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## New insights into the reduction of $\beta,\delta$ -diketo-sulfoxides

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**Abstract**—New developments in the reduction of  $\beta,\delta$ -diketo-sulfoxides, a reaction that affords important key intermediates for total synthesis, are described. We showed without ambiguity using NMR experiments, that the  $\beta$ -carbonyl group is totally enolised. This result is inconsistent with the previous hypothesis, which supposed the other tautomer (enolisation at the  $\delta$ -position) as the major one. We propose a rationale to explain the side reactions occurring during the reduction of unprotected  $\beta,\delta$ -diketo-sulfoxides and showed that judicious protection of the  $\delta$ -carbonyl group gave all diastereoisomers of  $\beta$ -hydroxy- $\delta$ -keto-sulfoxides. © 2003 Elsevier Science Ltd. All rights reserved.

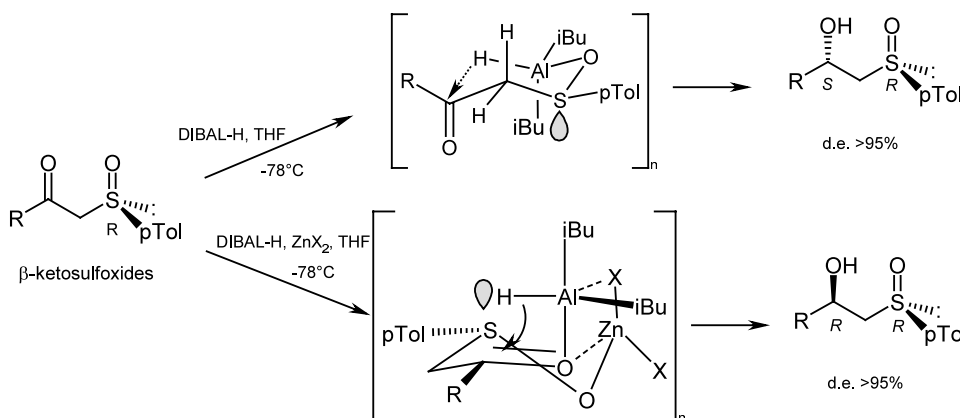
### 1. Introduction

In 1977 we published<sup>1</sup> the first asymmetric aldol-type condensation of  $\alpha$ -sulfinyl ester enolates giving  $\beta$ -hydroxy esters with high enantioselectivity (ee >85%). Since that time the use of chiral sulfoxides in asymmetric synthesis has increased greatly.<sup>2</sup>

One of the most useful results we obtained later was the stereoselective reduction of  $\beta$ -ketosulfoxides.<sup>3</sup> Their reduction with DIBAL-H and  $\text{ZnCl}_2/\text{DIBAL-H}$  occurred with the opposite diastereoselectivity (>95%) (Scheme 1). Most of the experimental results showed

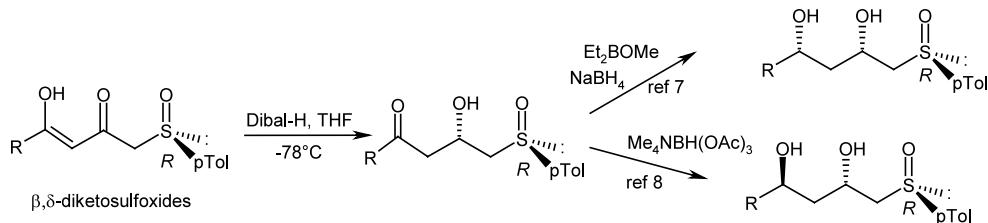
that chelated species and intramolecular hydride transfer are important factors for the control of the diastereoselectivity.<sup>3,4</sup>

$\beta,\delta$ -Diketosulfoxides, which are easily prepared<sup>5</sup> from the corresponding  $\beta$ -ketoesters or  $\beta$ -diketones, are excellent intermediates for the enantio- and diastereoselective synthesis of *syn*- and *anti*-1,3-diols.<sup>6</sup> It was shown that the  $\beta$ -carbonyl group could be reduced as in any  $\beta$ -ketosulfoxide with high stereoselectivity and that the resulting  $\beta$ -hydroxy- $\delta$ -ketosulfoxide could also be reduced to the corresponding *syn*- or *anti*-1,3-diols following literature procedures (Scheme 2).



Scheme 1.

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Scheme 2.

Despite several applications to the total synthesis of natural products,<sup>6</sup> this methodology is limited by the poor yields obtained for the first reduction when the  $\delta$ -carbonyl group is not protected. Furthermore, the  $\text{ZnX}_2$ -mediated reduction leading to the opposite configuration of the  $\beta$ -hydroxy group was not efficient in the case of  $\beta,\delta$ -diketosulfoxides as it only gave degradation products. No studies on the reduction of  $\delta$ -protected  $\beta,\delta$ -diketosulfoxides using  $\text{ZnX}_2/\text{DIBAL-H}$  system have been described so far.

In this regard, we now report the results we obtained in the reduction of  $\delta$ -protected  $\beta,\delta$ -diketosulfoxides to  $\beta$ -hydroxy- $\delta$ -ketosulfoxides in both absolute configurations. Accordingly, to gain a better understanding of the factors that govern the diastereoselective reduction of unprotected  $\beta,\delta$ -diketosulfoxides we undertook a study of this reduction and the keto-enol tautomerism of different  $\beta,\delta$ -diketosulfoxides.

## 2. Results and discussion

The  $\beta,\delta$ -diketosulfoxides **1a–h** (Table 1) were prepared in high yields either from  $\beta$ -diketone **2a**,  $\beta,\delta$ -diketoesters **2e,f** and menthyl-*p*-tolylsulfinylate **3**,  $\beta$ -ketoester **2b** and methyl-*p*-tolylsulfoxide **4** or from esters **2c,d,g,h** and 1-(*p*-tolylsulfinyl)propan-2-one **5** (Scheme 3). It should be noted that chromatographic purification of  $\beta,\delta$ -diketosulfoxides must be carried out on silica gel free of metallic impurities.<sup>9</sup>

The  $^1\text{H}$  NMR spectra of  $\beta,\delta$ -diketosulfoxides **1a–g** showed clearly that one of the two carbonyl groups is totally enolised (a singlet corresponding to one vinylic proton, 85% for **1h**). These spectra also show one AB pattern corresponding to the methylenic protons  $\alpha$  to the sulfoxide group (Fig. 1). Thus, two tautomeric

forms are possible. So far, the tautomer II, with the  $\delta$ -carbonyl enolised, has been supposed to be the major one in solution (Scheme 2). The enol form of the  $\beta$ -carbonyl group in tautomer I would impede its reduction to the alcohol.

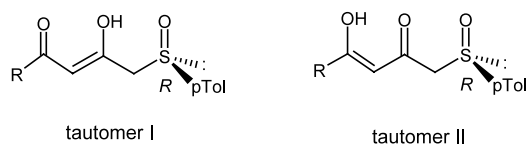


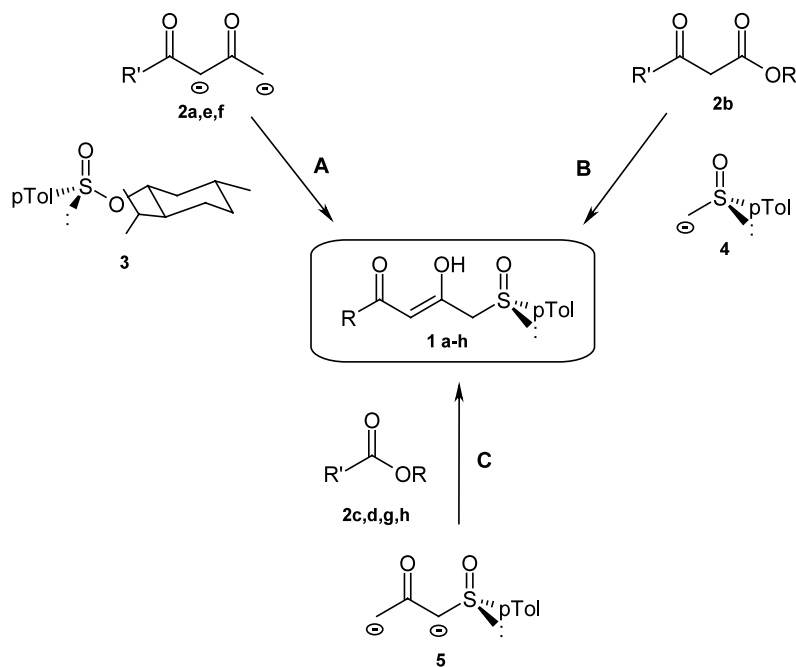
Figure 1.

This hypothesis is in agreement with previous results observed in the reduction of 4-sulfinyl-3-oxobutyric esters **6**.<sup>10</sup> In such substrates, the enol tautomer was present in a range of 20–30% depending on the nature of the solvent and the substrate itself, but attributed without any ambiguity at the  $\beta$ -position by NOESY correlation experiments. As the reduction of butyrates **6** using 1.2 equiv. of DIBAL-H in THF provided 20–30% of starting material, it was supposed that the enol tautomer led to unreactive aluminium enolates as intermediates (Scheme 4).

We tried to reduce the  $\beta$ -carbonyl group in the  $\beta,\delta$ -diketosulfoxides **1a–h** with DIBAL-H using the previously described conditions. Table 1 summarises the results obtained. Several notable features are evident: (i) 2 equiv. of DIBAL-H were necessary, probably due to an acid–base reaction between the hydride and the enolic proton; (ii) Only one diastereomer of the resulting  $\beta$ -hydroxy- $\delta$ -ketosulfoxide **7a–h** was detected by 200 MHz  $^1\text{H}$  NMR of the crude product; (iii) The  $^1\text{H}$  NMR of the crude product showed that all the starting material had reacted. However, the yield of the isolated

**Table 1.** Reduction of  $\beta,\delta$ -diketosulfoxides **1a–h** to the corresponding  $\beta$ -hydroxy- $\delta$ -ketosulfoxides **7a–h** by Dibal-H in THF

	R	Sulfoxide configuration	7 (Isolated yields); configuration
<b>1a</b>	CH <sub>3</sub>	(+)-(R)	35; R <sub>S</sub> ,2S
<b>1b</b>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	(-)-(S)	33; S <sub>S</sub> ,2R
<b>1c</b>	TBSO(CH <sub>2</sub> ) <sub>4</sub>	(+)-(R)	35; R <sub>S</sub> ,2S
<b>1d</b>	EtO <sub>2</sub> C(CH <sub>2</sub> ) <sub>3</sub>	(+)-(R)	33; R <sub>S</sub> ,2S
<b>1e</b>	EtO <sub>2</sub> CCH <sub>2</sub>	(+)-(R)	45; R <sub>S</sub> ,2S
<b>1f</b>	MeO <sub>2</sub> CCH <sub>2</sub>	(+)-(R)	44; R <sub>S</sub> ,2S
<b>1g</b>	BnOCH <sub>2</sub>	(+)-(R)	52; R <sub>S</sub> ,2S
<b>1h</b>	<i>t</i> BuO <sub>2</sub> CCH(Me)CO(CH <sub>2</sub> ) <sub>2</sub>	(-)-(S)	33; R <sub>S</sub> ,2S



Scheme 3.

$\beta$ -hydroxy- $\delta$ -ketosulfoxide **7a-h**, after purification by column chromatography using demetallated silica gel, was only 33–52%. Thus, we observed hydrogenolysis of the C–S bond leading to the corresponding  $\beta$ -diketones **2a-h** in 40–50% yield and the *p*-tolyl disulfide **8**; (iv) Even more intriguing was the improvement in the yield of the isolated  $\beta$ -hydroxy  $\delta$ -ketosulfoxides **7e-g** from **1e-g** bearing electron-withdrawing groups in the  $\eta$  position.

Additionally, the reduction of the  $\beta,\delta$ -diketosulfoxides **1a-h** using the system  $\text{ZnX}_2/\text{DIBAL-H}$ , in order to obtain the opposite absolute configuration of the stereogenic  $\beta$ -hydroxylic centre, led only to degradation products and/or a mixture of diastereoisomers in low yields.

We first carefully examined the enolate structure in the starting  $\beta,\delta$ -diketosulfoxides **1a,b,f,g** using NMR experiments. Thus, the HMBC spectrum ( $^1\text{H}$ – $^{13}\text{C}$  coupling) of compound **1b** for example in  $\text{CDCl}_3$  showed a correlation between C-2 and the AB-system of H-1 but not of H-5. Besides, a correlation of C-4 with C-5 and C-6 is also observed. No correlation between C-4 and H-1 can be distinguished. These observations would point to consider the tautomer I as the major form in the I–II equilibrium (Fig. 2). The same correlations are observed when the HMBC spectra are recorded in  $\text{THF-}d_8$  or toluene- $d_6$ .

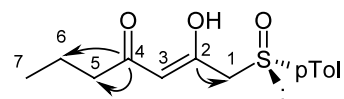
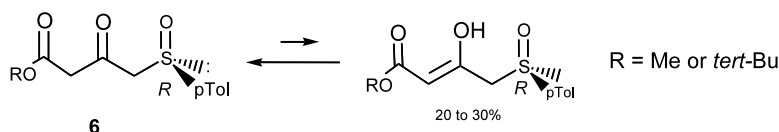


Figure 2. HMBC ( $^1\text{H}$ – $^{13}\text{C}$  NMR) of  $\beta,\delta$ -diketosulfoxide **1b** and corresponding correlations observed.

Additionally, we prepared the  $\delta$ -enol-methyl ether **10a** and **10b**<sup>11</sup> of the corresponding sulfoxides **1a** and **1b** in 73 and 65% yields by addition of 2 equiv. of the (*R*)- or (*S*)-*p*-tolylmethylsulfoxide lithium anion to a THF solution of **9a** and **9b**, respectively<sup>12</sup> at  $-78^\circ\text{C}$ . Reduction of **10a** and **10b**, in which the enolised carbonyl is fixed in the  $\delta$ -position, afforded the  $\beta$ -hydroxysulfoxides **11a-b** and **12a-b** (80% conversion) as 6/4 (*2S,R\_S*)/(*2R,R\_S*) and 7/3 (*2R,S\_S*)/(*2S,S\_S*) diastereomeric mixtures respectively using DIBAL-H. Pure (*2S,R\_S*)-**12a** and (*2R,S\_S*)-**12b** in 81 and 63% yields was isolated using  $\text{ZnI}_2/\text{DIBAL-H}$  system. Assignment of the configuration at C-2 based on the  $^1\text{H}$  NMR spectra<sup>13</sup> was confirmed by chemical correlation with the known  $\delta$ -keto- $\beta$ -hydroxy-sulfoxides **7a,b** and **16a,b** prepared by acidic treatment of compounds **11a,b** and **12a,b**. Diketone **2a-b** and *p*-tolyl disulfide **8** coming from the hydrogenolysis of C–S bond usually observed during the reduction of **1a-g**, were not present in  $^1\text{H}$  NMR of the crude reaction mixture (Scheme 5).



Scheme 4.

This last experiment suggested that the presence of the two side products **2** and **8** in the reduction of  $\beta,\delta$ -diketosulfoxides **1a–h** was dependent on the position of the enol function.

In fact, we propose that under the reaction conditions (THF,  $-78^\circ\text{C}$ ) even if the tautomer I is the major one,<sup>14</sup> the minor II is also present. The initially formed ratio could however be altered by addition of DIBAL-H to the mixture which could thus induce an irreversible reaction predominantly with the minor but more reactive tautomer II. In both cases, addition of the first equivalent of DIBAL-H would lead, after acid–base reaction, to the aluminium–enolates **A** and **B**. While in the case of **A**, addition of a second equivalent of DIBAL-H led to the  $\beta$ -hydroxy- $\delta$ -ketosulfoxide, in the case of **B**, the  $\beta$ -carbonyl was not available and after chelation of aluminium to the basic oxygen of the sulfoxide, an intramolecular hydride transfer took place with a C–S bond cleavage and the formation of the  $\beta$ -diketone **2** and *p*-tolylsulfenic acid which dimerised to *p*-tolyldisulfide **8** (Scheme 6).

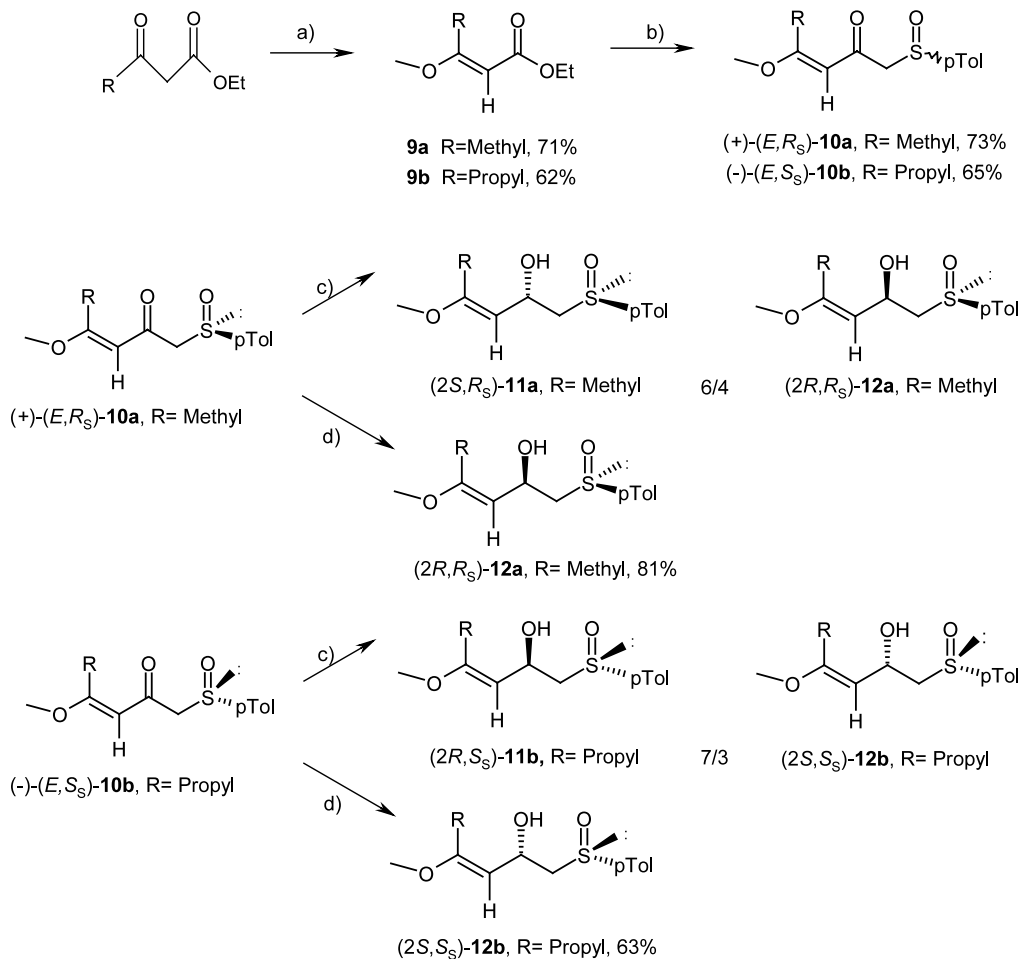
According to this hypothesis, the presence of electronegative groups in **1e–g** would displace the keto–enol equilibrium to the tautomer II leading to an improve-

ment in the yield of the  $\beta$ -hydroxy- $\delta$ -ketosulfoxide **7e–g**.

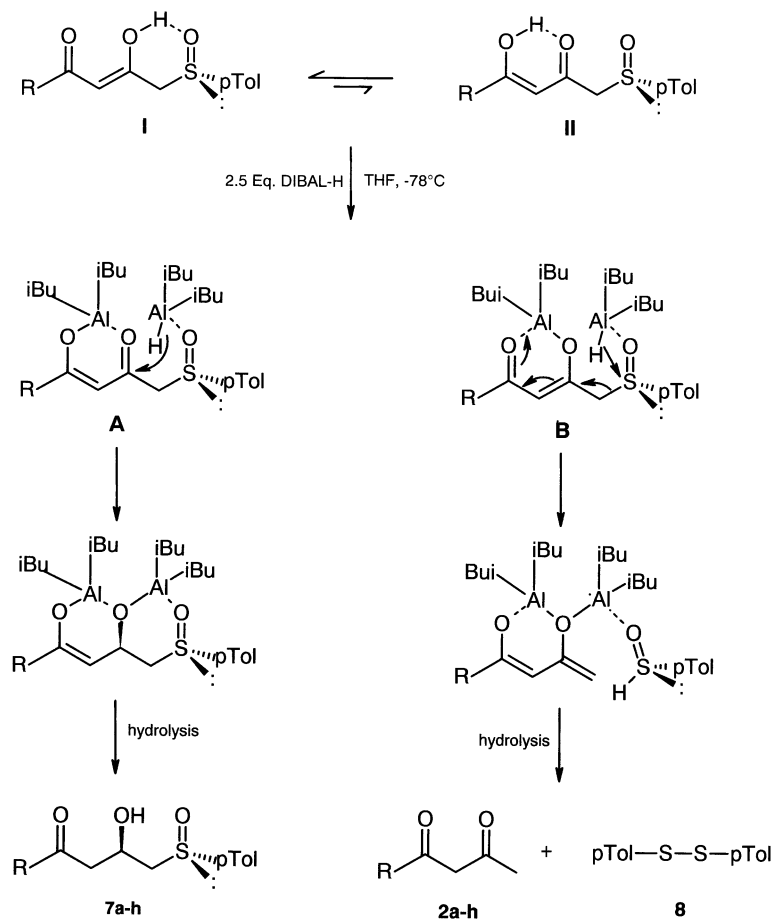
In protecting the  $\delta$ -carbonyl group one can avoid the formation of any enol tautomer. During our work on the asymmetric synthesis of Pamamycin-607,<sup>15</sup> we have used a dioxolane as protecting group for the  $\delta$ -carbonyl as previously mentioned in literature.<sup>16</sup>

Thus, by treatment of the  $\beta$ -keto- $\delta$ -dioxolanesulfoxide **13** prepared as previously described<sup>15</sup> with 2.5 equiv. of DIBAL-H in THF at  $-78^\circ\text{C}$ , we obtained the corresponding  $\beta$ -hydroxy- $\delta$ -dioxolanesulfoxide **14** with a de higher than 95%.<sup>17</sup> The *S* configuration of **14** was assigned according to the expected stereochemical course for DIBAL-H reduction of  $\beta$ -ketosulfoxides.<sup>13</sup> No degradation products were observed in this step. Hydrolysis of the ketal group was accomplished without prior isolation<sup>18</sup> of **14** yielding enantiomerically pure  $\beta$ -hydroxy- $\delta$ -ketosulfoxide **7b** in 80% yield from **13** (Scheme 7).

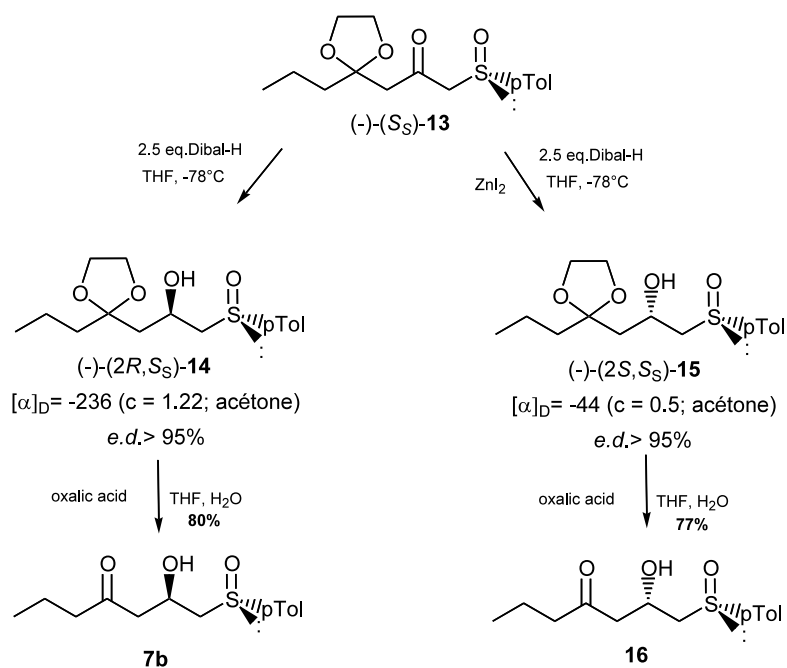
The (*S,S,2S*)-diastereomer **16b** was prepared in 77% yield by reduction of **13** with  $\text{ZnI}_2/\text{DIBAL-H}$  and subsequent hydrolysis of the ketal group.



**Scheme 5.** Reaction conditions: (a)  $\text{K}_2\text{CO}_3$ , DMSO,  $\text{Me}_2\text{SO}_4$ ; (b) (+)-(R) or (-) (*S*)-methyl-*p*-tolyl-sulfoxide (2 equiv.), LDA (2 equiv.), THF,  $-78^\circ\text{C}$ ; (c) Dibal-H 2.5 equiv., 90% (conversion), THF,  $-78^\circ\text{C}$ ; (d)  $\text{ZnI}_2$ , Dibal-H 2.5 equiv., THF,  $-78^\circ\text{C}$ .



Scheme 6.



Scheme 7.

We would also like to point out that the absence of degradation products allowed the purification of **14** and **15** simply by washing the crude products with ether instead of the usual laborious purification by column chromatography on metal-free silica gel.

### 3. Conclusions

In conclusion, we have demonstrated that  $\beta,\delta$ -diketosulfoxides have the  $\beta$ -carbonyl enolised in solution. This fact leads to the formation of side-products by reaction with DIBAL-H or  $\text{ZnX}_2/\text{DIBAL-H}$ . With the  $\delta$ -carbonyl functionality appropriately protected (as the enol ether or the dioxolane) side-reactions can be avoided in the reduction of  $\beta,\delta$ -diketosulfoxides improving yields, facilitating purification, and giving for the first time a high yielding method to access the (2*S*,*S*<sub>5</sub>)- or (2*R*,*R*<sub>5</sub>)- $\beta$ -hydroxy- $\delta$ -ketosulfoxides. A detailed study on the reduction of several functionalised  $\delta$ -enol methyl ether  $\beta$ -ketosulfoxides is now under investigation.

### 4. Experimental

#### 4.1. General

All reactions were carried out under dry argon. Standard syringe and cannula techniques were employed for transfer of dry solvents and air- or moisture-sensitive reagents. Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone, dichloromethane from phosphorus pentoxide, diisopropylamine from KOH. *n*-Butyllithium was purchased as a 1.6 M solution in hexane. Starting materials not mentioned below were commercially available. Enantiopure menthyl-*p*-tolylsulfonates **3** and methyl-*p*-tolylsulfoxides **4** in both configurations were prepared according to previously described methods.<sup>19</sup> Reactions were monitored by thin layer chromatography on silica gel plates (Merck 60F<sub>254</sub>) and stained by use of *p*-anisaldehyde. Merck silica gel 60H was used for column chromatography and demetallated following a known procedure<sup>20</sup> when required. NMR spectra were obtained at 200 MHz (<sup>1</sup>H) or 50 MHz (<sup>13</sup>C) and 400 MHz (<sup>1</sup>H) or 10 MHz (<sup>13</sup>C) on Bruker AC 200 and AC 400 instruments, with deuteriochloroform as solvent. Chemical shifts ( $\delta$ ) are given in ppm relative to tetramethylsilane ( $\delta=0$  ppm) or to residual protons in the solvent as internal standard. IR spectra were recorded with a Perkin–Elmer Spectrum One, and absorption bands are given in  $\text{cm}^{-1}$ . The Microanalyses Service of the Strasbourg Faculty of Chemistry performed microanalyses.

#### 4.2. (+)-(*R*<sub>5</sub>)-1-(*p*-Tolylsulfinyl)-2,4-pentanedione, **1a**

The  $\beta,\delta$ -diketosulfoxide **1a** was prepared according to literature methods<sup>5a</sup>

#### 4.3. (-)-(*S*<sub>5</sub>)-1-(*p*-Tolylsulfinyl)-2,4-heptanedione, **1b**

To a solution of LDA [prepared at  $-78^\circ\text{C}$  from diiso-

propylamine (0.48 ml; 3.5 mmol; 3.2 equiv.) and *n*-BuLi (2.2 ml of a 1.6 M solution in hexane, 3.56 mmol, 3.3 equiv.)] in THF (25 ml) at  $-78^\circ\text{C}$ , was added dropwise a solution of (-)-(*S*)-methyl-*p*-tolylsulfoxide (0.183 g; 1.19 mmol; 1.1 equiv.) in THF (3 ml). After stirring for 1 h at  $-78^\circ\text{C}$ , ethyl butyrylacetate (0.17 g; 1.08; 1 equiv.) was added and the resulting solution was stirred at rt for 4 h. The reaction mixture was then hydrolysed with saturated  $\text{NH}_4\text{Cl}$  (50 ml) and acidified to pH 3–4 with aqueous 10% HCl. The phases were separated and the aqueous layer was extracted with AcOEt (3×50 ml). The combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. The crude product was purified by column chromatography on metal-free silica gel (hexane:ethyl acetate, 4:1) to afford **1b** as a beige solid (0.190 g; 67%).  $R_f=0.59$  (ethyl acetate/dichloromethane, 1:1).  $[\alpha]_D^{20}=-131$  ( $c$  0.5, acetone).  $\text{Mp}=44\text{--}46^\circ\text{C}$ . <sup>1</sup>H NMR (200 MHz;  $\text{CDCl}_3$ ):  $\delta=0.94$  (t, 3H,  $J=7.3$  Hz), 1.64 (sext., 2H,  $J=7.3$  Hz), 2.28 (t, 2H,  $J=7.3$  Hz), 2.43 (s, 3H), 3.65 (AB system of the enol form, 1.9H,  $J_{\text{AB}}=12.8$  Hz,  $\Delta\nu=30.3$  Hz), 3.93 (AB system of the keto form, 0.1H,  $J_{\text{AB}}=13.5$  Hz,  $\Delta\nu=30.8$  Hz), 5.53 (s, 0.95H), 7.33 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.4$  Hz,  $\Delta\nu=41$  Hz), 7.54 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.4$  Hz,  $\Delta\nu=41$  Hz), 14.20 (broad s, 0.95H, enol) ppm. <sup>13</sup>C NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta=13.8, 19.0, 21.6, 40.6, 65.6, 101.9, 124.2, 130.1, 140.2, 142.2, 181.2, 196.5$  ppm. IR (film):  $\nu=3100\text{--}3000, 2980\text{--}2800, 1640\text{--}1580$   $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{14}\text{H}_{18}\text{O}_3\text{S}$  (266.35): C, 63.13; H, 6.81. Found: C, 63.00; H, 6.93%.

#### 4.4. Methyl 5-(*tert*-butyldimethylsilyloxy)pentanoate, **2c**

A solution of  $\delta$ -valerolactone (8 g; 79.9 mmol; 1 equiv.) in MeOH (260 ml) was treated with 10 drops of concentrated  $\text{H}_2\text{SO}_4$  and heated under reflux for 21 h. The mixture was cooled to rt and imidazole (275 mg) was added. After 15 min of stirring, methanol was evaporated and the resulting oil was suspended in 50 ml of DMF. Then imidazole (13.6 g; 0.2 mol; 1.5 equiv.) and TBSCl (18.1 g; 0.12 mol; 1.5 equiv.) were added and the mixture was stirred for 21 h at rt. The reaction mixture was hydrolysed at  $0^\circ\text{C}$  with  $\text{H}_2\text{O}$  (50 ml) and diluted with ether (50 ml). The stirring was continued until a clear phase-separation occurred. The aqueous layer was extracted with ether (2×50 ml). The combined organic phases were washed with saturated  $\text{NH}_4\text{Cl}$  (3×50 ml) and brine (2×50 ml), dried ( $\text{MgSO}_4$ ), and concentrated. The resulting yellow oil was purified by column chromatography on silica gel (hexane/ethyl acetate, 9:1) to afford methyl-5-(*t*-butyldimethylsilyloxy)pentanoate (10 g; 80%) as a yellow oil.  $R_f=0.52$  (ethyl acetate/hexane, 1:9). <sup>1</sup>H NMR (200 MHz;  $\text{CDCl}_3$ ):  $\delta=-0.05$  (s, 6H), 0.8 (s, 9H), 1.37–1.70 (m, 4H), 2.24 (t, 2H,  $J=7$  Hz), 3.53 (t, 2H,  $J=6$  Hz), 3.56 (s, 3H). <sup>13</sup>C NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta=-5.4, 18.2, 21.4, 25.9, 32.1, 33.7, 51.3, 62.6, 173.9$  ppm. IR (film):  $\nu=2960\text{--}2860, 1740\text{--}1720$   $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{12}\text{H}_{26}\text{O}_3\text{Si}$  (246.423): C, 58.49; H, 10.63. Found: C, 58.59; H, 10.74%.

#### 4.5. (+)-(R<sub>S</sub>)-1-(*p*-Tolylsulfinyl)-2,4-dioxo-8-(*t*-butyldimethylsilyloxy)octane, **1c**

To a solution of LDA [prepared at  $-15^{\circ}\text{C}$  from diisopropylamine (3.8 ml; 27 mmol; 4.4 equiv.) and *n*-BuLi (17 ml of a 1.55 M solution in hexane; 26.4 mmol; 4.3 equiv.) in THF (30 ml)] was added (+)-(R)-1-(*p*-tolylsulfinyl)-2-propanone **5<sup>5a</sup>** (2.5 g; 12.9 mmol; 2.1 equiv.) in THF (20 ml) at  $-15^{\circ}\text{C}$  via cannula. After stirring for 2 h at  $0^{\circ}\text{C}$ , the resulting orange solution was added dropwise to a solution of methyl-5-(*t*-butyldimethylsilyloxy)pentanoate **2c** (1.51 g; 6.1 mmol; 1 equiv.) in THF (20 ml) at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred for 1.5 h at  $-78^{\circ}\text{C}$  and hydrolysed with saturated  $\text{NH}_4\text{Cl}$  (140 ml) and acidified to pH 3 with 10% HCl. After extraction with ethyl acetate (3 $\times$ 100 ml), the organic phase was dried ( $\text{MgSO}_4$ ) and the solvent evaporated. Finally the crude product was purified by column chromatography on metal free silica gel (ethyl acetate/dichloromethane, 9:1) to afford **1c** as a beige solid (2 g, 80%).  $R_f=0.37$  (ethyl acetate/dichloromethane, 9:1).  $[\alpha]_{\text{D}}^{20}=+167$  (*c* 1,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=0.04$  (s, 6H), 0.89 (s, 9H), 1.44–1.72 (m, 4H), 2.32 (t, 2H,  $J=7$  Hz), 2.42 (s, 3H), 3.63 (AB system, 2H,  $J_{\text{AB}}=12.5$  Hz,  $\Delta\nu=29$  Hz), 3.61 (t, 2H,  $J=6$  Hz), 5.53 (s, 1H), 7.43 ((AB)<sub>2</sub> system, 4H,  $J_{\text{AB}}=8$  Hz,  $\Delta\nu=41$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=-5.4$ , 18.2, 21.4, 21.8, 25.9, 32.1, 38.3, 62.6, 65.5, 101.8, 124, 130, 139.8, 142.2, 181, 196.2 ppm. IR (film):  $\nu=3040$ –2840, 1600, 1090  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{21}\text{H}_{34}\text{O}_4\text{SSi}$  (410.645): C, 61.42; H, 8.35. Found: C, 61.38; H, 8.37%.

#### 4.6. Ethyl (R<sub>S</sub>)-5,7-dioxo-8-(*p*-tolylsulfinyl)octanoate, **1d**

Compound **1d** (0.450 g; 45%) was isolated as an orange oil from the starting materials (+)-(R)-1-(*p*-tolylsulfinyl)-2-propanone **5<sup>5a</sup>** (1.16 g; 5.9 mmol; 2 equiv.) and ethyl glutarate **2d** (0.54 ml; 2.95 mmol; 1 equiv.), by the method described for **1c**.  $R_f=0.56$  (ethyl acetate/dichloromethane, 1:1).  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=1.20$  (t, 3H,  $J=7$  Hz), 1.84 (m, 2H), 2.27 (t, 2H,  $J=7$  Hz), 2.30 (t, 2H,  $J=7$  Hz), 2.36 (s, 3H), 3.59 (AB system, 2H,  $J_{\text{AB}}=13$  Hz,  $\Delta\nu=24$  Hz), 4.07 (q, 2H,  $J=7$  Hz), 5.47 (s, 1H), 7.37 ((AB)<sub>2</sub> system, 4H,  $J_{\text{AB}}=8$  Hz,  $\Delta\nu=40$  Hz), 14.20 (broad s, 1H) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=14$ , 20.2, 21.2, 33, 37.5, 60.2, 65, 101.8, 129.8, 123.9, 142, 139.6, 172.6, 180.4, 195.3 ppm.

The preparation of **1e**,<sup>6b</sup> **1f**,<sup>6b</sup> **1g**<sup>6c</sup> and **1h**<sup>6a</sup> has been described elsewhere.

#### 4.7. (+)-(R<sub>S</sub>,2R)-1-(*p*-Tolylsulfinyl)-2-hydroxy-4-pentanone, **7a**

To a solution of  $\beta,\delta$ -diketosulfoxide **1a** (0.503 g; 2.11 mmol; 1 equiv.) in THF (30 ml) a solution of DIBAL-H (4.3 ml of a solution 1 M in toluene; 4.22 mmol; 2 equiv.) was added dropwise at  $-78^{\circ}\text{C}$ . Stirring was continued for 20 min at  $-78^{\circ}\text{C}$  before adding MeOH (15 ml) and then the solution was stirred for 30 min at rt. The solvent was evaporated and the residue was dissolved in AcOEt (100 ml), and saturated disodium

L-tartrate dihydrate (100 ml) was added. The stirring was continued until a clear phase-separation occurred. The aqueous layer was acidified to pH 5–6 with a 10% solution of  $\text{H}_2\text{SO}_4$  and extracted with AcOEt (3 $\times$ 100 ml). The combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated. The crude product was purified by column chromatography on metal-free silica gel (gradient hexane/dichloromethane, 4:1 to dichloromethane 100% for apolar products and dichloromethane/ethyl acetate, 4:1 to ethyl acetate 100% for the polar ones) to afford **7a** as a beige solid (177.5 mg, 35%).  $R_f=0.18$  (ethyl acetate/dichloromethane, 1:1).  $[\alpha]_{\text{D}}^{20}=+240$  (*c* 2, acetone). Mp = 94–95 $^{\circ}\text{C}$ .  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=2.12$  (s, 3H), 2.37 (s, 3H), 2.65 (AB fragment of an ABX system degenerated in A<sub>2</sub>, 2H), 2.85 (AB fragment of an ABX system, 2H,  $J_{\text{AX}}=9.5$  Hz,  $J_{\text{BX}}=3$  Hz,  $J_{\text{AB}}=13$  Hz,  $\Delta\nu=42$  Hz), 4.46 (s large, 1H), 4.60 (m, X of an ABX system, 1H), 7.39 ((AB)<sub>2</sub> system, 4H,  $J_{\text{AB}}=8$  Hz,  $\Delta\nu=38$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=21.3$ , 30.7, 49.4, 62.2, 62.9, 129.9, 123.9, 141.6, 139.7, 207.5 ppm. Anal. calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_3\text{S}$  (240.32): C, 59.97; H, 6.71. Found: C, 59.51; H, 6.82%.

#### 4.8. (+)-(R<sub>S</sub>,2S)-1-(*p*-Tolylsulfinyl)-8-(*t*-butyldimethylsilyloxy)-2-hydroxy-4-pentanone, **7c**

Compound **7c** (275 mg; 35%) was isolated as a beige solid from the starting material **1c** (0.783 g; 1.9 mmol; 1 equiv.), by the method described for **7a**.  $R_f=0.13$  (ethyl acetate/dichloromethane, 1:4). Mp = 64–65 $^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{20}=+87$  (*c* 1.14, chloroform).  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=0.005$  (s, 6H), 0.85 (s, 9H), 1.41–1.65 (m, 4H), 2.39 (s, 3H), 2.41 (t, 2H,  $J=7$  Hz), 2.63 (AB fragment of an ABX system degenerated in A<sub>2</sub>, 2H), 2.87 (AB fragment of an ABX system, 2H,  $J_{\text{AX}}=9.5$  Hz,  $J_{\text{BX}}=2.5$  Hz,  $J_{\text{AB}}=13$  Hz,  $\Delta\nu=49$  Hz), 3.56 (t, 2H,  $J=6$  Hz), 4.28 (s large, 1H), 4.60 (m, X of an ABX system, 1H), 7.41 ((AB)<sub>2</sub> system, 4H,  $J_{\text{AB}}=8$  Hz,  $\Delta\nu=37$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=-5.5$ , 18, 19.7, 21.2, 25.7, 31.9, 43.1, 48.4, 62.5, 62.8, 129.8, 133.7, 141.3, 139.8, 209.4 ppm. IR (film):  $\nu=3580$ –3260, 1705, 1100  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{21}\text{H}_{36}\text{O}_4\text{SSi}$  (412.66): C, 61.12; H, 8.79. Found: C, 60.94; H, 8.92%.

#### 4.9. (+)-(R<sub>S</sub>,5S)-Ethyl-5-oxo-7-hydroxy-8-(*p*-tolylsulfinyl)octanoate, **7d**

Compound **7d** (65 mg; 33%) was isolated as a yellow oil from the starting material **1d** (0.196 g; 0.58 mmol; 1 equiv.), by the method described for **7a**.  $R_f=0.28$  (ethyl acetate/dichloromethane, 1:1).  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=1.23$  (t, 3H,  $J=7$  Hz), 1.85 (q, 2H,  $J=7$  Hz), 2.28 (t, 2H,  $J=7$  Hz), 2.40 (s, 3H), 2.48 (t, 2H,  $J=7$  Hz), 2.70 (AB fragment of an ABX system degenerated in A<sub>2</sub>, 2H), 2.87 (AB fragment of an ABX system, 2H,  $J_{\text{AX}}=9.5$  Hz,  $J_{\text{BX}}=3$  Hz,  $J_{\text{AB}}=13.5$  Hz,  $\Delta\nu=56$  Hz), 4.09 (q, 2H,  $J=7$  Hz), 4.23 (d, 1H,  $J=3.5$  Hz), 4.61 (m, X of an ABX system, 1H), 7.42 ((AB)<sub>2</sub> system, 4H,  $J_{\text{AB}}=8$  Hz,  $\Delta\nu=36$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ): 14.2, 19.2, 21.1, 34.2, 42.35, 48.97, 51.89, 62.04, 69.88, 129.1, 132.9, 134.8, 142.2, 173.88, 207.3 ppm.

The preparation of **7e**,<sup>6b</sup> **7f**,<sup>6b</sup> **7g**<sup>14</sup> and **7h**<sup>6a</sup> has been described elsewhere.

#### 4.10. (*E*)-Ethyl 3-methoxy-2-butenolate, **9a**

To a solution of ethyl-acetoacetate (2 g; 0.016 mol; 1 equiv.) in DMSO (50 ml) was added K<sub>2</sub>CO<sub>3</sub> (3.17 g; 0.023 mol; 1.5 equiv.). After stirring for 1 h at rt, Me<sub>2</sub>SO<sub>4</sub> (1.30 ml; 0.021 mol, 1.3 equiv.) was added. The reaction was stirred 48 h and hydrolysed with water (50 ml) and diluted with ethyl acetate (50 ml). The aqueous layer was extracted with ethyl acetate (3×50 ml) and the combined organic layers were washed with brine (100 ml), dried (MgSO<sub>4</sub>) and concentrated. The crude oil was purified by column chromatography on silica gel (with hexane/ethyl acetate, 9:1 as eluent) to afford a colourless oil **9a** (1.63 g, 71%). *R*<sub>f</sub>=0.74 (ethyl acetate/hexane, 1:1). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ=1.27 (t, 3H, *J*=7 Hz), 2.22 (s, 3H), 3.63 (s, 3H), 4.16 (q, 2H, *J*=7 Hz), 5.01 (s, 1H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ=14.8, 19.22, 55.72, 59.68, 91.25, 168.2, 173.4 ppm. IR (film): ν=1700–1650, 1640–1600 cm<sup>-1</sup>. 230 mg of (*Z*)-isomer were also isolated. *R*<sub>f</sub>=0.44 (ethyl acetate/hexane, 1:1). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ=1.24 (t, 3H, *J*=7 Hz), 2.02 (s, 3H), 3.84 (s, 3H), 4.15 (q, 2H, *J*=7 Hz), 4.82 (s, 1H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ=14.5, 18.22, 55.4, 56.61, 97.4, 168.4, 169.46 ppm. IR (film): ν=1700–1650, 1640–1600 cm<sup>-1</sup>.

#### 4.11. (*E*)-Ethyl 3-methoxy-2-hexenoate, **9b**

To a solution of ethylbutyrylacetate (2 g; 0.013 mol; 1 equiv.) in DMSO (50 ml) was added K<sub>2</sub>CO<sub>3</sub> (2.62 g; 0.019 mol; 1.5 equiv.). After stirring for 1 h at rt, Me<sub>2</sub>SO<sub>4</sub> (1.20 ml; 0.017 mol, 1.3 equiv.) was added. The reaction was stirred 48 h and hydrolysed with water (50 ml) and diluted with ethyl acetate (50 ml). The aqueous layer was extracted with ethyl acetate (3×50 ml) and the combined organic layers were washed with brine (100 ml), dried (MgSO<sub>4</sub>) and concentrated. The crude oil was purified by column chromatography on silica gel (with hexane/ethyl acetate, 9:1 as eluent) to afford a colourless oil **9b** (1.31 g, 60%). *R*<sub>f</sub>=0.64 (ethyl acetate/hexane, 1:1). <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ=0.94 (t, 3H, *J*=7.3 Hz), 1.28 (t, 3H, *J*=7.3 Hz), 1.58 (sext, 2H, *J*=7.3 Hz), 2.71 (m, 2H), 3.63 (s, 3H), 4.14 (q, 2H, *J*=7.3 Hz), 4.99 (s, 1H) ppm. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ=13.8, 14.4, 20.9, 33.8, 55.3, 59.3, 90.5, 167.7, 176.7 ppm. IR (film): ν=1700–1650, 1640–1600 cm<sup>-1</sup>.

#### 4.12. (+)-(*E*,*R*<sub>S</sub>)-1-(*p*-Tolylsulfinyl)-4-methoxy-3-butene-2-one, **10a**

Compound **10a** (0.478 g; 55%) was isolated as a yellow oil from the starting materials (+)-(*R*)-methyl-*p*-tolylsulfoxide (1.2 g; 7.8 mmol; 2.1 equiv.) and **9a** (0.51 g; 3.1 mmol; 1 equiv.), by the method described for **1a**. *R*<sub>f</sub>=0.53 (ethyl acetate/dichloromethane, 1:1). [α]<sub>D</sub><sup>20</sup>=+262 (*c* 0.8 CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>):

δ=2.29 (s, 3H), 2.51 (s, 3H), 3.67 (s, 3H), 3.72 (B fragment of an AB system, 1H, *J*<sub>AB</sub>=21 Hz, Δγ=55 Hz), 3.92 (A fragment of an AB system, 1H, *J*<sub>AB</sub>=21 Hz, Δγ=55 Hz), 5.51 (s, 1H), 7.28 (B fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγ=68 Hz), 7.51 (A fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγ=68 Hz) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ=20.66, 21.81, 34.9, 56.29, 70.82, 99.74, 124.6, 130.3, 140.6, 142.4, 176.3, 188.81 ppm. IR (film): ν=1660–1640, 1620–1580 cm<sup>-1</sup>.

#### 4.13. (-)-(*E*,*R*<sub>S</sub>)-1-(*p*-Tolylsulfinyl)-4-methoxy-3-hexene-2-one, **10b**

Compound **10b** (0.478 g; 55%) was isolated as a yellow oil from the starting materials (-)-(*S*)-methyl-*p*-tolylsulfoxide (0.99 g; 6.48 mmol; 2.1 equiv.) and **9b** (0.53 g; 3.09 mmol; 1 equiv.), by the method described for **1b**. *R*<sub>f</sub>=0.43 (ethyl acetate/dichloromethane, 1:1). [α]<sub>D</sub><sup>20</sup>=-216 (*c* 1.14, CHCl<sub>3</sub>). <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ=0.89 (t, 3H, *J*=7.3 Hz), 1.50 (sext, 2H, *J*=7.3 Hz), 2.65 (m, 2H), 2.41 (s, 3H), 3.61 (s, 3H), 3.69 (B fragment of an AB system, 1H, *J*<sub>AB</sub>=19 Hz, Δγ=54 Hz), 3.88 (A fragment of an AB system, 1H, *J*<sub>AB</sub>=19 Hz, Δγ=54 Hz), 5.91 (s, 1H), 7.30 (B fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγ=68 Hz), 7.53 (A fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγ=68 Hz) ppm. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ=13.9, 20.6, 21.5, 34.9, 55.9, 70.6, 98.9, 124.3, 130.0, 140.2, 141.9, 179.7, 188.1 ppm. IR (film): ν=1660–1640, 1620–1580 cm<sup>-1</sup>.

#### 4.14. (*E*,2*S*,*R*<sub>S</sub>)-1-(*p*-Tolylsulfinyl)-4-methoxy-3-butene-2-ol, **11a**

Using the method described for **7a**, reduction of **10a** led to a 6/4 mixture of **11a** and **12a** with 20% of recovered starting material. A sample of compound **11b** could be separated from **12a** after flash chromatography, but contaminated by the corresponding enone **17a** resulting from its degradation on silica gel. *R*<sub>f</sub>=0.31 (ethyl acetate/dichloromethane, 1:1). <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ=2.12 (s, 3H), 2.42 (s, 3H), 2.88 (AB fragment of an ABX system, 2H, *J*<sub>AX</sub>=11.2 Hz, *J*<sub>BX</sub>=2 Hz, *J*<sub>AB</sub>=13.6 Hz, Δγ=118 Hz), 3.39 (s broad, 1H), 3.47 (s, 3H), 4.49 (d, 1H, *J*=12 Hz), 4.78–4.94 (m, X fragment of an ABX system, 1H), 7.39 (B fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγν=44 Hz), 7.58 (A fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγ=44 Hz) ppm.

#### 4.15. (*E*)-*S*(*R*)]-1-(*p*-Tolylsulfinyl)-4-oxo-2-butene, **17a**

Enone **17a** resulting from chromatography of **11a** was isolated as colourless oil. *R*<sub>f</sub>: 0.3 (dichloromethane/ethyl acetate: 3/2). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ=2.22 (s, 3H), 2.46 (s, 3H), 3.69 (AB fragment of an ABX system, 2H, *J*<sub>AX</sub>=*J*<sub>BX</sub>=8 Hz, *J*<sub>AB</sub>=13 Hz, Δγ=38 Hz), 6.09 (d, 1H, *J*<sub>trans</sub>=16 Hz), 6.58 (dt, X fragment of an ABX system, 1H, *J*<sub>BX</sub>=8 Hz, *J*<sub>trans</sub>=16 Hz), 7.37 (B fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγν=44 Hz), 7.56 (A fragment of an (AB)<sub>2</sub> system, 2H, *J*<sub>AB</sub>=8 Hz, Δγ=44 Hz) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ=1.4, 21.9, 27.65, 59.53, 124.51, 124.6, 130.4, 133.52, 137.6, 139.42, 142.56, 197.4 ppm. [α]<sub>D</sub><sup>20</sup>=+57 (*c* 0.15, CHCl<sub>3</sub>).

**4.16. (E,2R,S<sub>S</sub>)-1-(p-Tolylsulfinyl)-4-methoxy-3-hexene-2-ol, 11b**

Using the method described for **7a**, reduction of **10b** led to a 7/3 mixture of **11b** and **12b**. A sample of compound **11b** could be separated from **12b** after flash chromatography but contaminated traces of the corresponding enone **17b** resulting from its degradation on silica gel.  $R_f=0.34$  (ethyl acetate/dichloromethane, 1:1). <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>):  $\delta=0.72$  (t, 2H,  $J=7.3$  Hz), 1.12–1.50 (m, 2H), 1.79–1.96 (m, 2H), 2.41 (s, 3H), 2.75 (AB fragment of an ABX system, 2H,  $J_{AX}=10.4$  Hz,  $J_{BX}=2$  Hz,  $J_{AB}=13.2$  Hz,  $\Delta\nu=124$  Hz), 3.46 (s, 3H), 3.65 (s broad, 1H), 4.45 (d, 1H,  $J=11$  Hz), 4.70–4.90 (m, X fragment of an ABX system, 1H), 7.33 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8$  Hz,  $\Delta\gamma=44$  Hz), 7.53 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8$  Hz,  $\Delta\gamma=44$  Hz) ppm.

**4.17. (E,2R,R<sub>S</sub>)-1-(p-Tolylsulfinyl)-4-methoxy-3-butene-2-ol, 12a**

Compound **12a** (0.072 g; 81%) was isolated as a pale yellow oil from the starting material **10a** (0.084 g, 0.34 mmol), by the method described for **16b**. Purification was achieved by flash chromatography (ethyl acetate/hexane, 3/7).  $R_f=0.27$  (ethyl acetate/dichloromethane, 1:1). <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>):  $\delta=1.90$  (s, 3H), 2.41 (s, 3H), 2.97 (AB fragment of an ABX system, 2H,  $J_{AX}=9$  Hz,  $J_{BX}=4.1$  Hz,  $J_{AB}=13$  Hz,  $\Delta\nu=82$  Hz), 3.36 (d, 1H,  $J=2$  Hz), 3.5 (s, 3H), 4.51 (d, 1H,  $J=11$  Hz), 4.89–4.98 (m, X of an ABX system, 1H), 7.33 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8$  Hz,  $\Delta\gamma=44$  Hz), 7.5 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8$  Hz,  $\Delta\gamma=44$  Hz) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta=17.24, 21.82, 54.78, 66.8, 98.77, 124.3, 130.4, 141.2, 142.3, 158.02$  ppm.  $[\alpha]_D^{20}=+188$  ( $c$  0.9, CHCl<sub>3</sub>).

**4.18. (E,2S,S<sub>S</sub>)-1-(p-Tolylsulfinyl)-4-methoxy-3-hexene-2-ol, 12b**

Compound **12b** (0.042 mg; 63%) was isolated as a white solid from the starting material **10b** (0.058 g, 0.23 mmol), by the method described for **16b**. Purification was achieved by washing the crude product with ether.  $R_f=0.30$  (ethyl acetate/dichloromethane, 1:1). <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>):  $\delta=0.88$  (t, 2H,  $J=7.3$  Hz), 1.50 (m, 2H), 2.16 (t, 2H,  $J=7.3$  Hz), 2.41 (s, 3H), 2.95 (AB fragment of an ABX system, 2H,  $J_{AX}=8.5$  Hz,  $J_{BX}=3.7$  Hz,  $J_{AB}=13$  Hz,  $\Delta\gamma=84$  Hz), 3.30 (d, 1H,  $J=2$  Hz), 3.48 (s, 3H), 4.47 (d, 1H,  $J=11$  Hz), 4.85–4.99 (m, X of an ABX system, 1H), 7.34 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8$  Hz,  $\Delta\gamma=44$  Hz), 7.57 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8$  Hz,  $\Delta\gamma=44$  Hz) ppm. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta=13.9, 21.2, 21.6, 33.0, 54.5, 64.0, 66.2, 98.4, 124.1, 130.2, 140.8, 142.1, 161.2$  ppm. Anal. calcd for C<sub>15</sub>H<sub>22</sub>O<sub>3</sub>S (282.39): C, 63.80; H, 7.85. Found: C, 63.85; H, 8.02%.

**4.19. Ethyl 3-(1,3-dioxolane)hexanoate<sup>15</sup>**

A solution of ethyl butyrylacetate (4 g; 0.025 mol; 1 equiv.), freshly distilled ethylene glycol (3.1 ml; 0.05

mol; 2.2 equiv.) and TMSCl (14.1 ml; 0.11 mol; 4.4 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (120 ml) was heated at reflux under argon for 5 days. The mixture was cooled to rt and treated with saturated NaHCO<sub>3</sub> (200 ml). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were dried (MgSO<sub>4</sub>) and evaporated. The yellow oil obtained was purified by distillation to afford ethyl 3-(1,3-dioxolane)-hexanoate (4.44 g; 86%).  $R_f=0.27$  (ethyl acetate/hexane, 1:1). bp=107–110°C. <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>):  $\delta=0.92$  (t, 3H,  $J=7.3$  Hz), 1.26 (t, 3H,  $J=7.3$  Hz), 1.31–1.50 (m, 2H), 1.73–1.81 (m, 2H), 2.62 (s, 2H), 3.93–4.00 (m, 4H), 4.14 (q, 2H,  $J=7.3$  Hz) ppm. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta=13.5, 16.8, 39.9, 42.6, 60.4, 65.0, 109.4, 169.6$  ppm. IR (film):  $\nu=1720$  cm<sup>-1</sup>. Anal. calcd for C<sub>10</sub>H<sub>8</sub>O<sub>4</sub> (202.25): C, 59.39; H, 8.97. Found: C, 59.41; H, 8.91%.

**4.20. (-)-(S<sub>S</sub>)-1-(p-Tolylsulfinyl)-4-(1,3-dioxolane)-2-oxo-heptane, 13**

Compound **13** (3.13 g; 68%) was isolated as a yellow oil from the starting materials (+)-(S)-methyl-*p*-tolylsulfoxide (5.04 g; 32.7 mmol; 2.2 equiv.) and ethyl 3-(1,3-dioxolane)-hexanoate (3 g; 14.8 mmol; 1 equiv.), by the method described for **1b**.  $R_f=0.56$  (ethyl acetate/dichloromethane, 1:1).  $[\alpha]_D^{20}=-167$  ( $c$  1, acetone). <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>):  $\delta=0.86$  (t, 3H,  $J=7$  Hz), 1.22–1.42 (m, 2H), 1.49–1.59 (m, 2H), 2.40 (s, 3H), 2.72 (B fragment of an AB system, 1H,  $J_{AB}=13.52$  Hz,  $\Delta\gamma=18.6$  Hz), 2.85 (A fragment of an AB system, 1H,  $J_{AB}=13.52$  Hz,  $\Delta\gamma=18.6$  Hz), 3.91 (s, 4H), 3.97 (s, 2H), 7.32 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8.02$  Hz,  $\Delta\gamma=42.3$  Hz), 7.53 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{AB}=8.02$  Hz,  $\Delta\gamma=42.3$  Hz) ppm. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta=13.4, 16.0, 20.8, 39.5, 51.1, 64.2, 68.4, 108.8, 123.5, 129.4, 139.2, 141.4, 198.8$  ppm. Anal. calcd for C<sub>16</sub>H<sub>22</sub>O<sub>4</sub>S (310.41): C, 61.91; H, 7.14. Found: C, 61.76; H, 6.97%.

**4.21. (-)-(2R,S<sub>S</sub>)-1-(p-Tolylsulfinyl)-4-heptanone-2-ol, 7b**

To a solution of **13** (2.03 g; 6.55 mmol; 1 equiv.) in THF (100 ml) was added dropwise under argon and at -78°C a solution of DIBAL-H (10.9 ml of a 1 M solution in toluene; 16.0 mmol; 2.5 equiv.). Stirring was continued for 1.5 h at -78°C before adding MeOH (20 ml). Then the solvent was evaporated and the residue was dissolved in AcOEt (40 ml) and saturated disodium L-tartrate dihydrate (80 ml) was added. The stirring was continued until a clear phase separation occurred. The aqueous layer was extracted with AcOEt (3×100 ml). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. The yellow oil obtained (**14**) was suspended in a mixture of THF (20 ml) and water (15 ml) and oxalic acid (0.06 g; 0.6 mmol; 0.1 equiv.) was added. The mixture was refluxed for 2 h and treated with saturated NaHCO<sub>3</sub>. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), and concentrated. The crude product was washed with ether to afford **7b** (1.40 g; 80%) as a white solid. Compound **7b** could be also obtained from (-)-(S<sub>S</sub>)-1-(*p*-tolylsulfinyl)-2,4-heptanedione **1b** (33%) by

the method described for **7a**.  $R_f=0.42$  (ethyl acetate/dichloromethane, 1:1).  $[\alpha]_D^{20}=-222$  ( $c$  1, acetone). Mp = 80–83°C.  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=0.89$  (t, 3H,  $J=7.3$  Hz), 1.57 (sext, 2H, 7.3 Hz), 2.39 (t, 2H,  $J=7.3$  Hz), 2.43 (s, 3H), 2.64 (A<sub>2</sub> system, d, 2H,  $J=6.2$  Hz) 2.86 (AB fragment of an ABX system, 2H,  $J_{\text{AX}}=9.5$  Hz,  $J_{\text{BX}}=2.6$  Hz,  $J_{\text{AB}}=13.5$  Hz,  $\Delta\gamma=55$  Hz), 4.10 (s broad, 1H), 4.57–4.69 (m, X of an ABX system, 1H), 7.35 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.02$  Hz,  $\Delta\gamma=36$  Hz), 7.53 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.02$  Hz,  $\Delta\gamma=36$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=13.7, 17.1, 21.5, 45.6, 48.5, 61.5, 63.7, 124.1, 130.2, 139.8, 141.8, 210.3$  ppm. IR (film):  $\nu=3380, 2950, 1700, 1080$   $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{14}\text{H}_{20}\text{O}_3\text{S}$  (268.39): C, 62.66; H, 7.51. Found: C, 62.75; H, 7.67%.

#### 4.22. (–)-(2*R*,*S*<sub>5</sub>)-1-(*p*-Tolylsulfinyl)-4-(1,3-dioxolane)-heptane-2-ol, **14**

An analytical sample of **14** could be obtained by purification by column chromatography on silica gel (hexane/ethyl acetate 10:1) as a yellow oil.  $R_f=0.43$  (ethyl acetate/dichloromethane, 1:1).  $[\alpha]_D^{20}=-236$  ( $c$  1.22, acetone).  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=0.86$  (t, 3H,  $J=7.2$  Hz), 1.20–1.42 (m, 2H), 1.49–1.61 (m, 2H), 1.81 (AB fragment of a degenerated ABX system, 2H,  $J_{\text{AX}}=1.94$  Hz), 2.38 (s, 3H), 2.81 (m, 2H), 3.90 (s, 4H), 4.09 (s broad, 1H), 4.39–4.51 (m, 1H), 7.30 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.14$  Hz,  $\Delta\gamma=42.5$  Hz), 7.51 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.14$  Hz,  $\Delta\gamma=42.5$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=14.3, 17.1, 21.5, 39.6, 42.6, 63.1, 64.5, 64.7, 64.9, 111.4, 124.0, 130.0, 140.9, 141.4$  ppm. IR (film):  $\nu=3520$ –3480, 2980–2800  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{16}\text{H}_{24}\text{O}_4\text{S}$  (312.42): C, 61.51; H, 7.74. Found: C, 61.64; H, 7.83%.

#### 4.23. (–)-(2*S*,*S*<sub>5</sub>)-1-(*p*-Tolylsulfinyl)-4-heptanone-2-ol, **16**

To anhydrous  $\text{ZnI}_2$  (173 mg, 0.54 mmol; 1.1 equiv.), a solution of ketosulfoxide **13** (153 mg, 0.49 mmol; 1 equiv.) was added. After stirring for 30 min at rt, the solution was cooled to –78°C and (0.82 ml, 1.23 mmol; 2.5 equiv.) of a 1.5 M solution of DIBAL-H in toluene was added dropwise and stirred for 1 h. The reaction mixture was quenched with 10 ml of MeOH. The solvent was then evaporated and a saturated disodium L-tartrate dihydrate solution (30 ml) and 30 ml of ethyl acetate were added. The stirring was continued until a clear phase-separation occurred. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated. The yellow oil obtained (**15**) was suspended in a mixture of THF (20 ml) and water (15 ml) and oxalic acid (45 mg; 0.5 mmol; 0.1 equiv.) was added. The mixture was refluxed for 2 h and treated with a saturated solution of  $\text{NaHCO}_3$ . The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. The crude product was washed with ether to afford **16b**.  $R_f=0.22$  (ethyl acetate/dichloromethane, 1:1).  $[\alpha]_D^{20}=-184$  ( $c$

1.02, acetone).  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=0.90$  (t, 3H,  $J=7.3$  Hz), 1.58 (sext, 2H, 7.3 Hz), 2.40 (t, 2H,  $J=7.3$  Hz), 2.41 (s, 3H), 2.78 (AB fragment of an ABX system, 2H,  $J_{\text{AX}}=7.3$  Hz,  $J_{\text{BX}}=4.9$  Hz,  $J_{\text{AB}}=17.5$  Hz,  $\Delta\gamma=37.7$  Hz), 2.93 (AB fragment of an ABX system, 2H,  $J_{\text{AX}}=7.5$  Hz,  $J_{\text{BX}}=4.4$  Hz,  $J_{\text{AB}}=12.9$  Hz,  $\Delta\gamma=24$  Hz), 3.98 (d, 1H,  $J=2.7$  Hz), 4.50–4.55 (m, X of an ABX system, 1H), 7.32 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.22$  Hz,  $\Delta\gamma=41.5$  Hz), 7.53 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.22$  Hz,  $\Delta\gamma=41.5$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=13.7, 17.1, 21.5, 45.6, 48.4, 62.1, 64.8, 124.2, 130.2, 140.3, 142.0, 210.5$  ppm. Anal. calcd for  $\text{C}_{14}\text{H}_{20}\text{O}_3\text{S}$  (268.39): C, 62.66; H, 7.51. Found: C, 62.60; H, 7.46%.

#### 4.24. (–)-(2*S*,*S*<sub>5</sub>)-1-(*p*-Tolylsulfinyl)-4-(1,3-dioxolane)-heptane-2-ol, **15**

An analytical sample of **15** could be obtained by crystallisation in ether as a white solid.  $R_f=0.42$  (ethyl acetate/dichloromethane, 1:1).  $[\alpha]_D^{20}=-44$  ( $c$  0.5, acetone). Mp = 70–73°C.  $^1\text{H NMR}$  (200 MHz;  $\text{CDCl}_3$ ):  $\delta=0.90$  (t, 3H,  $J=7.2$  Hz), 1.20–1.48 (m, 2H), 1.55–1.67 (m, 2H), 1.91 (B fragment of an ABX system, 1H,  $J_{\text{BX}}=3.38$  Hz,  $J_{\text{AB}}=14.7$  Hz,  $\Delta\gamma=29$  Hz), 2.04 (A fragment of an ABX system, 1H,  $J_{\text{AX}}=8.56$  Hz,  $J_{\text{AB}}=14.7$  Hz,  $\Delta\gamma=29$  Hz), 2.41 (s, 3H), 2.85 (B fragment of an ABX system, 1H,  $J_{\text{BX}}=4.46$  Hz,  $J_{\text{AB}}=13.1$  Hz,  $\Delta\gamma=44.3$  Hz), 3.05 (A fragment of an ABX system, 1H,  $J_{\text{AX}}=7.08$  Hz,  $J_{\text{AB}}=13.1$  Hz,  $\Delta\gamma=44.3$  Hz), 3.95 (s, 4H), 4.02 (s broad, 1H), 4.19–4.31 (X fragment of a ABX system, m, 1H), 7.33 (B fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.14$  Hz,  $\Delta\gamma=42.5$  Hz), 7.57 (A fragment of an (AB)<sub>2</sub> system, 2H,  $J_{\text{AB}}=8.14$  Hz,  $\Delta\gamma=42.5$  Hz) ppm.  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta=14.3, 17.2, 21.5, 39.6, 42.3, 64.1, 64.2, 64.7, 64.9, 111.6, 124.3, 130.1, 140.8, 141.7$  ppm. IR (film):  $\nu=3520$ –3480, 2980–2800  $\text{cm}^{-1}$ . Anal. calcd for  $\text{C}_{16}\text{H}_{24}\text{O}_4\text{S}$  (312.42): C, 61.51; H, 7.74. Found: C, 61.39; H, 7.74%.

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