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Lithium 2,3-dihydro-1-benzothiophene-1,1-dioxide: synthesis, characterization, DFT calculations, and reactivity toward aldehydes and azomethines

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Abstract—The sulfonyl carbanion derived from 2,3-dihydro-1-benzothiophene-1,1-dioxide and its lithium salt has been investigated by DFT calculations. NMR and IR spectroscopic analyses showed that the lithium sulfonyl carbanion exists in solution as a monomer in equilibrium with a dimer. The lithium carbanion was treated with aldehydes and azomethynes to give chiral hydroxy and amino derivatives. The stereochemistry of the products and the diastereoselectivity of the reaction were investigated.

1. Introduction

Sulfones constitute an important class of organic compounds with pharmacological activity[1,2] and technological applications[3] and are useful intermediates in organic synthesis.[4,5] Among cyclic sulfones, 2,3-dihydrobenzo-1-thiophene-1,1-dioxide (**1**) has been recently studied as an acceptor chromophore in the construction of organic nonlinear optic (NLO) materials.[6]

In connection with our previous studies on benzocondensed sulfur heterocycles and their stereoselective functionalization,[7,8] we decided to examine the 2,3-dihydrobenzo-1-thiophene-1,1-dioxide by studying its functionalization by means of metalation reactions and deducing the structure of the intermediate lithium carbanion **3** by means of density functional theory (DFT) calculations and spectroscopic investigations.

The functionalization of **1** through metalation reactions has received little attention: the α-sulfonyl carbanion derived from tetrahydrothiophene-1,1-dioxide and Grignard reagents was reacted with aldehydes to give two diastereoisomeric β-hydroxysulfonic derivatives in a 50:50 ratio.[9] The benzocondensed compound was treated with Grignard reagents and then with aldehydes or ketones showing the same lack of diastereoselectivity.[10]

As regards the structures of sulfonyl carbanions, only some acyclic sulfones have been studied by NMR,[11,12] IR,[13] X-ray,[14–16] and by theoretical calculations,[17–22] while cyclic lithiated sulfones have been examined only to determine the hybridization state of the α-carbanion.[23–25] These studies indicated that lithium always interacts with the oxygen atoms[11,14–16] and that the carbanion is stabilized by Coulombic interactions, hyperconjugation, and polarization.[11,19] The thermodynamically more stable conformation of the carbanion showed the lone pair on the α carbon to assume a *gauche* conformation with respect to the sulfonyl oxygens.[19,20]

2. Results and discussion

2.1. Structural elucidation of the lithiated sulfone

The sulfonyl carbanions derived from acyclic sulfones are chiral and 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.[12,16] Corey[23,24] and then Whitney[25] from base-catalyzed hydrogen–deuterium exchange and racemization experiments, deduced that the sulfonyl carbanion obtained

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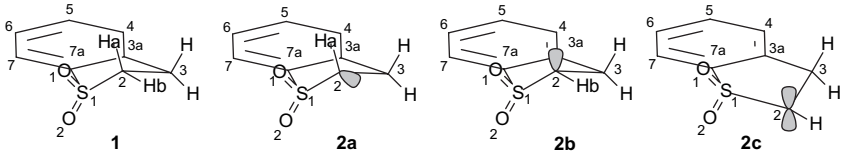


Figure 1.

by decarboxylation of the 2-methyl-2,3-dihydrobenzothiophene-2-carboxylic acid was planar and therefore achiral.

Geometry optimizations carried out with Gaussian03[26] on the cyclic sulfone **1** gave a non-planar structure with the α hydrogens H_a and H_b diastereotopics (Fig. 1). By removing either the hydrogen H_b or H_a, the carbanions **2a** and **2b** were originated: geometry optimization gave two structures with almost equal energy and with the C_2 atom pyramidal (Table 1). Geometry optimization of **2** starting from a planar arrangement at C_2 led to the structure **2c** with an energy value close to **2a** and **2b** (Fig. 1 and Table 1).

Geometry optimization of the lithiated sulfone starting from **2a–c** and with the lithium ion located between an oxygen and the C_2 gave three structures (**3a–c**) showing the cation interacting with one oxygen atom and the C_2 pyramidal (Fig. 2). When the lithium atom was placed between the two oxygen atoms in **2c**, the geometry optimization gave the planar structure **3d** featuring a slightly higher energy (0.56 kcal/mol).

The NMR spectroscopic analysis consisted in recording several spectra of the lithiated sulfone at different temperatures (−30/−80 °C) and concentrations (0.30, 0.15, and 0.08 M corresponding to samples 1, 2, and 3). The ^{13}C NMR chemical shift values and the coupling constants were quite constant through the various samples.

The ^1H NMR spectrum of **3** showed all signals as broad singlets: the comparison with the spectrum of the sulfone **1** revealed an upfield shift at all aromatic protons, except at H_7, that resulted shifted downfield: the deshielding effect at H_7 can be due to the closeness of the positive lithium atom (Table 3).[11] The ^7Li NMR spectrum showed a single signal at −0.48 ppm, $W_{1/2}$=18 Hz: this value is consistent with an ionic bond, as demonstrated by the bond lengths values obtained with DFT calculations (Table 2). The value does not change significantly on changing the temperature or concentration, thus indicating a slightly different chemical environment.

Several ^1H NMR spectra of **3** were recorded at different temperatures (−30, −60, and −80 °C) and concentrations (0.30, 0.15, and 0.08 M corresponding to samples 1, 2, and 3 in Table 4). The chemical shifts of the three samples did not differ in the temperature range −30 to −60 °C. The sample 1 does not show any change even at −80 °C. At −80 °C samples 2 and 3 showed the signals of H_2, H_3 and, H_7 splitted in doublets (δ_a and δ_b) while the remaining aromatic protons did not change their aspect (Table 4). The data reported in Table 4 showed that this splitting ($\Delta=\delta_a-\delta_b$) follows the order $\Delta H_7>\Delta H_2>\Delta H_3$. Because of the poor resolution of these doublets it was impossible to determine the integral value exactly, however, for the sample 2 the downfield peak area is about twice the other. For the sample 3 the chemical shift values remained unchanged but the integral ratio is inverted.

The data reported in Table 4 clearly indicate that the splitting of H_2 and H_7 signals depends upon both the temperature and the concentration, and ΔH_7 is greater than ΔH_2. Therefore, it is likely that an equilibrium between a monomeric and a dimeric form exists in solution (Fig. 3), the former being described by structure **3d**. Moreover, the C_2–H_2 coupling constant in the lithiated sulfone is 29.54 Hz higher than that in the sulfone, suggesting that the carbanion should be planar.[12,27] The literature reports that the lithium salts of

Table 1. Relative energies Δ*E* (kcal/mol), selected bond lengths (Å; Wiberg bond indexes in parentheses) and angles (°), and NBO charges *Q* (e) calculated for **1** and **2a–c**

	1	**2a**	**2b**	**2c**
Δ*E*	—	−0.063	0	0
$S–O_1$	1.442 (1.273)	1.463 (1.193)	1.468 (1.175)	1.468 (1.175)
$S–O_2$	1.445 (1.259)	1.464 (1.168)	1.479 (1.130)	1.479 (1.130)
$C_2–S$	1.814 (0.825)	1.690 (1.083)	1.682 (1.116)	1.682 (1.116)
$C_{7a}–S$	1.778 (0.834)	1.818 (0.768)	1.790 (0.817)	1.790 (0.817)
$C_{7a}–S–C_2–C_3$	25.11	22.61	24.19	24.18
Ha(SC_2C_3)	115.30	120.15	140.90	143.31
Hb(SC_2C_3)	118.39			
$Q(C_2)$	−0.592	−0.868	−0.841	−0.841
Q(S)	2.163	2.142	2.114	2.114
$Q(O_1)$	−0.941	−1.010	−1.013	−1.013
$Q(O_2)$	−0.945	−1.011	−1.031	−1.031

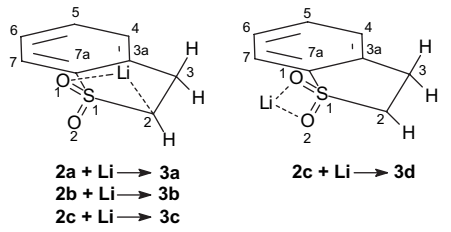


Figure 2.

acyclic sulfones in solution exist as monomers[22,28–30] or as dimers in equilibrium with monomers:[11] in this case it was impossible to detect these two forms by NMR spectroscopy not even at −110 °C. In the solid state, they were detected by XRD only as dimers.[14–16]

Unfortunately, in contrast with the reported acyclic lithiated sulfones, which are stable even at room temperature, thus allowing for the determination of their structure by XRD, lithiated sulfone **3** was quite unstable under these conditions.

The DFT calculations allowed us to determine geometrical parameters (bond lengths and angles) of the intermediate **3** hardly measurable otherwise because of its instability.

These calculations stated the lacking of the stabilizing n_c–$\sigma^*_{C7a–S}$ interaction, typical of acyclic sulfones, in the cyclic **3** and its replacement with a n_c–$\sigma^*_{S–O}$ interaction leading to a lengthening of the S–O bond with its consequent instability.

In fact the lithium salt **3** was prepared at −60 °C by treating **1** with MeLi in diethyl ether to give, after quickly evaporating the solvent at low temperature, a yellow-brown solid, subsequently used to record IR and Raman spectra. After spectra recording, the sample was dissolved in anhydrous THF at low temperature and then treated with D_2O: analysis of this mixture revealed only the monodeuterated sulfone and other products derived from carbanion decomposition.

The experimental frequency values for C–H_{arom} and C–H_{aliph} Raman-active stretching modes and IR-active symmetric and asymmetric SO_2 stretching modes of sulfone **1** are in good agreement with the scaled values calculated at DFT level. The same frequencies calculated for **3** are in good agreement with the experimental ones. Although the lithium salt of the sulfone in the solid state is probably a dimer, analogously to the reported acyclic sulfones, the presence of IR bands corresponding to those calculated showed that the sulfonic group structure does not change significantly between the two structures (monomer–dimer).

Table 2. Relative energies Δ*E* (kcal/mol), selected bond lengths (Å; Wiberg bond indexes in parentheses) and angles (°), NBO charges *Q* (e) and hyperconjugative interactions (kcal/mol) calculated for **3a–d**

	3a	**3b**	**3c**	**3d**
Δ*E*	0	0	0	0.56
S–O_1	1.449 (1.254)	1.502 (1.050)	1.502 (1.050)	1.521 (1.000)
S–O_2	1.502 (1.050)	1.450 (1.254)	1.450 (1.254)	1.521 (0.999)
C_2–S	1.730 (1.027)	1.730 (1.027)	1.730 (1.028)	1.618 (1.322)
C_{7a}–S	1.775 (0.848)	1.775 (0.848)	1.775 (0.848)	1.760 (0.893)
Li–O_1	3.680	1.827	1.827	1.827
Li–O_2	1.827	3.680	3.681	1.827
Li–C_2	2.097	2.097	2.097	3.761
Li–H_2	2.687	2.686	2.686	4.027
Li–H_{7a}	4.655	4.653	4.651	3.563
C_{7a}–S–C_2–C_3	20.24	20.36	20.38	0.05
Ha(SC_2C_3)	121.77	—	—	179.69
Hb(SC_2C_3)	—	121.81	121.86	—
Q(C_2)	−0.978	−0.978	−0.978	−0.761
Q(S)	2.106	2.106	2.107	2.034
Q(O_1)	−0.944	−0.944	−1.101	−1.120
Q(O_2)	−1.101	−0.101	−0.944	−1.120
Q(Li)	0.914	0.915	0.915	0.947
n_c–$\sigma^*_{S–O1}$	11.11	7.23	7.24	18.17
n_c–$\sigma^*_{S–O2}$	7.25	11.15	11.18	18.20
n_c–$\sigma^*_{C7a–S}$	0.00	0.00	0.00	0.00
n_c–Li	17.72	17.72	17.72	0

Table 3. ^{1}H NMR, ^{13}C NMR, and ^{7}Li NMR data of sulfone **1** and lithiated sulfone **3**[a]

	δH_2	δH_3	δH_4	δH_5	δH_6	δH_7	δC_2	^1J C_2–H_2	δLi[b]
1	t 3.70	t 3.52	d 7.67	t 7.80	t 7.68	d 7.92	t 50.54	143.02	
3[c]	s 2.52	s 3.62	s 7.40	s 7.40	s 7.40	s 8.22	d 39.40	172.56	−0.48
Δ(3−1)	−1.18	0.10	−0.27	−0.40	−0.28	0.30	−11.14	29.54	

[a] Chemical shift values δ are given in parts per million relative to TMS; coupling constants *J* are given in hertz.
[b] Shift value given in parts per million relative to a LiCl saturated solution in H_2O.
[c] Compound **3** of 0.30 M in THF-d_8 at −60 °C.

Table 4. ^{1}H NMR data of lithium sulfone **3** at −60/−80 °C

Sample	Concentration (M)[a]	δH_2 (ppm)		Ia/Ib	δH_3 (ppm)		δH_7 (ppm)		Ia/Ib
		−60 °C	−80 °C		−60 °C	−80 °C	−60 °C	−80 °C	
1	0.30	2.52	2.54		3.62	3.64	8.22	8.23	
2	0.15	2.61	δ_a 2.64 δ_b 2.60	2	3.71	δ_a 3.75 δ_b 3.71	8.29	δ_a 8.36 δ_b 8.29	2
3	0.08	2.61	δ_a 2.63 δ_b 2.58	0.5	3.71	δ_a 3.74 δ_b 3.71	8.27	δ_a 8.36 δ_b 8.28	0.5

[a] Solutions in THF-d_8.

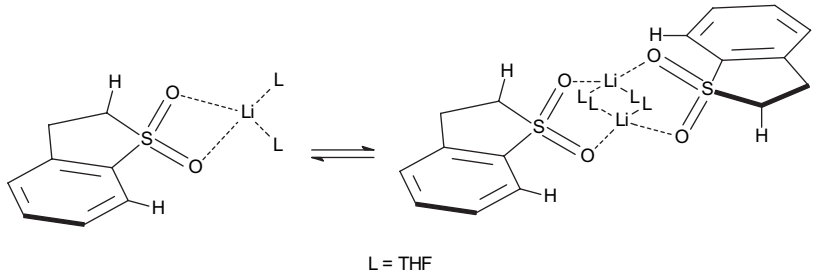


Figure 3.

To obtain a better insight into the carbanion structure we tried to prepare its potassium salt using the method reported by Chassing et al. for the methylphenylsulfone.[13] When **1** was treated with KH in THF at low temperature no reaction occurred even after 8 h; at room temperature the reaction was slow and did not afford the desired potassium salt. If D_2O was added to the reaction mixture, a rapid reaction occurred giving the multi-deuterated sulfone. By treating **1** with the potassium salt of dimethylsulfoxide in DMSO, as reported by Bordwell,[31–33] a rapid transformation occurred not giving the desired product: in fact, immediately after adding D_2O, the deuterated sulfone was not obtained, and the addition of a stronger acid such as CH_3COOH[34] did not give the starting material.

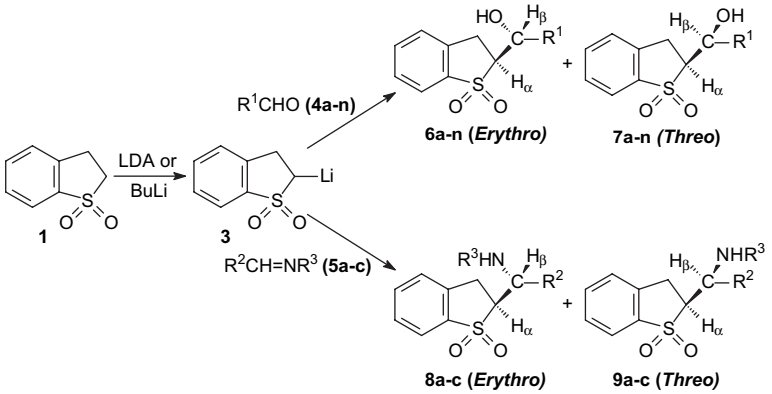
The low stability of the potassium salt of **1** can hardly explain the pK_a value (28.7) reported by Bordwell[31–35] in order to prove that the *gauche* conformation of the lone pair with respect to the sulfonyl oxygens was the one kinetically favored but not the thermodynamically more stable.[19]

2.2. Reaction of 3 with electrophiles

Sulfone **1** was metalated with BuLi or LDA to give the lithium intermediate **3**, which was reacted with aldehydes (**4a–n**) or azomethines (**5a–c**) as electrophiles to give two series of diastereomeric hydroxy derivatives **6a–n** and **7a–n**, and two series of diastereomeric amino derivatives **8a–c** and **9a–c**, respectively (Scheme 1).

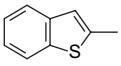
The *erythro* structure of **6a–n** and **8a–c** and the *threo* structure of **7a–n** and **9a–c** have been assigned on the basis of the H_α–H_β coupling constant values (see ^{1}H NMR data in Section 4).

The product distribution for the reactions with aldehydes is reported in Table 5. The *erythro* diastereoisomer always prevailed over the *threo* one (except in the case of 4-*N*,*N*-dimethylaminobenzaldehyde **4a**), the diastereomeric ratios ranges from *erythro*/*threo*=54:46 for the 4-methoxybenzaldehyde (**4b**) to *erythro*/*threo*=69:31 for the 1-benzothiophene-2-carbaldehyde (**4n**).



Scheme 1.

Table 5. Distribution of the products obtained by reacting **1** and **4a–n**

R^1CHO	R^1	Starting material (%)	Global yield (%)	**6** *erythro* (%)	**7** *threo* (%)
4a[a]	4-$Me_2NC_6H_4$	0	42	40	60
4a[b]	4-$Me_2NC_6H_4$	4	86	26	74
4b[a]	4-$MeOC_6H_4$	0	70	54	46
4b[b]	4-$MeOC_6H_4$	2	50	54	46
4c[a]	4-MeC_6H_4	0	50	54	46
4c[b]	4-MeC_6H_4	0	56	68	32
4d[a]	C_6H_5	0	56	66	34
4d[b]	C_6H_5	0	34	65	35
4e[a]	4-FC_6H_4	0	40	66	34
4e[b]	4-FC_6H_4	3	44	66	34
4f[a]	4-$CF_3C_6H_4$	9	40	54	46
4f[b]	4-$CF_3C_6H_4$	3	75	59	41
4g[a]		0	74	60	40
4h[a]		0	43	60	40
4i[a]	Me_2CH	25	75	58	42
4i[b]	Me_2CH	3	77	59	41
4l[a]	*n*-C_5H_{11}	100	0	0	0
4l[c]	*n*-C_5H_{11}	0	57	53	47
4l[d]	*n*-C_5H_{11}	15	40	53	47
4m[b]	$CH_3CH_2CH_2$	6	74	64	36
4n[b]		13	77	69	31

[a] Compound **1** of 3 mmol in 10 mL THF, 2.50 equiv LDA, −60 °C, **4** after 10 min, hydrolysis after 10 min.
[b] Compound **1** of 6 mmol in 10 mL THF, 1.75 equiv LDA, −60 °C, **4** after 10 min, hydrolysis after 10 min.
[c] Compound **1** of 3 mmol in 10 mL THF, 2.50 equiv LDA, −60 °C, **4l** after 10 min (−30 °C), hydrolysis after 45 min.
[d] Compound **1** of 6 mmol in 10 mL THF, 1.75 equiv LDA, −60 °C, **4l** after 10 min (−30 °C), hydrolysis after 45 min.

The structures of the obtained compounds were assigned by means of NMR spectroscopic analysis. The magnetic equivalence of the *ortho* protons in the phenyl group (R^1), due to free rotation of the phenyl ring, can be achieved only for an antiperiplanar arrangement of the phenyl ring and the sulfonyl group (Fig. 4).

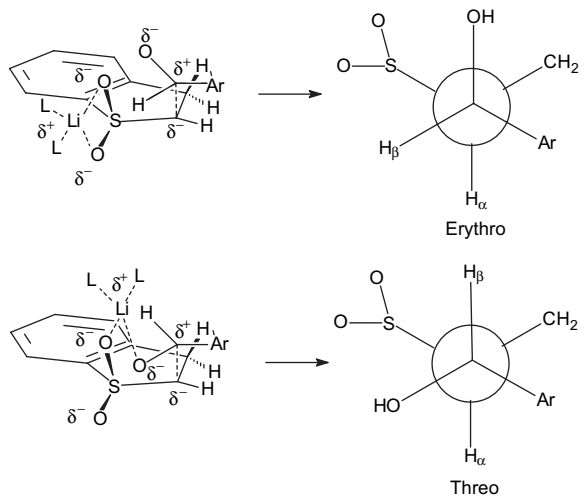


Figure 4.

Since the spectroscopic and theoretical investigations on the lithium salt **3** suggested an equilibrium between the monomeric and dimeric forms, all reactions were performed by using different concentrations of **1** and of the metalating reagent, with the aim of testing the effect of the aggregation state on the diasteroselectivity (Table 5).

Butyl- (**4m**) and isobutylaldehyde (**4i**) showed reactivity analogous to that of the aromatic aldehydes. The increase of number of the carbon atoms lowered the reactivity: in fact *n*-hexanal (**4l**) needed a longer reaction time and higher temperature to react (Table 5).

4-*N*,*N*-Dimethylaminobenzaldehyde (**4a**) gave a greater amount of *threo* isomer (*erythro*/*threo*=40:60): this result became even more evident (*erythro*/*threo*=24:76) performing the reaction with a greater concentration of both metalating reagent and substrate (Table 5).

These results can be rationalized by hypothesizing that the electrophile can approach the lithiated anion according to two different ways (Fig. 4): with a direct interaction between the carbonyl carbon and the C_2, with the carbonyl oxygen pointing toward the aromatic benzothiophene ring (*erythro* derivative), or with the carbonyl oxygen coordinating the lithium ion (*threo* derivative) (Fig. 4). We believe that the first one is the preferred by analogy with the cyclic sulfoxides studied in our previous works.[7,8]

When the electrophilic character of the carbonyl carbon is high (high value of σ_p) and the nucleophilicity of the carbonyl oxygen is low, the *erythro* transition state is favored with respect to the *threo* one, so among arylaldehydes the 4-trifluoromethylphenyl should have given the highest *erythro*/*threo* diastereoselectivity. Indeed, this is not the case because the *erythro* diastereoisomer is the kinetic product while the *threo* is the thermodynamic one. This was proved by reacting the *erythro* isomer (**6f**) in the reaction conditions as reported in Table 5 and finding that it converted 65% into the *threo* (**7f**) (Table 6). When the reaction was performed at −80 °C (keeping all other parameters constant) the diastereoselectivity remained unchanged (*erythro*/*threo*=54:46).

At this temperature the *erythro* is converted more slowly into the *threo* isomer: since the ratio between the diastereoisomer is constant, the rate of formation of the *erythro* isomer must be lowered as compared to that of the *threo* isomer. Such a behavior could be explained by assigning to the *erythro* isomer a greater activation energy and a higher pre-

Table 6. Equilibrium between *erythro* and *threo* diastereoisomers (LDA in THF)

Compound	σ_p	Initial ratio *erythro*/*threo* %	Final ratio *erythro*/*threo* %
6a	−0.83	100:0	56:44
7a		0:100	12:82
6b	−0.27	100:0	45:55
6b[a]		100:0	61:39
7b		0:100	22:78
6f	0.54	100:0	35:65
7f		0:100	30:70

[a] Solvent: THF/HMPA 1:5.

exponential factor than the *threo*. The two possible transition states should confirm the proposed mechanism (Fig. 4), with the *erythro* isomer being derived by a direct attack of the carbonyl carbon on the carbanion (statistically more probable) and the *threo* isomer derived from a six-centered transition state (less probable). In the reaction conditions reported in Table 5, we found the *erythro–threo* interconversion to occur to a lesser extent as the electron withdrawing power decreases (Table 6). This explains the similar diastereoselectivity observed for all arylaldehydes.

A peculiar case is constituted by the 4-*N*,*N*-dimethylamino group where the *threo* isomer is the kinetically and thermodynamically favored product. Consequently the diastereomeric ratios are the highest obtained (Table 5). As expected, by increasing the reaction time (30 min+30 min) we observed the disappearance of the starting material **1** and the decrease of the *erythro*/*threo* ratio (*erythro*/*threo*=50:50).

Probably, the lack of diastereoselectivity observed in previous studies[9,10] was due to the interconversion between diastereoisomers caused by higher temperatures and longer reaction times.

With the aim of achieving a better diastereoselectivity, we changed the solvent polarity. An increase in the polarity resulted in an increase in the diastereoselectivity under the reaction conditions reported in Table 5, but the yield was significantly reduced for the solvent mixture THF/HMPA=1:5 (Table 7).

The higher diastereoselectivity obtained in the more polar solvent can be ascribed to a destabilization of the *threo* transition state, due to a competition in the coordination of lithium ion between the aldehydic oxygen atom and the HMPA (Fig. 4). Furthermore the *erythro* isomer (**6b**) showed a greater stability in the mixture THF/HMPA=1:5 than in THF alone (Table 7).

Table 7. Distribution of the products obtained by reacting **1** and **4b** in various THF/HMPA ratios[a]

Solvent	Starting material (%)	Global yield (%)	**6b** *erythro* (%)	**7b** *threo* (%)
THF	0	70	54	46
THF/HMPA 4:1	0	71	59	41
THF/HMPA 1:5	0	39	68	32

[a] Compound **1** of 3 mmol in 10 mL of solvent, 2.5 equiv LDA, −60 °C, **4b** in THF/HMPA after 10 min, hydrolysis after 10 min.

Finally, the intermediate **3** was made to react with aromatic imines **5a–c** to give two series of diastereomeric amino derivatives **8a–c** and **9a–c** (Scheme 1 and Table 8): imines **5b** and **5c** gave a slightly lower diastereoselectivity compared with the same reactions in the same conditions with the corresponding aldehydes. The lower diastereoselectivity can be ascribed to the stronger electrophilic character of nitrogen with respect to oxygen that, by increasing the coordination to lithium, gives mainly the *threo* isomer. Contrary to the reactions of **3** with aldehydes, these reactions are not reversible (Table 8).

3. Conclusions

The lithium carbanion optimized structures **3a–d** turned out to be nearly isoenergetic, and none of them presented a significant hyperconjugative interaction $n_c–\sigma^*_{S–C}$ (Table 2). The structure **3d** showed two hyperconjugative contributions $n_c–\sigma^*_{S–O}$ of 18.20 kcal/mol; in the structures **3a–c** these contributions are smaller (11.18 and 7.24 kcal/mol), but there is another stabilization n_c–Li of 17.72 kcal/mol (Table 2).

All four structures **3a–d** resulted are equally stabilized by hyperconjugation, but the lithium atom preferred to form a O–Li–O scissor-like contact ion pair with the O atoms showing the higher negative charges (structure **3d**). Moreover, the structure **3d** well agrees with NMR chemical shifts and coupling constants typical of a planar structure (Table 3).

A comparison of these data with those reported in the literature pointed out that the structure of **3** does not differ from those of the lithium salts of acyclic sulfones.[11] Acyclic lithiated sulfones are stable at room temperature and have been examined both in the solid state and in solution, for example, the carbanion of methylphenyl sulfone (slightly different from **3**) resulted quite stable as lithium or potassium salt, or in polar solvents such as DMSO.[12,31]

The lower stability of **3** with respect to lithium salts of acyclic sulfones can be due to the higher stability of the transformation products of **3d**, or due to the loss of sulfonyl oxygens caused by the decreased bond order S–O, derived by the Li–O interaction or by the $n_c–\sigma^*_{S–O}$ hyperconjugation. A comparison of the S–O bond lengths in the sulfone **1** and in the lithiated sulfone **3**, showed a lengthening of 0.077 Å: the corresponding difference between methylphenyl sulfone and the lithium salt of methylphenyl sulfone, where $n_c–\sigma^*_{S–O}$ hyperconjugation is absent, is only 0.001 Å.[16] As a proof, when **3** in the solid state was treated with D_2O, we detected a discrete amount of deuterated benzothiophene (10% with respect to the deuterated sulfone).

Table 8. Distribution of the products obtained by reacting **1** and **4a–c**[a]

$R^2CH=NR^3$	R^2	R^3	Starting material recovered (%)	Global yield (%)	**8** *erythro* (%)	**9** *threo* (%)
5a	4-$MeOC_6H_4$	4-$MeOC_6H_4$	12	74	54	46
5b	C_6H_5–	4-$MeOC_6H_4$	8	52	62	38
5c	4-FC_6H_4	4-$MeOC_6H_4$	0	67	58	42

[a] Compound **1** of 6 mmol in 10 mL THF, 1.75 equiv BuLi, −60 °C, **5a–c** after 10 min, hydrolysis after 10 min.

As regards the low diastereoselectivity of the reaction of **3** with aldehydes it can be better ascribed to the smooth transformation *erythro*→*threo* than to the slightly different rate of formation of the two diastereoisomers. The rate of this transformation is higher for stronger electron withdrawing substituents on the phenyl ring of the aldehyde, thus leveling the distereoselectivity for different substituents.

4. Experimental section

4.1. General

Commercially available reagent-grade starting materials and solvents were used. Solutions of butyllithium in hexane were obtained from Aldrich Chemical Company and were analyzed before use.[36] Imines **5a–c** were prepared from 4-methoxybenzaldehyde and 4-methoxyaniline, aniline, and 4-fluoroaniline, respectively.[37] The compound **1** was prepared by literature methods.[38] NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. IR spectra were recorded on a FTIR Bruker Equinox 55 spectrophotometer. Raman spectra were recorded on a FT-Raman Bruker RFS 100/S spectrophotometer. The GC–MS analyses were performed with a Hewlett-Packard 5989A MS spectrometer using the direct insertion probe (DIP) method. All chromatographies were performed on silica gel 60, 0.04–0.063 (Fluka). Microanalyses were carried out with a Carlo Erba 1106 elemental analyzer. Melting points were obtained on a Kofler hot stage microscope and are uncorrected. In order to determine yields and molar fractions HPLC analyses were performed by a Waters 600 HPLC instrument employing a Spherisorb-CN normal phase column of 250 mm length and 4.6 mm id, hexane/isopropanol (75:25) as eluant (1 mL/min). The UV detector diode array was positioned at λ_{max}. All determinations were carried out on the basis of calibration plots of the pure compounds. Quantum-chemical DFT calculations were carried out with the commercial suite Gaussian03[26] on the sulfone **1**, on its deprotonated anionic derivatives **2a–c**, and on the corresponding lithium salts **3a–d** (Fig. 2). All calculations exploited the well-known three parameters hybrid functional B3LYP.[39] For all atoms the valence triple-zeta 6-311++G-(3df,3pd) basis set including extended and polarization functions was used throughout.[40,41] Force constants and the resulting vibrational IR- and Raman-active frequencies were computed by analytically determining the second derivatives of the energy with respect to the Cartesian nuclear coordinates at the optimized geometries. Vibrational frequencies were scaled by a factor of 0.963, obtained by comparing selected groups of calculated and experimental frequencies measured for **1**. For all compounds NBO populations[42] and Wiberg bond indexes[43] were also calculated at the optimized geometries.[44] The programs Gabedit 2.0.7[45] and Molden 4.6[46] were used to investigate the charge distributions and MO's shapes.

4.1.1. Synthesis of the lithiated sulfone (3) for NMR analysis. An amount of **1** (50, 25, or 12 mg) was dissolved in THF-d_8 (0.5 mL) in an NMR tube equipped with screw cap and Teflon septum. The solution was cooled to −60 °C and a 0.66 M solution of methyl lithium in THF-d_8 (0.5 mL), cooled at −20 °C, was slowly added by a syringe through the septum. The methyl lithium solution was prepared by dissolving solid MeLi (7.3 mg), obtained by diethyl ether evaporation from a commercial 1.5 M solution (0.22 mL), in THF-d_8 (0.5 mL).

All samples were prepared in a dry box (1 ppm H_2O, 1 ppm O_2), and in 10 min the NMR spectra were recorded.

4.1.2. Synthesis of the lithiated sulfone (3) for IR and Raman analysis. To a solution of **1** (3 mmol) in dry diethyl ether (20 mL) cooled at −60 °C, was added dropwise a stirred solution of MeLi (4.0 mmol). After stirring for 10 min at the same temperature the diethyl ether was evaporated in vacuum in a dry box. One portion of the yellow solid was mixed with Nujol for the IR spectra, another portion was placed in a capillary tube (then flame sealed) for the Raman spectra.

After IR measurements, the solid was poured into anhydrous THF and D_2O at −60 °C and the organic layer was analyzed by GC–MS: the MS spectrum showed the presence of the deuterated molecular ion (*m*/*z* 169).

4.1.2.1. 2,3-Dihydro-1-benzothiophene-1,1-dioxide (1). IR (Nujol) 1600, 1580, 1411, 1292, 1265, 1196, 1147, 1119, 1059, 982, 852, 787, 747, 697, 599, 549, 517, 453, 436, 378 cm^{-1}; Raman (solid) 3076, 3056, 3010, 2959, 2943, 1600, 1582, 1442, 1414, 1285, 1195, 1146, 1113, 1021, 982, 790, 698, 598, 546, 521, 454, 378, 249, 193, 134 cm^{-1}; δ_H (300 MHz, THF-d_8, −60 °C): 7.83 (1H, d, J=7.8 Hz, H_7), 7.73 (1H, t, J=7.5 Hz, H_6), 7.64–7.58 (2H, m, H_4–H_5), 3.62–3.57 (2H, m, H_2), 3.52–3.48 (2H, m, H_3); δ_C (75.4 MHz, THF-d_8, −60 °C): 138.5 (s, C_{7a}), 137.0 (s, C_{3a}), 133.2 (dd, ^1J=161.8 Hz, ^2J=7.3 Hz, C_5), 128.5 (dd, ^1J=165.3 Hz, ^2J=6.1 Hz, C_4), 127.1 (dd, ^1J=163.1 Hz, ^2J=7.3 Hz, C_6), 121.0 (dd, ^1J=167.2 Hz, ^2J=8.5 Hz, C_7), 50.4 (d, ^1J=143.0 Hz, C_2), 25.1 (t, ^1J=136.2 Hz, C_3).

4.1.2.2. Lithium-2,3-dihydro-1-benzothiophene-1,1-dioxide (3). IR (Nujol) 1299, 1264, 1190, 1097, 1058, 972, 884, 811, 748, 703, 657, 546, 521, 438 cm^{-1}; Raman (solid) 3059, 2941, 1588, 1544, 1439, 1310, 1195, 1160, 1038, 1019, 796, 706, 491, 454, 84 cm^{-1}; δ_H (300 MHz, THF-d_8, −60 °C): 8.22 (1H, br s, $W_{1/2}$ 26.6 Hz, H_7), 7.40 (3H, br s, $W_{1/2}$ 14.9 Hz, H_4, H_5, H_6), 3.62 (2H, br s, $W_{1/2}$ 20.3 Hz, H_3), 2.52 (1H, br s, $W_{1/2}$ 29.8 Hz, H_2); δ_C (75.4 MHz, THF-d_8, −60 °C) 144.5 (s, C_{7a}), 141.7 (s, C_{3a}), 128.9 (d, ^1J=164.7 Hz, C_4), 127.7 (d, ^1J=162.7 Hz, C_6), 126.5 (d, ^1J=156.6 Hz, C_5), 121.5 (d, ^1J=170.0 Hz, C_7), 39.4 (d, ^1J=172.6 Hz, C_2), 33.0 (t, ^1J=132.7 Hz, C_3).

4.2. General procedure

To a stirred solution of LDA (11 mL, 7.5 mmol) or *n*-BuLi (4.8 mL, 7.5 mmol) in dry THF (5 mL), cooled at −60 °C, a solution of **1** (0.5 g, 3 mmol) in dry THF (10 mL) was added dropwise. After stirring for 10 min at the same temperature, the aldehydes (**4a–n**) (3.3 mmol) were added. The stirring was continued for further 10 min and the reaction was quenched at −60 °C with aqueous saturated NH_4Cl, extracted with dichloromethane, dried with Na_2SO_4, filtered, and the solvent removed in vacuo.

In order to increase the reaction diastereoselectivity different temperatures, concentrations, and solvent polarities were used, as reported in Tables 5 and 7.

When the reactions were performed on 6 mmol of substrate in 5 mL of dry THF, 10.5 mmol of LDA in 10 mL of dry THF or 10.5 mmol of BuLi, and 6.6 mmol of aldehyde were employed.

When imines **5a–c** were employed as electrophiles, after adding the electrophile the temperature was kept at −30 °C, the stirring was continued for 45 min, and the reaction was quenched at −30 °C with aqueous saturated NH_4Cl and worked up in the same manner.

The following compounds were isolated as racemic mixtures.

4.2.1. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(4-dimethylaminophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6a). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 424 mg, yield 22%, mp 152–153 °C (EtOH/H_2O). IR (Nujol) 3500, 1290, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.70 (1H, d, *J*=7.5 Hz, Ar*H*), 7.55 (1H, t, *J*=7.5 Hz, Ar*H*), 7.43 (1H, t, *J*=7.5 Hz, Ar*H*), 7.34 (1H, d, *J*=7.5 Hz, Ar*H*), 7.30 (2H, d, *J*=8.8 Hz, Ar*H*), 6.74 (2H, d, *J*=8.8 Hz, Ar*H*), 5.57 (1H, d, *J*=1.8 Hz, C*H*OH), 3.72 (1H, m, SO_2CH), 3.63 (1H, dd, *J*=7.5, 15.9 Hz, CH_2), 3.11 (1H, dd, *J*=7.8, 15.9 Hz, CH_2), 3.07 (1H, s, O*H*, D_2O exchangeable), 2.95 (6H, s, CH_3); δ_C (75.4 MHz, $CDCl_3$): 151.2, 138.2, 134.8, 133.3, 132.2, 131.7, 127.8, 127.1, 121.4, 111.8, 72.9, 67.4, 40.0, 30.3; *m/z* (EI) 317 (22, M^+), 299 (21), 150 (100), 120 (12), 77 (11%). Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41; S, 10.10. Found: C, 64.15; H, 6.08; N, 4.56; S, 10.15.

4.2.2. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(4-dimethylaminophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7a). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 1210 mg, yield 64%, mp 151–152 °C (EtOH). IR (Nujol) 3480, 1300, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.78 (1H, d, *J*=7.5 Hz, Ar*H*), 7.49 (2H, m, Ar*H*), 7.29 (2H, d, *J*=9.0 Hz, Ar*H*), 7.20 (1H, d, *J*=7.5 Hz, Ar*H*), 6.74 (2H, d, *J*=9.0 Hz, Ar*H*), 5.05 (1H, d, *J*=9.6 Hz, C*H*OH), 3.90 (1H, m, SO_2CH), 3.37 (1H, s, O*H*, D_2O exchangeable), 2.98 (6H, s, CH_3), 2.93 (2H, m, CH_2); δ_C (75.4 MHz, $CDCl_3$): 150.7, 139.1, 135.7, 133.3, 128.6, 127.7, 127.3, 126.8, 121.7, 112.4, 72.9, 67.2, 40.3, 29.9; *m/z* (EI) 318 (28), 317 (30, M^+), 300 (17), 150 (100), 120 (15), 77 (7%). Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41; S, 10.10. Found: C, 64.45; H, 5.98; N, 4.36.

4.2.3. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(4-methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6b). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 346 mg, yield 38%, mp 127–129 °C (EtOH). IR (Nujol) 3525, 1295, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.69 (1H, d, *J*=7.5 Hz, Ar*H*), 7.55 (1H, t, *J*=7.5 Hz, Ar*H*), 7.43 (1H, t, *J*=7.5 Hz, Ar*H*), 7.34 (3H, m, Ar*H*), 6.91 (2H, d, *J*=8.7 Hz, Ar*H*), 5.59 (1H, s, C*H*OH), 3.80 (3H, s, OCH_3), 3.70 (1H, m, SO_2CH), 3.59 (1H, dd, *J*=7.8, 16.2 Hz, CH_2), 3.51 (1H, d, *J*=2.7 Hz, O*H*, D_2O exchangeable), 3.06 (1H, dd, *J*=8.1, 16.2 Hz CH_2); δ_C (75.4 MHz, $CDCl_3$): 159.3, 138.4, 136.9, 133.6, 131.7, 128.6, 127.3, 126.8, 121.4, 114.0, 67.9, 66.3, 55.2, 25.7; *m/z* (EI) 304 (7, M^+), 287 (12), 137 (100), 135 (74), 109 (30), 94 (19), 77 (40%). Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53. Found: C, 63.02; H, 5.35; S, 10.56.

4.2.4. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(4-methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7b). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 291 mg, yield 32%, mp 146–147 °C (EtOH/H_2O). IR (Nujol) 3465, 1305, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.77 (1H, d, *J*=7.5 Hz, Ar*H*), 7.50 (2H, m, Ar*H*), 7.36 (2H, d, *J*=8.7 Hz, Ar*H*), 7.22 (1H, d, *J*=7.5 Hz, Ar*H*), 6.94 (2H, d, *J*=8.7 Hz, Ar*H*), 5.09 (1H, dd, *J*=3.0, 9.8 Hz, C*H*OH), 3.86 (1H, m, SO_2CH), 3.83 (3H, s, OCH_3), 3.26 (1H, d, *J*=3.0 Hz, O*H*, D_2O exchangeable), 2.89 (2H, m, CH_2); δ_C (75.4 MHz, $CDCl_3$): 160.1, 139.0, 135.7, 133.5, 131.9, 128.9, 128.2, 126.9, 122.0, 114.4, 73.0, 67.3, 55.3, 29.9; *m/z* (EI) 304 (8, M^+), 137 (100), 135 (23), 109 (14), 86 (20), 77 (19%). Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53. Found: C, 62.94; H, 5.36; S, 10.44.

4.2.5. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(4-methylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6c). Purified by chromatography (diethyl ether/petroleum ether, 1:1); white crystals, 657 mg, yield 38%, mp 138–140 °C (EtOH). IR (Nujol) 3570, 1300, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.65 (1H, d, *J*=7.5 Hz, Ar*H*), 7.52 (1H, t, *J*=7.5 Hz, Ar*H*), 7.39 (1H, t, *J*=7.5 Hz, Ar*H*), 7.29 (3H, m, Ar*H*), 7.17 (2H, d, *J*=7.8 Hz, Ar*H*), 5.56 (1H, s, C*H*OH), 3.68 (1H, m, SO_2CH), 3.56 (1H, dd, *J*=7.5, 16.5 Hz, CH_2), 3.54 (1H, d, *J*=3.0 Hz, O*H*, D_2O exchangeable), 3.01 (1H, dd, *J*=8.4, 16.5 Hz, CH_2), 2.33 (3H, s, CH_3); δ_C (75.4 MHz, $CDCl_3$): 138.4, 137.6, 136.9, 136.7, 133.5, 129.2, 128.5, 127.2, 125.5, 121.4, 68.1, 66.3, 25.6, 21.0; *m/z* (EI) 288 (1, M^+), 271 (29), 121 (84), 119 (100), 93 (48), 91 (79), 77 (75%). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; S, 11.12. Found: C, 66.47; H, 5.50; S, 11.06.

4.2.6. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(4-methylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7c). Purified by chromatography (diethyl ether/petroleum ether, 1:1); white crystals, 553 mg, yield 18%, mp 195–197 °C (EtOH/H_2O). IR (Nujol) 3430, 1300, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.76 (1H, d, *J*=7.5 Hz, Ar*H*), 7.49 (2H, m, Ar*H*), 7.32 (2H, d, *J*=7.8 Hz, Ar*H*), 7.22 (3H, m, Ar*H*), 5.10 (1H, d, *J*=9.6 Hz, C*H*OH), 3.87 (1H, dd, *J*=8.1, 9.6 Hz, SO_2CH), 3.27 (1H, br s, O*H*, D_2O exchangeable), 2.89 (2H, m, CH_2), 2.37 (3H, s, CH_3); δ_C (75.4 MHz, $CDCl_3$): 139.0, 138.9, 136.8, 135.7, 133.5, 129.7, 128.9, 126.9, 126.8, 121.9, 73.2, 67.2, 29.8, 21.2; *m/z* (EI) 288 (6, M^+), 121 (100), 119 (23), 93 (28), 91 (29), 77 (29%). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; S, 11.12. Found: C, 66.51; H, 5.64; S, 11.19.

4.2.7. (2*S*)-2-[(1*R*)-1-Hydroxy-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6d). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 304 mg, yield 37%, mp 134–136 °C (EtOH/H_2O).

IR (Nujol) 3485, 1290, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.68 (1H, d, *J*=8.1 Hz, Ar*H*), 7.54 (1H, t, *J*=7.5 Hz, Ar*H*), 7.36 (7H, m, Ar*H*), 5.63 (1H, s, C*H*OH), 3.72 (1H, m, SO_2CH), 3.59 (1H, dd, *J*=7.8, 16.2 Hz, CH_2), 3.58 (1H, d, *J*=3.0 Hz, O*H*, D_2O exchangeable), 3.00 (1H, dd, *J*=8.4, 16.2 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 139.6, 138.2, 136.9, 133.6, 128.6, 128.5, 127.9, 127.2, 125.5, 121.4, 68.1, 66.2, 25.4; *m*/*z* (EI) 274 (13, M^+), 257 (71), 238 (47), 223 (15), 207 (27), 168 (98), 151 (34), 137 (52), 107 (63), 105 (100), 91 (36), 77 (95%). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69. Found: C, 65.79; H, 5.21; S, 11.52.

4.2.8. (2*S*)-2-[(1*S*)-1-Hydroxy-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7d). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 156 mg yield 19%, mp 138–140 °C (EtOH/H_2O). IR (Nujol) 3450, 1295, 1140 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.69 (1H, t, *J*=7.5 Hz, Ar*H*), 7.50 (1H, t, *J*=7.5 Hz, Ar*H*), 7.37 (6H, m, Ar*H*), 7.18 (1H, d, *J*=7.5 Hz, Ar*H*), 5.12 (1H, d, *J*=10.2 Hz, CHO*H*), 3.85 (1H, dd, *J*=8.5, 10.2 Hz, SO_2CH), 3.66 (1H, br, O*H*, D_2O exchangeable), 2.84 (2H, d, *J*=8.5 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 139.8, 138.9, 135.5, 133.4, 128.8, 128.7, 128.6, 126.9, 126.8, 121.7, 73.0, 67.1, 29.6; *m*/*z* (EI) 274 (13, M^+), 257 (100), 168 (68), 137 (29), 107 (44), 105 (37), 91 (21), 77 (51%). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69. Found: C, 65.80; H, 5.23; S, 11.59.

4.2.9. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(4-fluorophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6e). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 508 mg, yield 29%, mp 43–45 °C (EtOH/H_2O); IR (Nujol) 3420, 1295, 1155 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.59 (1H, d, *J*=7.5 Hz, Ar*H*), 7.52 (1H, t, *J*=7.5 Hz, Ar*H*), 7.34 (6H, m, Ar*H*), 5.49 (1H, s, C*H*OH), 3.65 (1H, m, SO_2CH), 3.48 (1H, dd, *J*=8.0, 16.4 Hz, CH_2), 3.40 (1H, s, O*H*, D_2O exchangeable), 3.03 (1H, dd, *J*=8.4, 16.4 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 162.0 (J_{CF}= 246.6 Hz), 138.0, 136.6, 135.5 (J_{CF}=2.4 Hz), 133.6, 128.5, 127.4 (J_{CF}=8.6 Hz), 127.2, 121.2, 115.3 (J_{CF}=22.0 Hz), 67.8, 66.1, 25.8; *m*/*z* (EI) 292 (4, M^+), 275 (47), 256 (28), 241 (13), 225 (21), 210 (17), 168 (57), 151 (30), 137 (39), 125 (67), 123 (100), 109 (41), 97 (51), 95 (28), 77 (30%). Anal. Calcd for $C_{15}H_{13}FO_3S$: C, 61.63; H, 4.48; F, 6.50; S, 10.97. Found: C, 61.78; H, 4.55; F, 6.43; S, 10.89.

4.2.10. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(4-fluorophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7e). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 262 mg, yield 15%, mp 204–206 °C (EtOH/H_2O). IR (Nujol) 3445, 1305, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.78 (1H, d, *J*=7.8 Hz, Ar*H*), 7.50 (4H, m, Ar*H*), 7.24 (1H, d, *J*=7.5 Hz, Ar*H*), 7.11 (2H, m, Ar*H*), 5.14 (1H, d, *J*=9.9 Hz, C*H*OH), 3.85 (1H, m, SO_2CH), 3.42 (1H, br s, O*H*, D_2O exchangeable), 2.91 (2H, m, CH_2); δ_C (75.4 MHz, $CDCl_3$): 163.3 (J_{CF}=247.8 Hz), 138.8, 135.6 (J_{CF}=3.7 Hz), 135.5, 133.7, 129.0, 128.7 (J_{CF}=8.5 Hz), 127.0, 122.0, 116.0 (J_{CF}=20.7 Hz), 72.7, 67.2, 29.8; *m*/*z* (EI) 292 (14, M^+), 168 (100), 137 (30), 125 (47), 123 (36), 109 (18), 97 (31), 95 (21), 77 (36%). Anal. Calcd for $C_{15}H_{13}FO_3S$: C, 61.63; H, 4.48; F, 6.50; S, 10.97. Found: C, 61.46; H, 4.43; F, 6.49; S, 10.91.

4.2.11. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(4-trifluoromethylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6f). Purified by chromatography (diethyl ether/petroleum ether, 1:1); white crystals, 902 mg, yield 44%, mp 158–160 °C (EtOH/H_2O). IR (Nujol) 3440, 1325, 1160 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.65 (1H, d, *J*=7.5 Hz, Ar*H*), 7.59 (2H, d, *J*=8.4 Hz, Ar*H*), 7.50 (3H, m, Ar*H*), 7.39 (1H, t, *J*=7.5 Hz, Ar*H*), 7.26 (1H, d, *J*=7.5 Hz, Ar*H*), 5.67 (1H, s, C*H*OH), 3.67 (1H, m, SO_2CH), 3.61 (1H, d, *J*=2.7 Hz, O*H*, D_2O exchangeable), 3.51 (1H, dd, *J*=7.5, 16.4 Hz, CH_2), 2.93 (1H, dd, *J*=8.4, 16.4 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 143.6, 138.1, 136.6, 133.9, 130.3 (J_{CF}=33.0 Hz), 128.8, 127.4, 126.0, 125.7 (J_{CF}=3.7 Hz), 123.8 (J_{CF}=272.3 Hz), 121.6, 67.7, 65.9, 25.2; *m*/*z* (EI) 342 (2, M^+), 324 (12), 306 (16), 275 (10), 260 (16), 173 (38), 168 (100), 151 (17), 145 (21), 137 (37), 127 (34), 91 (20), 77 (35%). Anal. Calcd for $C_{16}H_{13}F_3O_3S$: C, 56.14; H, 3.83; F, 16.65; S, 9.37. Found: C, 55.96; H, 3.79; F, 16.53; S, 9.48.

4.2.12. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(4-trifluoromethylphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7f). Purified by chromatography (diethyl ether/petroleum ether, 1:1); white crystals, 636 mg, yield 31%, mp 163–164 °C (EtOH). IR (Nujol) 3480, 1330, 1160 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.68 (1H, d, *J*=7.5 Hz, Ar*H*), 7.60 (2H, d, *J*=8.1 Hz, Ar*H*), 7.52 (2H, d, *J*= 8.1 Hz, Ar*H*), 7.47 (1H, t, *J*=7.5 Hz, Ar*H*), 7.39 (1H, t, *J*= 7.5 Hz, Ar*H*), 7.17 (1H, d, *J*=7.5 Hz, Ar*H*), 5.17 (1H, dd, *J*=3.6, 9.6 Hz, C*H*OH), 3.80 (1H, m, SO_2CH), 3.76 (1H, br s, O*H*, D_2O exchangeable), 2.84 (2H, d, *J*=8.1 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 143.8, 138.7, 135.3, 133.6, 130.9 (J_{CF}=32.9 Hz), 128.9, 127.3, 127.0, 125.8 (J_{CF}= 3.7 Hz), 123.8 (J_{CF}=272.3 Hz), 121.8, 72.5, 66.9, 29.6; *m*/*z* (EI) 342 (2, M^+), 168 (100), 145 (11), 137 (28), 127 (22), 91 (15), 77 (25%). Anal. Calcd for $C_{16}H_{13}F_3O_3S$: C, 56.14; H, 3.83; F, 16.65; S, 9.37. Found: C, 56.31; H, 3.89; F, 16.53; S, 9.36.

4.2.13. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(2-furyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6g). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 348 mg, yield 44%, mp 94–96 °C (EtOH/H_2O). IR (Nujol) 3410, 1285, 1140 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.71 (1H, d, *J*=7.5 Hz, Ar*H*), 7.58 (1H, t, *J*=7.5 Hz, Ar*H*), 7.42 (3H, m, Ar*H*), 6.40 (2H, m, Ar*H*), 5.61 (1H, s, C*H*OH), 3.92 (1H, m, SO_2CH), 3.68 (1H, dd, *J*=7.0, 16.6 Hz, CH_2), 3.34 (2H, m, O*H*, D_2O exchangeable, CH_2); δ_C (75.4 MHz, $CDCl_3$): 152.0, 142.6, 138.2, 136.9, 133.7, 128.6, 127.3, 121.5, 110.5, 107.8, 64.0, 63.4, 26.5; *m*/*z* (EI) 264 (5, M^+), 247 (11), 246 (11), 228 (73), 213 (18), 197 (66), 151 (38), 135 (40), 97 (81), 95 (100), 91 (18), 77 (39%). Anal. Calcd for $C_{13}H_{12}O_4S$: C, 59.08; H, 4.58; S, 12.13. Found: C, 59.07; H, 4.49; S, 12.26.

4.2.14. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(2-furyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7g). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 237 mg, yield 30%, mp 147–148 °C (EtOH/H_2O). IR (Nujol) 3485, 1305, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.70 (1H, d, *J*=7.5 Hz, Ar*H*), 7.49 (1H, m, Ar*H*), 7.41 (2H, m, Ar*H*), 7.21 (1H, d, *J*=7.5 Hz, Ar*H*), 6.36 (2H, m, Ar*H*), 5.14 (1H, dd, *J*=4.0, 9.4 Hz, C*H*OH), 4.02 (1H, m,

SO_2CH), 3.34 (1H, d, J=4.0 Hz, O*H*, D_2O exchangeable), 3.12 (1H, dd, J=8.4, 16.6 Hz, CH_2), 2.90 (1H, dd, J=8.0, 16.6 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 152.2, 143.2, 138.7, 135.5, 133.7, 128.9, 127.0, 121.9, 110.5, 108.8, 66.8, 64.8, 29.3; *m/z* (EI) 264 (8, M^+), 247 (28), 228 (52), 213 (12), 197 (42), 168 (23), 151 (25), 137 (29), 97 (100), 95 (49), 77 (29%). Anal. Calcd for $C_{13}H_{12}O_4S$: C, 59.08; H, 4.58; S, 12.13. Found C, 58.91; H, 4.63; S, 12.03.

4.2.15. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(2-thienyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6h). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 218 mg, yield 26%, mp 93–94 °C (EtOH). IR (Nujol) 3430, 1300, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.71 (1H, d, J=7.5 Hz, Ar*H*), 7.58 (1H, t, J=7.5 Hz, Ar*H*), 7.45 (1H, t, J=7.5 Hz, Ar*H*), 7.36 (1H, d, J=7.5 Hz, Ar*H*), 7.31 (1H, t, J=4.5 Hz, Ar*H*), 7.04 (2H, m, Ar*H*), 5.89 (1H, s, C*H*OH), 3.84 (1H, m, SO_2CH), 3.67 (1H, dd, J=7.2, 16.6 Hz, CH_2), 3.60 (1H, d, J=2.4 Hz, O*H*, D_2O exchangeable), 3.26 (1H, dd, J=8.0, 16.6 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 143.1, 139.8, 136.7, 133.7, 128.6, 127.3, 126.9, 126.2, 125.8, 121.4, 71.5, 65.9, 26.1; *m/z* (EI) 280 (7, M^+), 263 (67), 262 (24), 244 (41), 229 (14), 213 (51), 151 (38), 113 (78), 111 (100), 85 (41), 77 (22%). Anal. Calcd for $C_{13}H_{12}O_3S_2$: C, 55.69; H, 4.31; S, 22.87. Found: C, 55.80; H, 4.39; S, 22.75.

4.2.16. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(2-thienyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7h). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 142 mg, yield 17%, mp 93–94 °C (EtOH/H_2O). IR (Nujol) 3440, 1305, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.78 (1H, d, J=7.5 Hz, Ar*H*), 7.57 (1H, t, J=7.5 Hz, Ar*H*), 7.49 (1H, t, J=7.5 Hz, Ar*H*), 7.39 (1H, d, J=5.1 Hz, Ar*H*), 7.28 (1H, d, J=7.5 Hz, Ar*H*), 7.14 (1H, d, J=3.0 Hz, Ar*H*), 7.04 (1H, m, Ar*H*), 5.49 (1H, dd, J=3.3, 9.6 Hz, C*H*OH), 3.95 (1H, m, SO_2CH), 3.62 (1H, d, J=3.3 Hz, O*H*, D_2O exchangeable), 3.13 (1H, dd, J=8.2, 16.8 Hz, CH_2), 2.98 (1H, dd, J=8.2, 16.8 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 143.2, 138.8, 135.4, 133.6, 128.9, 127.0, 126.9, 126.4, 125.8, 121.9, 69.2, 67.3, 29.9; *m/z* (EI) 280 (9, M^+), 263 (13), 244 (17), 213 (19), 168 (21), 151 (18), 137 (20), 113 (100), 111 (53), 85 (33), 77 (23%). Anal. Calcd for $C_{13}H_{12}O_3S_2$: C, 55.69; H, 4.31; S, 22.87. Found: C, 55.67; H, 4.21; S, 22.95.

4.2.17. (2*S*)-2-[(1*R*)-1-Hydroxy-2-methylpropyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6i). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 648 mg, yield 45%, mp 105–107 °C (EtOH/H_2O). IR (Nujol) 3480, 1285, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.59 (1H, d, J=7.5 Hz, Ar*H*), 7.46 (1H, t, J=7.5 Hz, Ar*H*), 7.33 (1H, t, J=7.5 Hz, Ar*H*), 7.28 (1H, d, J=7.5 Hz, Ar*H*), 4.02 (1H, d, J=7.2 Hz, CHO*H*), 3.55 (1H, m, SO_2CH), 3.48 (1H, dd, J=7.5, 15.6 Hz, CH_2), 3.18 (1H, dd, J=8.0, 15.6 Hz, CH_2), 3.03 (1H, d, J=3.0 Hz, O*H*, D_2O exchangeable), 1.76 (1H, m, C*H*), 0.98 (3H, d, J=6.6 Hz, CH_3), 0.88 (3H, d, J=6.6 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$): 138.2, 137.0, 133.5, 128.5, 127.2, 121.3, 71.7, 62.6, 32.0, 26.0, 18.9, 18.4; *m/z* (EI) 241 (1, MH^+), 222 (16), 197 (100), 168 (28), 151 (45), 143 (34), 137 (23), 135 (31), 115 (24), 105 (37), 91 (38), 77 (56), 55 (27), 43 (66%). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; S, 13.34. Found: C, 60.12; H, 6.79; S, 13.22.

4.2.18. (2*S*)-2-[(1*S*)-1-Hydroxy-2-methylpropyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7i). Purified by chromatography (diethyl ether/petroleum ether, 2:1); white crystals, 460 mg, yield 32%, mp 182–184 °C (EtOH). IR (Nujol) 3480, 1300, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.66 (1H, d, J=7.5 Hz, Ar*H*), 7.49 (1H, t, J=7.5 Hz, Ar*H*), 7.38 (1H, t, J=7.5 Hz, Ar*H*), 7.28 (1H, d, J=7.5 Hz, Ar*H*), 3.85 (1H, m, CHO*H*), 3.66 (1H, m, SO_2CH), 3.20 (2H, m, CH_2), 2.78 (1H, d, J=7.2 Hz, O*H*, D_2O exchangeable), 1.95 (1H, m, C*H*), 1.04 (3H, d, J=6.6 Hz, CH_3), 0.97 (3H, d, J=6.6 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$): 139.0, 135.9, 133.5, 128.8, 127.0, 121.6, 74.8, 64.0, 31.4, 29.2, 19.8, 16.2; *m/z* (EI) 241 (4, MH^+), 223 (6), 197 (100), 168 (13), 105 (14), 91 (10), 77 (14), 43 (16), 41 (14%). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; S, 13.34. Found: C, 59.93; H, 6.62; S, 13.19.

4.2.19. (2*S*)-2-[(1*R*)-1-Hydroxyhexyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6l). Purified by chromatography (diethyl ether/petroleum ether, 1:1); oil, 241 mg, yield 30%, n_D=1.5335. IR (neat) 3510, 1295, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.70 (1H, d, J=7.5 Hz, Ar*H*), 7.57 (1H, t, J=7.5 Hz, Ar*H*), 7.44 (1H, t, J=7.5 Hz, Ar*H*), 7.39 (1H, d, J=7.5 Hz, Ar*H*), 4.48 (1H, m, CHO*H*), 3.59 (1H, dd, J=7.5, 15.4 Hz, CH_2), 3.50 (1H, m, SO_2CH), 3.29 (1H, dd, J=7.5, 15.4 Hz, CH_2), 3.04 (1H, d, J=3.0 Hz, O*H*, D_2O exchangeable), 1.68 (2H, m, $CH_3(CH_2)_3CH_2CHOH$), 1.53 (2H, m, $CH_3(CH_2)_2CH_2CH_2CHOH$), 1.34 (4H, m, $CH_3CH_2CH_2(CH_2)_2CHOH$), 0.91 (3H, t, J=6.2 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$): 138.4, 136.9, 133.6, 128.6, 127.3, 121.4, 66.7, 64.6, 34.8, 31.4, 25.7, 25.2, 22.5, 13.9; *m/z* (EI) 269 (4, MH^+), 251 (10), 250 (11), 197 (27), 168 (43), 151 (25), 137 (34), 129 (47), 115 (23), 104 (36), 91 (43), 77 (54), 55 (50), 43 (100), 41 (89%). Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51; S, 11.95. Found: C, 62.47; H, 7.44; S, 11.94.

4.2.20. (2*S*)-2-[(1*S*)-1-Hydroxyhexyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7l). Purified by chromatography (diethyl ether/petroleum ether, 1:1); white crystals, 277 mg, yield 27%, mp 90–92 °C (H_2O). IR (Nujol) 3480, 1310, 1155 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.58 (1H, d, J=7.5 Hz, Ar*H*), 7.45 (1H, t, J=7.5 Hz, Ar*H*), 7.33 (1H, t, J=7.5 Hz, Ar*H*), 7.25 (1H, d, J=7.5 Hz, Ar*H*), 4.01 (1H, m, CHO*H*), 3.49 (1H, m, SO_2CH), 3.23 (2H, m, CH_2), 3.11 (1H, s, O*H*, D_2O exchangeable), 1.59 (2H, m, $CH_3(CH_2)_3CH_2CHOH$), 1.47 (2H, m, $CH_3(CH_2)_2CH_2CH_2$-CHOH), 1.23 (4H, m, $CH_3CH_2CH_2(CH_2)_2CHOH$), 0.81 (3H, t, J=6.3 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$): 138.8, 135.7, 133.2, 128.4, 126.9, 121.2, 70.0, 65.9, 34.5, 31.3, 29.1, 24.6, 22.3, 13.8; *m/z* (EI) 269 (4, MH^+), 251 (8), 250 (13), 197 (95), 168 (68), 151 (24), 137 (39), 129 (40), 115 (25), 105 (36), 91 (50), 77 (64), 55 (56), 43 (100), 41 (96%). Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51; S, 11.95. Found: C, 62.43; H, 7.47; S, 12.04.

4.2.21. (2*S*)-2-[(1*R*)-1-Hydroxybutyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6m). Purified by chromatography (diethyl ether/petroleum ether, 3:1); oil, 677 mg, yield 47%, n_D=1.5430. IR (neat) 3520, 1290, 1150 cm^{-1};

δ_H (300 MHz, $CDCl_3$): 7.64 (1H, d, J=7.5 Hz, Ar*H*), 7.52 (1H, t, J=7.5 Hz, Ar*H*), 7.37 (2H, m, Ar*H*), 4.38 (1H, m, CHO*H*), 3.48 (2H, m, CH_2 and SO_2C*H*), 3.29 (2H, m, O*H*, D_2O exchangeable and CH_2), 1.50 (4H, m, CH_2CH_2CH$_3$), 0.94 (3H, t, J=6.8 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$): 138.2, 136.8, 133.3, 128.2, 127.1, 121.0, 66.5, 64.5, 36.8, 26.0, 18.4, 13.5; *m*/*z* (EI) 241 (5, MH^+), 223 (13), 222 (9), 197 (27), 168 (35), 158 (25), 151 (34), 137 (35), 129 (75), 115 (24), 105 (32), 91 (48), 77 (67), 55 (42), 43 (100), 41 (81%). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; S, 13.34. Found: C, 60.14; H, 6.59; S, 13.45.

4.2.22. (2*S*)-2-[(1*S*)-1-Hydroxybutyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7m). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 389 mg, yield 27%, mp 116–118 °C (H_2O). IR (Nujol) 3475, 1305, 1155 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.72 (1H, d, J=7.5 Hz, Ar*H*), 7.56 (1H, t, J=7.5 Hz, Ar*H*), 7.46 (1H, t, J=7.5 Hz, Ar*H*), 7.35 (1H, d, J=7.5 Hz, Ar*H*), 4.12 (1H, m, CHO*H*), 3.59 (1H, m, SO_2C*H*), 3.28 (2H, m, CH_2), 3.13 (1H, d, J=7.2 Hz, O*H*, D_2O exchangeable), 1.64 (4H, m, CH_2CH_2-CH$_3$), 0.81 (3H, t, J=7.1 Hz, CH_3); δ_C (75.4 MHz, $CDCl_3$): 139.1, 136.0, 133.5, 128.8, 127.1, 121.6, 70.3, 66.0, 37.0, 29.4, 18.6, 13.8; *m*/*z* (EI) 222 (7), 197 (100), 168 (50), 151 (18), 137 (28), 129 (27), 115 (21), 105 (36), 91 (41), 77 (63), 55 (36), 43 (69), 41 (59%). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; S, 13.34. Found: C, 59.95; H, 6.65; S, 13.31.

4.2.23. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(2,3-dihydrobenzothien-2-yl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (6n). Purified by chromatography (diethyl ether/petroleum ether, 4:1); pale yellow crystals, 1049 mg, yield 53%, mp 134–136 °C (EtOH). IR (Nujol) 3500, 1290, 1145 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.88 (1H, d, J=6.9 Hz, Ar*H*), 7.80 (1H, d, J=6.9 Hz, Ar*H*), 7.74 (1H, d, J=7.5 Hz, Ar*H*), 7.61 (1H, s, Ar*H*), 7.55 (1H, t, J=7.5 Hz, Ar*H*), 7.40 (3H, m, Ar*H*), 7.32 (1H, d, J=7.5 Hz, Ar*H*), 6.05 (1H, s, CHO*H*), 3.93 (1H, m, SO_2C*H*), 3.68 (1H, dd, J=7.5, 16.6 Hz, CH_2), 3.62 (1H, d, J=2.7 Hz, O*H*, D_2O exchangeable), 3.00 (1H, dd, J=8.7, 16.6 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 140.8, 138.3, 136.9, 135.7, 134.1, 133.7, 128.7, 127.3, 124.8, 124.5, 123.7, 123.2, 121.5, 121.1, 64.8, 64.0, 25.6; *m*/*z* (EI) 330 (16, M^+), 313 (53), 163 (100), 161 (78), 147 (15), 135 (64), 91 (76), 77 (43%). Anal. Calcd for $C_{17}H_{14}O_3S_2$: C, 61.80; H, 4.27; S, 19.41. Found: C, 61.69; H, 4.35; S, 19.52.

4.2.24. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(2,3-dihydrobenzothien-2-yl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (7n). Purified by chromatography (diethyl ether/petroleum ether, 4:1); pale yellow crystals, 475 mg, yield 24%, mp 198–200 °C (EtOH/H_2O). IR (Nujol) 3500, 1300, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.08 (1H, m, Ar*H*), 7.90 (1H, m, Ar*H*), 7.80 (1H, d, J=7.2 Hz, Ar*H*), 7.52 (3H, m, Ar*H*), 7.41 (2H, m, Ar*H*), 7.20 (1H, d, J=7.2 Hz, Ar*H*), 5.56 (1H, dd, J=3.6, 9.6 Hz, CHO*H*), 4.23 (1H, m, SO_2C*H*), 3.51 (1H, d, J=3.6 Hz, O*H*, D_2O exchangeable), 2.96 (2H, m, CH_2); δ_C (75.4 MHz, $CDCl_3$): 140.9, 138.8, 136.9, 135.5, 134.7, 133.6, 128.9, 127.0, 125.2, 124.9, 124.5, 123.1, 122.6, 121.9, 68.9, 66.1, 29.8; *m*/*z* (EI) 330 (14, M^+), 163 (100), 161 (23), 135 (48), 91 (42), 77 (21%). Anal. Calcd for $C_{17}H_{14}O_3S_2$: C, 61.80; H, 4.27; S, 19.41. Found: C, 61.99; H, 4.35; S, 19.30.

4.2.25. (2*S*)-2-[(1*R*)-1-(4-Methoxyphenylamino)-1-(4-methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (8a). Purified by chromatography (diethyl ether/petroleum ether, 1:1); white crystals, 984 mg, yield 40%, mp 152–154 °C (EtOH). IR (Nujol) 3360, 1305, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.64 (1H, d, J=7.5 Hz, Ar*H*), 7.48 (1H, t, J=7.5 Hz, Ar*H*), 7.38 (1H, t, J=7.5 Hz, Ar*H*), 7.32 (2H, d, J=8.4 Hz, Ar*H*), 7.26 (1H, d, J=7.5 Hz, Ar*H*), 6.82 (2H, d, J=8.4 Hz, Ar*H*), 6.61 (2H, d, J=8.7 Hz, Ar*H*), 6.46 (2H, d, J=8.7 Hz, Ar*H*), 4.93 (1H, d, J=6.3 Hz, CHN*H*), 3.77 (1H, m, SO_2C*H*), 3.72 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.54 (1H, dd, J=8.7, 16.6 Hz, CH_2), 3.21 (1H, dd, J=8.1, 16.6 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 159.2, 153.0, 140.5, 139.3, 136.2, 133.4, 131.7, 128.7, 128.1, 127.2, 121.6, 116.6, 114.5, 114.3, 66.7, 56.6, 55.6, 55.2, 28.7; *m*/*z* (EI) 410 (23), 409 (61, M^+), 287 (57), 242 (100), 121 (23), 77 (7%). Anal. Calcd for $C_{23}H_{23}NO_4S$: C, 67.29; H, 5.56; N, 3.45; S, 7.90. Found: C, 67.46; H, 5.66; N, 3.42; S, 7.83.

4.2.26. (2*S*)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-(4-methoxyphenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (9a). Purified by chromatography (diethyl ether/petroleum ether, 1:1); white crystals, 836 mg, yield 34%, mp 215–216 °C (EtOH). IR (Nujol) 3360, 1265, 1155 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.68 (1H, d, J=7.5 Hz, Ar*H*), 7.43 (1H, t, J=7.5 Hz, Ar*H*), 7.36 (1H, t, J=7.5 Hz, Ar*H*), 7.26 (2H, d, J=8.7 Hz, Ar*H*), 7.13 (1H, d, J=7.5 Hz, Ar*H*), 6.81 (2H, d, J=8.7 Hz, Ar*H*), 6.58 (2H, d, J=9.3 Hz, Ar*H*), 6.53 (2H, d, J=9.3 Hz, Ar*H*), 4.77 (1H, d, J=9.6 Hz, CHN*H*), 3.72 (1H, m, SO_2C*H*), 3.71 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.00 (1H, dd, J=8.0, 16.4 Hz, CH_2), 2.75 (1H, dd, J=10.0, 16.4 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 159.4, 152.9, 140.3, 139.8, 135.6, 133.3, 131.9, 128.8, 128.2, 126.9, 121.8, 116.6, 114.6, 114.5, 67.0, 58.5, 55.6, 55.2, 31.2; *m*/*z* (EI) 410 (10), 409 (35, M^+), 287 (25), 242 (100), 121 (22), 77 (8%). Anal. Calcd for $C_{23}H_{23}NO_4S$: C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.25; H, 5.56; N, 3.41; S, 7.89.

4.2.27. (2*S*)-2-[(1*R*)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (8b). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 727 mg, yield 32%, mp 182–184 °C (EtOH). IR (Nujol) 3370, 1305, 1165 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.70 (1H, d, J=7.5 Hz, Ar*H*), 7.47 (3H, m, Ar*H*), 7.31 (4H, m, Ar*H*), 6.65 (3H, m, Ar*H*), 6.52 (2H, d, J=8.7 Hz, Ar*H*), 5.05 (1H, d, J=5.4 Hz, CHN*H*), 4.47 (1H, s, N*H*), 3.84 (1H, m, SO_2C*H*), 3.67 (3H, s, OCH_3), 3.62 (1H, dd, J=8.7, 16.5 Hz, CH_2), 3.25 (1H, dd, J=8.0, 16.5 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 153.1, 140.6, 139.9, 139.3, 136.2, 133.5, 129.0, 128.8, 128.1, 127.2, 127.0, 121.6, 116.6, 114.6, 66.6, 57.0, 55.6, 28.4; *m*/*z* (EI) 379 (17, M^+), 212 (100), 122 (11), 91 (6), 77 (6%). Anal. Calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69; S, 8.45. Found: C, 69.85; H, 5.63; N, 3.63; S, 8.38.

4.2.28. (2*S*)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (9b). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 454 mg, yield 20%, mp 284–286 °C (EtOH). IR (Nujol) 3350, 1290, 1150 cm^{-1}; δ_H

(300 MHz, $CDCl_3$): 7.68 (1H, d, J=7.5 Hz, Ar*H*), 7.40 (3H, m, Ar*H*), 7.26 (2H, d, J=8.7 Hz, Ar*H*), 7.13 (1H, d, J=7.5 Hz, Ar*H*), 6.81 (2H, d, J=8.7 Hz, Ar*H*), 6.58 (2H, d, J=9.3 Hz, Ar*H*), 6.53 (2H, d, J=9.3 Hz, Ar*H*), 4.89 (1H, d, J=10.2 Hz, CHN*H*), 3.78 (1H, m, SO_2CH), 3.67 (3H, s, OCH_3), 3.10 (1H, dd, J=9.9, 16.2 Hz, CH_2), 2.80 (1H, dd, J=7.8, 16.2 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 159.4, 152.9, 140.3, 139.8, 135.6, 133.3, 129.0, 128.8, 128.2, 127.0, 126.9, 121.8, 116.6, 114.6, 66.9, 59.1, 55.6, 31.1; *m*/*z* (EI) 379 (2, M^+), 212 (100), 122 (32), 91 (37), 77 (42%). Anal. Calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69; S, 8.45. Found: C, 69.53; H, 5.64; N, 3.65; S, 8.56.

4.2.29. (2*S*)-2-[(1*R*)-1-(4-Methoxyphenylamino)-1-(4-fluorophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (8c). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 929 mg, yield 39%, mp 74–75 °C (EtOH/H_2O). IR (Nujol) 3370, 1310, 1165 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.70 (1H, d, J=7.8 Hz, Ar*H*), 7.56 (1H, t, J=7.5 Hz, Ar*H*), 7.46 (3H, m, Ar*H*), 7.35 (1H, d, J=7.5 Hz, Ar*H*), 7.04 (2H, m, Ar*H*), 6.67 (2H, d, J=9.0 Hz, Ar*H*), 6.51 (2H, d, J=9.0 Hz, Ar*H*), 5.02 (1H, d, J=6.0 Hz, CHN*H*), 3.81 (1H, m, SO_2CH), 3.69 (3H, s, OCH_3), 3.59 (1H, dd, J=8.7, 16.5 Hz, CH_2), 3.29 (1H, dd, J=7.5, 16.5 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 158.9 (J_{CF}=270.0 Hz), 153.2, 140.1, 139.2, 136.0, 135.4 (J_{CF}=2.4 Hz), 133.6, 128.8, 128.6 (J_{CF}=8.5 Hz), 127.2, 121.6, 116.6, 116.0 (J_{CF}=20.6 Hz), 114.6, 66.7, 56.6, 55.6, 28.7; *m*/*z* (EI) 397 (5, M^+), 230 (11), 169 (100), 137 (22), 120 (45), 103 (46), 91 (29), 78 (49), 77 (30%). Anal. Calcd for $C_{22}H_{20}FNO_3S$: C, 66.48; H, 5.07; F, 4.78; N, 3.52; S, 8.07. Found: C, 66.26; H, 5.15; F, 4.84; N, 3.43; S, 8.01.

4.2.30. (2*S*)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-(4-fluorophenyl)-methyl]-2,3-dihydro-1-benzothiophene-1,1-dioxide (9c). Purified by chromatography (diethyl ether/petroleum ether, 3:1); white crystals, 666 mg, yield 28%, mp 239–241 °C (EtOH). IR (Nujol) 3340, 1290, 1150 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.76 (1H, d, J=7.5 Hz, Ar*H*), 7.48 (4H, m, Ar*H*), 7.24 (1H, d, J=7.5 Hz, Ar*H*), 7.07 (2H, t, J=8.6 Hz, Ar*H*), 6.68 (2H, d, J=9.0 Hz, Ar*H*), 6.64 (2H, d, J=9.0 Hz, Ar*H*), 4.89 (1H, d, J=9.6 Hz, CHN*H*), 3.78 (1H, m, SO_2CH), 3.69 (3H, s, OCH_3), 3.12 (1H, dd, J=9.9, 16.4 Hz, CH_2), 2.85 (1H, dd, J=8.0, 16.4 Hz, CH_2); δ_C (75.4 MHz, $CDCl_3$): 162.42 (J_{CF}=248.9 Hz), 141.0, 140.0, 139.5, 135.6, 135.4, 133.5, 128.9, 128.7 (J_{CF}=7.3 Hz), 126.9, 121.9, 116.5, 116.1 (J_{CF}=20.8 Hz), 114.7, 66.9, 58.4, 55.6, 31.0; *m*/*z* (EI) 397 (28, M^+), 230 (100), 122 (19), 91 (5), 77 (8%). Anal. Calcd for $C_{22}H_{20}FNO_3S$: C, 66.48; H, 5.07; F, 4.78; N, 3.52; S, 8.07. Found: C, 66.38; H, 5.17; F, 4.69; N, 3.47; S, 8.07.

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References and notes

1. Roy, K.; Leonard, J. T. *Bioorg. Med. Chem.* **2004**, *12*, 745–754.
2. Ghosh, A. K.; Thompson, W. J.; Munson, P. M.; Liu, W.; Huff, J. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 83–88.
3. Xu, K. *J. Electrochem. Soc.* **2002**, *149*, A920–A926.
4. Mori, K.; Aki, S.; Kido, M. *Liebigs Ann. Chem.* **1993**, 83–89.
5. Caldwell, J. J.; Craig, D.; East, S. P. *Synlett* **2001**, 1602–1604.
6. Hu, Z.; Fort, A.; Barzoukas, M.; Jen, A. K.; Barlow, S.; Marder, S. R. *J. Phys. Chem.* **2004**, *108*, 8626–8630.
7. Cabiddu, S.; Cadoni, E.; Melis, S.; Gelli, G.; Cabiddu, M. G.; Fattuoni, C.; De Montis, S.; Ianelli, S. *Tetrahedron* **2001**, *57*, 10365–10375.
8. Cabiddu, S.; Cadoni, E.; Ianni, A.; Gelli, G.; Melis, S.; Bernard, A. M.; Cabiddu, M. G.; De Montis, S.; Fattuoni, C. *Eur. J. Org. Chem.* **2002**, 3393–3401.
9. Truce, W. E.; Klinger, T. C. *J. Org. Chem.* **1970**, *35*, 1834–1838.
10. Grandclaudon, P.; Lablache-Combier, A. *J. Org. Chem.* **1983**, *48*, 4129–4131.
11. Gais, H. S.; Van Gumpel, M.; Raabe, G.; Muller, J.; Braum, S.; Lindner, H. J.; Rohs, S.; Runsink, J. *Eur. J. Org. Chem.* **1999**, 1627–1651.
12. Chassing, G.; Marquet, A. *Tetrahedron* **1978**, *34*, 1399–1404.
13. Chassing, G.; Marquet, A.; Corset, J.; Froment, F. *J. Organomet. Chem.* **1982**, *232*, 293–313.
14. Gais, H. G.; Volhardt, J.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 939–940.
15. Gais, H. G.; Muller, J.; Volhardt, J. *J. Am. Chem. Soc.* **1991**, *113*, 402–403.
16. Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277–297.
17. Pietro, W. J.; Francl, M. M.; Hehre, W. J.; DeFrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039–5048.
18. Wolfe, S.; Stolow, A.; LaJohn, L. A. *Tetrahedron Lett.* **1983**, *24*, 4071–4074.
19. Bors, A. D.; Streitwieser, A. *J. Am. Chem. Soc.* **1986**, *108*, 1397–1404.
20. Koch, R.; Anders, E. *J. Org. Chem.* **1994**, *59*, 4529–4534.
21. Raabe, G.; Gais, H. G.; Fleischhauer, J. *J. Am. Chem. Soc.* **1996**, *118*, 4622–4630.
22. Piffl, M.; Westo, J.; Gunther, W.; Anders, E. *J. Org. Chem.* **2000**, *65*, 5942–5950.
23. Corey, E. J.; Lowry, T. H. *Tetrahedron Lett.* **1965**, *13*, 793–801.
24. Corey, E. J.; Lowry, T. H. *Tetrahedron Lett.* **1965**, *13*, 803–809.
25. Cram, D. J.; Whitney, T. A. *J. Am. Chem. Soc.* **1967**, *89*, 4651–4661.
26. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.;

Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.

27. Gais, H. G.; Volhardt, J.; Kruger, C. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1092–1094.
28. Kaufman, M. J.; Gronert, S.; Bors, D. A.; Streitwieser, A. *J. Am. Chem. Soc.* **1987**, *109*, 602–603.
29. Gais, H. G.; Hellmann, G.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 10103–10112.
30. Streitwieser, A.; Peng Wang, G.; Bors, D. A. *Tetrahedron* **1997**, *53*, 10103–10112.
31. Bordwell, F. G.; Branca, J. C.; Johnson, C. R.; Vanier, N. R. *J. Org. Chem.* **1980**, *45*, 3884–3889.
32. Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295–3299.
33. Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299–3305.
34. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
35. Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.
36. Duhamel, L.; Plaquevent, J. C. *J. Org. Chem.* **1979**, *44*, 3404–3405.
37. Nongkunsarn, P.; Ramsden, C. A. *Tetrahedron* **1997**, *53*, 3805–3830.
38. Bordwell, F. G.; McKellin, W. H. *J. Am. Chem. Soc.* **1950**, *72*, 1985–1988.
39. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789; (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200–1211; (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.
40. (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654; (b) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294–301; (c) Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1992**, *197*, 499–505; (d) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265–3269.
41. Basis sets were obtained from the Extensible Computational Chemistry Environment Basis Set Database, Version 02/02/06, as developed and distributed by the Molecular Science Computing Facility, Environmental and Molecular Sciences Laboratory, which is part of the Pacific Northwest Laboratory, PO Box 999, Richland, Washington 99352, USA, and funded by the U.S. Department of Energy. The Pacific Northwest Laboratory is a multi-program laboratory operated by Battelle Memorial Institute for the U.S. Department of Energy under contract DE-AC06–76RLO 1830. Contact Karen Schuchardt for further information.
42. (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066–4073; (b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746; (c) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.
43. Wiberg, K. *Tetrahedron* **1968**, *24*, 1083–1096.
44. Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO Version 3.1.
45. Gabedit is a free Graphical User Interface for computational chemistry packages. It is written by Abdul-Rahman Allouche. Gabedit is available from http://lasim.univ-lyon1.fr/allouche/gabeditb
46. Schaftenaar, G.; Noordik, J. H. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 123–134.