $^{13}$C-NMR 181.1, 181.0, 159.5, 152.1, 147.9, 134.6, 134.3, 133.8, 133.7, 119.8, 119.1, 117.5, 56.3, 34.1, 33.7, 24.6, 24.5. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.69; H, 5.26. Found: C, 76.84; H, 5.46.

**(−)-(1*R*,4*S*)-1,4-Ethano-5-methoxy-1,4-dihydro-9,10-anthraquinone (10).** Compound (−)-**10** was obtained following method C from 98 mg of **1c** (63 mg, 79% yield, $[\alpha]^{20}_D$ −4° ($c$ = 1, $CHCl_3$)) or following method B from 98 mg of **1c** and cyclohexadiene carrying out the reaction at rt, after flash chromatography (eluent $CH_2Cl_2$:hexane = 1:1) of the crude reaction (64 mg, 80% yield, $[\alpha]^{20}_D$ −8° ($c$ = 1, $CHCl_3$)).

***endo*-1,4-Ethano-5-hydroxy-1,4,4a,9a-tetrahydro-9,10-anthraquinone (19).** A solution of juglone (**18**) (100 mg, 0.57 mmol) and cyclohexadiene (0.2 mL, 11.4 mmol) was refluxed in 10 mL of $CHCl_3$. After 3 days, the solvent was evaporated to afford compound **19** (130 mg, 90% yield) which could be used without further purification: mp 89–90 °C (methanol); IR (KBr) 1670, 1620, 1350, 1260, 1165, 800, 690 cm$^{-1}$; MS $m/z$ (relative intensity) 254 ($M^+$, 29), 224 (15), 120 (14), 97 (15), 80 (100), 69 (45), 59 (77); $^1$H-NMR $\delta$ 1.41 and 1.79 (4 H, 2m, $H_{11a}$, $H_{11b}$, $H_{12a}$, and $H_{12b}$), 3.15 and 3.24 (2 H, 2dd, $J$ = 2.4 and 9.4 Hz, $H_{4a}$ and $H_{9a}$), 3.36 (2 H, m, $H_1$ and $H_4$), 6.19 (2 H, m, $H_2$ and $H_3$), 7.21 (1 H, dd, $J$ = 1.7 and 7.6 Hz, $H_6$), 7.55 (1 H, dd, $J$ = 1.7 and 7.6 Hz, $H_8$), 7.62 (1 H, t, $J$ = 7.6 Hz, $H_7$), 12.60 (1 H, s, OH); $^{13}$C-NMR $\delta$ 24.5, 24.7, 35.7, 35.8, 49.5, 49.9, 117.8, 122.9, 133.0, 133.4, 133.7, 135.0, 136.6, 161.5, 196.7, 204.3. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.59; H, 6.51. Found: C, 75.37; H, 5.64.

**1,4-Ethano-5-hydroxy-1,4-dihydro-9,10-anthraquinone (20).** A solution of **19** (100 mg, 0.39 mmol) in 10 mL of THF and $K_2CO_3$ (1 g, 8.20 mmol) in 10 mL of water was stirred at rt for 12 h. After workup, compound **20** (85 mg, 87% yield) was obtained as a yellow solid: mp 158–160 °C (methanol); IR (KBr) 1630, 1450, 1335, 1245, 765, 720 cm$^{-1}$; MS $m/z$ (relative intensity) 252 ($M^+$, 19), 224 (100), 196 (13), 168 (26), 139 (37), 63 (12); $^1$H-NMR $\delta$ 1.30–1.70 (4 H, m, $H_{11a}$, $H_{11b}$, $H_{12a}$, and $H_{12b}$), 4.52 (2 H, m, $H_1$ and $H_4$), 6.44 (2 H, m, $H_2$ and $H_3$), 7.19 (1 H, dd, $J$ = 2.1 and 7.7 Hz, $H_6$), 7.5–7.7 (2 H, m, $H_7$ and $H_8$), 12.11 (1 H, s, OH); $^{13}$C-NMR $\delta$ 24.4, 24.5, 33.4, 34.2, 114.6, 118.9, 124.0, 132.2, 133.5, 133.6, 135.7, 150.2, 151.7,

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161.2, 180.4, 186.4. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.19; H, 4.76. Found: C, 75.98; H, 5.00.

**(±)-1,4-Ethano-5-methoxy-1,4-dihydro-9,10-anthraquinone (10).** A suspension of **20** (50 mg, 0.2 mmol), $Ag_2O$ (460 mg, 1.98 mmol), and MeI (0.4 mL, 6.42 mmol) in 10 mL of dry $CH_2Cl_2$ was vigorously stirred at rt. After 24 h, the solution was filtered and the solvent evaporated to afford compound (±)-**10** (49 mg, 93% yield): mp 148–149 °C (methanol).

**(+)-(1*R*,4*S*)-1,4-Ethano-1-methoxy-1,4-dihydro-9,10-anthraquinone (12a).** Compound (+)-**12a** was obtained following method D from 89 mg of **1a** (56 mg, 78% yield): mp 124–125 °C (methanol); $[\alpha]^{20}_D$ +114° (*c* = 1, $CHCl_3$); IR (KBr) 1660, 1590, 1280, 720 $cm^{-1}$; MS *m/z* (relative intensity) 266 ($M^+$, 3), 238 (100), 209 (46), 181 (20), 152 (32); $^1$H-NMR δ 1.40–1.90 (4 H, m, $H_{11a}$, $H_{11b}$, $H_{12a}$, and $H_{12b}$), 3.70 (3 H, s, $CH_3O$), 4.50 (1 H, ddt, *J* = 1.6, 6.1, and 2.6 Hz, $H_4$) 6.42 (1 H, dd, *J* = 6.1 and 7.8 Hz, $H_3$), 6.63 (1 H, dd, *J* = 1.6 and 7.8 Hz, $H_2$), 7.70 (2 H, m, $H_6$ and $H_7$), 8.07 (2 H, m, $H_5$ and $H_8$); $^{13}$C-NMR δ 24.8, 31.0, 33.4, 55.6, 85.0, 125.7, 126.3, 130.0, 131.2, 132.9, 133.6, 135.1, 136.3, 147.5, 150.4, 180.8, 181.1. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.69; H, 5.26. Found: C, 76.80; H, 5.25.

**(+)-(1*R*,4*S*)-1,4-Ethano-1,5-dimethoxy-1,4-dihydro-9,10-anthraquinone (12b).** Compound (+)-**12b** was obtained following method D from 98 mg of **1b** (63 mg, 77% yield): 122–123 °C (methanol); $[\alpha]^{20}_D$ +55° (*c* = 0.5, $CHCl_3$); IR (KBr) 1651, 1585, 1472, 1290, 1057 $cm^{-1}$; MS *m/z* (relative intensity) 296 ($M^+$, 4), 268 (42), 253 (100), 209 (23), 180 (21), 152 (35), 139 (15); $^1$H-NMR δ 1.30–1.90 (4 H, m, $H_{11a}$, $H_{11b}$, $H_{12a}$, and $H_{12b}$), 3.67 and 3.99 (6 H, 2s, $2CH_3O$), 4.50 (1 H, m, $H_4$), 6.38 (1 H, dd, *J* = 6.1 and 7.8 Hz, $H_3$), 6.60 (1 H, dd, *J* = 1.6 and 7.8 Hz, $H_2$), 7.23 (1 H, dd, *J* = 1.4 and 8.2 Hz, $H_6$) 7.63 (1 H, dd, *J* = 7.7 and 8.2 Hz, $H_7$), 7.73 (1 H, dd, *J* = 1.4 and 7.7 Hz, $H_8$); $^{13}$C-NMR δ 25.1, 31.2, 33.7, 55.6, 56.4, 84.9, 117.0, 119.2, 119.3, 131.5, 134.7, 135.3, 135.6, 145.4, 152.1, 159.3, 180.7, 180.8. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 73.11; H, 5.50.

**(+)-(1*R*,4*S*)-1,4-Ethano-1,8-dimethoxy-1,4-dihydro-9,10-anthraquinone (12c).** Compound (+)-**12c** was obtained following method D from 98 mg of **1c** (65 mg, 80% yield): mp 120–121 °C (methanol); $[\alpha]^{20}_D$ +76° (*c* = 0.5, $CHCl_3$); IR (KBr) 1660, 1580, 1470, 1295, 1050 $cm^{-1}$; MS *m/z* (relative intensity) 296 ($M^+$, 3), 268 (36), 253 (100), 236 (12), 209 (12), 180 (13), 152 (27), 139 (28); $^1$H-NMR δ 1.30–1.90 (4 H, m, $H_{11a}$, $H_{11b}$, $H_{12a}$, and $H_{12b}$), 3.69 and 3.97 (6 H, 2s, $2CH_3O$), 4.41 (1 H, m, $H_4$), 6.38 (1 H, dd, *J* = 6.1 and 7.8 Hz, $H_3$), 6.59 (1 H, dd, *J* = 1.6 and 7.8 Hz, $H_2$), 7.26 (1 H, dd, *J* = 1.4 and 8.2 Hz, $H_7$), 7.59 (1 H, dd, *J* = 7.6 and 8.2 Hz, $H_6$), 7.69 (1 H, dd, *J* = 1.4 and 7.6 Hz, $H_5$); $^{13}$C-NMR δ 25.2, 31.4, 33.3, 55.7, 56.6, 85.4, 123.8, 124.9, 125.5, 130.1, 131.5, 133.9, 135.5, 137.1, 140.2, 148.0, 181.1, 181.5. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 72.80; H, 5.59.

**1,5-Dimethoxy-9,10-anthraquinone (14).** Compound **12b** (55mg, 0.2 mmol) was heated at 110 °C in vacuo (6 mmHg) to give, after crystallization of the residue, compound **14** (39 mg, 72% yield): mp 234–235 °C (methanol) (lit.[24] mp 237 °C); MS *m/z* (relative intensity) 268 ($M^+$, 38), 253 (100), 152 (35), 139 (39); $^1$H-NMR δ 4.04 (6 H, s, $2CH_3O$), 7.28 (2 H, dd, *J* = 1.2 and 8.4 Hz, $H_2$ and $H_6$), 7.70 (2 H, dd, *J* = 7.8 and 8.4 Hz, $H_3$ and $H_7$), 7.91 (2 H, dd, *J* = 1.2 and 7.8 Hz, $H_4$ and $H_8$); $^{13}$C-NMR δ 56.4 (2 C), 116.7 (2 C), 119.7 (2 C), 123.9 (2 C), 135.0 (2 C), 137.4 (2 C), 159.7 (2 C), 182.7 (2 C). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.48. Found: C, 71.48; H, 4.33.

**1,8-Dimethoxy-9,10-anthraquinone (15).** Compound **12c** (55 mg, 0.2 mmol) was heated at 120 °C in vacuo (8 mmHg) to give, after crystallization of the residue, compound **15** (40 mg, 75% yield): mp 222–223 °C (methanol) (lit.[25] mp 223 °C); MS *m/z* (relative intensity) 268 ($M^+$, 100), 254 (59), 237 (50), 209 (31), 181 (24), 152 (57), 139 (70); $^1$H-NMR δ 4.01 (6 H, s, $2CH_3O$), 7.30 (2 H, dd, *J* = 1.2 and 8.4 Hz, $H_2$ and $H_7$), 7.63 (2 H, dd, *J* = 7.8 and 8.4 Hz, $H_3$ and $H_6$), 7.85 (2 H, dd, *J* = 1.2 and 7.8 Hz, $H_4$ and $H_5$); $^{13}$C-NMR δ 56.4 (2 C), 118.0 (2 C), 118.8 (2 C), 124.0 (2 C), 133.8 (2 C), 134.7 (2 C), 159.4 (2 C), 182.8, 183.9. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.48. Found: C, 71.71; H, 4.43.

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**Supplementary Material Available:** $^1$H NMR spectra of **2a–c**, **3a–c**, and **11a,b** (11 pages). This material is contained in many 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.

# Structure–Activity Relationships of Illudins: Analogs with Improved Therapeutic Index

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Illudin S and M are extremely toxic sesquiterpenes produced by *Omphalotus illudens*. At low pH they behave as bifunctional alkylating agents, but at physiological pH they do not react with oxygen or nitrogen nucleophiles. Illudins react spontaneously with sulfur nucleophiles, glutathione or cysteine, at or slightly below pH 7, and toxicity to HL 60 cells can be modulated by altering glutathione levels in cells. Analogs of illudin M, e.g. the deoxy and, particularly, the dehydro derivatives, are less reactive to thiols and correspondingly less toxic to HL 60 cells than the parent compound. Dehydroilludin M has been found to be quite effective at inhibiting tumor growth in vivo at doses well tolerated by athymic nude mice.

## Introduction

The poisonous nature of the jack-o'-lantern mushroom, *Omphalotus illudens* (formerly *Clitocybe illudens*), has been known for a long time. For example, there were reports in the *New York Botanical Garden Journal* in 1938 and 1939 of persons who became ill after eating the mushroom.[2] Fortunately, they vomited, and so recovered quickly. In a report in *Nature* in 1963 on the isolation of an antitumor substance from *Lampteromyces japonicus* (synonymous with *O. illudens*), a bioluminescent mushroom,[3] it was stated that the mushroom was known in

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