Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4357–4367

TETRAHEDRON: *ASYMMETRY*

On the mechanism and diastereoselectivity of 2,3-dihydrobenzofuran formation from sulfinylbenzoquinones and 2-trimethylsilyloxyfuran

M. Carmen Carreño,* José L. García Ruano,* Antonio Urbano, Cynthia Z. Remor † and Yolanda Arroyo ‡

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

Received 8 October 1999; accepted 19 October 1999

Abstract

A mechanistic study of the reactions between 2-trimethylsilyloxyfuran **1** and (S*S*)-2-(arylsulfinyl)-1,4-benzoquinones **2a** and **2b**, giving rise to the diastereoselective formation of [3a*S*,8b*S*,S*S*]-3a,8b-dihydro-7-hydroxy-8-(arylsulfinyl)furo[3,2-*b*]benzofuran-2(3*H*)-ones **3a** and **3b**, is reported. The detection and ^{1}H NMR characterization of several precursors of **3a** and **3b** accounts for a Michael-type initial reaction which dictates the final diastereoselection of the process. A significant improvement of the stereoselectivity (up to 96% de) in the formation of the *tert*-butylsulfinyl substituted derivative **3c** was achieved by using 2-(*tert*-butylsulfinyl)-1,4-benzoquinone **2c** as the starting quinone.

1. Introduction

The 2,3-dihydrobenzofuran moiety is found in a number of natural products[1] which show significant biological properties. Two general synthetic approaches are available to date to construct this fragment. One of them, mainly exploited by Engler,[2] is based on a Lewis acid promoted reaction between a methoxy substituted *p*-benzoquinone and a styrene or stilbene derivative. The other relies on the reaction between a benzoquinone bearing an electron-withdrawing substituent and an electron-rich diene and has been studied by different research groups.[3] With 2-trimethylsilyloxyfuran **1**, this reaction gives rise to a *cis*-3a,8b-dihydrofuro[3,2-*b*]benzofuran-2(3*H*)-one[4] (Scheme 1). An asymmetric version of this process has been studied by Brimble using quinones bearing differently substituted esters as chiral auxiliaries[5] or in the presence of chiral catalysts.[6] Although optically active derivatives were obtained in all cases, the

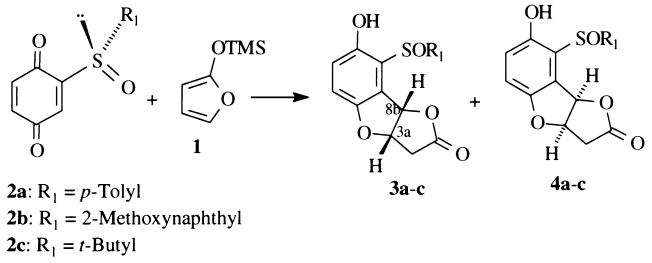
* Corresponding authors. E-mail: carmen.carrenno@uam.es

† On leave from Instituto de Química/UFRGS, Porto Alegre (RS), Brazil.

‡ On leave from Departamento de Química Orgánica (E.T.S.I.I.), Universidad de Valladolid, Spain.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00460-7

diastereoselectivities achieved were not good enough for preparative purposes. When the reaction was carried out between **1** and enantiopure (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **2a**[7] in acetonitrile, a 77:23 mixture of diastereomers **3a** and **4a** was obtained (Scheme 1). To date, such diastereoselectivity has not been improved due to the unknown mechanistic and stereochemical course of the process, since either an initial Diels–Alder reaction[3b,d,f] or a Michael-type addition process is consistent with the observed results.[5b]

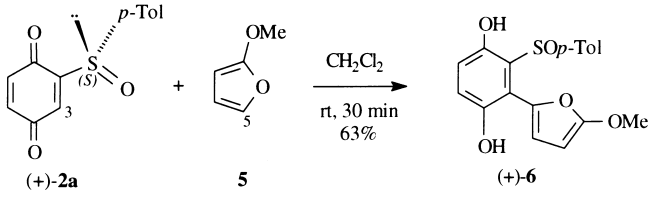


Scheme 1.

In the course of our studies devoted to asymmetric Diels–Alder reactions with enantiomerically pure (S*S*)-2-(*p*-tolylsulfinyl)-1,4-quinones,[8] we had observed excellent levels of π-facial diastereoselection for cycloadditions with a wide range of dienes. Based on our results, the stereoselectivity reported for the reaction of **2a** with 2-trimethylsilyloxyfuran **1** was suggesting a non concerted reaction course in the initial step. To clarify the mechanism, we undertook a detailed study of the reaction between **2a** and 2-substituted furan derivatives with the aim of gaining an improvement of the diastereoselectivity obtained previously. We report herein evidence of a Michael-type initial reaction which dictates the stereoselectivity of the process as well as the way to improve the final diastereoselection.

2. Results and discussion

We first carried out the reaction of **2a**[9] with 2-methoxyfuran **5** (Scheme 2). Working under very mild conditions (CH_2Cl_2, rt, 30 min), (S*S*)-3-(5-methoxy-2-furanyl)-2-(*p*-tolylsulfinyl)-1,4-dihydroxybenzene **6** could be isolated in 63% yield, after flash chromatography. The formation of compound **6** must be the consequence of a Michael-type attack of the furan from its nucleophilic C-5 position to the more deficient C-3 of the quinone, followed by aromatization of the initial intermediate.



Scheme 2.

We then repeated the reaction reported by Brimble[7] between (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **2a** and 2-trimethylsilyloxyfuran **1** in CH_2Cl_2 at rt and obtained a complex reaction mixture which, after flash chromatography, evolved into a 80:20 ratio of **3a**[10] and **4a**[10] in 59% yield (Scheme 1, Table 1, entry 1). The course of the reaction was then monitored by ^1H NMR (CD_3CN at rt), recording a spectrum every 10 min until the disappearance of **2a** signals (1 h 40 min). The evolution showed the progressive formation of epimeric compounds **7a** and **8a** in a 75:25 ratio (Scheme 3), which were stable enough to be characterized. The mixture of **7a** and **8a** could be transformed into desilylated

Table 1
Reactions of 2-trimethylsilyloxyfuran **1** and sulfinylbenzoquinones **2a–c**

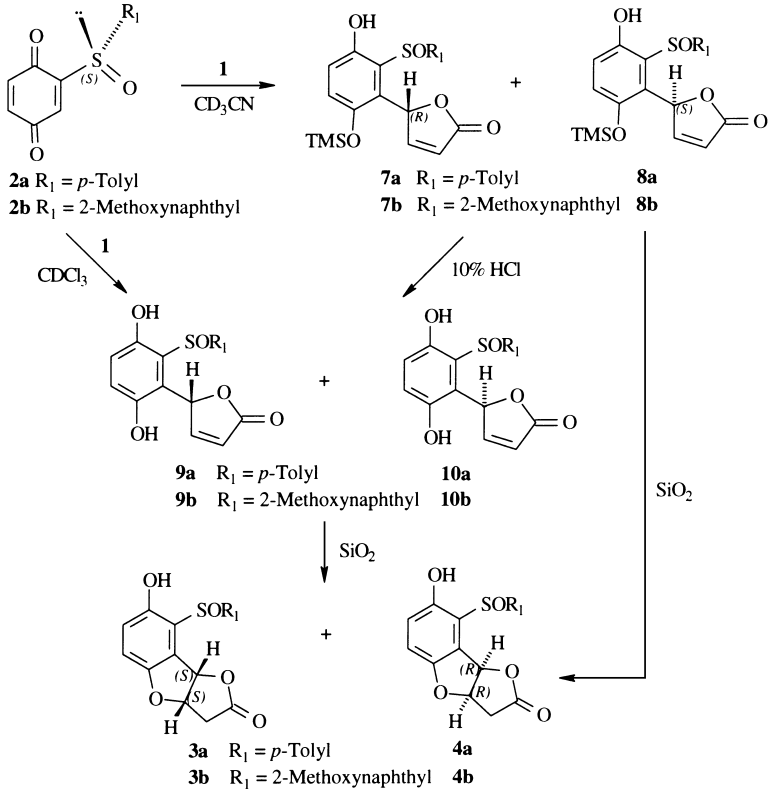
Entry	Quinone	Solvent	T (°C)	Time (h)	**3** : **4**	Yield (%)
1	**2a**	CH_2Cl_2	25	0.25	80 : 20	59 [a]
2	**2a**	CH_2Cl_2	-78	0.5	83 : 17	82[b]
3	**2a**	CH_2Cl_2/Eu(fod)$_3$	-20	0.4	59 : 41[c]	--[d]
4	**2a**	CH_2Cl_2/$ZnBr_2$	25	0.05	71 : 29[c]	--[d]
5	**2b**	CH_2Cl_2	0	1.25	85 : 15	59 [a]
6	**2b**	EtOH	0	1	69 : 31	62 [a]
7	**2b**	$CHCl_3$	-20	3	90 : 10	90[e]
8	**2c**	$CHCl_3$	-20	0.3	98 : 2	52[f]

[a]Mixture of **3** and **4** after flash chromatography. [b]69% for **3a** and 13% for **4a** isolated yields. [c]Diastereoisomeric ratio determined by ^{1}H-NMR of the crude reaction mixture containing **9a** and **10a**. [d]Not determined. [e]82% for **3b** and 8% for **4a** isolated yields. [f]Yield of pure **3c**.

derivatives **9a** and **10a** (75:25) by treatment with 10% HCl. When the same ^{1}H NMR monitoring was effected in $CDCl_3$, a mixture of compounds **9a** and **10a** (80:20) was detected. This evolution could be a consequence of the acid traces always present in $CDCl_3$. After flash chromatography, both mixtures of **7a**–**8a** and **9a**–**10a** evolved into **3a** and **4a** as a consequence of an intramolecular conjugate addition to the α,β-unsaturated butyrolactone moiety, which also occurs stereoselectively, giving rise to the corresponding *cis*-fused compounds (Scheme 3).

In accordance with these observations, the diastereoselectivity achieved must be initially defined in the Michael-type starting reaction. The stereochemical course of the process could be explained taking into account a sterically favored approach of 2-trimethylsilyloxyfuran **1** to sulfinylquinone **2a** from the less hindered face which supports the lone electron pair at sulfur. Three conformers A, B and C (Scheme 4) could participate in the conformational equilibrium of **2a**. Nevertheless, only A and C show a steric differentiation between both diastereotopic faces of **2a**. Thus, the attack of 2-trimethylsilyloxyfuran **1** would preferentially occur from the upper face of conformation A and from the bottom one of conformation C. Although rotamer B could also be considered,[11] steric and stereoelectronic grounds suggest a lower participation. The conjugate addition through transition states TSI and TSII, with an antiperiplanar relationship between the nucleophilic and electrophilic double bonds, must be favored over the approach shown as TSIII with an antiperiplanar arrangement of the furan oxygen and the quinonic double bond. The latter must be strongly destabilized by electronic repulsions between proximal oxygens. The expected higher reactivity of *s-cis* conformation A[12] as well as its higher stability due to minimum electrostatic repulsions allowed us to assume its preferred evolution. Moreover, a higher stability of TSI can be predicted since steric interactions between the approaching furan and the sulfinylic oxygen must be lower than those existing in TSII, where furan is interacting with the bulky tolyl ring. Thus, reaction through TSI accounts for the major formation of diastereoisomer **7a**, a precursor of compound **3a** bearing the (*S*,*S*) absolute configuration in the new stereogenic centers.

According with this mechanism, all factors increasing the population of conformer A in the conformational equilibrium of sulfinylquinone **2a** or steric interactions in the corresponding transition states would improve the diastereoselectivity of the process. As shown in Table 1, a decrease in the reaction temperature (CH_2Cl_2, −78°C) slightly improved the diastereoselectivity in favor of **3a** (83:17, entry 2), as could be expected assuming an increased participation of A in the conformational equilibrium shown in Scheme 4. The use of chelating Lewis acids such as Eu(fod)$_3$ and $ZnBr_2$ (Table 1, entries 3 and 4)



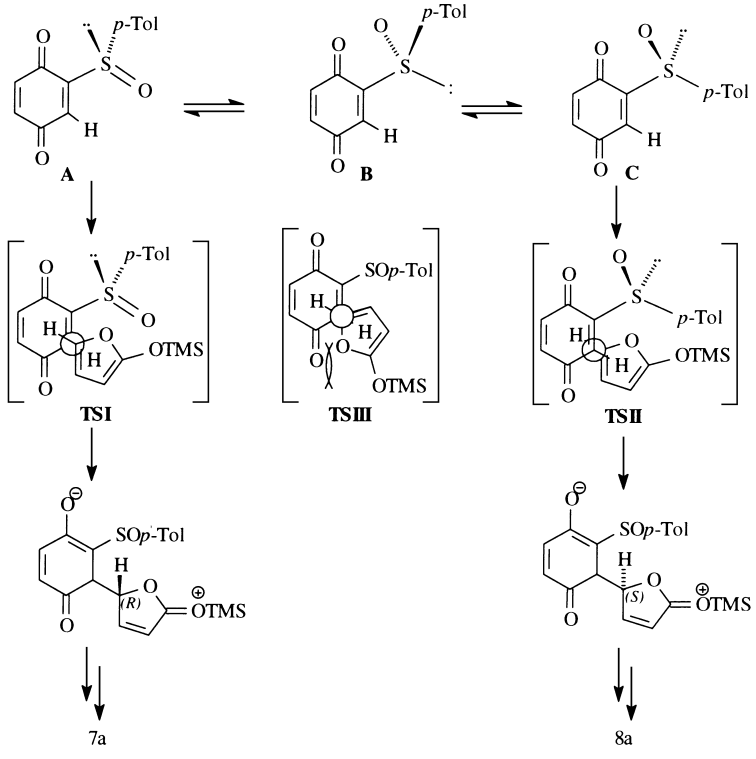
Scheme 3.

decreased the diastereoselection as a consequence of the higher participation of an *s-trans* conformation such as C.

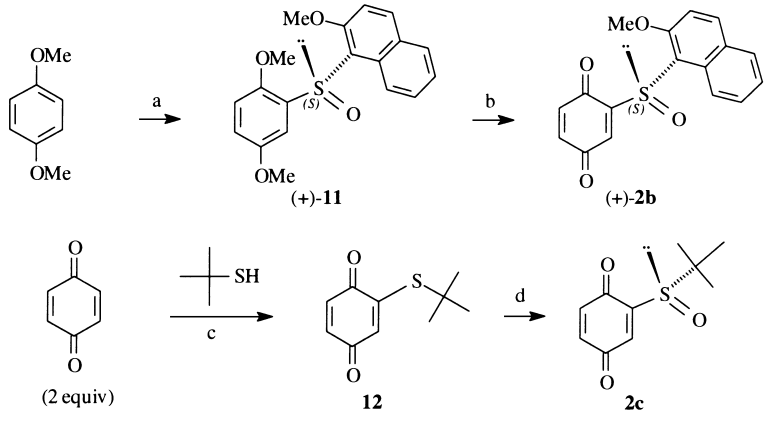
In order to evaluate the role of steric effects in the relative stability of the different transition states, we reasoned that the use of quinones bearing a sulfinyl substituent bulkier than the tolyl group could be appropriate. With this aim, (*SS*)-2-(2′-methoxynaphthylsulfinyl)-1,4-benzoquinone **2b** and 2-(*tert*-butylsulfinyl)-1,4-benzoquinone **2c** were prepared (Scheme 5). The synthesis of (+)-**2b** was carried out following the two-step general methodology described previously by us[9] for the synthesis of (+)-**2a**, based on Andersen's synthesis.[13] Thus, the direct metallation of 1,4-dimethoxybenzene with *n*-BuLi at rt, followed by reaction with (−)-(*SS*)-menthyl-2-methoxy-1-naphthylsulfinate[14] as sulfinylating agent, afforded derivative (+)-**11** in 60% yield (Scheme 5). Ammonium cerium (IV) nitrate (CAN) cleanly oxidized compound **11** at rt into enantiopure sulfinylquinone (+)-**2b** in 90% yield.

The *tert*-butylsulfinyl derivative **2c** was prepared in racemic form as outlined in Scheme 5 from the corresponding thioether **12**. Thus, 2-(*tert*-butylthio)-1,4-benzoquinone **12** was prepared in 50% isolated yield according to an old reported procedure[15] based on the reaction between 2 equiv. of 1,4-benzoquinone and *tert*-butylthiol. Direct controlled oxidation of compound **12** with 1 equiv. of *m*-CPBA in $CHCl_3$ at 0°C yielded a 75% yield of 2-(*tert*-butylsulfinyl)-1,4-benzoquinone **2c**. The results obtained in the reactions of sulfinylbenzoquinones (+)-**2b** and **2c** and 2-trimethylsilyloxyfuran **1** are collected in Table 1.

As expected, reaction of quinone (+)-**2b** in CH_2Cl_2 at rt gave, after flash chromatography, a better diastereoselection (85:15) of the corresponding derivatives (+)-**3b** and (+)-**4b** (Scheme 1, Table 1, entry 5) if compared with the same reaction with quinone **2a** (entry 1). The use of a polar solvent such as EtOH



Scheme 4.



Scheme 5. (a) (i) *n*-BuLi, THF, rt, 1 h; (ii) (−)-(S*S*)-menthyl-2-methoxy-1-naphthalenesulfinate, THF, −78°C, 2 h, 60%; (b) CAN, CH_3CN, H_2O, rt, 1 h, 90%; (c) EtOH, rt, 4 h, 50%; (d) *m*-CPBA, CH_2Cl_2, 0°C, 1 h, 93%

decreased the diastereoselectivity (69:31, Table 1, entry 6). This result is in agreement with a diminished presence of conformation A (Scheme 4) due to minimization of dipolar repulsion between the C=O and S=O groups induced by polar solvents. The best result, 90:10 ratio of **3b** and **4b**, was obtained working in $CHCl_3$ at −20°C (Table 1, entry 7). The mechanistic pathway proposed for the formation of **3a** and **4a** could be corroborated for **3b** and **4b** in a similar ^1H NMR monitoring of the reaction between **2b** and **1** (Scheme 3). In this case, compounds **7b** and **8b** (80:20 ratio) were initially detected in CD_3CN and **9b** and **10b** (90:10) in $CDCl_3$. Derivatives **7b** and **8b** can be transformed into **9b** and **10b** after hydrolysis with 10% HCl and compounds **3b** and **4b** were obtained diastereoisomerically pure after flash

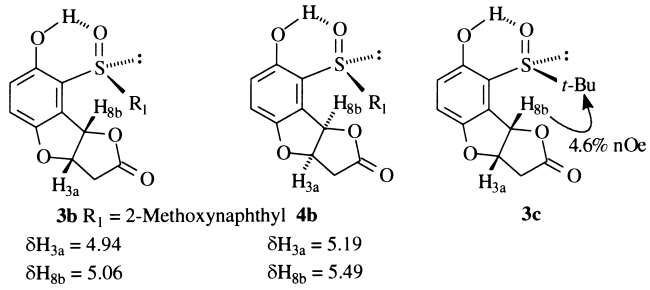


Figure 1. ^{1}H NMR parameters and NOE experiment used for configurational assignment

chromatography of the mixtures of **7b**–**8b** or **9b**–**10b**. The assignment of the correct stereochemistry at the bridgehead positions of **3b** and **4b** was effected taking into account the fixed *s-trans* conformation of the sulfinyl group in both derivatives due to the hydrogen bonding formed between the phenolic proton and the sulfinyl oxygen (Fig. 1).[16] In this conformation, the bulky 2-methoxynaphthyl substituent of the sulfoxide is directed to the upper face of the dimethoxy substituted aromatic ring and the lone electron pair to the lower one. In this situation, protons H_{3a} and H_{8b} in diastereoisomer **3b** are shielded by the naphthalene ring appearing further upfield in the ^{1}H NMR spectrum relative to the equivalent protons in the other diastereoisomer **4b** (0.25 ppm shielding for H_{3a} and 0.43 for H_{8b}, see Fig. 1).

Finally, reaction of 2-(*tert*-butylsulfinyl)-1,4-benzoquinone **2c** with **1** was effected in $CHCl_3$ at −20°C (Scheme 1, Table 1, entry 8). Under these conditions and after flash chromatography, a 98:2 mixture of derivatives **3c** and **4c** was formed, allowing us to isolate compound **3c** diastereoisomerically pure in 52% yield. This excellent result demonstrates that steric effects are essential in controlling the π-facial diastereoselectivity of the initial conjugate addition. Configurational assignment of **3c** was mainly based on an NOE experiment.[17] Thus, selective irradiation on bridgehead hydrogen H_{8b} showed a relevant 4.6% NOE enhancement between this proton and the *tert*-butyl substituent of the sulfinyl moiety, indicating the spatial closeness of both groups in the fixed *s-trans* conformation of the *tert*-butyl sulfinyl substituent depicted for **3c** in Fig. 1.

3. Conclusion

We have proposed a mechanistic and stereochemical rationale for the diastereoselective formation of [3a*S*,8b*S*,S*S*]-3a,8b-dihydro-7-hydroxy-8-(aryl- and *tert*-butylsulfinyl)furo[3,2-*b*]benzofuran-2(3*H*)-ones **3a**–**c** based on a sterically controlled diastereoselective conjugate addition of 2-trimethylsilyloxyfuran on sulfinylquinones as the key step. A significant improvement of the stereoselectivity (up to 96% de) was achieved by using the *tert*-butylsulfinyl group on the starting quinone. We are now proceeding to apply these good results to the asymmetric synthesis of natural products.

4. Experimental

4.1. General methods

Melting points were obtained in open capillary tubes and are uncorrected. IR spectra were obtained as $CHCl_3$ solutions and are given in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Diastereoisomeric adducts ratios were established by integration of well-

separated signals in the crude reaction mixtures and are listed in Table 1. 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. Dry THF was distilled from sodium/benzophenone ketyl. CH_2Cl_2 and $CHCl_3$ were dried over P_2O_5. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2, and solvent dryness with Na_2SO_4.

*4.2. (SS)-2-(5-Methoxy-2-furanyl)-3-(*p*-tolylsulfinyl)-1,4-dihydroxybenzene **6***

To a solution of (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **2a** (500 mg, 2.0 mmol) in dry CH_2Cl_2 (10 ml), 2-methoxyfuran (200 μl, 2.2 mmol) was added. After stirring at rt for 30 min, the solvent was evaporated and the residue purified by flash chromatography (eluent hexane:EtOAc 3:1) to obtain pure **6** as a solid in 60% yield: mp 126–127°C; $[\alpha]_D^{20}=-403$ (*c* 0.5, acetone); ^{1}H NMR δ 10.54 (s, 1H), 7.55 and 7.26 (AA′BB′ system, 4H), 6.98 and 6.82 (AB system, 2H, *J*=8.6 Hz), 6.41 (d, 1H, *J*=3.1 Hz), 5.75 (s, 1H), 5.29 (d, 1H, *J*=3.1 Hz), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR δ 162.3, 153.8, 147.1, 142.1, 140.6, 134.9, 130.2, 130.0, 126.0, 120.9 (2C), 120.8 (2C), 114.8, 81.6, 57.7, 21.3; IR ν_{max} 3500, 3040, 2960, 2290, 1490, 1460, 1355, 1315, 1150, 790; EI-MS *m/z* (%) 344 (M^+, 21), 328 (9), 285 (100), 269 (37), 193 (18), 165 (18), 139 (13), 123 (14), 91 (28). Anal. calcd for $C_{18}H_{16}O_5S$: C, 62.78; H, 4.69; S, 9.29. Found: C, 62.47; H, 4.55; S, 8.94.

*4.3. (5*R,*SS)- and (5*S,*SS)-5-[3-Hydroxy-6-trimethylsilyloxy-2-(*p*-tolylsulfinylphenyl)]furan-2(5*H*)-one **7a** and **8a***

These compounds were detected by ^{1}H NMR monitoring after mixing (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**2a**) (10.8 mg, 0.04 mmol) and 2-trimethylsilyloxyfuran **1** (8.1 μl, 0.05 mmol) in CD_3CN at rt as a 75:25 mixture of epimers at C_5. Compound **7a**: ^{1}H NMR (CD_3CN) δ 10.34 (s, 1H), 7.66 and 7.38 (AA′BB′ system, 4H), 7.62 (dd, 1H, *J*=1.8 and 5.9 Hz), 7.04 and 6.81 (AB system, 2H, *J*=9.4 Hz), 6.64 (dd, 1H, *J*=1.8 and 2.4 Hz), 6.31 (dd, 1H, *J*=2.4 and 5.3 Hz), 2.41 (s, 3H), 0.09 (s, 9H). Compound **8a**: ^{1}H NMR (CD_3CN) δ 10.26 (s, 1H), 7.72 (dd, 1H, *J*=1.8 and 5.9 Hz), 7.57 and 7.40 (AA′BB′ system, 4H), 6.95 and 6.80 (AB system, 2H, *J*=9.4 Hz), 6.58 (dd, 1H, *J*=1.8 and 2.4 Hz), 6.18 (dd, 1H, *J*=2.4 and 5.3 Hz), 2.38 (s, 3H), 0.29 (s, 9H); EI-MS (from the mixture of **7a** and **8a**) *m/z* (%) 402 (M^+, 2), 346 (6), 330 (100), 314 (14), 185 (21), 267 (40), 248 (42), 194 (24), 139 (31), 123 (29), 108 (43), 91 (87), 77 (34).

*4.4. (5*R,*SS)- and (5*S,*SS)-5-[3,6-Dihydroxy-2-(*p*-tolylsulfinylphenyl)]furan-2(5*H*)-one **9a** and **10a***

To a solution of (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **2a** (25 mg, 0.1 mmol) in dry CH_2Cl_2 (5 ml), 2-trimethylsilyloxyfuran **1** (20 μl, 0.12 mmol) was added. The mixture was stirred at rt for 15 min and 5 ml of 10% HCl were added. After workup, compounds **9a** and **10a** were obtained as an 80:20 mixture of epimers at C_5. These compounds were also detected by ^{1}H NMR after mixing (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **2a** (10.8 mg, 0.04 mmol) and 2-trimethylsilyloxyfuran **1** (8.1 μl, 0.05 mmol) in $CDCl_3$ at rt as a 85:15 mixture. Compound **9a**: ^{1}H NMR δ 10.43 (s, 1H), 7.72 and 7.31 (AA′BB′ system, 4H), 7.52 (dd, 1H, *J*=1.8 and 5.9 Hz), 6.92 and 6.79 (AB system, 2H, *J*=8.8 Hz), 6.64 (dd, 1H, *J*=1.6 and 2.3 Hz), 6.31 (dd, 1H, *J*=2.3 and 5.7 Hz), 2.39 (s, 3H). Compound **10a**: ^{1}H NMR δ 10.14 (s, 1H), 7.65 (dd, 1H, *J*=1.6 and 5.7 Hz), 7.56 and 7.31 (AA′BB′ system, 4H), 6.92 and 6.79 (AB system, 2H, *J*=9.4 Hz),

6.59 (dd, 1H, *J*=1.6 and 2.3 Hz), 6.17 (dd, 1H, *J*=2.3 and 5.7 Hz), 2.39 (s, 3H); EI-MS (from the mixture of **9a** and **10a**) *m/z* (%) 330 (M^+, 100), 314 (14), 285 (21), 267 (37), 194 (20), 139 (16), 123 (18).

*4.5. (3a*S*,8b*S*,*SS*)-3a,8b-Dihydro-7-hydroxy-8-(2′-methoxy-1-naphthylsulfinyl)furo[3,2-*b*]benzofuran-2(3*H*)-one **3a***

To a solution of (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone **2a** (50 mg, 0.20 mmol) in dry CH_2Cl_2 (5 ml) cooled to −78°C, 2-trimethylsilyloxyfuran **1** (38 μl, 0.22 mmol) was added under argon. The mixture was stirred at −78°C for 30 min and the solvent evaporated under reduced pressure. After flash chromatography (eluent CH_2Cl_2:acetone 40:1), compound (−)-**3a** was isolated diastereoisomerically pure in 69% yield: $[\alpha]_D^{20}$=−268 (*c* 0.41, CH_2Cl_2) [(lit.[7] $[\alpha]_D^{20}$=−240 (*c* 0.34, CH_2Cl_2)].

*4.6. (3a*R*,8b*R*,*SS*)-3a,8b-Dihydro-7-hydroxy-8-(*p*-tolylsulfinyl)furo[3,2-*b*]benzofuran-2(3*H*)-one **4a***

Compound (+)-**4a** was obtained diastereoisomerically pure as above in 13% yield: $[\alpha]_D^{20}$=+4.8 (*c* 0.30, CH_2Cl_2) [(lit.[7] $[\alpha]_D^{20}$=+4.2 (*c* 0.24, CH_2Cl_2)].

*4.7. (SS)-1,4-Dimethoxy-2-(2′-methoxynaphthylsulfinyl)benzene **11***

To a solution of 2.4 M *n*-BuLi (4.2 ml, 10 mmol) in dry THF (20 ml), 1,4-dimethoxybenzene (1.37 g, 9.9 mmol) in dry THF (20 ml) was added dropwise at rt under argon. The mixture was stirred for 1 h, cooled to −78°C and then added via cannula to a precooled (−78°C) and vigorously stirred solution of (−)-(S*S*)-menthyl-2-methoxy-1-naphthalenesulfinate[15] (3.0 g, 10.2 mmol) in dry THF (50 ml). The mixture was stirred at −78°C for 2 h and quenched with water (200 ml). After workup and crystallization, pure **11** was obtained as a white solid in 60% yield: mp 165–167°C; $[\alpha]_D^{20}$=+327 (*c* 1, $CHCl_3$); ^{1}H NMR δ 8.67 (dd, 1H, *J*=1.1 and 8.6 Hz), 7.92 (d, 1H, *J*=9.1 Hz), 7.79 (dd, 1H, *J*=1.1 and 8.1 Hz), 7.75 (d, 1H, *J*=3.2 Hz), 7.54 (dt, 1H, *J*=1.1 and 8.1 Hz), 7.37 (dt, 1H, *J*=1.1 and 8.1 Hz), 7.21 (d, 1H, *J*=9.1 Hz), 6.87 (dd, 1H, *J*=3.2 and 8.6 Hz), 6.66 (d, 1H, *J*=9.1 Hz), 3.90, 3.87 and 3.32 (3s, 9H); ^{13}C NMR δ 157.6, 153.9, 149.2, 134.3, 132.3, 128.7, 128.3, 127.50, 124.1, 123.2, 117.0, 113.7, 112.3, 111.7, 56.5, 56.0, 55.8; IR ν_{max} 1620, 1590, 1510, 1480, 1460, 1435, 1380, 1350, 1275, 1150, 1140, 1090, 910, 810, 710. Anal. calcd for $C_{19}H_{18}O_4S$: C, 65.65; H, 5.30; S, 9.35. Found: C, 65.67; H, 5.01; S, 9.15.

*4.8. (SS)-2-(2′-Methoxynaphthylsulfinyl)-1,4-benzoquinone **2b***

To a solution of (+)-**11** (752 mg, 2.2 mmol) in CH_3CN (50 ml), ammonium cerium (IV) nitrate (5.5 g, 10 mmol) in H_2O (150 ml) was added at rt. After stirring for 1 h, workup and crystallization (ethyl ether), pure **2b** was obtained as an orange solid in 90% yield: mp 102–103°C; $[\alpha]_D^{20}$=+960 (*c* 0.1, $CHCl_3$); ^{1}H NMR δ 8.52 (d, 1H, *J*=8.1 Hz), 8.00 (d, 1H, *J*=8.9 Hz), 7.81 (d, 1H, *J*=8.1 Hz), 7.64 (dt, 1H, *J*=1.2 and 8.1 Hz), 7.59 (d, 1H, *J*=2.8 Hz), 7.44 (dt, 1H, *J*=1.2 and 8.1 Hz), 7.27 (d, 1H, *J*=8.9 Hz), 6.79 (dd, 1H, *J*=2.8 and 10.1 Hz), 6.63 (d, 1H, *J*=10.1 Hz), 4.00 (s, 3H, OCH_3); ^{13}C NMR δ 185.0, 183.30, 158.3, 153.0, 136.9, 136.3, 134.0, 132.2, 128.8, 128.6, 128.50, 124.5, 122.5, 113.4, 56.6; IR ν_{max} 1655, 1585, 1500, 1465, 1315, 1270, 1215, 1130, 1070, 980, 810, 720, 670. Anal. calcd for $C_{17}H_{12}O_4S$: C, 65.37; H, 3.87; S, 10.26. Found: C, 65.02; H, 4.14; S, 9.99.

*4.9. (5*R*,SS)- and (5*S*,SS)-5-[3-Hydroxy-6-trimethylsilyloxy-2-(2′-methoxynaphthylsulfinyl)phenyl]-furan-2(5*H*)-one **7b** and **8b***

These compounds were detected by ^{1}H NMR monitoring after mixing (S*S*)-2-(2′-methoxynaphthylsulfinyl)-1,4-benzoquinone **2b** (11.0 mg, 0.03 mmol) and 2-trimethylsilyloxyfuran **1** (6.5 μl, 0.04 mmol) in CD_3CN at rt as a 80:20 mixture of epimers at C_5. Compound **7b**: ^{1}H NMR (CD_3CN) δ 11.13 (s, 1H), 8.6–7.4 (m, 6H), 6.9–6.7 (m, 2H), 5.93 (dd, 1H, *J*=1.8 and 2.3 Hz), 5.78 (dd, 1H, *J*=2.3 and 5.9 Hz), 5.63 (dd, 1H, *J*=1.8 and 5.9 Hz), 3.90 (s, 3H), 0.08 (s, 9H). Compound **8b**: ^{1}H NMR (CD_3CN) δ 11.27 (s, 1H), 8.7–7.4 (m, 6H), 6.9–6.7 (m, 2H), 6.12 (dd, 1H, *J*=1.8 and 5.9 Hz), 5.97 (dd, 1H, *J*=2.3 and 5.9 Hz), 5.86 (dd, 1H, *J*=1.8 and 2.3 Hz), 3.95 (s, 3H), 0.29 (s, 9H).

*4.10. (5*R*,SS)- and (5*S*,SS)-5-[3,6-Dihydroxy-2-(2′-methoxynaphthylsulfinyl)phenyl]furan-2(5*H*)-one **9b** and **10b***

To a solution of (S*S*)-2-(2′-methoxynaphthylsulfinyl)-1,4-benzoquinone **2b** (30.8 mg, 0.10 mmol) in dry CH_2Cl_2 (5 ml), 2-trimethylsilyloxyfuran **1** (16.25 μl, 0.11 mmol) was added. The mixture was stirred at rt for 1 h and 5 ml of 10% HCl were added. After workup, compounds **9b** and **10b** were obtained as a 85:15 mixture of epimers at C_5. These compounds were also detected by ^{1}H NMR monitoring after mixing (S*S*)-2-(2′-methoxynaphthylsulfinyl)-1,4-benzoquinone **2b** (11.0 mg, 0.03 mmol) and 2-trimethylsilyloxyfuran **1** (6.5 μl, 0.04 mmol) in $CDCl_3$ at rt as a 90:10 mixture. Compound **9b**: ^{1}H NMR δ 11.10 (s, 1H), 8.6–7.2 (m, 6H), 6.72 and 6.66 (AB system, 2H, *J*=9.2 Hz), 5.92 (dd, 1H, *J*=1.6 and 2.1 Hz), 5.73 (dd, 1H, *J*=2.1 and 5.4 Hz), 5.34 (dd, 1H, *J*=1.6 and 5.4 Hz), 3.90 (s, 3H). Compound **10b**: ^{1}H NMR δ 11.18 (s, 1H), 8.6–7.2 (m, 6H), 6.79 and 6.73 (AB system, 2H, *J*=9.2 Hz), 6.15 (dd, 1H, *J*=1.8 and 5.4 Hz), 5.98 (dd, 1H, *J*=2.1 and 5.4 Hz), 5.84 (dd, 1H, *J*=1.8 and 2.1 Hz), 3.85 (s, 3H).

*4.11. (3a*S*,8b*S*,SS)-3a,8b-Dihydro-7-hydroxy-8-(2′-methoxy-1-naphthylsulfinyl)furo[3,2-*b*]benzofuran-2(3*H*)-one **3b***

To a solution of (S*S*)-2-(2′-methoxynaphthylsulfinyl)-1,4-benzoquinone **2b** (154 mg, 0.5 mmol) in dry $CHCl_3$ (10 ml) cooled to −20°C, 2-trimethylsilyloxyfuran **1** (80 μl, 0.55 mmol) was added under argon. The mixture was stirred at −20°C for 4 h and the solvent evaporated under reduced pressure. After flash chromatography (eluent CH_2Cl_2:acetone 20:1), compound (+)-**3b** was isolated diastereoisomerically pure as an oil in 82% yield: $[\alpha]_D^{20}$=+62 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 10.70 (s, 1H), 8.66. (d, 1H, *J*=8.2 Hz), 8.09 (d, 1H, *J*=8.8 Hz), 7.86 (d, 1H, *J*=8.2 Hz), 7.69 (dt, 1H, *J*=8.2 and 1.2 Hz), 7.47 (dt, 1H, *J*=8.2 and 1.2 Hz), 7.34 (d, 1H, *J*=8.8 Hz), 6.91 and 6.78 (AB system, 2H, *J*=8.8 Hz), 5.06 (d, 1H, *J*=6.4 Hz), 4.95 (m, 1H), 4.00 (s, 3H), 2.84 (m, 2H); ^{13}C NMR δ 174.1, 158.6, 156.3, 153.5, 136.2, 132.8, 132.6, 129.7, 128.8, 128.3, 124.8, 122.7, 121.5, 117.7, 117.2, 113.9, 113.5, 81.7, 81.0, 56.3, 34.9; IR ν_{max} 3650, 3000, 2910, 1780, 1595, 1460, 1300, 1160, 1140, 1105. Anal. calcd for $C_{21}H_{16}O_6S$: C, 63.63; H, 4.07; S, 8.09. Found: C, 63.50; H, 4.08; S, 7.95.

*4.12. (3a*R*,8b*R*,SS)-3a,8b-Dihydro-7-hydroxy-8-(2′-methoxy-1-naphthylsulfinyl)furo[3,2-*b*]benzofuran-2(3*H*)-one **4b***

Compound (+)-**4b** was obtained diastereoisomerically pure as above in 8% yield: $[\alpha]_D^{20}$=+267 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 10.82 (s, 1H), 8.57 (d, 1H, *J*=8.2 Hz), 8.12 (d, 1H, *J*=9.4 Hz), 7.87 (d, 1H, *J*=8.2 Hz), 7.60 (dt, 1H, *J*=8.2 and 1.2 Hz), 7.40 (dt, 1H, *J*=8.2 and 1.2 Hz), 7.31 (d, 1H, *J*=9.4 Hz), 6.92 and

6.80 (AB system, 2H, *J*=8.8 Hz), 5.49 (d, 1H, *J*=5.9 Hz), 5.14 (m, 1H), 3.97 (s, 3H), 2.67 (m, 2H); ^{13}C NMR δ 173.1, 158.9, 155.9, 154.1, 136.9, 132.4, 129.3, 128.9, 128.8, 124.3, 122.7, 121.7, 121.2, 118.2, 117.5, 113.9, 113.1, 81.7, 81.1, 56.3, 34.9. Anal. calcd for $C_{21}H_{16}O_6S$: C, 63.63; H, 4.07; S, 8.09. Found: C, 63.78; H, 4.15; S, 8.23.

*4.13. 2-(*tert*-Butylthio)-1,4-benzoquinone **12***

To a suspension of 1,4-benzoquinone (2.36 g, 21.8 mmol) in EtOH (35 ml), 1,1-dimethylethanethiol (1.23 ml, 10.9 mmol) was added at rt. After stirring for 4 h and evaporation of the solvent, the residue was purified by flash chromatography (eluent hexane:EtOAc 85:15) to afford pure **12** as a red solid in 50% yield: mp 64–65°C (ethyl ether/hexane); ^{1}H NMR δ 6.8–6.6 (m, 3H), 1.53 (s, 9H); ^{13}C NMR δ 184.4, 184.2, 150.9, 136.9, 136.6, 128.2, 46.5, 30.0 (3C); EI-MS *m/z* (%) 196 (M^+, 11), 174 (10), 142 (25), 57 (100); HRMS (EI) calcd for $C_{10}H_{12}O_2S$ 196.05580, found 196.05568.

4.14. (SS)-2-(*tert*-Butylsulfinyl)-1,4-benzoquinone **2c***

To a solution of thioether **12** (100 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) cooled at 0°C, *m*-CPBA (150 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) was added. The mixture was stirred at 0°C for 1 h and treated with saturated aqueous solution of $NaHCO_3$. After workup and crystallization (CH_2Cl_2:hexane), pure **2c** was obtained as an orange solid in 93% yield: mp 139–140°C; ^{1}H NMR δ 7.28 (d, 1H, *J*=1.7 Hz), 6.87 (dd, 1H, *J*=1.7 and 9.5 Hz), 6.84 (d, 1H, *J*=9.5 Hz), 1.26 (s, 9H); ^{13}C NMR δ 184.6, 184.4, 152.9, 137.5, 136.9, 136.7, 52.1, 23.6 (3C); EI-MS *m/z* (%) 212 (M^+, 1), 158 (21), 140 (15), 112 (24), 57 (100); HRMS (EI) calcd for $C_{10}H_{12}O_3S$ 212.05072, found 212.05058.

4.15. (3aS,8bS*,SS*)-3a,8b-Dihydro-7-hydroxy-8-(*tert*-butylsulfinyl)furo[3,2-*b*]benzofuran-2(3H)-one **3c***

To a solution of 2-(*tert*-butylsulfinyl)-1,4-benzoquinone **2c** (28 mg, 0.13 mmol) in dry $CHCl_3$ (5 ml) cooled to −20°C, 2-trimethylsilyloxyfuran (1) (24 μl, 0.14 mmol) was added under argon. The mixture was stirred at −20°C for 1 h and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (eluent hexane:EtOAc 50:50) to obtain diastereoisomerically pure **3c** as a white solid in 52% yield: mp 168–169°C; ^{1}H NMR δ 10.50 (s, 1H), 6.90 and 6.89 (AB system, 2H, *J*=9.0 Hz), 5.94 (d, 1H, *J*=5.9 Hz), 5.32 (dt, 1H, *J*=5.9 and 3.2 Hz), 4.00 (s, 3H), 2.98 (m, 2H), 1.38 (s, 9H); ^{13}C NMR δ 174.1, 157.6, 154.1, 124.3, 121.1, 116.1, 114.6, 83.2, 81.7, 61.0, 34.5, 23.6 (3C); EI-MS *m/z* (%) 296 (M^+, 2), 240 (42), 224 (31), 194 (100), 179 (32), 149 (32), 84 (16), 69 (10), 57 (81); HRMS (EI) calcd for $C_{14}H_{16}O_5S$ 296.07185, found 296.07120.

Acknowledgements

We thank Dirección General de Investigación Científica y Técnica (Grants PB95-0174 and PB96-0035) for financial support.

References

1. Sotheeswaran, S.; Pasupathy, V. *Phytochemistry* **1993**, *32*, 1083–1092.
2. (a) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch Jr., K. O.; Ray, J. E. *J. Org. Chem*. **1994**, *59*, 6567–6587. (b) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem*. **1994**, *59*, 6588–6599. (c) Engler, T. A.;

Gfesser, G. A.; Draney, B. W. *J. Org. Chem*. **1995**, *60*, 3700–3706. (d) Engler, T. A.; Iyengar, R. *J. Org. Chem*. **1998**, *63*, 1929–1934. (e) Engler, T. A.; Letavic, M. A.; Iyengar, R.; LaTessa, K. O.; Reddy, J. P. *J. Org. Chem*. **1999**, *64*, 2391–2405.

3. (a) Bird, C. W.; Brown, A. L.; Chan, C. C.; Lewis, A. *Tetrahedron Lett*. **1989**, *30*, 6223–6226. (b) Fariña, F.; Paredes, M. C.; Valderrama, J. *Synth. Commun*. **1989**, *19*, 3301–3312. (c) Kraus, G. A.; Shi, J.; Reynolds, D. *J. Org. Chem*. **1990**, *55*, 1105–1106. (d) Fariña, F.; Paredes, M. C.; Valderrama, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, *48*, 2345–2346. (e) Rupprecht, K. M.; Boger, J.; Hoogsteen, K.; Nachbar R. B.; Springer, J. P. *J. Org. Chem*. **1991**, *56*, 6180–6188. (f) Fariña, F.; Paredes, M. C.; Valderrama, J. *Tetrahedron* **1992**, *48*, 4629–4640.
4. Brimble, M. A.; Elliot, R. J. R. *Tetrahedron* **1997**, *53*, 7715–7730 and references cited therein.
5. (a) Brimble, M. A.; Duncalf, L. J.; Reid, D. C. W.; Roberts, T. R. *Tetrahedron* **1998**, *6*, 5363–5374. (b) Brimble, M. A.; McEwan, J. F.; Turner, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1257–1267.
6. Brimble, M. A.; McEwan, J. F. *Tetrahedron: Asymmetry* **1997**, *8*, 4069–4078.
7. Brimble, M. A.; Duncalf, L. J.; Reid, D. C. W. *Tetrahedron: Asymmetry* **1995**, *6*, 263–269.
8. For an overview of our work, see: (a) Carreño, M. C. *Chem. Rev*. **1995**, *95*, 1717–1760. For more recent references, see: (b) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A.; Urbano, A.; Remor, C. Z.; Stefani, V.; Fischer, J. *J. Org. Chem*. **1996**, *61*, 503–509. (c) Carreño, M. C.; Urbano, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1621–1623. (d) Carreño, M. C.; Urbano, A.; Di Vitta, C. *J. Org. Chem*. **1998**, *63*, 8320–8330. (e) Carreño, M. C.; Hérnandez-Sánchez, R.; Mahugo, J.; Urbano, A. *J. Org. Chem*. **1999**, *64*, 1387–1390. (f) Carreño, M. C.; Urbano, A.; Di Vitta, C. *Chem. Commun*. **1999**, 817–818.
9. Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Synthesis* **1992**, 651–653.
10. The absolute configuration of **3a** and **4a** had been established previously (see Ref. 7).
11. Kahn, S. D.; Here, W. J. *J. Am. Chem. Soc*. **1986**, *108*, 7399–7400.
12. Higher reactivity had been evidenced for the *s-cis* conformer in Michael additions of vinyl sulfoxides (see Ref. 11) and Diels–Alder reactions of sulfinyl quinones (see Ref. 8).
13. Andersen, K. K.; Gafield, W.; Papanicolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc*. **1964**, *86*, 5637–5646.
14. Pyne, S. G.; Hajipour, A. R.; Prabakaran, K. *Tetrahedron Lett*. **1994**, *35*, 645–648.
15. Snell, J. M.; Weissberger, A. *J. Am. Chem. Soc.* **1939**, *61*, 450.
16. The presence of this hydrogen bonding was evident from the ^{1}H NMR spectra of **3b** and **4b**, where the phenolic proton appears very deshielded at 10.70 and 10.82 ppm, respectively.
17. This NOE experiment was performed in $CDCl_3$ at 500 MHz.