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Efficient and highly diastereoselective preparation of a myrtenal derived bis-sulfoxide and its preliminary evaluation as chiral acyl donor

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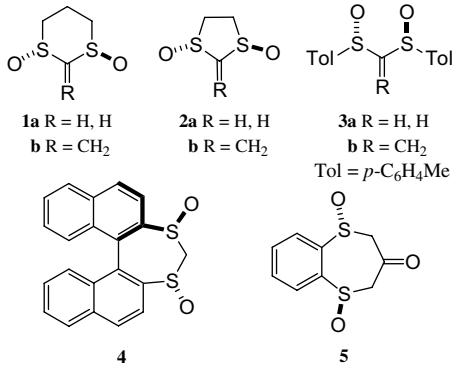
Abstract—Treatment of disulfide **7** with $NaIO_4$ in EtOH at rt gave monosulfoxide **8** (95%), while at 50 °C it gave *trans*-bis-sulfoxide **6a** (84%, >99% de). In contrast, treatment of **7** with MCPBA gave bis-sulfone **9** (95%). The anion of **6a** reacted with benzaldehyde affording carbinol **10** (76%, >99% de). The absolute configuration of **8**, **6a**, and **10** was established by single crystal X-ray diffraction analyses.

Since the earlier applications of chiral sulfoxides,[1] they have become one of the most broadly used functional group in asymmetric synthesis. A recent review summarizes the synthesis of chiral sulfoxides and their vast application in stereoselective contemporary organic synthesis.[2] The structural assortment of chiral sulfoxides has significantly grown during the last 10 years, which has increased the number of available chiral synthetic procedures. A particular interest has been focused by several authors[3–5] in using C_2-symmetric bis-sulfoxides to achieve a great variety of asymmetric transformations through a chiral auxiliary-based approach.

The structures of the most common C_2-symmetric chiral bis-sulfoxides are shown in Scheme 1. Their synthetic utility has mainly been addressed for the enantioselective preparation of α-hydroxycarbonyl derivatives, by condensing the corresponding sulfoxide-stabilized anion of compounds **1a**–**3a**, and **4** with aldehydes,[3,6,7] while bis-sulfinylethylenes **1b**–**3b** have successfully been used as dipolarophiles and dienophiles in 1,3-dipolar[8] and Diels–Alder[9] reactions, respectively. The utility of the corresponding anion of **3a** in stereoselective 1,4-additions to stabilized Michael acceptors was also demonstrated.[10] On the other hand, an interesting application of bis-sulfoxide **5** as a chiral desymmetrization agent of *meso*-1,2-diols was described.[11] In addition, organometallic complexes of bis-sulfoxides with Pd(II), Rh(I), and Ru(II) have encountered noteworthy synthetic applications in catalytic hydrogenation and Diels–Alder reactions.[12] The last complexes have shown binding



Scheme 1. Most common bis-sulfoxides used as chiral auxiliaries.

Keywords: Bis-sulfoxide; Chiral auxiliary; Acyl donor; (1*R*)-(−)-Myrtenal; Diastereoselective nucleophilic addition.
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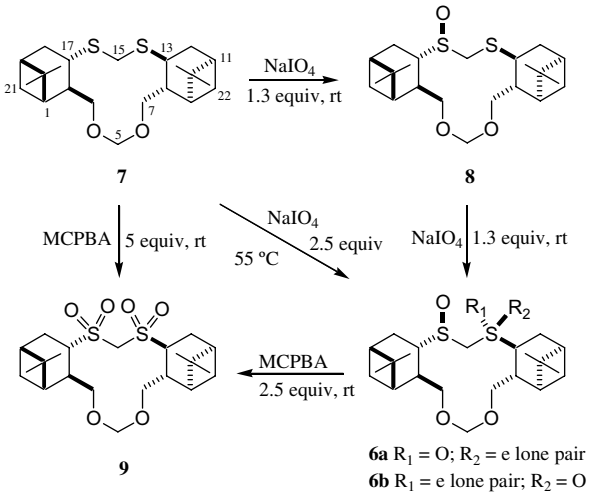
ability to DNA, indicating their potential use as anticancer agents.[13]

In light of the above synthetic applications of chiral bis-sulfoxides, we were encouraged to develop an efficient protocol to prepare the optically pure new chiral *trans* bis-sulfoxide **6a** starting from bis-sulfide **7**, described by Solladié-Cavallo et al.[14] and by us,[15] as well as to evaluate the behavior of its corresponding anion in condensations with aldehydes. This study forms part of our research to develop new chiral auxiliaries derived from commercially available natural occurring (1*R*)-(−)-myrtenal.[16]

An important fact to be considered, is that the preparation of enantiomerically pure bis-sulfoxides **1a**–**2a** was achieved through the enantioselective oxidation of their corresponding bis-sulfide precursors using Modena and co-workers[17] or Kagan and co-workers[18] reaction conditions, since the former is the most efficient to achieve asymmetric oxidations on sulfide derivatives. More recently, a promising method to prepare optically pure chiral bis-sulfoxide through dynamic kinetic transformation of sulfinyl chlorides was described, although this was only implemented for 1,4-bis-sulfides.[19] In our case the bisulfide **7** is intrinsically chiral since it was synthesized from naturally occurring (1*R*)-(−)-myrtenal, and therefore its oxidation was conducted employing achiral, traditional sulfide-oxidizing reagents like H_2O_2, MCPBA (*m*-chloroperbenzoic acid), and $NaIO_4$, which normally involve simple and mild reaction protocols. To the best of our knowledge, this is the first synthesis of a C_2-symmetric 1,3-bis-sulfoxide whose precursor bis-sulfide possesses intrinsic chirality derived from its natural origin.

The oxidation of C_2-symmetric bis-sulfides normally engages several competing procedures involving the formation of monosulfoxide, *cis* and/or *trans* bis-sulfoxides, monosulfoxide–monosulfone, and the fully oxidized bis-sulfone. The nature and the amount of the oxidizing agent usually allow control of the desired oxidation extent. Accordingly, in order to optimize the selective preparation of monosulfoxide **8**, *trans* bis-sulfoxide **6a**, or bis-sulfone **9**, several assays with variable amounts of the oxidizing agents MCPBA, H_2O_2, and $NaIO_4$ were carried out (Scheme 2). The oxidation outcomes and reaction conditions are summarized in Table 1. Thus, oxidation with MCPBA in CH_2Cl_2 (entry 2) showed the lowest selectivity, since even using 1.3 equiv after 15 min formed a mixture of monosulfoxide **8**, *trans* bis-sulfoxide **6a**, and bis-sulfone **9**, **8** being the dominant product. Using more oxidizing equivalents pushes the reaction to the exclusive formation of sulfone **9** (entry 3). A slightly lower reaction rate was observed using H_2O_2 in EtOH at room temperature (entry 1), however, it showed a similar low selectivity as MCPBA leading to the simultaneous formation of monosulfoxide **8** and *trans* bis-sulfoxide **6a**, even with 1 equiv of H_2O_2. When $NaIO_4$ was used, a substantial improvement in selectivity was observed. Thus, treatment of dimer **7** with 1.3 equiv of $NaIO_4$ (entry 4) in EtOH at room temperature yielded almost quantitatively monosulfoxide **8**,



Scheme 2. Reaction conditions to selectively prepare monosulfoxide **8**, *trans* bis-sulfoxide **6a**, and sulfone **9**.

Table 1. Reaction conditions for the selective formation of sulfoxides **6a** and **8**, bis-sulfone **9** from disulfide **7**

Entry	Oxidant	Conditions	Ratio **8**:**6a**:**6b**:**9**[a]
1	H_2O_2[b]	EtOH, 30 min	70:20:0:10
2	MCPBA[b]	CH_2Cl_2, 15 min	55:30:0:15
3	MCPBA[c]	CH_2Cl_2, 1.5 h	0:0:0:100
4	$NaIO_4$[b]	EtOH, 1.5 h	95:5:0:0
5	$NaIO_4$[d]	EtOH, 55 °C, 6 h	0:90:10:0

[a] Measured by ^{1}H NMR.
[b] 1.3 equiv.
[c] 5.0 equiv.
[d] 2.5 equiv.

while using 2.5 equiv of $NaIO_4$ at 55 °C (entry 5) allowed the formation of *trans* bis-sulfoxide **6a** (90%) admixed with a small amount of *cis* bis-sulfoxide **6b**.

During the course of the oxidation, and according to their differential formation, monosulfoxide **8**, *trans* and *cis* bis-sulfoxides **6a** and **6b**, and sulfone **9** were clearly distinguished, their respective R_f values being 0.42, 0.38, 0.36, and 0.65 (EtOAc–hexane, 2:3). Their structural relationship was established by controlling the amount and the type of oxidizing agent.

Thus, further oxidation of **8** with 1.3 equiv of $NaIO_4$ gave **6a** and **6b** in the same ratio as obtained when dimer **7** was directly treated with 2.5 equiv of $NaIO_4$ (Scheme 2). Similarly, oxidation of the mixture of **6a** and **6b** with 2.5 equiv of MCPBA yielded bis-sulfone **9**. It was noteworthy that *cis* bis-sulfoxide **6b** was only detected in small amounts perhaps since this compound is converted into a sulfoxide–sulfone, which in turn would rapidly be transformed into bis-sulfone **9**.

The structure of **6a**,**b**, **8**, and **9** was verified from their spectroscopic data. The extent of oxidation was determined by HRMS, confirming the presence of one, two, two, and four oxygen atoms in monosulfoxide **8**, *trans* and *cis* bis-sulfoxide **6a** and **6b**, and bis-sulfone **9**, respectively. In addition, Figure 1 shows the multiplici-

ties and some relevant features in the respective ^{1}H NMR spectra, which allowed differentiation of each of the above compounds by applying chemical shift and symmetry criteria. Figure 1 shows the down-field set of signals (3.20–4.85 ppm) belonging to the 12-membered heterocycle protons, excluding the H-2 and H-8 signals, which appear up-field. Thus, the lower trace shows the signals of monosulfoxide **8**, revealing two AB systems for the O–CH_2–O and CH_2–S groups. The large chemical shift difference between H-17 (4.01 ppm) and H-13 (3.54 ppm), as well as between H-15a (3.92 ppm) and H-15b (3.47 ppm), denotes the strong anisotropic influence of the sulfoxide group.

The stereochemical discrimination between *trans* and *cis* bis-sulfoxides **6a** and **6b** (traces b and c, respectively) is easily achieved from their nonsymmetric and symmetric signal distribution, respectively. For instance, the coincidence of the NMR signals of each monomeric moiety of *trans* bis-sulfoxide **6a** matches with its C_2-symmetry, giving a highly symmetric ^{1}H NMR spectrum. Conversely, the ^{1}H NMR spectrum of *cis* bis-sulfoxide **6b** shows different anisotropic environments for each monomeric moiety due to lack of C_2-symmetry. The almost coincident chemical shifts (4.32 and 4.28 ppm) and down-field displacement of H-13 and H-17 in **6b**, as compared to the same protons in disulfide **7** (3.69 ppm), reveals the proximity to their respective sulfoxide groups. Similarly to *trans* bis-sulfoxide **6a**, the ^{1}H NMR spectrum of bis-sulfone **9** also shows a simplified distribution of signals due to its C_2-symmetry. The presence of sulfone groups causes larger down-field shifts of the H-13, H-17, and S–CH_2–S signals, as compared to those of *trans* and *cis* bis-sulfoxides **6a** and **6b**.

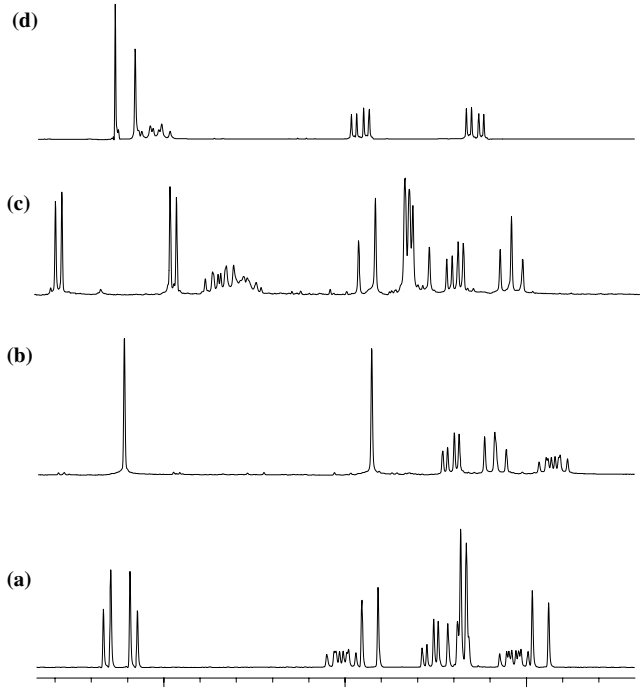


Figure 1. ^{1}H NMR signals of (a) monosulfoxide **8**, (b) *trans* bis-sulfoxide **6a**, (c) *cis* bis-sulfoxide **6b**, and (d) bis-sulfone **9**. Only 3.20–4.85 ppm regions are showed.

The absolute configuration of **8** was verified by single crystal X-ray diffraction analysis[20] (Fig. 2), where the *R* configuration of the sulfoxide group can be appreciated. Figure 2 also compares the X-ray perspective views of **7** and **8**. In both compounds a closely related conformation can be visualized for the 12-membered ring in the solid state, which allows one to envisage the oxidation preference on going from **7** to **8**. Thus, the *pro-R* electron lone pair at any sulfur in bis-sulfide **7** points *exo* of the 12-membered ring, while the *pro-S* electron lone pair points *endo*. This fact makes the *pro-R* electron lone pair more available for the oxidation process. The same reason could be applicable for the second oxidation to give *trans* bis-sulfoxide **6a**.

The utility of *trans* bis-sulfoxide **6a** as a chiral acyl donor was explored by condensing its derived anion with benzaldehyde in THF at −78 °C, giving carbinol **10** in 76% yield and >99% de (Scheme 3).

Figure 3 shows the X-ray structure[20] of carbinol **10**, where the *R* configuration at the new stereogenic center can be appreciated, revealing that nucleophilic approach took place from the *si* face of the carbonyl group.

A reasonable chair-like six-membered transition state, keeping a close structural analogy with the X-ray perspective view of carbinol **10**, is proposed (Fig. 4). Therein the axial-like arrangement of the phenyl group, which minimizes steric interactions with the β oxygen of the

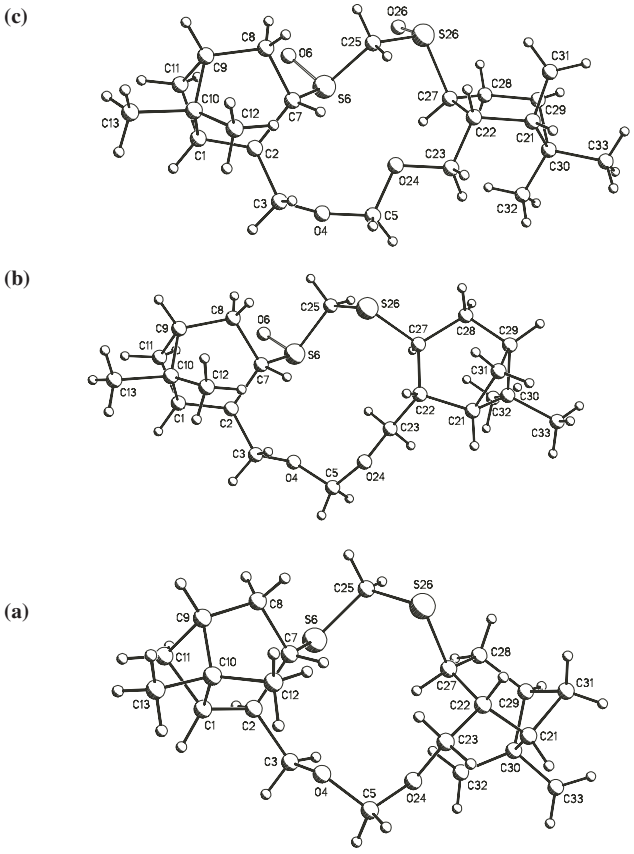
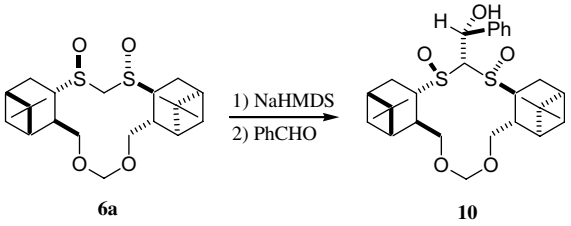


Figure 2. X-ray structures of (a) bis-sulfide **7**, (b) monosulfoxide **8**, and (c) bis-sulfoxide **6a**.



Scheme 3. Highly diastereoselective addition of the anion of **6a** to benzaldehyde.

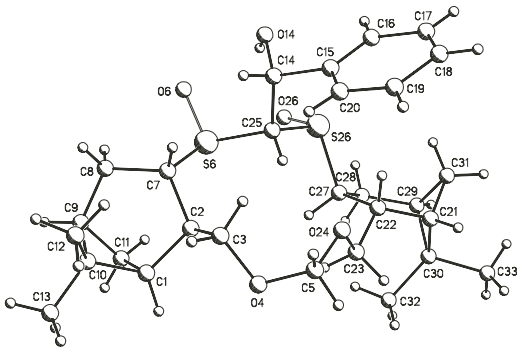


Figure 3. X-ray structure of carbinol **10**.

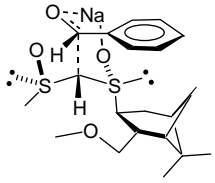


Figure 4. Transition state explaining the highly preferred stereochemical outcome of the nucleophilic addition to benzaldehyde.

nonchelated sulfoxide, can be appreciated. Accordingly, it can be inferred that nucleophilic addition by the *si* face is disfavored.

In conclusion, the easy preparation of bis-sulfoxide **6a** as compared to bis-sulfoxides **1a**–**3a**, is emphasized, since in the latter it is necessary to introduce a carboethoxy group at C-2 to get the best enantiomeric excess, thus increasing the number of steps starting from the respective disulfide. In addition, the oxidation protocol of the later involves the more sophisticated Modena reaction conditions.[17] Due to its high optical purity and straightforward preparation, the new bis-sulfoxide **6a** provides a promising synthetic alternative to be used as a synthetic tool in a similar way as the bis-sulfoxides in Scheme 1 were used.

Acknowledgements

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