Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 5807–5810
Tetrahedron Letters

Preparation of enantiomerically pure (*E*)-β-sulfinylenones from β-ketoesters

Naïma Khiri, Amandine Lefranc, Guy Solladié and Gilles Hanquet*

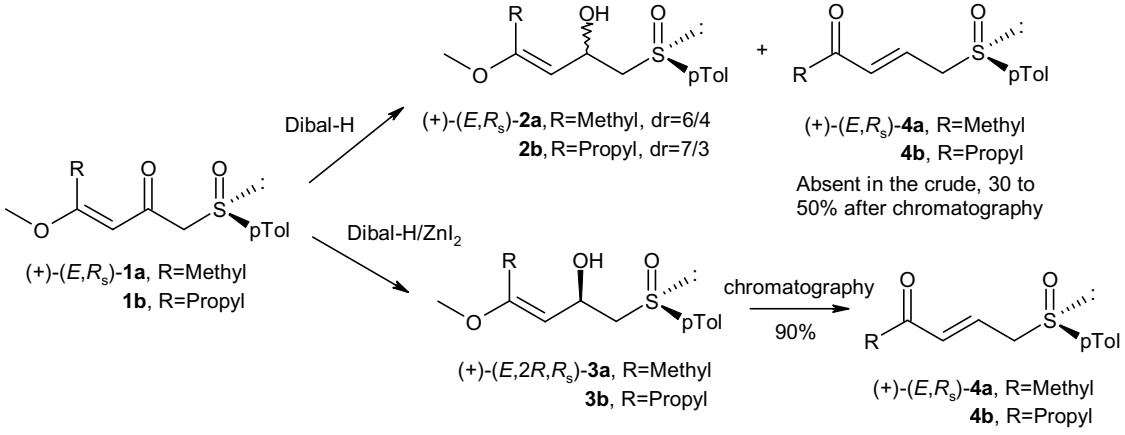
Laboratoire de Stéréochimie associéau CNRS, ECPM, Université Louis Pasteur, 25 rue Becquerel, 67087 Strasbourg, France

Received 20 April 2005; revised 28 June 2005; accepted 28 June 2005

Abstract—Enantiomerically pure (*E*)-β-sulfinylenones are smoothly prepared from β-ketoesters in three steps with good overall yield. Since they can be the substrates of many diastereoselective reactions, they represent versatile precursors of a wide range of chiral building blocks. We propose a rationale to explain the formation of (*E*)-β-sulfinylenones from the corresponding δ-enol-methylethers.

We recently reported that enantiomerically pure δ-protected β,δ-diketosulfoxides[1] were important building blocks for the preparation of polyhydroxylated compounds.[2] We pointed out that the choice of the δ-protecting group was important to obtain good yields and high diastereoselectivity in the DIBAL-H or DIBAL-H/ZnX_2 reductions of such compounds. During these investigations, we observed in the case of the reduction of δ-enol-methylether **1a**,**b**, that the purification of the resulting β-hydroxysulfoxides **2a**,**b** and **3a**,**b** on silica gel delivered the corresponding β-sulfinylenones **4a**,**b** as side products (Scheme 1).

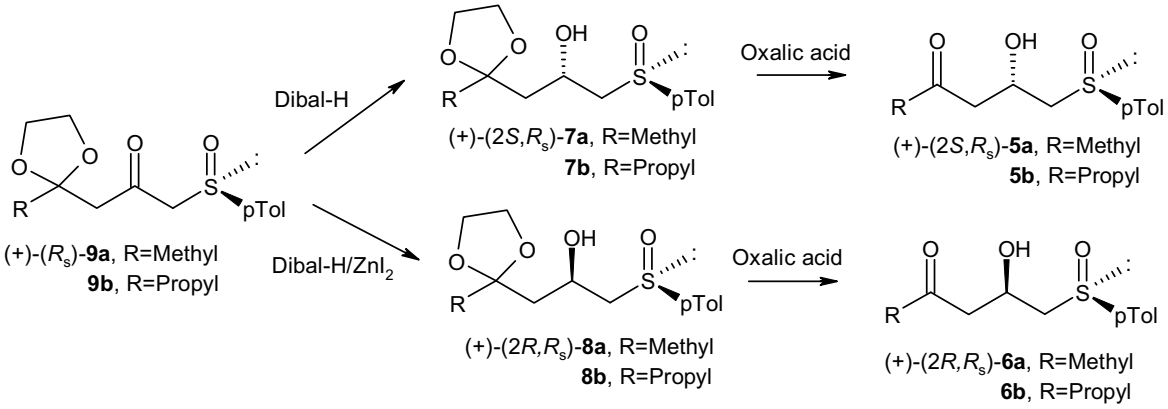
Such enones bearing a chiral non racemic sulfinyl moiety at β-position are potentially versatile building blocks as they are the substrate for several diastereoselective reactions (e.g., cycloadditions, 1,4- or 1,2-additions, Baylis Hillman reactions). The β-sulfinylenone **4a** has already



Scheme 1.

Keywords: (*E*)-β-Sulfinylenones; β-Ketoesters.
* Corresponding author. Tel.: +33 390242746; fax: +33 390242742; e-mail: ghanquet@chimie.u-strasbg.fr

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.151



Scheme 2.

been briefly mentioned in the literature by Bravo et al.[3] as a side product of the 1,4-addition of methylsulfoxide anion on (*E*)-4-ethoxy-3-buten-2-one.

In this regard, we report in this paper some mechanistic insights which rationalise the acid-catalysed formation of the β-sulfinylenones **4a**,**b** from β-hydroxysulfoxides **2a**,**b** and **3a**,**b** and the extension to the preparation of several analogues from different β-ketoesters.

Our first hypothesis to explain the formation of the β-sulfinylenones **4a**,**b** from **2a**,**b** and **3a**,**b** on silica gel was the hydrolysis of the enol–ether moiety followed by an elimination of the hydroxy group. However, we were able to prepare δ-keto-β-hydroxysulfoxides **5a**,**b** and **6a**,**b** following previously described procedure[1] and their purification on silica gel did not result in the formation of the corresponding β-sulfinylenones **4a**,**b** (Scheme 2).

Furthermore, stronger acidic treatment (HCl 5%/THF/water) of compounds **5a**,**b** or **6a**,**b** resulted in very low yields of β-sulfinylenones **4a**,**b** (10%).

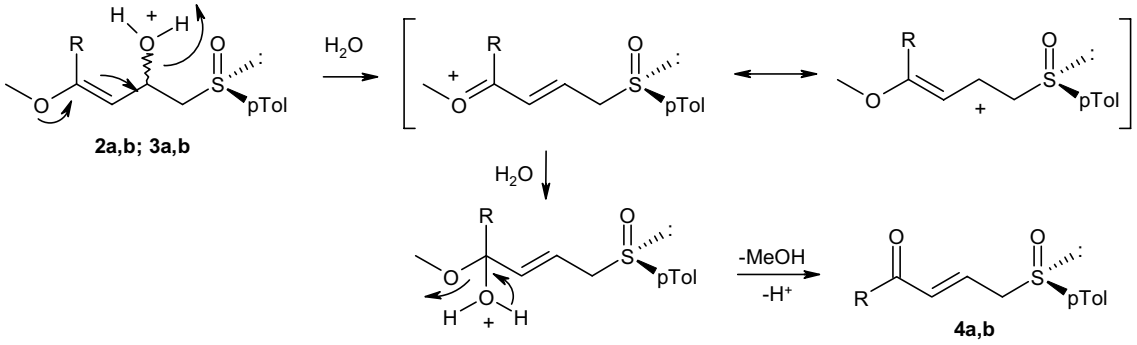
Additionally, we observed that the diastereoisomers **3a**,**b** were more readily transformed on silica gel to the corresponding β-sulfinylenones **4a**,**b** than the C-2 epimers **2a**,**b** (Scheme 1). Diastereoisomers **2a**,**b** could be isolated from the crude reduction mixture by flash chromatography whereas purification of **3a**,**b** afforded large amounts of β-sulfinylenones **4a**,**b**.

In fact, we propose a protonation of the hydroxyl group and subsequent formation of a carbocation with release of water which is able to hydrolyse the oxonium moiety and give the conjugated carbonyl derivative (Scheme 3).

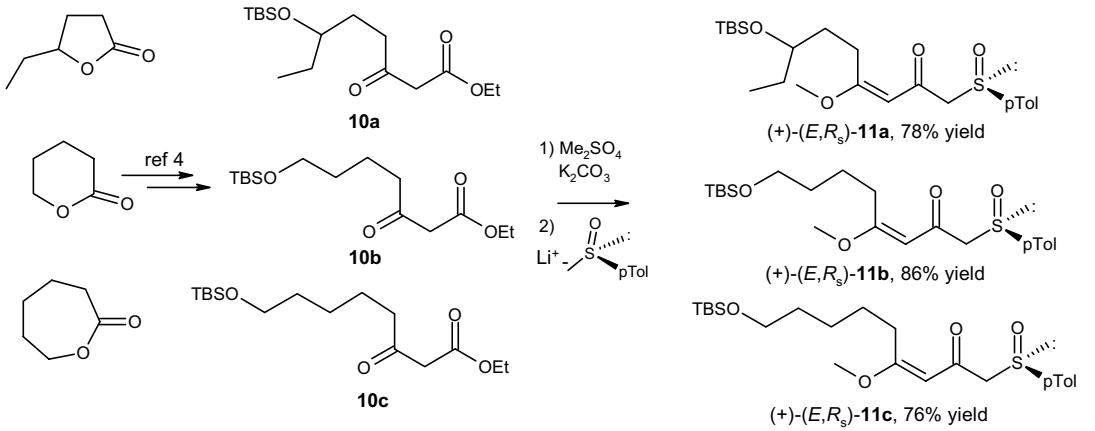
$NaBH_4$ reduction of **1a**,**b** afforded a 1/1 diastereoisomeric mixture of β-hydroxysulfoxides **2a**,**b** and **3a**,**b**. In this case, the higher proportion of the 2*S* diastereoisomer in the mixture retarded the subsequent elimination and required a stronger acid than silica gel (Amberlyst®) to obtain in good yields (71% and 78%, respectively) the corresponding β-sulfinylenones **4a**,**b**.

We described a few months ago a straightforward access to the 5-, 6- or 7-silyloxy-3-ketoesters **10a**–**c** by enolate ring-opening of the corresponding γ-, δ- and ε-lactones.[4] We thought that such β-ketoesters could be good candidates for the extension of our methodology to prepare functionalised enantiomerically pure β-sulfinylenones. β-Ketoesters **10a**–**c** were transformed into the corresponding methyl enol–ethers and condensed with the (*R*)-methylsulfoxide anion to give the δ-protected β,δ-diketosulfoxides **11a**–**c** (Scheme 4) with excellent overall yields.[5]

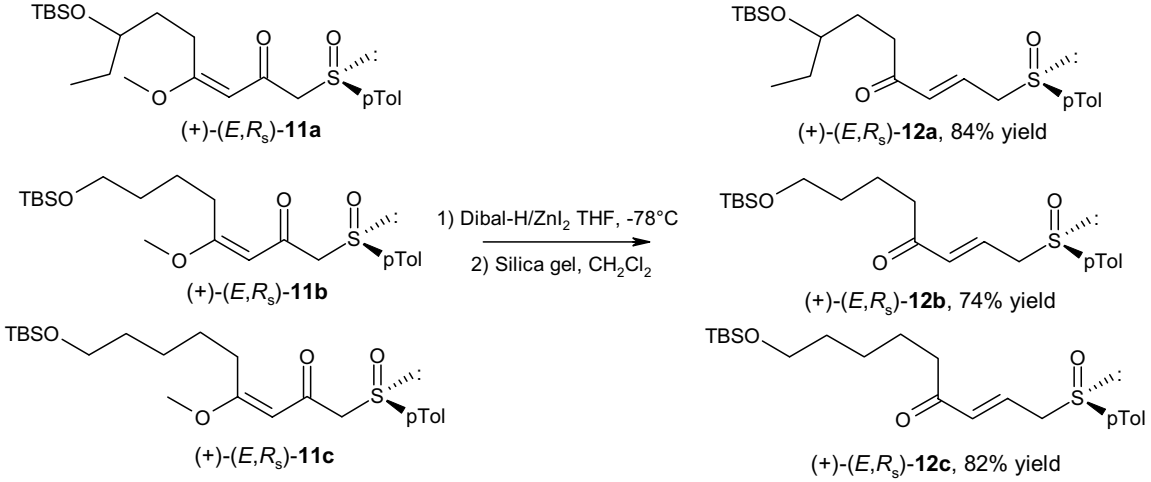
The reduction of compounds **11** by DIBAL-H/ZnI_2 (1.5 equiv)[6] followed by overnight stirring with silica gel in dichloromethane led directly to the formation of β-sulfinylenones **12a**–**c** in good yields after chromatography (Scheme 5).[7] The use of diastereoselective conditions for the reduction was essential to avoid the use of



Scheme 3.



Scheme 4.



Scheme 5.

strong acid during the elimination step which resulted in the deprotection of the silyl ether.

In conclusion, we have described an efficient preparation of enantiomerically pure β-sulfinylenones **4a**,**b** and **12a**–**c** which represent potentially versatile precursors of a wide range of chiral building blocks. Diastereoselective transformations of these substrates are now under investigation in our laboratory.

References and notes

1. Hanquet, G.; Salom-Roig, X. R.; Lanners, S.; Solladié, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1291–1301.
2. Hanquet, G.; Colobert, F.; Lanners, S.; Solladié, G. *ARKIVOC* **2003**, *vii*, 328.
3. Bravo, P.; Bruché, L.; Farina, A.; Gerus, I. I.; Kolytcheva, M. T.; Kukhar, V. P.; Meille, S. V.; Viani, F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1667–1670.
4. Lanners, S.; Khiri, N.; Hanquet, G.; Solladié, G. *Tetrahedron Lett.* **2005**, *46*, 619–622.
5. Compound **11a**: $[\alpha]_D$ +132 (*c* 2, acetone); compound **11b**: $[\alpha]_D$ +108 (*c* 2, acetone); compound **11c**: $[\alpha]_D$ +167 (*c* 2, acetone).
6. In contrast with previously described conditions,[1] the use of 1.5 equiv instead of 2.5 equiv of DIBAL-H 1 M in toluene for reduction of compounds **11** gave better isolated yields.
7. Typical procedure for β-sulfinylenone preparation from δ-enol-methylether **10**: to a solution of diisopropylamine (2.3 equiv) dissolved in dry THF (40 ml) under argon, cooled to −78 °C and *n*-BuLi (1.6 M in hexane; 2.3 equiv) was added dropwise over 15 min, a solution of (+)-methyl-*p*-tolylsulfoxide (2.1 equiv) in 30 ml of anhydrous THF via cannula. After 1 h in the same temperature, the methyl enol ether **10** (9.07 mmol; 1 equiv) in 40 ml THF anhydrous was added over 10 min. The reaction mixture was gradually allowed to return to room temperature and stirred for a further period of 4 h at room temperature. The reaction mixture was then quenched with aqueous saturated NH_4Cl (20 ml) and washed with AcOEt and brine (10 ml). The organic layer was dried over sodium sulfate and evaporated under vacuum. The crude product was purified by gradient chromatography on demetalled[8] silica gel using cyclohexane/AcOEt as eluent to give pure products **11**.

To anhydrous ZnI_2 (1.1 equiv), a solution of ketosulfoxide **11** (1 equiv) was added. After stirring for 30 min at room temperature, the solution was cooled to −78 °C and (1.5 equiv) of a solution of DIBAL-H in toluene was added dropwise and stirred for 1 h. The reaction mixture was quenched with (15 ml) of MeOH. The solvent was then evaporated and a saturated disodium L-tartrate dihydrate and ethyl acetate were added (15 ml each). 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 ($MgSO_4$) and evaporated, the crude product mixture was treated with silica gel. After stirring for 14 h at room temperature, the silica gel was filtrated and washed twice with a small amount of ethyl acetate. The solvent was removed under reduced pressure. The obtained residue was finally purified by gradient column chromatography on demetalled[8] silica gel (cyclohexane/AcOEt as eluent) to give the corresponding (*E*)-β-sulfinylenones **12**.

(+)-(*E*,R_S)-1-(*p*-Tolylsulfinyl)-7-(*tert*-butyldimethylsilyloxy)-2-nonene-4-one **12a**: yield: 84% $R_f = 0.66$ (1/1 CH_2Cl_2/AcOEt). $[\alpha]_D^{20}$ +103 (*c* 1, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.047$ (s, 6H), 0.89 (s, 9H), 0.86 (t, 3H, $J = 7.4$ Hz), 1.44 (m, 2H), 1.68 (m, 2H), 2.42 (s, 3H), 2.55 (m, 2H), 3.65 (m, 3H), 6.14 (td, 1H, $J_{trans} = 15.5$ Hz, 0.4Hz), 6.55 (td, 1H, $J = 7$ Hz, 7.5 Hz), 7.34 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 7.8$ Hz, $\Delta\nu = 42$ Hz), 7.5 (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 7.8$ Hz, $\Delta\nu = 42$ Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.1$, 142.1, 139, 136.5, 132.45, 129.95, 124.15, 72.35, 59.22, 36.22, 29.70, 29.68, 25.88, 21.44, 18.08, 9.52, −4.45 ppm.

(+)-(*E*,R_S)-1-(*p*-Tolylsulfinyl)-8-(*tert*-butyldimethylsilyloxy)-2-octene-4-one **12b**: yield: 74% $R_f = 0.52$ (1/1 CH_2Cl_2/AcOEt). $[\alpha]_D^{20}$ +60 (*c* 0.2, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.9 (s, 9H), 1.55 (m, 2H), 1.65 (m, 2H), 2.42 (s, 3H), 2.57 (t, 2H, $J = 7$ Hz), 3.55 to 3.7 (m, 5H), 6.1 (td, 1H, $J_{trans} = 16$ Hz, 0.7 Hz), 6.6 (td, 1H, $J = 16$ Hz, 7.5 Hz), 7.35 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 7.9$ Hz, $\Delta\nu = 42$ Hz), 7.46 (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 7.9$ Hz, $\Delta\nu = 42$ Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199$, 142.1, 139, 136.5, 131.9, 130, 124.15, 62.7, 59.2, 40.25, 32.2, 26.9, 25.9, 21.45, 18.3, −3.6 ppm.

(+)-(*E*,R_S)-1-(*p*-Tolylsulfinyl)-9-(*tert*-butyldimethylsilyloxy)-2-nonene-4-one **12c**: yield: 82% $R_f = 0.6$ (1/1 CH_2Cl_2/AcOEt). $[\alpha]_D^{20}$ +91 (*c* 0.5, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.9 (s, 9H), 1.55 (m, 2H), 1.59 (m, 2H), 2.43 (s, 3H), 2.51 (t, 2H, $J = 7.1$ Hz), 3.52 to 3.75 (m, 5H), 6.1 (td, 1H, $J = 16$ Hz, 1 Hz), 6.55 (td, 1H, $J_{trans} = 16$ Hz, 7.5 Hz), 7.32 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 7.8$, $\Delta\nu = 42$ Hz), 7.56 (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 7.8$ Hz, $\Delta\nu = 42$ Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.1$, 142.1, 139, 136.5, 131.9, 130, 124.1, 62.9, 59.15, 40.5, 32.5, 25.9, 25.45, 23.7, 21.4, 18.3, −5.3 ppm.

Sulfinylenone **4a**,**b** were obtained from **1a**,**b** by $NaBH_4$ reduction, followed by Amberlyst® treatment of the crude mixture.

(+)-(*E*,R_S)-1-(*p*-Tolylsulfinyl)-4-oxo-2-butene **4a**: yield: 71% $R_f = 0.3$ (dichloromethane/ethyl acetate 1/1). $[\alpha]_D^{20}$ +57 (*c* 0.15, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.22$ (s, 3H), 2.46 (s, 3H), 3.69 (AB fragment of an ABX system, 2H, $J_{AX} = J_{BX} = 8$ Hz, $J_{AB} = 13$ Hz, $\Delta\nu = 38$ Hz), 6.09 (d, 1H, $J_{trans} = 16$ Hz), 6.58 (dt, 1H, $J_{BX} = 8$ Hz, $J_{trans} = 16$ Hz), 7.37 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 34$ Hz), 7.56 (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 34$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 1.4$, 21.9, 27.6, 59.5, 124.5, 124.6, 130.4, 133.52, 137.6, 139.4, 142.5, 197.4 ppm.

(+)-(*E*,R_S)-1-(*p*-Tolylsulfinyl)-4-oxo-2-hexene **4b**: yield: 78% $R_f = 0.24$ (dichloromethane/ethyl acetate 1/1). $[\alpha]_D^{20}$ +67 (*c* 0.25, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, 3H, $J = 7.3$ Hz), 1.6 (m, 2H), 2.41 (s, 3H), 2.45 (t, 2H, $J = 7.3$ Hz), 3.61 (AB fragment of an ABX system, 2H, $J_{AX} = J_{BX} = 8$ Hz, $J_{AB} = 12.8$ Hz, $\Delta\nu = 39$ Hz), 6.07 (td, 1H, $J_{trans} = 16$ Hz, 1.1 Hz), 6.54 (dt, 1H, $J_{BX} = 8$ Hz, $J_{trans} = 16$ Hz), 7.32 (B fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 27$ Hz), 7.46 (A fragment of an $(AB)_2$ system, 2H, $J_{AB} = 8$ Hz, $\Delta\nu = 27$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 142, 199.3 ppm.

8. Hubbard, J. S.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2566–2570.