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Synthesis and Diels-Alder Reactions of (S)-3-Chloro and (S)-3-Ethyl-2-p-tolylsulfinyl-1,4-benzoquinones†

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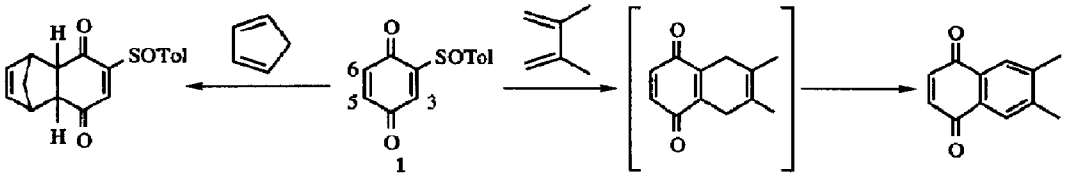
Abstract: The synthesis of the title compounds in enantiomerically pure form is described. Their cycloadditions with cyclopentadiene and 2,3-dimethyl-1,3-butadiene in the presence of $ZnBr_2$ take place on the unsubstituted dienophilic double bond C_5-C_6 giving access to optically active 4a,5,8,8a-tetrahydronaphthoquinones with a diastereoisomeric excess ranging from 40 to 72%.

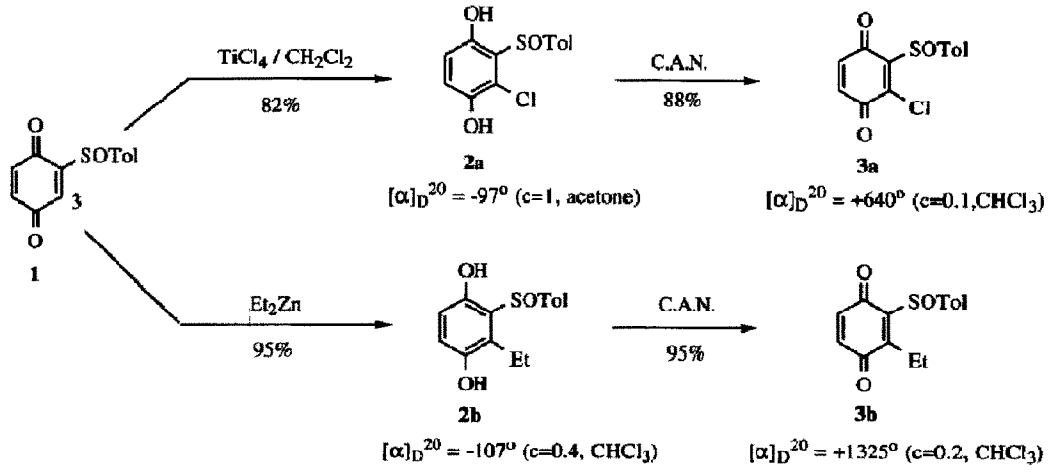
The ability of the sulfinyl group to control the π-facial diastereoselectivity of Diels-Alder cycloadditions when situated both on the dienophile[1] and on the diene[2] partner has been subjected to considerable study in recent years. High diastereoselectivities could be achieved both in thermal and catalytic processes by using sulfinyl dienophiles, being possible to get both configurations of the new chiral centers generated by choosing the appropriate experimental conditions[1a-c]. Our previous work on asymmetric Diels-Alder reactions of sulfinylnaphthoquinones[1b] illustrated the successful use of these chiral synthons for the construction of enantiomerically pure 1,4-dihydro-9,10-anthraquinones in both configurations through the tandem cycloaddition/pyrolytic sulfoxide elimination. The potential synthetic usefulness of enantiomerically pure 2-p-tolylsulfinyl-1,4-benzoquinone derivatives as chiral synthons of p-benzoquinones, prompted us to undertake the investigation of their dienophilic behaviour. Our preliminary results[1a] on the simplest (S)-2-p-tolylsulfinyl-1,4-benzoquinone (**1**) showed a higher reactivity of the unsubstituted dienophilic double bond C_5-C_6 with cyclic dienes (Scheme 1). High π-facial diastereoselectivities were achieved in the reaction of **1** with cyclopentadiene and the relative configuration of the resulting adducts could be controlled by using different Lewis acids. Acyclic dienes reacted with **1** through the sulfinyl substituted double bond C_2-C_3 but the instantaneous sulfoxide elimination and subsequent aromatization prevented the isolation of chiral products.



Scheme 1

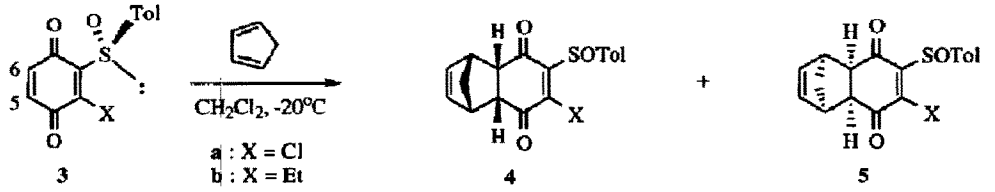
In order to avoid the undesired evolution of these adducts, we thought of introducing different substituents on C_3 of the sulfinylquinone system. With this aim, we decided to study the dienophilic behaviour of 3-chloro and 3-ethyl-2-p-tolylsulfinyl-1,4-benzoquinones **3a** and **3b** which would give rise to optically active substituted tetrahydro-1,4-naphthoquinones. The results are described herein.

The synthesis of compounds **3** (Scheme 2) was achieved in good optical and chemical yields starting from enantiomerically pure **1** which had been previously obtained[3]. Reaction of **1** with $TiCl_4$ afforded (S)-3-chloro-1,4-dihydroxy-2-p-tolylsulfinylbenzene (**2a**)[4] in 82% yield, whereas the addition of $ZnEt_2$ to **1** gave 3-ethyl substituted sulfinylhydroquinone **2b**[4] in 95% yield. Although the starting quinone **1** showed several reactive positions, only the products resulting from reaction on C_3 were detected, probably due to the previous association of the reagents to the sulfinylic oxygen. Oxidation of hydroquinones **2** with cerium (IV) ammonium nitrate (CAN) gave the desired sulfinylquinones **3a** and **3b**[4] in 88% and 95% yield respectively (Scheme 2).



Scheme 2

The cycloadditions of **3a** and **3b** with cyclopentadiene, chosen as a model cyclic diene, were carried out in CH_2Cl_2 at -20°C and afforded mixtures of two diastereoisomeric *endo* adducts **4**[4] and **5**[4] respectively (Scheme 3) that could be separated by flash chromatography (CH_2Cl_2:acetone 45:1). Their relative ratios were determined from the ^{1}H-NMR spectra of the crude reaction mixtures by integration of well separated signals and are recorded in Table 1. Compounds **4** and **5** resulted from the reaction on the unsubstituted dienophilic double bond C_5-C_6 of the p-benzoquinone systems, the best facial diastereoselectivity of the process being achieved in the presence of $ZnBr_2$.



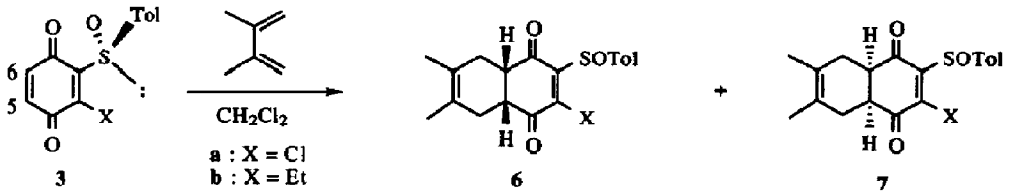
Scheme 3

Table 1. Diels-Alder reactions of **3a** and **3b** with cyclopentadiene (4-5 eq) at -20°C.

Entry	Substrate	Cat (eq)	Time	Yield(%)	Adducts	Ratio	d.e.
1	**3a**	-----	1 h	85	**4a : 5a**	50 : 50	0
2	**3a**	$ZnBr_2$ (2)	5 min	90	**4a : 5a**	80 : 20	60
3	**3b**	-----	1 h	90	**4b : 5b**	50 : 50	0
4	**3b**	$ZnBr_2$ (2)	5 min	87	**4b : 5b**	70 : 30	40

The absolute configuration of *endo* adducts **4b** and **5b** was deduced from the similarity of their ^{1}H-NMR parameters with those of the adducts resulting in the reaction of (S)-2-p-tolylsulfinyl-1,4-benzoquinone (1) with cyclopentadiene[1a]. This criterium was not valid for chloroderivatives and their configurational assignment was established by chemical correlation[5]. Thus, compounds **4** show the $R_{4a},S_5,R_8,S_{8a},S_S$ and **5** the $S_{4a},R_5,S_8,R_{8a},S_S$ configuration in their chiral centers.

The reaction of quinones **3** with 2,3-dimethyl-1,3-butadiene, used as a model acyclic diene, afforded mixtures of diastereoisomeric tetrahydronaphthoquinones **6** and **7** (Scheme 4) that could not be separated by flash chromatography and whose relative ratios depended on reactions conditions (Table 2).



3 6 7

Scheme 4

Table 2. Diels-Alder reactions of **3a** and **3b** with 2,3-dimethyl-1,3-butadiene (10 eq) at -20ºC.

Entry	Substrate	Cat (eq)	Time	Yield(%)	Adducts	Ratio	d.e.
1	**3a**	-----	2 d	92	**6a : 7a**	67 : 33	34
2	**3a**	$ZnBr_2$ (2)	1 h	87	**6a : 7a**	86 : 14	72
3	**3b**[a]	-----	4 d	94	**6b : 7b**	60 : 40	20
4	**3b**	$ZnBr_2$ (2)	6 h	85	**6b : 7b**	70 : 30	40

a. This reaction was carried out at 0ºC.

Contrary to the results obtained in the reactions of **1** with there kind of dienes[1a], 2,3-dimethyl-1,3-butadiene reacted with quinones **3** only through C_5-C_6 unsubstituted double bond indicating that steric and electronic effects of the substituents on C_2 and C_3 rendes difficult the approach of the acyclic diene to the later. The configurational assignment of adducts **6** and **7** was based on the similar behaviour of quinones **3** in the cycloaddition with cyclopentadiene and 2,3-dimethyl-1,3-butadiene in the presence of $ZnBr_2$ (the interactions present in the transition state for both dienes must be very similar).

The π-facial diastereoselectivities achieved in the reactions of quinones **3** with these dienes in the presence of $ZnBr_2$, although moderate (d.e. 40-72%), were surprising considering the distance existing between the reactive double bond C_5-C_6 and the chiral sulfinyl inductor. This remote asymmetric induction could be a consequence of a stereoelectronic approach control with the origin in a non-equivalent extension of the π orbital system[7] imposed by the remote asymmetric sulfoxide determining the preferred diene approach from one of the diastereotopic faces of the chelate between **3** and $ZnBr_2$. A similar asymmetric distribution of the π-orbital could be invoked to explain the π-facial diastereoselectivity observed in cycloadditions of **1** with cyclopentadiene[1a] which was previously justified on steric grounds. We are now undertaking a study of Diels-Alder reactions on compound **1** and other sulfinylquinones such as sulfinylnaphthazarins[8] to obtain experimental evidence supporting this hypothesis.

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†.- In memory of Prof. Francisco Fariña.

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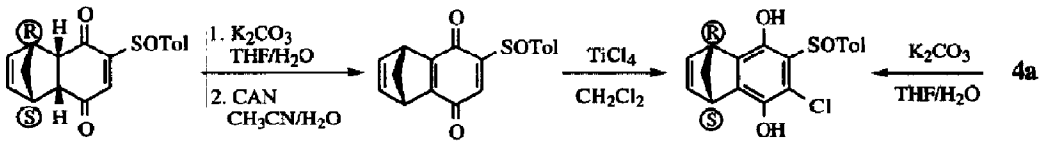
4.- All new compounds described in this paper were fully characterized on the basis of their IR, ^{1}H-NMR (200 MHz, $CDCl_3$), ^{13}C-NMR (50.3 MHz, $CDCl_3$) spectral data and elemental analysis / HRMS. **2a**: m.p. 179-81ºC (CH_2Cl_2); $[\alpha]_D^{20}$ -97º (c=1, acetone); ^{1}H-NMR δ 10.85 (broad s, 1H, asociated OH), 7.74 and 7.31 (AA'BB' system, 4H, tolyl group), 7.01 and 6.77 (AB system, 2H, J = 9.1 Hz, H_5 and H_6), 5.44 (broad s, 1H, OH), 2.40 (s, 3H, CH_3Ar); ^{13}C-NMR (d_6-acetone) δ 154.1, 145.1, 143.0, 139.1, 131.3, 130.3, 126.0, 120.6, 120.2, 119.1, 21.4. **2b**: m.p. 156-8ºC (CCl_4); $[\alpha]_D^{20}$ -107º (c=0.4, $CHCl_3$); ^{1}H-NMR δ 10.43 (broad s, 1H, asociated OH), 7.49 and 7.18 (AA'BB' system, 4H, tolyl group), 6.82 and 6.64 (AB system, 2H, J = 8.8 Hz, H_5 and H_6), 6.08 (broad s, 1H, OH), 2.68 (m, 2H, Et), 2.38 (s, 3H, CH_3Ar), 1.12 (t, 3H, J = 7.4 Hz, Et); ^{13}C-NMR δ 153.7, 146.7, 142.6, 140.0, 135.1, 130.3, 128.8, 126.3, 120.7, 117.5, 21.4, 20.4, 13.8. **3a**: mp 118-20ºC (ethylic ether); $[\alpha]_D^{20}$ +640º (c=0.1, $CHCl_3$); ^{1}H-NMR δ 7.73 and 7.34 (AA'BB' system, 4H, tolyl group), 6.93 and 6.79 (AB system, 2H, J = 9.1 Hz, H_5 and H_6), 2.41 (s, 3H, CH_3Ar); ^{13}C-NMR δ 181.0, 177.7, 142.4, 137.8, 137.1, 135.8, 132.8, 131.5, 130.1, 125.0, 21.4. **3b**: mp 73-5ºC (ethylic ether); $[\alpha]_D^{20}$ +1325º (c=0.2, $CHCl_3$); ^{1}H-NMR δ 7.64 and 7.31 (AA'BB' system, 4H, tolyl group), 6.79 and 6.69 (AB system, 2H, J = 10.0 Hz, H_5 and H_6), 3.10 (q, 2H, J = 7.4 Hz, Et), 2.39 (s, 3H, CH_3Ar), 1.12 (t, 2H, J = 7.4 Hz, Et); ^{13}C-NMR δ 185.7, 184.4, 152.2, 141.5, 136.9, 136.1, 130.1, 130.0, 125.8, 124.8, 21.3, 17.1, 14.5. **4a**: $[\alpha]_D^{20}$ +132º (c=0.75, $CHCl_3$); ^{1}H-NMR δ 7.67 and 7.30 (AA'BB' system, 4H, tolyl group), 6.00 (dd, 1H, J = 2.8 and 5.6 Hz, H_6), 5.85 (dd, 1H, J = 2.8 and 5.6 Hz, H_7), 3.51 (m, 2H, H_5 and H_8) 3.34 (2dd, 2H, J = 3.7 and 8.5 Hz, H_{4a} and H_{8a}), 2.40 (s, 3H, CH_3Ar), 1.53 (dt, 1H, J = 1.7 and 9.0 Hz, H_{9b}), 1.43 (m, 1H, H_{9a}); ^{13}C-NMR δ 192.3, 189.7, 152.0, 148.1, 142.1, 138.0, 135.6, 134.9, 129.9, 125.1, 50.2, 50.1, 49.6, 49.2, 48.3, 21.4. **5a**: $[\alpha]_D^{20}$ +90º (c=0.5, $CHCl_3$); ^{1}H-NMR δ 7.67 and 7.30 (AA'BB' system, 4H, tolyl group), 6.05 (dd, 1H, J = 2.8 and 5.6 Hz, H_6), 5.93 (dd, 1H, J = 2.8 and 5.6 Hz, H_7), 3.51 (m, 2H, H_5 and H_8), 3.34 (m, 2H, H_{4a} and H_{8a}) 2.40 (s, CH_3Ar), 1.53 (m, H_{9b}), 1.43 (m, H_{9a}). **4b**: mp 102-4ºC (hexane); $[\alpha]_D^{20}$ +375º (c=0.2, $CHCl_3$); ^{1}H-NMR δ 7.58 and 7.30 (AA'BB' system, 4H, tolyl group), 5.92 (dd, 1H, J = 3.0 and 5.7 Hz, H_6), 5.57 (dd, 1H, J = 3.0 and 5.6 Hz, H_7), 3.48 and 3.42 (2m, 2H, H_{4a} and H_{8a}), 3.25 (m, 2H, H_5 and H_8), 3.04 (q, 2H, J = 7.4 Hz, Et), 2.40 (s, 3H, CH_3Ar), 1.50-1.35 (m, 2H, H_{9a} and H_{9b}), 0.98 (t, 3H, J = 7.4 Hz, Et); ^{13}C-NMR δ 197.2, 196.1, 157.9, 151.8, 141.2, 139.6, 135.1, 135.0, 129.8, 124.8, 49.3, 49.1, 49.0, 48.9, 48.7, 21.3, 16.7, 13.8. **5b**: $[\alpha]_D^{20}$ +296º (c=0.5, $CHCl_3$); ^{1}H-NMR δ 7.60 and 7.29 (AA'BB' system, 4H, tolyl group), 6.06 (t, 2H, J = 1.8 Hz, H_6 and H_7), 3.50 (m, 2H, H_5 and H_8), 3.24 and 3.17 (2dd, 2H, J = 3.8 and 8.7 Hz, H_{4a} and H_{8a}), 2.97 (m, 2H, Et), 2.39 (s, 3H, CH_3Ar), 1.54 and 1.40 (2dt, 2H, J = 2.0 and 8.9 Hz, H_{9a} and H_{9b}), 1.03 (t, 3H, J = 7.3 Hz, Et); ^{13}C-NMR δ 197.1, 195.9, 158.2, 151.5, 141.2, 139.6, 135.3, 135.2, 129.8, 124.7, 49.1, 49.0 (2C), 48.9, 48.8, 21.2, 17.2, 13.6.

5.- Chemical correlation of **4a** with (S_5,R_8,S_S)-3-chloro-5,8-methano-2-p-tolylsulfinyl-5,8-dihydro-1,4-naphthalene (**10**), obtained from (R_{4a},S_5,R_8,S_{8a},S_S)-5,8-methano-2-p-tolylsulfinyl-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (**8**)[1a] whose stereochemistry had been unequivocally established by X-ray[6], was carried out as follows:



8 **9** **10**

The treatment of **8** with K_2CO_3 and further CAN oxidation yielded **9** which upon reaction with $TiCl_4$ evolved into **10**. The same compound **10** was isolated in the treatment of **4a** with K_2CO_3. As the stereochemistry of C-5 and C-8 of **8** and **4a** remained unaltered along the transformations, we could assign the 5S,8R configuration to **10** and then, the R_{4a},S_5,R_8,S_{8a},S_S configuration to **4a**.

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