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Reactivity of lithium 2,3-dihydro-1-benzothiophene-1-oxide toward aldehydes and imines and DFT calculations

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ABSTRACT

The sulfinyl carbanion derived from 2,3-dihydro-1-benzothiophene-1-oxide and its lithium salt has been investigated by DFT calculations. The lithium carbanion was treated with aldehydes and imines to give chiral hydroxy and amino derivatives, with high stereoselectivity at the carbon α to the sulfoxide group (trans diastereoisomers), but with low diastereoselectivity at the hydroxyl or amine group. DFT calculations were used to rationalize the different stereochemical behavior of cyclic and acyclic lithiated sulfoxides in the reaction with aldehydes and azomethines.

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1. Introduction

Sulfoxides represent an important class of organic compounds exhibiting biological activity[1–5] and widely used as chiral auxiliaries in asymmetric organic synthesis.[6] Cyclic sulfoxides have been less studied than their acyclic analogous compounds. In connection with our previous studies on benzocondensed sulfur heterocycles and their stereoselective functionalization,[7–9] we decided to examine the 2,3-dihydrobenzo-1-thiophene-1-oxide (**1**) by studying its functionalization through lithiation reactions and deducing the structure of the intermediate lithium carbanion **3** by means of Density Functional Theory (DFT) calculations.

Only a few acyclic lithiated sulfoxides have been studied by NMR spectroscopy,[10] IR spectroscopy,[11] and theoretical calculations,[12–15] and only one XRD structure is present in literature.[16] Among cyclic analogues, only the lithiated sulfoxide of thiacyclohexane has been examined.[17] In all cases, the lithium atom was found to interact with the oxygen atom,[11–16] the carbanion being stabilized by Coulombic interactions, hyperconjugation, and polarization,[18] analogously to lithiated sulfones.

2. Results and discussion

2.1. DFT calculation of the lithiated sulfoxide

Geometry optimization carried out on the cyclic sulfoxide **1** with Gaussian 03[19] gave a non-planar structure for the penta-atomic moiety with diastereotopic α hydrogens H_a and H_b (Fig. 1). By removing either the hydrogen H_b or H_a, the carbanion **2a** or **2b** was formed, respectively, featuring very close energies and with the C_2 atom showing a pyramidal geometry (Fig. 1 and Table 1).

It is worth noting that the geometry optimization carried out on **2a** leads to inversion of configuration of the C_2 atom with respect to the starting sulfoxide. An examination of the occupied frontier Kohn–Sham orbitals calculated for **2a** shows that HOMO-1 and HOMO (Fig. 2) are mainly localized on the sulfur and the C_2 atoms, respectively. In particular, the NBO analysis shows that the HOMO calculated for **2a** basically consists of a lone pair (NBA population 1.63*e*) of p nature (92.45%) localized on the C_2 atom, while HOMO-1 (1.96*e*) is built up almost equally of the s and p AOs (46.45 and 53.33%, respectively) of the sulfur atom. The same orbitals can also be envisaged for **2b** (Fig. 2; NBA: LP on C_2: 1.81*e*, s 21.82%, p 76.95%; LP on S: 1.95*e*, s 46.40%, p 53.40%): in this case, the two lone pairs show a nearly eclipsed arrangement.

As a consequence of deprotonation at the C_2 atom, the C_2–S bond distance is shortened on passing from **1** to **2**, this change being more evident in **2a** than in **2b** (Wiberg bond index WBI:

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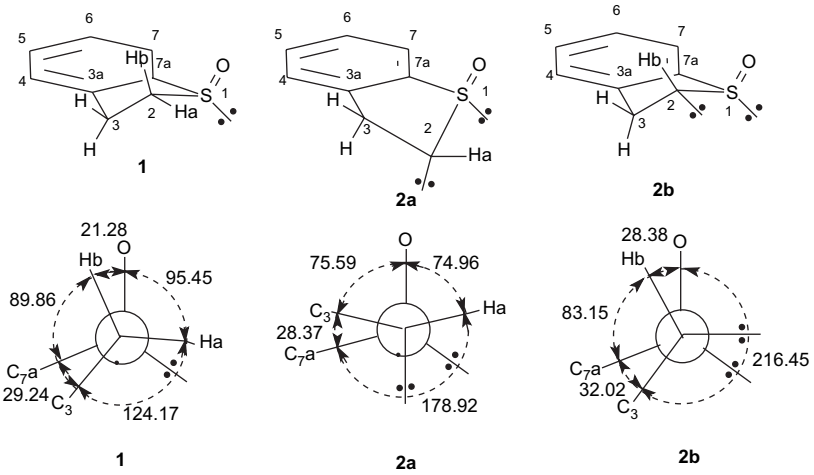


Figure 1.

Table 1
Relative energies ΔE (kcal mol^{-1}), selected bond lengths (Å) and angles (°), and NBO charges $Q(e)$ calculated for **1**, **2a**, and **2b**

	1	2a	2b
ΔE	—	−0.72	0.00
S–O	1.509	1.529	1.510
C_2–S	1.875	1.704	1.762
C_{7a}–S	1.824	1.815	1.857
C_3–C_2–S	107.71	114.33	103.54
OSC_7	109.62	103.40	108.47
H_a–C_2–S	108.80	116.54	
H_a–C_2–C_3	114.67	121.72	
H_b–C_2–S	102.24		104.62
H_b–C_2–C_3	112.79		109.94
(C_3C_2S)–H_a	−124.86	150.55	
(C_3C_2S)–H_b	119.04		115.17
C_{7a}–S–C_2–C_3	29.40	−28.37	32.02
Q (C_2)	−0.545	−0.812	−0.852
Q (S)	+1.249	+1.157	+1.204
Q (O)	−0.977	−1.088	−1.038
$n_{C-\sigma^*S-O}$		21.02	—

0.887 in **1**, 1.202 in **2a**, 1.040 in **2b**), while the S–O bond is longer in **2a** than in **2b** (WBI: 1.247 in **1**, 1.064 in **2a**, 1.178 in **2b**). In **2a**, the antiperiplanar arrangement between the oxygen atom and the C_2 lone pair allows for a stronger hyperconjugation within the C_2–SO bond, evaluated at the NBO level (Table 1). The structure calculated for the isomer **2a** is slightly more stable than that of **2b** (Table 1). The sulfinyl carbanions derived from acyclic sulfoxides have been reported to show a hybridization state intermediate between sp^2 and sp^3, or pure sp^2 when the α carbon is bound to a phenyl group.[18] The conformation along the C–S axis showed the lone pair on the C_2 rotated by 20.5° away from the position antiperiplanar to the S–O bond: this position represents a compromise between the maximization of the $n_{C-\sigma^*S-O}$ and $n_{C-\sigma^*S-R}$ stabilization and minimization of lone pair repulsion.[12,18]

DFT calculations were used to evaluate geometrical parameters (bond lengths and angles) of the intermediate **3**, hardly measurable otherwise because of its instability. In fact, the lithium salt, generated by reaction of **1** with LDA, is unstable at temperatures above

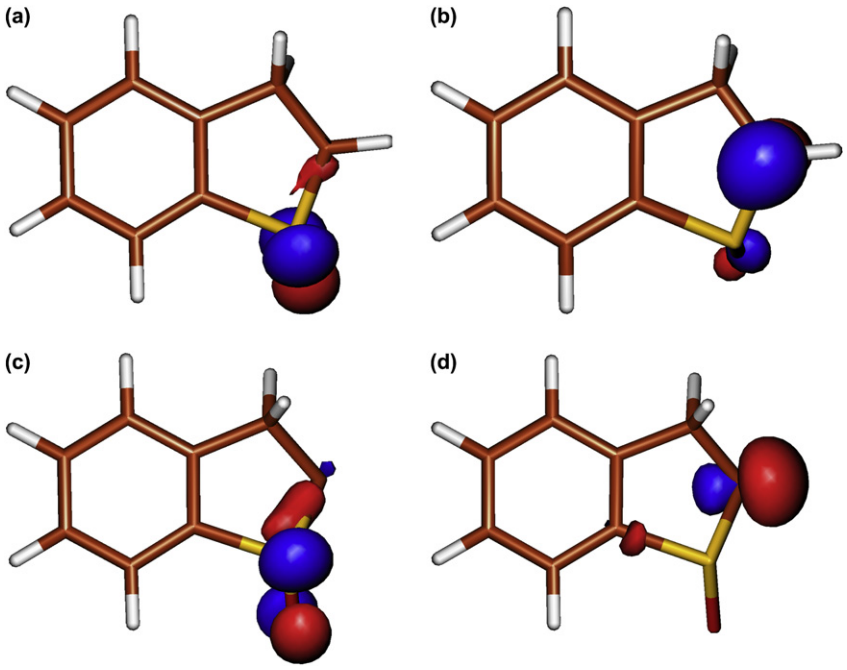


Figure 2. Drawings of Kohn–Sham HOMO-1s (a, c) and HOMOs (b, d) calculated for **2a** (top) and **2b** (bottom; cut off value 0.1e).

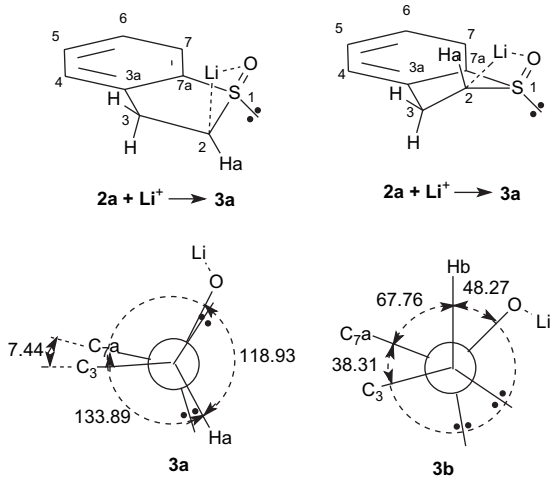


Figure 3.

−40 °C. Furthermore, the NMR spectroscopic analysis at low temperature (−70/−80 °C) is troublesome: the reaction of LDA with **1** produces diisopropylamine interfering in interpreting the spectrum of the lithium sulfinyl carbanion, while treatment of **1** with MeLi or BuLi leads to cleavage of the C_{Ar}–S bond.[20]

Geometry optimization was also performed on the lithium salts of **2a** and **2b** (**3a** and **3b**, respectively) showing different energies and the cation interacting with both the oxygen and the C_2 atoms.

It is interesting to underline that the optimization of **3a** starting from **2a** occurs with configuration inversion on the C_2 atom. The C_2–S bond is calculated to be shorter in **3a** than in **3b** (WBI: 0.935 and 0.899, respectively) while the S–O bond shows an opposite trend in the two structures (WBI: 1.011 and 1.082 for **3a** and **3b**, respectively): these data can be explained by considering that the interaction between the lithium atom and the oxygen is stronger in **3a** than that in **3b** and that **3a** shows a hyperconjugative contribution n_C–BD^*_{S-O} (10.14 kcal mol^{-1}), while in **3b** this contribution is completely missing (Fig. 3, Table 2).

Compounds **3a** and **3b** have different energies (by 18 kcal mol^{-1}), and none of them present a significant hyperconjugative interaction n_C–σ^*_{S-C} (Table 2). Both salts are stabilized by the interaction between C_2 and Li^+, this contribution being greater in the case of the former isomer than in the latter. By comparing the structure of **2a** (free carbanion) with that of **3a** (lithiated carbanion) it is evident a greater pyramidal character in **3a**, attributable to the interaction between the lithium cation and C_2.

Table 2
Relative energies ΔE (kcal mol^{-1}), selected bond lengths (Å) and angles (°), NBO charges $Q(e)$, and hyperconjugative interactions (kcal mol^{-1}) calculated for **3a** and **3b**

	3a	3b
ΔE	−18.10	0.00
S–O	1.558	1.545
C_2–S	1.759	1.782
C_{7a}–S	1.790	1.810
Li–O	1.804	1.883
Li–C_2	2.114	2.037
OSC_7	105.76	114.77
C_3–C_2–S	111.24	102.17
H_a–C_2–S	108.93	
H_a–C_2–C_3	113.97	
H_b–C_2–S		99.12
H_b–C_2–C_3		103.52
(C_3C_2S)–H_a	126.45	
(C_3C_2S)–H_b		106.07
C_{7a}–S–C_2–C_3	7.44	38.31
$Q(C_2)$	−0.926	−0.917
Q(S)	+1.184	+1.197
Q(O)	−1.135	−1.102
Q(Li)	+0.879	+0.911
n_C–BD^*_{S-O}	10.14	—
C_2–Li	18.40	13.45

Theoretical calculations indicate that the carbanion **2a** adopts a conformation analogous to the free methyl sulfinyl carbanion (C–S bond), but in **2a** the negative hyperconjugation is due only to n_C–σ^*_{S-O} and not to n_C–σ^*_{S-C} and n_C–σ^*_{S-O} as in the methyl sulfinyl carbanion.[18] The lithium salt **3a** adopts a different conformation (C–S bond) with respect to the lithium carbanion derived from the acyclic sulfoxide {Li_2[PhC(CH_3)SO_2Ph]$_2$·2TMEDA} in the solid state,[18] but it has the same conformation of the calculated lithium methyl sulfoxide.[15] Furthermore C_2 in **3a** has a greater pyramidal character than in the above cited lithium sulfoxide[18] and in the lithium phenylmethyl sulfoxide.[17]

2.2. Reactions of 3 with electrophiles

Sulfoxide **1** was metalated with LDA to give the lithium intermediate **3**, which in turn was reacted with aldehydes (**4a–f**) or imines (**5a–c**) as electrophiles to give four series of diastereomeric hydroxy-derivatives, **6a–f** and **7a–f** with the carbinolic group trans to the sulfoxide oxygen, while **8a** and **9a** are cis diasteroisomers, and four series of amino compounds where **10a–c** and **11a** and **11c** are trans derivatives while **12b** and **13b** are cis (Scheme 1).

The structures of the obtained compounds were assigned by means of NMR spectroscopic analysis. The trans structures of **6a–f** and **7a–f** and the cis structures of **8a** and **9a** have been assigned on the basis of the different chemical shifts values of C_2 and H_2: the signals of C_2 and H_2 in **6** and **7** are shifted downfield with respect to those of **8a** and **9a** (Table 3), a trend analogous to that reported for aldehydic derivatives of 1,3-benzoxathiol-3-oxide,[7] whose relative configurations were also confirmed by XRD.

Moreover, **6** can be distinguished from **7** on the basis of the different coupling constant values J_{H2-H8}: by assuming that the trans diastereoisomers adopt a conformation allowing the aromatic ring to displace as far as possible from the bulky SO group, the H_8 would be antiperiplanar to H_2 in **7** (higher J value), while in **6** H_2 and H_8 would display a *syn* arrangement (lower J value) (Fig. 4, Table 3).

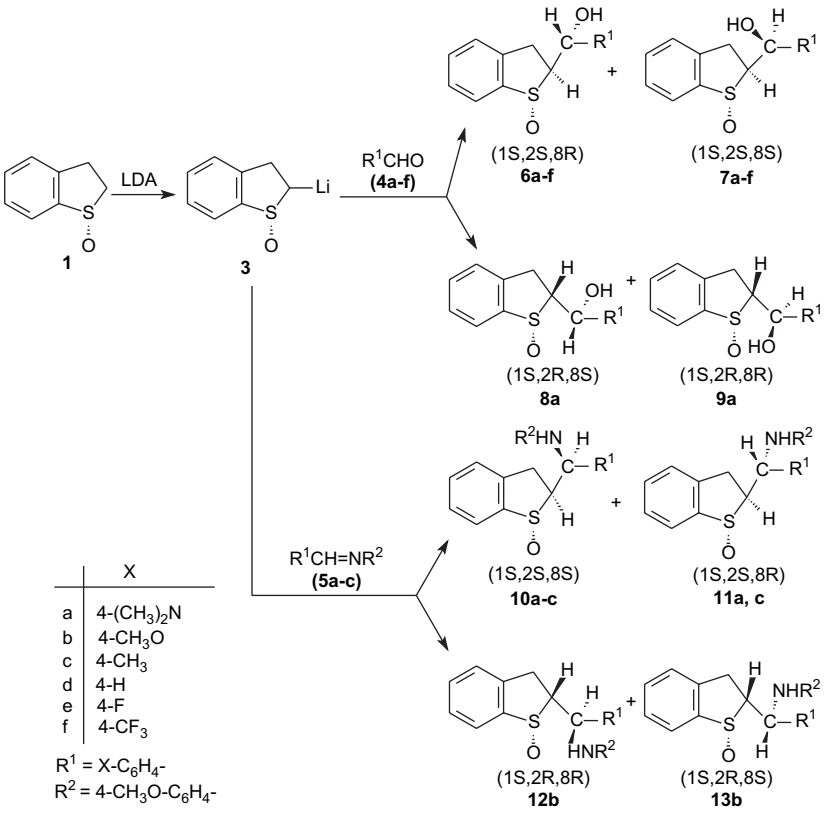
Moreover, the repulsion between the hydroxyl oxygen atom and the lone pair on the sulfur atom in **7** caused the aryl group to move closer to H_{3a}, which resulted in an upfield shift with respect to the analogous protons in **6** (Fig. 4, Table 3).

Both cis diastereoisomers **8a** and **9a** show the same coupling constant J_{H2-H8}=8.1 Hz: the only two possible conformations are those reported in Figure 5 showing the H_2 and H_8 in an antiperiplanar arrangement. The signal due to H_{3a} in the ^{1}H NMR spectrum is shifted more upfield in **9a** (2.61 ppm) than in **8a** (3.49 ppm) because of its proximity to the shielding cone of the aromatic ring (Table 3 and Fig. 4).

The trans diastereoisomers **6** and **7** (electrophilic attack opposite to the sulfoxide oxygen) always prevailed over the cis ones (except in the case of the reaction with the 4-*N*,*N*-dimethylaminobenzaldehyde **4a**), the diastereomeric ratios ranging between trans/cis=42:58 and 40:60, at −60 and −78 °C, respectively, for the 4-*N*,*N*-dimethylaminobenzaldehyde (**4a**) to trans=100% for **4b–f** (Table 4).

The ratio trans/cis does not change for different temperatures, except for the reaction of **3** with **4a** (Table 4). Furthermore, increasing the temperature from −78 to −60 °C the global yield decreases, but the amount of the diastereoisomer **6** increases (Table 4).

With the exception of the reaction with the 4-*N*,*N*-dimethylaminobenzaldehyde, which has a strong electron-releasing group



Scheme 1.

Table 3
^{1}H and ^{13}C NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) of diastereoisomers **6** [1*S*,2*S*,8*R*+1*R*,2*R*,8*S*], **7** [1*S*,2*S*,8*S*+1*R*,2*R*,8*R*], **8** [1*S*,2*R*,8*S*+1*R*,2*S*,8*R*], and **9** [1*S*,2*R*,8*R*+1*R*,2*S*,8*S*]

	H_2	C_2	H_8		C_8	H_{3a}	H_{3s}
	δ	δ	δ	$^{3}J_{H2-H8}$	δ	δ	δ
6a	3.60	77.6	5.02	4.5	69.8	3.24	3.37
6b	3.62	77.6	5.12	4.5	69.9	3.21	3.41
6c	3.63	77.1	5.15	4.5	69.5	3.25	3.42
6d	3.66	77.2	5.22	4.5	69.8	3.25	3.31
6e	3.67	77.0	5.22	4.8	69.4	3.34	3.46
6f	3.72	76.7	5.39	4.3	69.4	3.24	3.32
7a	3.62	77.8	4.64	8.1	72.6	2.92	3.26
7b	3.64	77.8	4.76	8.1	72.4	2.95	3.35
7c	3.61	77.4	5.18	8.0	69.8	2.95	3.32
7d	3.67	77.6	4.83	7.8	72.8	3.02	3.39
7e	3.67	77.5	4.89	7.8	71.9	3.14	3.48
7f	3.74	77.6	5.04	7.8	72.1	3.01	3.37
8a	3.44	70.5	4.89	8.1	68.1	3.49	3.64
9a	3.47	69.4	4.76	8.1	68.7	2.61	3.30

(dimethylamino group $\sigma_p=-0.83$), the carbonyl carbon mainly approaches the carbanion on the opposite side with respect to the sulfoxide oxygen and the lithium atom (bonded to the oxygen). As a consequence, the lithium atom poorly affects the stereochemistry of the C_2 reaction, in contrast with the behavior of acyclic sulfoxides.[21]

The analysis of the diastereoselectivity among the trans adducts reveals that the amount of **7** increases as the electron-withdrawing power of the substituent on the aromatic ring increases. The aldehyde can approach the carbanion placing its aromatic group as far as possible from the sulfoxide group and between the CH_2 and the H_2. This arrangement can be adopted by two different transition states, one leading to derivatives **6** and the other to derivatives **7** (Fig. 6).

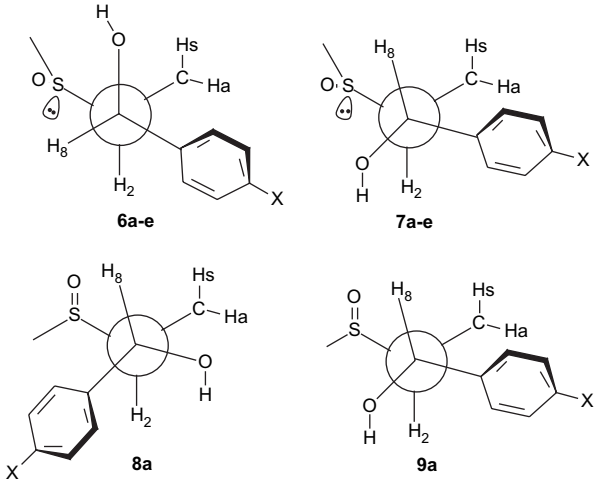


Figure 4.

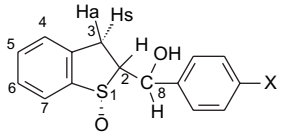


Figure 5.

The reactions run under kinetic control conditions, since no diastereoisomeric interconversion was observed when each diastereoisomer was subjected to LDA under the same reaction conditions.

Table 4
Product distribution for **1**+**4a–f** in THF

R^1CHO	Molar fraction[a]				Global yield[c] (%)
	6	**7**	**8**	**9**	
4a[b]	0.30	0.12	0.41	0.17	30
4a[c]	0.25	0.15	0.38	0.22	55
4b[b]	0.67	0.33			36
4b[c]	0.59	0.41			66
4c[b]	0.66	0.34			53
4c[c]	0.58	0.42			71
4d[b]	0.58	0.42			35
4d[c]	0.51	0.49			56
4e[b]	0.54	0.46			47
4e[c]	0.49	0.51			65
4f[b]	0.46	0.54			58
4f[c]	0.43	0.57			77

[a] Determined by HPLC analyses.
[b] Reaction temperature=−60 °C.
[c] Reaction temperature=−78 °C.

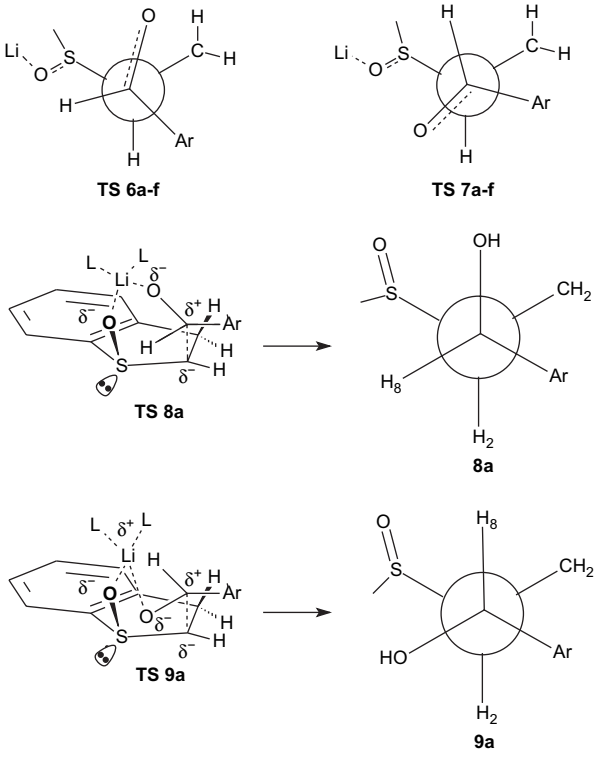


Figure 6.

For the cis isomers (only **8a** and **9a** were obtained), it can be noticed that the approach of the electrophile from the same side of the sulfoxide oxygen can proceed through two different six-center transition states (Fig. 6) involving the sulfoxide oxygen, the lithium cation, the aldehydic oxygen, the sulfur atom, C_2 and C_8.[18]

The comparison between the diastereoselectivity on the C_2 atom in the reactions of **3** with aldehydes and the corresponding reactions of lithium 1,3-benzoxathiol-3-oxide with the same aldehydes show some differences only with regards to **4b** and **4c**.[7] The diastereoselectivity at the carbonyl carbon in the reactions of 1,3-benzoxathiol-3-oxide was constant for different substituents on the aldehyde ring,[7] while in the case of 2,3-dihydro-1-benzothiophene-1-oxide the amount of the isomer **7** increases as the electron-withdrawing power of the substituent increases (Table 4).

To get a better insight into the behavior of the lithiated **3** toward electrophiles, the reactions with aldehydes were carried out under different experimental conditions, i.e., changing concentrations and temperatures (Table 5). When **3** was reacted with the 4-methylbenzaldehyde **4c** at −60 °C using a higher substrate concentration and a lower LDA/substrate ratio, the diastereoselectivity did not change but the yield increased. This effect disappeared when the reaction was performed at −78 °C. 4-*N*,*N*-Dimethylaminobenzaldehyde **4a** showed the same behavior.

The reaction of **3** with **4b** at −40 °C showed a total conversion of the substrate, but no diastereoisomer was isolated. This is consistent with the lowering of the yield as the temperature lowers from −78 to −60 °C and can tentatively be explained by the low stability of the lithiated intermediate **3**. Moreover, when the same reaction was performed at −60 °C and the electrophile **4b** was dissolved in the mixture of solvents HMPA/THF the reaction yield lowered, the selectivity on C_2 remained unchanged, but the amount of the isomer **6** increased (Table 5).

When **3** was allowed to react with aromatic azomethines **5a–c**, the reaction yields increased as the electron-withdrawing power of the substituent on the ring increases, with also an increasing diastereoselectivity on the C_8 for the trans isomers (Table 6).

The HPLC analysis of the reaction mixture of **3** with **5a** showed four peaks with identical UV spectral features attributable to four possible diastereoisomers: the first two were isolated and identified as **10a** and **11a**, while the other two could not be isolated even after repeated reactions and chromatographies, and were assigned the structures **12a** and **13a** by analogy with the reaction products of **3** with **5b**. In the reaction of **3** with **5b** only the product **12b** could not be isolated. The relative configuration assignment was made referring to the products derived from the reaction of **3** with aldehydes and of the lithiated 1,3-benzoxatiol-3-oxide with the same azomethines.[8] Therefore, the trans isomers were distinguished from the cis ones on the basis of their higher chemical shift values

Table 6
Product distribution for **1**+**5a–c** in THF at −60 °C[a]

$R^1CH{=}NR^2$	R^1	R^2	**10** (%)	**11** (%)	**12** (%)	**13** (%)	Global yield[c] (%)
5a	4-$MeOC_6H_4$	4-$MeOC_6H_4$	55	31	9[b]	5[b]	26
5b	C_6H_5	4-$MeOC_6H_4$	62	12[b]	9	17	38
5c	4-$CF_3C_6H_4$	4-$MeOC_6H_4$	94	6			68

[a] Compound **1** (3 mmol) in 10 mL THF, 2.5 equiv LDA, **5** after 10 min, hydrolysis after 10 min.
[b] Not isolated products.
[c] Referred to pure isolated products.

Table 5
Yields and selectivity for the reactions of **1** with different aldehydes R^1CHO at −60 °C in different experimental conditions

R^1	mol $L^{-1}\times10^{-3}$	LDA/**1**	Solvent	*T* (°C)	**6** (%)	**7** (%)	**8** (%)	**9** (%)	Global yield (%)
4-$Me_2NC_6H_4$	3.28	2.5	THF	−60	30	12	41	17	30
4-$Me_2NC_6H_4$	6.56	1.75	THF	−60	28	13	40	19	51
4-MeC_6H_4	3.28	2.5	THF	−60	66	34			53
4-MeC_6H_4	6.56	1.75	THF	−60	64	36			69
4-$MeOC_6H_4$	3.28	2.5	THF	−60	66	34			36
4-$MeOC_6H_4$	3.28	2.5	THF	−40					—
4-$MeOC_6H_4$	3.28	2.5	HMPA/THF 3:1	−60	59	41			32

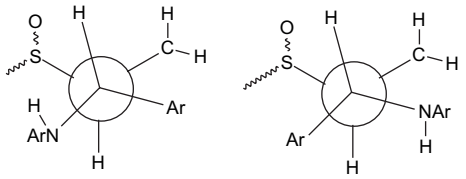


Figure 7.

at C_2. The $^3J_{H2-H8}$ coupling constants ranged between 9.0 and 10.0 Hz, therefore H_2 and H_8 must be in an antiperiplanar arrangement: the only two possible conformations are those reported in Figure 7. In the conformation **10–12**, the protons on C_3 are shifted upfield with respect to those in conformation **11–13** because of the shielding effect of the closer aromatic ring. On the other side, the N–H protons in **10–12** are more deshielded than in **11–13** by the proximity of the sulfoxide group (see Section 4).

These reactions are likely to proceed through a mechanism analogous to that reported for the reaction of 1,3-benzoxathiol-3-oxide with azomethines.[8]

3. Conclusions

We are assuming that in THF the lithium sulfoxide **3** adopts the structure **3a**, which is from the calculations, more stable than **3b**. When compared with the acyclic sulfoxides described in the literature, **3** showed a greater instability: in fact **3** decomposed at temperatures above −40 °C, while the lithium phenyl methyl sulfinyl carbanion was stable even at 30 °C.[17]

The distance Li–C in **3a** is somewhat shorter than that calculated by Wolfe for the lithium methyl sulfoxide,[15] and is considerably shorter than the Li–C distance determined by Boche for the lithium α-sulfinyl carbanion through XRD analysis.[16]

Finally, there must be a substantial difference between lithiated acyclic and cyclic sulfoxides in solution: in fact, the reactions with electrophiles, able to coordinate the lithium atom, as aldehydes and imines, lead to retention of configuration for the acyclic[15,18] and to inversion for the cyclic ones so far examined. Lithiated acyclic sulfoxides would be supposed to have, in solution, a weak or may be no[22] interaction Li–C_2 to allow coordination of the lithium atom with the nucleophile (e.g., the aldehydic oxygen) and the simultaneous attack of the electrophilic carbon to the carbanion, as extensively reported in the literature.[6,18] The lithiated cyclic sulfoxides are characterized by a calculated Li–C_2 interaction of 18.40 kcal mol^{-1}. In such sulfoxides the attack will mainly take place on the opposite side with respect to the sulfoxide oxygen giving a global configurational inversion at C_2. Only when the heteroatom (bond to electrophile) is nucleophile enough to compete with the carbanion in the coordination of the lithium cation, the electrophile attack will take place on the same side of the sulfoxide oxygen (e.g., reactions with strong electron-releasing substituted aldehydes).

4. Experimental section

The compound **1** was prepared by literature methods.[23] For materials, instruments, and calculation approach see our previous work.[9]

4.1. General procedure

To a vigorously stirred solution of LDA (8 mmol), **1** (0.5 g, 3 mmol) in dry THF (10 mL) was added dropwise at −60 °C (−80 °C) under argon. After 15 min, a solution of the electrophile (4 mmol) in dry THF (5 mL) was added dropwise and the reaction was completed by vigorous stirring for 15 min at the same temperature. The cooling bath was removed, the reaction mixture was hydrolyzed with brine, and the pH adjusted to 4–5 by addition of 10% aqueous hydrochloric acid. The organic layer was separated, the aqueous layer extracted with (3×20 mL) of CH_2Cl_2, and the organic solutions were combined and dried (Na_2SO_4).

In this manner the following compounds were isolated as racemic mixture and characterized.

*4.1.1. (1S,2S)-2-[(1R)-1-Hydroxy-1-(4-N,N-dimethylaminophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**6a**)*

This compound was obtained using 4-*N*,*N*-dimethylaminobenzaldehyde as electrophile. Purified by chromatography (ethyl acetate); white crystals, 138 mg (14%), mp 152–154 °C. IR (Nujol) 3370, 1600, 1455, 1360, 1145, 1070, 735 cm^{-1}; δ_H (300 MHz, DMSO): 7.14 (1H, d, *J*=9.3 Hz, Ar*H*), 7.43 (3H, m, Ar*H*), 7.23 (2H, d, *J*=8.4 Hz, Ar*H*), 6.71 (2H, d, *J*=8.4 Hz, Ar*H*), 5.75 (1H, t, O*H*, *J*=4.5 Hz, D_2O exchangeable), 5.02 (1H, t, *J*=4.5 Hz, C*H*OH), 3.60 (1H, m, C*H*SO), 3.37 (1H, dd, *J*=8.4, 16.8 Hz, CH_2), 3.24 (1H, dd, *J*=8.4, 16.8 Hz, CH_2), 2.88 (6H, s, CH_3); δ_C (75.4 MHz, DMSO): 149.6, 144.1, 142.5, 131.6, 130.1, 128.0, 127.8, 127.4, 126.9, 112.1, 77.6, 69.8, 40.5, 31.3; *m*/*z* (EI) 301 (M$^+$, 21), 284 (19), 267 (18), 162 (41), 148 (100), 134 (53), 121 (44), 91 (36), 77 (42%). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 58.89; H, 3.98; S, 9.81. Found: C, 58.80; H, 3.90; S, 9.70.

*4.1.2. (1S,2S)-2-[(1S)-1-Hydroxy-1-(4-N,N-dimethylaminophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**7a**)*

This compound was obtained using 4-*N*,*N*-dimethylaminobenzaldehyde as electrophile. Purified by chromatography (ethyl acetate); white crystals, 59 mg (6%), mp 163–166 °C. IR (Nujol) 3360, 1620, 1460, 1365, 1135, 1080, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.74 (1H, d, *J*=8.1 Hz, Ar*H*), 7.44 (3H, m, Ar*H*), 7.72 (2H, d, *J*=8.4 Hz, Ar*H*), 6.24 (2H, d, *J*=8.4 Hz, Ar*H*), 5.76 (1H, d, *J*=4.8 Hz, O*H*, D_2O exchangeable), 4.64 (1H, dd, *J*=4.5, 8.1 Hz, C*H*OH), 3.62 (1H, m, C*H*SO), 3.26 (1H, m, CH_2), 2.92 (1H, m, CH_2), 2.89 (6H, s, CH_3); δ_C (75.4 MHz, DMSO): 150.0, 144.5, 141.9, 131.6, 130.3, 128.1, 127.4, 126.9, 126.3, 112.2, 77.8, 72.6, 40.3, 34.2; *m*/*z* (EI) 301 (M$^+$, 39), 284 (11), 267 (36), 162 (90), 150 (93), 148 (92), 134 (100), 121 (49), 91 (41), 77 (55%). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 58.89; H, 3.98; S, 9.81. Found: C, 58.78; H, 3.88; S, 9.69.

*4.1.3. (1S,2R)-2-[(1S)-1-Hydroxy-1-(4-N,N-dimethylaminophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**8a**)*

This compound was obtained using 4-*N*,*N*-dimethylaminobenzaldehyde as electrophile. Purified by chromatography (ethyl acetate/light petroleum, 1:5); white crystals, 206 mg (21%), mp 145–148 °C. IR (Nujol) 3380, 1610, 1450, 1370, 1150, 1060, 720 cm^{-1}; δ_H (300 MHz, DMSO): 7.78 (1H, d, *J*=7.2 Hz, Ar*H*), 7.55 (3H, m, Ar*H*), 7.34 (2H, d, *J*=8.4 Hz, Ar*H*), 6.73 (2H, d, *J*=9.0 Hz, Ar*H*), 5.51 (1H, d, *J*=4.8 Hz, O*H*, D_2O exchangeable), 4.89 (1H, dd, *J*=4.8, 8.1 Hz, C*H*OH), 3.64 (1H, m, CH_2), 3.44 (1H, m, C*H*SO), 3.49 (1H, m, CH_2), 2.89 (6H, s, CH_3); δ_C (75.4 MHz, DMSO): 150.2, 145.3, 145.0, 132.3, 130.7, 127.8, 127.5, 126.7, 126.5, 112.1, 70.5, 68.1, 40.3, 34.8; *m*/*z* (EI) 301 (M$^+$, 6), 284 (15), 267 (5), 148 (100), 135 (50), 121 (50), 91 (27), 77 (28%). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 58.89; H, 3.98; S, 9.81. Found: C, 58.84; H, 3.91; S, 9.73.

*4.1.4. (1S,2R)-2-[(1R)-1-Hydroxy-1-(4-N,N-dimethylaminophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**9a**)*

This compound was obtained using 4-*N*,*N*-dimethylaminobenzaldehyde as electrophile. Purified by chromatography (ethyl acetate); white crystals, 119 mg (12%), mp 170–172 °C. IR (Nujol) 3370, 1610, 1440, 1350, 1135, 1080, 720 cm^{-1}; δ_H (300 MHz, DMSO): 7.90 (1H, d, *J*=7.2 Hz, Ar*H*), 7.44 (3H, m, Ar*H*), 7.30 (2H, d, *J*=8.1 Hz,

Ar*H*), 6.73 (2H, d, *J*=8.1 Hz, Ar*H*), 5.75 (1H, s, O*H*, D_2O exchangeable), 4.76 (1H, m, *J*=8.1 Hz, C*H*OH), 3.47 (1H, m, C*H*SO), 3.30 (1H, dd, *J*=6.4, 16.5 Hz, CH_2), 2.89 (6H, s, CH_3), 2.61 (1H, dd, *J*=6.3, 16.5 Hz, CH_2); δ_C (75.4 MHz, DMSO): 150.1, 144.9, 142.5, 132.1, 129.8, 127.9, 127.5, 126.9, 126.3, 112.2, 69.4, 68.7, 40.5, 34.5; *m*/*z* (EI) 301 (M^+, 20), 284 (19), 267 (17), 162 (41), 148 (100), 134 (56), 121 (49), 91 (36), 77 (42%). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 58.89; H, 3.98; S, 9.81. Found: C, 58.83; H, 3.89; S, 9.71.

4.1.5. (1S,2S)-2-[(1R)-1-Hydroxy-1-(4-methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**6b**)

This compound was obtained using 4-methoxylbenzaldehyde as electrophile. Purified by chromatography (diethyl ether); white crystals, 369 mg (39%), mp 174–176 °C. IR (Nujol) 3160, 2960, 1465, 1370, 1305, 1260, 1090, 100, 770, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.72 (1H, d, *J*=7.8 Hz, Ar*H*), 7.46 (3H, m, Ar*H*), 7.35 (2H, d, *J*=8.7 Hz, Ar*H*), 6.92 (2H, d, *J*=8.7 Hz, Ar*H*), 5.91 (1H, d, *J*=8.7 Hz, O*H*, D_2O exchangeable), 5.12 (1H, t, *J*=4.5 Hz, C*H*OH), 3.75 (3H, s, CH_3), 3.62 (1H, dd, *J*=4.5, 7.2 Hz, C*H*SO), 3.41 (1H, dd, *J*=6.7, 16.8 Hz, CH_2), 3.21 (1H, dd, *J*=6.9, 16.8 Hz, CH_2); δ_C (75.4 MHz, DMSO): 158.1, 144.4, 142.8, 135.0, 132.0, 128.4, 127.8, 126.7, 114.0, 77.6, 69.9, 55.4, 31.5; *m*/*z* (EI) 288 (M^+, 4), 271 (5), 253 (2), 241 (12), 226 (3), 180 (5), 135 (100), 109 (16), 91 (20), 77 (50%). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 44.44; H, 5.55; S, 11.11. Found: C, 44.39; H, 5.52; S, 11.07.

4.1.6. (1S,2S)-2-[(1S)-1-Hydroxy-1-4-(methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**7b**)

This compound was obtained using 4-methoxylbenzaldehyde as electrophile. Purified by chromatography (ethyl acetate); white crystals, 256 mg (27%), mp 173–176 °C. IR (Nujol) 3260, 2950, 1580, 1480, 1440, 1360, 1230, 1150, 1040, 1000, 815, 990, 750, 700 cm^{-1}; δ_H (300 MHz, DMSO): 7.65 (1H, d, *J*=7.2 Hz, Ar*H*), 7.48 (3H, m, Ar*H*), 7.38 (2H, d, *J*=8.7 Hz, Ar*H*), 6.94 (2H, d, *J*=8.7 Hz, Ar*H*), 5.94 (1H, d, *J*=5.1 Hz, O*H*, D_2O exchangeable), 4.76 (1H, dd, *J*=4.8, 8.1 Hz, C*H*OH), 3.76 (3H, s, CH_3), 3.64 (1H, dd, *J*=7.7, 7.8 Hz, C*H*SO), 3.35 (1H, dd, *J*=6.7, 16.8 Hz, CH_2), 2.95 (1H, dd, *J*=6.6, 16.8 Hz, CH_2); δ_C (75.4 MHz, DMSO): 158.8, 144.4, 141.9, 135.1, 131.7, 128.2, 127.9, 126.5, 126.3, 113.7, 77.8, 72.4, 55.2, 34.2; *m*/*z* (EI) 288 (M^+, 5), 271 (4), 253 (2), 241 (12), 226 (4), 180 (4), 135 (100), 109 (17), 91 (20), 77 (49%). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 44.44; H, 5.55; S, 11.11. Found: C, 44.41; H, 5.50; S, 11.05.

4.1.7. (1S,2S)-2-[(1R)-1-Hydroxy-1-(4-methylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**6c**)

This compound was obtained using 4-methylbenzaldehyde as electrophile. Purified by chromatography (diethyl ether/light petroleum, 40:1); white crystals, 368 mg (41%), mp 194–197 °C. IR (Nujol) 3460, 2960, 1500, 1410, 1330, 1290, 1020, 790, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.72 (1H, d, *J*=7.2 Hz, Ar*H*), 7.45 (3H, m, Ar*H*), 7.32 (2H, d, *J*=8.1 Hz, Ar*H*), 7.17 (2H, d, *J*=7.8 Hz, Ar*H*), 5.95 (1H, d, *J*=4.5 Hz, O*H*, D_2O exchangeable), 5.15 (1H, t, *J*=4.5 Hz, C*H*OH), 3.63 (1H, td, *J*=4.5, 7.2 Hz, C*H*SO), 3.42 (1H, dd, *J*=6.6, 16.8 Hz, CH_2), 3.25 (1H, dd, *J*=6.7, 16.8 Hz, CH_2), 2.29 (3H, s, CH_3); δ_C (75.4 MHz, DMSO): 143.8, 142.3, 139.5, 136.3, 131.5, 128.6, 127.9, 126.2, 126.2, 125.9, 77.1, 69.5, 30.8, 20.6; *m*/*z* (EI) 272 (M^+, 5), 254 (13), 237 (6), 135 (71), 119 (100), 91 (91), 77 (67%). Anal. Calcd for $C_{16}H_{16}O_2S$: C, 74.41; H, 5.88; S, 11.76. Found: C, 74.42; H, 5.90; S, 11.71.

4.1.8. (1S,2S)-2-[(1S)-1-Hydroxy-1-(4-methylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**7c**)

This compound was obtained using 4-methylbenzaldehyde as electrophile. Purified by chromatography (diethyl ether/light petroleum, 50:1); white crystals, 268 mg (30%), mp 192–194 °C. IR (Nujol) 3450, 2980, 1515, 1430, 1330, 1290, 1050, 775, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.73 (1H, d, *J*=7.1 Hz, Ar*H*), 7.44 (3H, m, Ar*H*), 7.33 (2H, d, *J*=8.1 Hz, Ar*H*), 7.17 (2H, d, *J*=8.1 Hz, Ar*H*), 5.95 (1H, d, *J*=5.2 Hz, O*H*, D_2O exchangeable), 5.18 (1H, dd, *J*=4.8, 7.8 Hz, C*H*OH), 3.61 (1H, dd, *J*=6.8, 7.8 Hz, C*H*SO), 3.32 (1H, dd, *J*=6.6, 16.7 Hz, CH_2), 2.95 (1H, dd, *J*=6.7, 16.8 Hz, CH_2), 2.30 (3H, s, CH_3); δ_C (75.4 MHz, DMSO): 144.2, 142.6, 139.8, 136.6, 131.8, 129.0, 128.2, 126.7, 126.5, 126.3, 77.4, 69.8, 30.6, 20.9; *m*/*z* (EI) 272 (M^+, 6), 254 (12), 237 (7), 135 (72), 119 (100), 91 (92), 77 (68%). Anal. Calcd for $C_{16}H_{16}O_2S$: C, 74.41; H, 5.88; S, 11.76. Found: C, 74.39; H, 5.92; S, 11.75.

4.1.9. (1S,2S)-2-[(1R)-1-Hydroxy-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1-oxide (**6d**)

This compound was obtained using benzaldehyde as electrophile. Purified by chromatography (diethyl ether/light petroleum, 20:1); white crystals, 243 mg (28%), mp 135–138 °C. IR (Nujol) 3200, 2975, 1470, 1385, 1240, 1210, 1680, 1160, 1110, 1000, 1060, 770, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.73 (1H, d, *J*=6.9 Hz, Ar*H*), 7.39 (8H, m, Ar*H*), 6.01 (1H, d, *J*=4.5 Hz, O*H*, D_2O exchangeable), 5.22 (1H, t, *J*=4.5 Hz, C*H*OH), 3.66 (1H, td, *J*=4.5, 7.2 Hz, C*H*SO), 3.31 (1H, dd, *J*=7.8, 16.5 Hz, CH_2), 3.25 (1H, dd, *J*=7.4, 17.1 Hz, CH_2); δ_C (75.4 MHz, DMSO): 144.0, 142.7, 142.5, 131.7, 128.3, 128.1, 127.4, 126.4, 126.3, 126.2, 77.2, 69.8, 31.0; *m*/*z* (EI) 258 (M^+, 6), 240 (12), 223 (6), 135 (100), 91 (84), 77 (62), 91 (24), 77 (22%). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.76; H, 5.42; S, 12.40. Found: C, 69.66; H, 5.36; S, 12.31.

4.1.10. (1S,2S)-2-[(1S)-1-Hydroxy-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1-oxide (**7d**)

This compound was obtained using benzaldehyde as electrophile. Purified by chromatography (diethyl ether/light petroleum, 30:1); white crystals, 245 mg (27%), mp 152–155 °C. IR (Nujol) 3220, 2975, 1450, 1365, 1240, 1210, 1680, 1150, 1060, 770, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.75 (1H, d, *J*=7.5 Hz, Ar*H*), 7.42 (8H, m, Ar*H*), 6.06 (1H, d, *J*=4.8 Hz, O*H*, D_2O exchangeable), 4.83 (1H, dd, *J*=5.1, 7.8 Hz, C*H*OH), 3.67 (1H, m, C*H*SO), 3.91 (1H, dd, *J*=6.4, 17.1 Hz, CH_2), 3.00 (1H, dd, *J*=6.3, 17.1 Hz, CH_2); δ_C (75.4 MHz, DMSO): 144.4, 143.0, 142.0, 131.7, 128.4, 128.2, 127.7, 126.7, 126.5, 126.3, 77.6, 72.8, 34.3; *m*/*z* (EI) 258 (M^+, 5), 240 (12), 223 (7), 135 (100), 91 (83), 77 (65), 91 (24), 77 (23%). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.76; H, 5.42; S, 12.40. Found: C, 69.62; H, 5.31; S, 12.33.

4.1.11. (1S,2S)-2-[(1R)-1-(Hydroxy)-1-[4-(fluoro)phenyl]methyl 2,3-dihydro-1-benzothiophene-1-oxide (**6e**)

This compound was obtained using 4-fluorobenzaldehyde as electrophile. Purified by chromatography (diethyl ether); white crystals, 289 mg (32%), mp 150–152 °C. IR (Nujol) 3320, 2970, 1600, 1460, 1380, 1305, 1225, 1160, 1070, 1030, 780, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.73 (1H, d, *J*=7.5 Hz, Ar*H*), 7.46 (3H, m, Ar*H*), 7.18 (4H, t, *J*=9.0 Hz, Ar*H*), 6.06 (1H, d, *J*=3.9 Hz, O*H*, D_2O exchangeable), 5.22 (1H, m, C*H*OH), 3.67 (1H, dd, *J*=4.8, 7.8 Hz, C*H*SO), 3.38 (1H, dd, *J*=6.4, 16.5 Hz, CH_2), 3.21 (1H, dd, *J*=6.6, 16.5 Hz, CH_2); δ_C (75.4 MHz, DMSO): 161.5 (J_{CF}=242.9 Hz), 144.1, 142.5, 138.9 (J_{CF}=2.4 Hz), 131.8, 128.3 (J_{CF}=8.5 Hz), 128.1, 126.4, 115.0 (J_{CF}=22.0 Hz), 77.0, 69.4, 31.1; *m*/*z* (EI) 276 (M^+, 2), 258 (13), 241 (10), 210 (7), 152 (5), 135 (100), 123 (39), 109 (26), 91 (31), 77 (41%). Anal. Calcd for $C_{15}H_{13}FO_2S$: C, 65.21; H, 4.71; S, 11.59. Found: C, 65.17; H, 4.70; S, 11.53.

4.1.12. (1S,2S)-2-[(1S)-1-Hydroxy-1-(4-fluorophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**7e**)

This compound was obtained using 4-fluorobenzaldehyde as electrophile. Purified by chromatography (ethyl acetate); white crystals, 301 mg (33%), mp 170–172 °C. IR (Nujol) 3280, 2960, 1600, 1455, 1390, 1220, 1160, 1065, 1010, 770, 725 cm^{-1}; δ_H (300 MHz, DMSO): 7.74 (1H, d, *J*=7.2 Hz, Ar*H*), 7.47 (3H, m, Ar*H*), 7.20 (4H, t, *J*=9.0 Hz, Ar*H*), 6.11 (1H, d, *J*=5.1 Hz, O*H*, D_2O exchangeable), 4.89 (1H, dd, *J*=5.1, 7.8 Hz, C*H*OH), 3.67 (1H, dd, *J*=7.4, 7.8 Hz, C*H*SO), 3.48 (1H, dd, *J*=6.2, 17.1 Hz, CH_2), 3.01 (1H, dd,

J=6.6, 17.1 Hz, CH_2); δ_C (75.4 MHz, DMSO): 161.4 (J_{CF}=243.0 Hz), 144.1, 141.7, 139.0 (J_{CF}=3.7 Hz), 131.5, 128.5 (J_{CF}=8.5 Hz), 128.0, 126.3, 126.1, 114.9 (J_{CF}=20.7 Hz), 77.5, 71.9, 34.0; m/z (EI) 276 (M^+, 3), 258 (13), 241 (10), 210 (6), 152 (4), 135 (100), 123 (39), 109 (25), 91 (31), 77 (42%). Anal. Calcd for $C_{15}H_{13}FO_2S$: C, 65.21; H, 4.71; S, 11.59. Found: C, 65.15; H, 4.67; S, 11.55.

4.1.13. (1S,2S)-2-[(1R)-1-Hydroxy-1-(4-trifluoromethylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**6f**)

This compound was obtained using 4-trifluoromethylbenzaldehyde as electrophile. Purified by chromatography (diethyl ether); white crystals, 354 mg (33%), mp 158–160 °C. IR (Nujol) 3300, 2970, 1495, 1410, 1370, 1190, 1140, 1090, 1040, 845, 785, 740 cm^{-1}; δ_H (300 MHz, DMSO): 7.72 (5H, m, ArH), 7.46 (3H, m, ArH), 6.24 (1H, d, J=4.5 Hz, OH, D_2O exchangeable), 5.39 (1H, t, J=4.3 Hz, CHOH), 3.72 (1H, dd, J=3.9, 4.5 Hz, CHSO), 3.32 (1H, dd, J=3.9, 17.0 Hz, CHSO), 3.24 (1H, dd, J=4.5, 17.0 Hz, CH_2); δ_C (75.4 MHz, DMSO): 147.5, 144.0, 142.4, 131.8, 128.2 (J_{CF}=16.6 Hz), 128.1, 127.1, 126.4, 126.3, 125.2 (J_{CF}=3.7 Hz), 124.4 (J_{CF}=272.2 Hz), 76.7, 69.4, 30.8; m/z (EI) 326 (M^+, 1), 308 (6), 291 (3), 239 (2), 173 (11), 145 (18), 135 (100), 91 (29), 77 (16%). Anal. Calcd for $C_{16}H_{13}F_3O_2S$: C, 58.89; H, 3.98; S, 9.81. Found: C, 58.82; H, 3.94; S, 9.76.

4.1.14. (1S,2S)-2-[(1S)-1-Hydroxy-1-(4-trifluoromethylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**7f**)

This compound was obtained using 4-trifluoromethylbenzaldehyde as electrophile. Purified by chromatography (ethyl acetate); white crystals, 397 mg (44%), mp 208–210 °C. IR (Nujol) 3280, 2960, 1450, 1370, 1170, 1110, 1065, 1010, 860, 830, 730 cm^{-1}; δ_H (300 MHz, DMSO): 7.74 (5H, m, ArH), 7.47 (3H, m, ArH), 6.28 (1H, d, J=5.1 Hz, OH, D_2O exchangeable), 5.04 (1H, m, CHOH), 3.74 (1H, dd, J=7.5, 7.8 Hz, CHSO), 3.41 (1H, dd, J=8.4, 16.8 Hz, CH_2), 3.10 (1H, dd, J=6.6, 16.5 Hz, CH_2); δ_C (75.4 MHz, DMSO): 147.8, 144.3, 141.9, 131.7, 128.3 (J_{CF}=31.8 Hz), 128.2, 127.5, 126.5, 125.3 (J_{CF}=4.9 Hz), 124.4 (J_{CF}=272.3 Hz), 77.6, 72.1, 34.2; m/z (EI) 326 (M^+, 1), 308 (7), 291 (3), 239 (2), 173 (11), 145 (18), 135 (100), 91 (29), 77 (16%). Anal. Calcd for $C_{16}H_{13}F_3O_2S$: C, 58.89; H, 3.98; S, 9.81. Found: C, 58.84; H, 3.91; S, 9.73.

4.1.15. (1S,2S)-2-[(1S)-1-(4-Methoxyphenylamino)-1-(4-methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**10a**)

This compound was obtained using 4-methoxy-*N*-[(4-methoxyphenyl)methylidene]aniline as electrophile. Purified by chromatography (ethyl acetate/light petroleum, 5:1); white crystals, 183 mg (14%), mp 192–194 °C. IR (Nujol) 3280, 2970, 1610, 1580, 1510, 1450, 1370, 1230, 1130, 1030, 825, 725 cm^{-1}; δ_H (300 MHz, DMSO): 7.75 (1H, d, J=6.9 Hz, ArH), 7.44 (5H, m, ArH), 6.86 (2H, d, J=9.0 Hz, ArH), 6.62 (4H, m, ArH), 6.22 (1H, d, J=12.0 Hz, NH, D_2O exchangeable), 4.67 (1H, t, J=10.5 Hz, CHNH), 3.72 (1H, m, CHSO), 3.70 (3H, s, CH_3), 3.58 (3H, s, CH_3), 3.15 (1H, dd, J=8.1, 16.8 Hz, CH_2), 2.91 (1H, dd, J=8.1, 16.8 Hz, CH_2); δ_C (75.4 MHz, DMSO): 158.5, 151.3, 144.6, 141.4, 140.7, 133.7, 131.6, 128.5, 128.4, 126.5, 126.3, 115.1, 114.4, 113.9, 76.7, 58.0, 55.3, 55.0, 34.4; m/z (EI) 393 (M^+, 21), 242 (100), 134 (40), 91 (30), 77 (36%). Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.23; H, 5.85; S, 8.14. Found: C, 70.17; H, 5.84; S, 8.11.

4.1.16. (1S,2S)-2-[(1R)-1-(4-Methoxyphenylamino)-1-(4-methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**11a**)

This compound was obtained using 4-methoxy-*N*-[(4-methoxyphenyl)methylidene]aniline as electrophile. Purified by chromatography (ethyl acetate/light petroleum, 5:1); white crystals, 103 mg (8%), mp 185–187 °C. IR (Nujol) 3350, 2900, 2840, 1500, 1450, 1380, 1310, 1270, 1190, 1130, 1050, 900, 810, 720, 630 cm^{-1}; δ_H (300 MHz, DMSO): 7.71 (1H, d, J=7.2 Hz, ArH), 7.49 (3H, m, ArH), 7.39 (2H, d, J=8.4 Hz, ArH), 6.87 (2H, d, J=9.0 Hz, ArH), 6.62 (2H, d, J=9.0 Hz, ArH), 6.54 (2H, d, J=9.0 Hz, ArH), 6.00 (1H, d, J=9.0 Hz, NH, D_2O exchangeable), 4.75 (1H, t, J=8.4 Hz, CHNH), 3.73 (1H, m, CHSO), 3.71 (3H, s, CH_3), 3.58 (3H, s, CH_3), 3.53 (1H, dd, J=8.4, 16.8 Hz, CH_2), 3.43 (1H, dd, J=8.4, 16.6 Hz, CH_2); δ_C (75.4 MHz, DMSO): 158.4, 151.1, 144.0, 141.8, 141.4, 133.3, 131.7, 128.5, 128.2, 126.5, 114.5, 113.8, 77.2, 56.3, 55.3, 55.0, 33.2; m/z (EI) 393 (M^+, 26), 242 (100), 134 (35), 91 (27), 77 (40%). Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.23; H, 5.85; S, 8.14. Found: C, 70.15; H, 5.87; S, 8.08.

4.1.17. (1S,2S)-2-[(1S)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1-oxide (**10b**)

This compound was obtained using 4-methoxy-*N*-(phenylmethylidene)aniline as electrophile. Purified by chromatography (ethyl acetate/light petroleum, 1:5); white crystals, 282 mg (23%), mp 199–202 °C. IR (Nujol) 3290, 2970, 1460, 1380, 1035, 835, 765, 725 cm^{-1}; δ_H (300 MHz, DMSO): 7.75 (1H, d, J=7.5 Hz, ArH), 7.36 (8H, m, ArH), 6.62 (4H, s, ArH), 6.32 (1H, d, J=10.5 Hz, NH, D_2O exchangeable), 4.74 (1H, t, J=10.5 Hz, CHNH), 3.75 (1H, td, J=7.8, 10.5 Hz, CHSO), 3.58 (3H, s, CH_3), 3.13 (1H, dd, J=8.1, 17.1 Hz, CH_2), 2.92 (1H, dd, J=7.8, 16.5 Hz, CH_2); δ_C (75.4 MHz, DMSO): 151.3, 144.5, 141.9, 141.3, 140.7, 131.6, 128.5, 128.4, 127.4, 126.5, 126.3, 114.9, 114.4, 76.6, 58.6, 55.0, 34.3; m/z (EI) 363 (M^+, 24), 346 (3), 212 (100), 122 (30), 91 (28), 77 (23%). Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.72; H, 5.78; S, 8.81. Found: C, 72.68; H, 5.68; S, 8.69.

4.1.18. (1S,2R)-2-[(1R)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1-oxide (**12b**)

This compound was obtained using 4-methoxy-*N*-(phenylmethylidene)aniline as electrophile. Purified by chromatography (diethyl ether/light petroleum, 8:1); white crystals, 41 mg (4%), mp 198–200 °C. IR (Nujol) 3250, 2990, 1500, 1415, 1050, 765 cm^{-1}; δ_H (300 MHz, DMSO): 7.94 (1H, d, J=7.2 Hz, ArH), 7.40 (8H, m, ArH), 6.65 (2H, d, J=9.3 Hz, ArH), 6.60 (2H, d, J=9.3 Hz, ArH), 6.42 (1H, d, J=10.8 Hz, NH, D_2O exchangeable), 4.69 (1H, t, J=10.8 Hz, CHNH), 3.58 (3H, s, CH_3), 3.33 (1H, m, CHSO), 3.79 (1H, m, CHSO), 3.33 (1H, dd, J=6.6, 16.5 Hz, CH_2), 2.63 (1H, dd, J=6.6, 16.5 Hz, CH_2); δ_C (75.4 MHz, DMSO): 151.3, 144.9, 141.2, 141.2, 132.4, 128.5, 128.1, 127.7, 127.4, 127.1, 126.5, 115.0, 114.5, 67.5, 55.3, 55.0, 35.1; m/z (EI) 363 (M^+, 22), 346 (4), 212 (100), 122 (32), 91 (29), 77 (24%). Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.72; H, 5.78; S, 8.81. Found: C, 72.68; H, 5.64; S, 8.65.

4.1.19. (1S,2R)-2-[(1S)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1-oxide (**13b**)

This compound was obtained using 4-methoxy-*N*-(phenylmethylidene)aniline as electrophile. Purified by chromatography (diethyl ether/light petroleum, 8:1); white crystals, 76 mg (7%), mp 172–175 °C. IR (Nujol) 3350, 2950, 1460, 1380, 1300, 1025, 725 cm^{-1}; δ_H (300 MHz, DMSO): 7.86 (1H, d, J=7.5 Hz, ArH), 7.44 (8H, m, ArH), 6.65 (2H, d, J=9.0 Hz, ArH), 6.57 (2H, d, J=8.7 Hz, ArH), 6.25 (1H, d, J=9.6 Hz, NH, D_2O exchangeable), 4.69 (1H, t, J=6.3 Hz, CHNH), 3.68 (1H, m, CHSO), 3.58 (3H, s, CH_3), 3.39–3.58 (2H, m, CH_2); δ_C (75.4 MHz, DMSO): 165.6, 145.0, 144.7, 142.4, 141.6, 132.6, 128.4, 128.0, 127.7, 127.5, 126.9, 126.5, 114.6, 114.3, 68.8, 56.1, 55.3, 35.7; m/z (EI) 363 (M^+, 22), 346 (4), 212 (100), 122 (33), 91 (28), 77 (23%). Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.72; H, 5.78; S, 8.81. Found: C, 72.70; H, 5.66; S, 8.66.

4.1.20. (1S,2S)-2-[(1S)-1-(4-Methoxyphenylamino)-1-(4-trifluoromethylphenyl)methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**10c**)

This compound was obtained using 4-methoxy-*N*-{[4-(trifluoromethyl)phenyl]methylidene}aniline as electrophile. Purified by chromatography (ethyl acetate/light petroleum, 5:1); white

crystals, 907 mg (64%), mp 193–195 °C. IR (Nujol) 3250, 2950, 1620, 1460, 1370, 1160, 1020, 720 cm^{-1}; δ_H (300 MHz, DMSO): 7.74 (5H, m, Ar*H*), 7.45 (3H, m, Ar*H*), 6.65 (4H, s, Ar*H*), 6.45 (1H, d, *J*=10.8 Hz, N*H*, D_2O exchangeable), 4.98 (1H, t, *J*=10.8 Hz, C*H*NH), 3.81 (1H, dd, *J*=8.4, 10.8 Hz, C*H*SO), 3.58 (3H, s, CH_3), 3.16 (1H, dd, *J*=8.1, 16.5 Hz, CH_2), 2.96 (1H, dd, *J*=8.4, 16.5 Hz, CH_2); δ_C (75.4 MHz, DMSO): 151.5, 146.8, 144.4, 140.9, 140.4, 131.6, 128.3, 128.2, 128.0 (J_{CF}=31.7 Hz), 126.3, 126.3, 125.4 (J_{CF}=3.6 Hz), 124.5 (J_{CF}=308.3 Hz), 115.0, 114.5, 76.3, 58.2, 55.2, 34.1; *m*/*z* (EI) 431 (M^+, 19), 280 (100), 135 (48), 122 (48), 91 (24), 77 (34%). Anal. Calcd for $C_{23}H_{20}F_3NO_2S$: C, 64.03; H, 4.64; S, 7.42. Found: C, 64.01; H, 4.60; S, 7.39.

*4.1.21. (1S,2S)-2-[(1R)-1-(4-Methoxyphenylamino)-1-(4-trifluoromethylphenyl)methyl]-2,3-dihydro-1-benzothiophene-1-oxide (**11c**)*

This compound was obtained using 4-methoxy-*N*-{[4-(trifluoromethyl)phenyl]methylidene}aniline as electrophile. Purified by chromatography (ethyl acetate/light petroleum, 5:1); white crystals, 56 mg (4%), mp 187–189 °C. IR (Nujol) 3235, 2960, 1630, 1465, 1375, 1155, 1020, 720 cm^{-1}; δ_H (300 MHz, DMSO): 7.71 (5H, m, Ar*H*), 7.49 (3H, m, Ar*H*), 6.60 (4H, m, Ar*H*), 6.18 (1H, d, *J*=9.0 Hz, N*H*, D_2O exchangeable), 5.02 (1H, t, *J*=9.0 Hz, C*H*NH), 3.80 (1H, dd, *J*=8.4, 9.0 Hz, C*H*SO), 3.58 (3H, s, CH_3), 3.55 (1H, dd, *J*=8.1, 16.5 Hz, CH_2), 3.41 (1H, dd, *J*=8.4, 16.5 Hz, CH_2); δ_C (75.4 MHz, DMSO): 151.2, 146.3, 143.7, 141.3, 140.8, 131.6, 128.2, 128.1, 127.9 (J_{CF}=32.8 Hz), 126.3, 126.2, 125.2 (J_{CF}=3.2 Hz), 124.1 (J_{CF}=272.3 Hz), 114.4, 114.3, 76.5, 56.4, 55.1, 33.0; *m*/*z* (EI) 431 (M^+, 21), 280 (100), 135 (52), 122 (51), 91 (25), 77 (35%). Anal. Calcd for $C_{23}H_{20}F_3NO_2S$: C, 64.03; H, 4.64; S, 7.42. Found: C, 64.15; H, 4.62; S, 7.45.

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