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Conjugate Additions of Me_2CuLi to Enantiopure γ-Hydroxy-δ-sulfinyl and Sulfonyl Pentenoates

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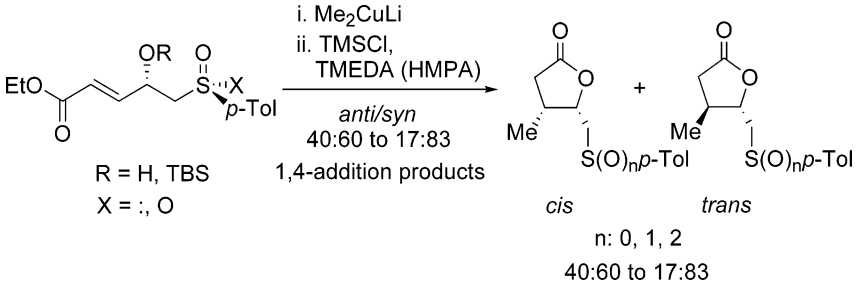

A systematic study of dimethyl cuprate conjugate additions to diastereoisomeric ethyl γ-hydroxy (or *tert*-butyldimethylsilyloxy)-δ-*p*-tolylsulfinyl-2-pentenoates and the analoguous sulfones showed mainly 3,4-anti diastereoselectivity when the reaction occurred in the presence of TMSCl. The π-facial diastereoselection is mainly governed by the γ-hydroxy or silyloxy group, whereas the role of the sulfur functionality is to increase the reactivity of the pentenoate system, probably by assisting the transfer of the alkyl group from the cuprate. This was evidenced by the reactions on similar systems that lack the sulfur functions. The appropriate choice of NH_4OH or HCl hydrolysis in the workup allowed direct access to the open chain products or the lactones.

Introduction

Asymmetric conjugate additions have been efficiently achieved by using chiral electrophiles, nucleophiles,[1] and chiral catalysts.[1,2] The sulfinyl group situated on either the acceptor[3] or the nucleophile[4] can control the diastereofacial selectivity of this synthetically useful C−C bond-formation reaction.[5] In connection with our investigations devoted to the use of sulfoxides in asymmetric synthesis,[6] we have explored the 1,4-conjugate addition on (*R*)-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone derivatives.[7] Such substrates, bearing an OH at C-4 and a sulfoxide in a remote position from the α,β-unsaturated moiety,

(1) Reviews: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (b) Tomkinson, N. C. O. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Sainsbury, M., Ed.; Elsevier: Oxford, U.K., 2001; Vol. 5, Chapter 6, pp 199−258. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (d) Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem*. **1998**, 2051−2061. (e) Leonard, J. *Contemp. Org. Synth*. **1994**, *1*, 387−415. (f) Rossiter, B. E.; Swingle, N. M. *Chem. Rev*. **1992**, *92*, 771−806. (g) Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992. (h) Schmalz, H. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4, Chapter 1.5.

(2) Reviews: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem*. **2002**, *19*, 3221−3236. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed*. **2001**, *40*, 4591−4597. (c) Feringa, B. L. *Acc. Chem. Res*. **2000**, *33*, 346−343. (d) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 569−592. (e) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp 1121−1139. (f) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp 1105−1120. (g) Alexakis, A. In *Transition Metal Catalyzed Reactions*; Murahashi, S. I., Davies, S. G., Eds.; IUPAC Blackwell Science: Oxford, U.K., 1999; Chapter 15, pp 303−316. (h) Krause, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 283−285.

(3) (a) Review: Posner, G. H. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons: New York, 1988; Chapter 16, pp 823−849. Recent examples: (b) Brebion, F.; Delouvrié, B.; Nájera, F.; Fenstebank, L.; Malacria, M.; Vaissermann, J. *Angew. Chem., Int. Ed*. **2003**, *42*, 5342−5345 and references therein. (c) Paquette, L. A.; Tae, M. P.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 2742−2748.

(4) (a) Review: Hua, D. H. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: London, 1992; Vol. 1, pp 249−281. Recent examples: (b) Nakamura, S.; Uchiyama, Y.; Ishikawa, S.; Fukinbara, R.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **2002**, *43*, 2381−2383. (c) Marco, J. L.; Fernández, I.; Khiar, N.; Fernández, P.; Romero, A. *J. Org. Chem*. **1995**, *60*, 6678−6679.

(5) For a recent review on asymmetric synthesis based on sulfoxides: Fernández, I.; Khiar, N. *Chem. Rev*. **2003**, *103*, 3651−3705.

(6) For an overview of our work see: (a) Carreño, M. C. *Chem. Rev*. **1995**, *95*, 1717−1760. For more recent references see: (b) Carreño, M. C.; Ribagorda, M.; Sanz-Cuesta, M. J. *Chem. Commun.* **2005**, 1007−1009. (c) Carreño, M. C.; González-López, M.; Urbano, A. *Chem. Commun.* **2005**, 611−613. (d) Carreño, M. C.; Colobert, F.; des Mazery, R.; Solladié, G.; Urbano, A. *Org. Lett.* **2005**, *7*, 2039−2042. (e) Carreño, M. C.; Ribagorda, M.; Somoza, A.; Urbano, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2755−2757.

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were able to give exclusive 1,4-conjugate addition products upon reaction with organoaluminum reagents in the absence of any other metal catalysts, in good yields and under mild conditions. Moreover, we observed an efficient desymmetrization of the prochiral dienone moiety because the 1,4-addition occurred from the pro-*R* double bond syn to the face containing the C-4 OH in a highly diastereoselective manner.[8] The observed desymmetrization is due to the presence of the β-hydroxy sulfinyl moiety, which directs the organometallic attack exclusively to one of the prochiral double bonds, and assists with the alkyl transfer. The essential role of the γ-hydroxy group in directing the site and face selectivity of 1,4-conjugate additions has been pointed out in reactions of similar *p*-quinol derivatives[9] and acyclic systems[10] with Grignard and organolithium reagents. Organocopper reagents also react diastereoselectively with γ-alkoxy-α,β-unsaturated esters[11] and other γ-substituted pentenoates.[12] Remote asymmetric inductions have also been observed on 4-keto acrylates bearing a NBn_2 substituent α to the carbonyl group.[13] Such conjugate additions are of particular importance because they allow the stereocontrolled introduction of functional diversity in acyclic carbon chains leading to interesting targets for synthesis.[10a] Although a γ-alkoxy group is able to direct the conjugate addition on this acyclic system, the influence of a combined γ-oxygenated substituent with a sulfur function at the δ carbon in acyclic Michael type acceptors is unknown. Recently, we have synthesized and studied the reactions of diastereoisomeric hydroxy sulfinyl pentenoates **1**−**4** and sulfones **5** and **6** with $AlMe_3$, and found that exclusive addition to the ester group occurred in a rather selective process.[14] The usefulness of the 1,4-adducts resulting from **1**−**4** as building blocks for chiral targets prompted us to study the conjugate additions on these substrates. Compounds **5** and **6**, bearing an enantiopure hydroxy sulfone, were also of interest as the sulfonyl group[15] is very useful for further synthetic transformations. The diastereofacial selectivity of conjugate additions in such acyclic systems is more difficult to control than in the cyclic series, because of their greater flexibility and possibility for geometrical isomerization of the double bond under the reaction conditions. In this paper, we disclose our results on organometallic additions to chiral epimeric sulfinyl pentenoates **1**−**4** and sulfones **5** and **6** (Figure 1).

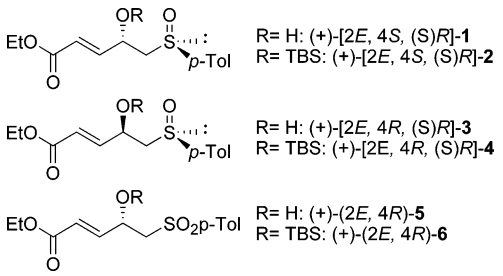


FIGURE 1.

Results and Discussion

Enantiomerically pure ethyl 4-hydroxy-5-(*p*-tolylsulfinyl)-2-pentenoates **1**−**4** and the corresponding sulfones **5** and **6** were synthesized as previously reported.[13]

We began the study of organometallic additions with organocuprates[1,2,16] generated from equimolecular amounts of MeMgBr and CuI. In the presence of a large excess of the resulting species (4 and 8 equiv), compound **1** was recovered unchanged after several days. When TMSCl and Et_3N,[17] which are known to accelerate conjugated additions, were added to the reaction medium, only 13% conjugate addition products were formed.

We later studied the reactions of hydroxy sulfoxide **1** with an excess of Me_2CuLi, generated from MeLi (12 equiv) and CuI (6 equiv). In the absence of any additive, the reaction occurred at room temperature, and after acidic hydrolysis, a 79:21[18] mixture of lactones **7** and **8**, resulting from a sequential 1,4-conjugate addition, lactonization of the hydroxy ester, and reduction of the sulfoxide to thioether, was isolated, but in low yield (Table 1, entry 1). The relative cis:trans ratio (79:21) reflected the diastereoisomeric ratio of the initial 1,4-addition products (syn:anti). The order of these reactions could not be established unequivocally at this stage. The acidic workup was essential for facilitating the straightforward formation and isolation of the lactones, probably because of the activation of the ester moiety. The reactivity of Me_2CuLi has been known to be influenced by the Cu(I) salt used for the preparation of the reagent.[19] In our case, the use of $CuBr{\cdot}Me_2S$ afforded similar results, but in even poorer yields. The addition of TMSCl/TMEDA, which also activates the organocuprate 1,4-

(7) (a) Carreño, M. C.; Pérez González, M.; Ribagorda, M.; Houk, K. N. *J. Org. Chem*. **1998**, *63*, 3687−3693. (b) Carreño, M. C.; Pérez González, M.; Ribagorda, M.; Fischer, J. *J. Org. Chem*. **1996**, *61*, 6758−6759.

(8) A high π-facial diastereoselectivity was also observed in Diels−Alder cycloadditions: (a) Carreño, M. C.; Pérez González, M.; Fischer, J. *Tetrahedron Lett*. **1995**, *36*, 4893−4896. (b) Carreño, M. C.; Pérez González, M.; Houk, K. N. *J. Org. Chem*. **1997**, *62*, 9128−9137.

(9) (a) Fleming, F. F.; Wang, Q.; Zhang, Z.; Steward, O. W. *J. Org. Chem.* **2002**, *67*, 5953−5956. (b) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D. C.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc*. **1988**, *110*, 3702−3704. (c) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc*. **1990**, *112*, 9393−9394.

(10) (a) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 4235−4238. (b) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127−131.

(11) (a) Hanessian, S. M. J.; Wang, W. *J. Am. Chem. Soc*. **2001**, *123*, 10200−10206 and references therein. (b) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc*. **1992**, *114*, 7652−7660.

(12) Yamamoto, K.; Ogura, H.; Jukuta, J.; Inoue, H.; Hamada, K.; Sugiyama, Y.; Yamada, S. *J. Org. Chem*. **1998**, *63*, 4449−4458.

(13) Captain, L. F.; Xia, X.; Liotta, D. C. *Tetrahedron Lett*. **1996**, *37*, 4293−4296.

(14) Carreño, M. C.; Sanz-Cuesta, M. J.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 3537−3540.

(15) Recent reviews: (a) Chinchilla, R.; Nájera, C. *Recent Res. Dev. Org. Chem.* **1998**, *2*, (Part 2), 637−683. (b) Nájera, C.; Sansano, M. J. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 437−467.

(16) (a) Lipshutz, B. H. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 167−187. (b) Lipshutz, B. H. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley & Sons: Chichester, U.K., 1994. (c) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; John Wiley & Sons: New York, 1980.

(17) Sha, C. K.; Santhosh, K. C.; Lih, S. H. *J. Org. Chem.* **1998**, *63*, 2699−2704.

(18) The diastereomeric ratios were determined by integration of well-differentiated signals in the ^1H NMR spectrum of the crude reaction mixtures.

(19) (a) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251−4254. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005−5038. (c) Lipshutz, B. H.; Wilhelm, R. S.; Floyd D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672−7674.

SCHEME 1. Reaction of Ethyl γ-TBDMSO-δ-*p*-tolylsulfinyl Pentenoate 2 with Me_2CuLi in the Presence of TMSCl, Followed by NH_4OH Hydrolysis

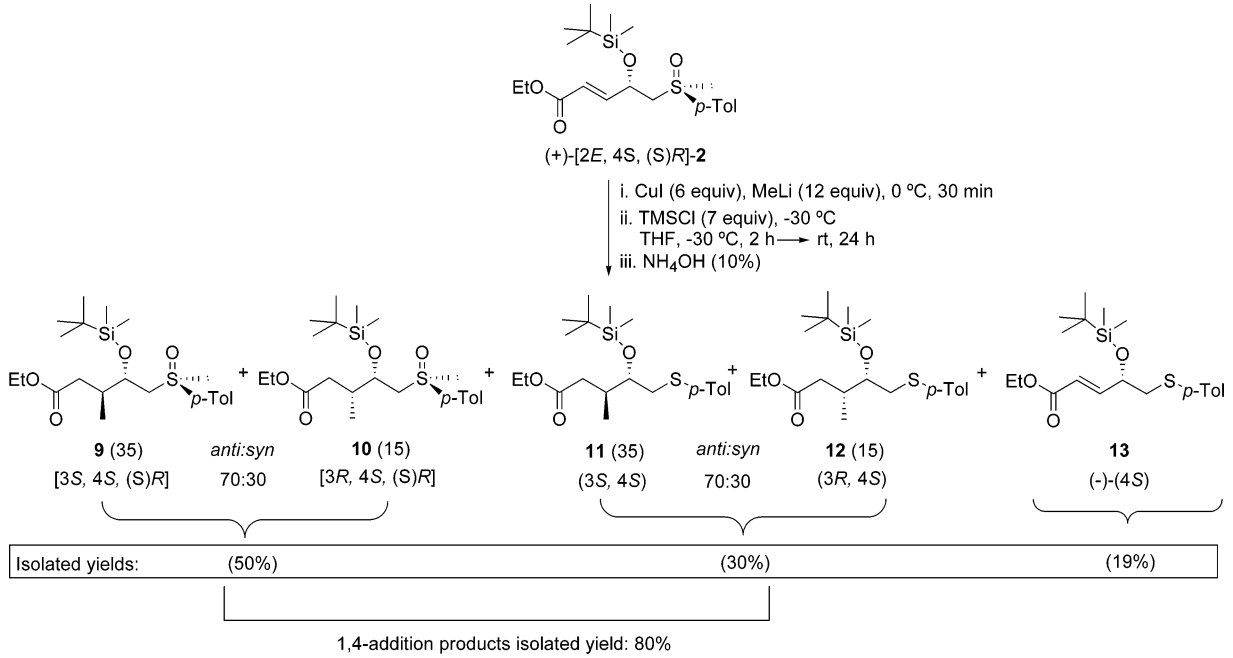
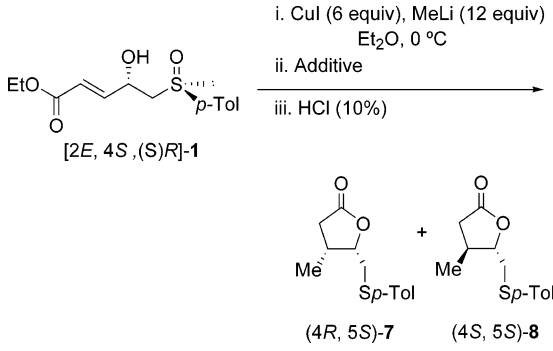


TABLE 1. 1,4-Conjugate Additions of Me_2CuLi to Ethyl γ-Hydroxy-δ-*p*-tolylsulfinyl Pentenoate 1



entry	compound	additive (TMSCl/TMEDA)	*T* (°C)	time	yield (%)	dr[a] (**7**:**8**)
1	**1**	none	0 → rt	18 h	22	79:21
2	**1**	7 equiv/7 equiv	−78	15 min	46	18:82

[a] Diastereomeric ratio.

additions,[11,20] significantly increased the reaction rate under conditions shown in Table 1. Thereby, the 1,4-addition/lactonization and sulfoxide reduction domino sequence was completed in 15 min at −78 °C. An 18:82 mixture of disatereomeric lactones **7** and **8** was isolated in a 46% yield (Table 1, entry 2). The stereoselectivity of the process in the presence of TMSCl and TMEDA was inverted with respect to the similar reaction in the absence of additives.

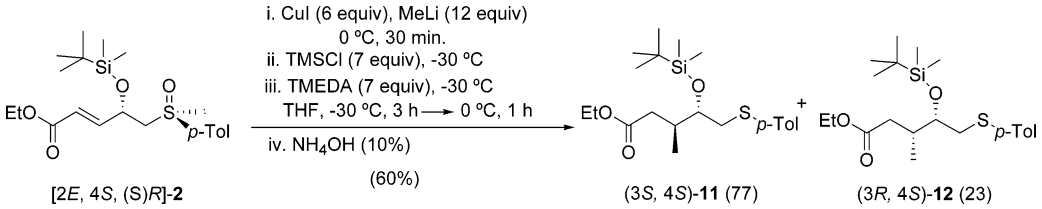
Under similar conditions, without additives, the OTBS-protected pentenoate **2** did not react. We then tried the reaction of **2** in the presence of TMSCl. When **2** was treated with an excess of Me_2CuLi (6 equiv) and TMSCl (7 equiv) and worked up with a NH_4OH solution, we observed the formation of the mixture shown in Scheme 1 after 24 h, working from −30 °C up to room temperature.

The major components of the mixture corresponded to the expected 1,4-addition products **9** and **10**, epimers at the new stereogenic carbon C-3, which were isolated in a 50% yield by column chromatography as a 70:30 mixture. The major component corresponded to the anti relative configuration. The thioethers **11** and **12**, corresponding to the 1,4-addition products and reduction of the sulfinyl group of **9** and **10**, could also be isolated in a 30% yield as a 70:30 mixture of anti:syn diastereomers. The major component also corresponded to (3*S*,4*S*)-**11** showing again the anti relative configuration. Thus, the 1,4-conjugate addition occurred in an 80% isolated yield with a 70:30 anti:syn selectivity. Nineteen percent pentenoate **13**, with the sulfoxide reduced to thioether function, could also be isolated. The competitive reduction of the sulfoxide under these conditions to give **11** and **12** could occur on the starting material **2** to give the pentenoate **13**, which could later evolve to the 1,4-addition product, and/or once the 1,4-addition had occurred. However, the isolation of **13** suggested that this system did not give the conjugate addition under these conditions. Therefore, the sulfoxide-bearing pentenoate **2** must be the reactive species and not the thioether **13**, which remained unchanged once formed. The conjugate addition at the pentenoate **2** occurred preferentially from the si-face to give the major formation of the anti adduct.

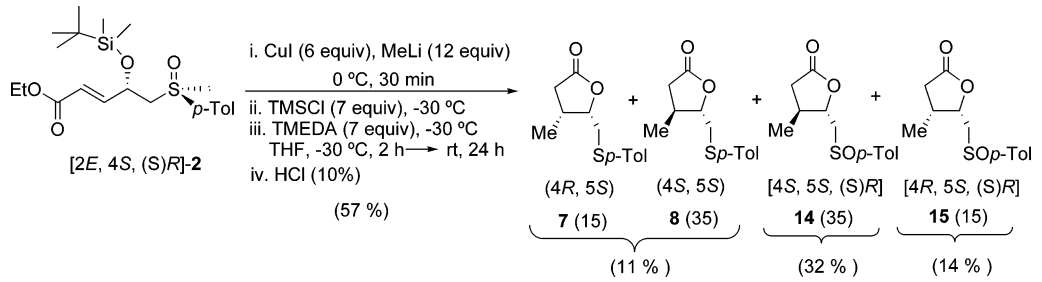
The presence of TMEDA in addition to the TMSCl further accelerated the 1,4-addition of Me_2CuLi to the sulfinyl pentenoate **2** as well as the rate of sulfoxide-to-thioether reduction. Under these conditions, the reaction of [2*E*,4*S*,(S)*R*]-**2** with the cuprate was completed in 1 h at −30 to 0 °C, with the sole products detected being thioethers *anti*-(3*S*,4*S*)-**11** and *syn*-(3*R*,4*S*)-**12**. The major diastereomer was the *anti*-(3*S*,4*S*)-**11**, and the **11**:**12** (77:23) mixture was isolated in a 60% yield (Scheme 2).

(20) Chounan, Y.; Yamamoto, Y. *Chemtracts: Org Chem* **1993**, *6*, 310−314.

SCHEME 2. Reaction of Ethyl γ-TBDMSO-δ-*p*-tolylsulfinyl Pentenoate 2 with Me_2CuLi in the Presence of TMSCl and TMEDA, Followed by NH_4OH Hydrolysis



SCHEME 3. Reaction of Ethyl γ-TBDMSO-δ-*p*-tolylsulfinyl Pentenoate 2 with Me_2CuLi in the Presence of TMSCl and TMEDA, Followed by HCl Hydrolysis



Thus, the presence of TMEDA slightly increased the diastereofacial selectivity of the cuprate reaction, but the preference for the si-face addition to the unsaturated ester remained.

When the crude mixture resulting from the Me_2CuLi/TMSCl/TMEDA treatment of **2** was hydrolyzed with HCl (10%) instead of the routinely used NH_4OH, a mixture of lactones **7**, **8**, **14**, and **15** was formed (Scheme 3). The relative ratio of the *trans*-thioether **8** and the *trans*-sulfoxide **14**, bearing the 4*S*, 5*S* absolute configurations at the stereogenic carbons, with respect to the analogue cis-epimers (4*R*,5*S*)-**7** and -**15** was 70:30[23] (**8**+**14** (4*S*,5*S*): **7**+**15** (4*R*,5*S*)). The final 70:30 trans:cis diastereoselectivity is a consequence of the initial anti:syn diastereoselectivity. A chromatographic separation allowed for the isolation of the 70:30 mixture of thioethers **7** and **8** (11% yield) as well as diastereomerically pure sulfoxides **14** and **15** in 32 and 14% yield, respectively.

The absolute configuration of the major sulfinyl butanolide [4*S*, 5*S*, (S)*R*]-**14** was unequivocally established by X-ray diffraction.[21]

Taking into account the 4*S*,(S)*R* configuration of the starting protected hydroxy-substituted sulfinyl pentenoate **2**, we assigned the configuration 4*R*,5*S*,(S)*R* to the minor epimeric lactone **15**. The absolute configuration of **7** and **8** was established later by chemical correlation (see below).

Surprisingly, the [2*E*,4*R*,(S)*R*]-4-hydroxy-5-*p*-tolylsulfinyl-2-pentenoate epimers **3** and **4** did not react with either Me_2CuLi or Me_2CuLi/TMSCl/TMEDA under similar conditions. These results suggest a cooperative effect of the relative configuration of the hydroxylic center and the sulfoxide, which must favor the conjugate addition when the configurations at the stereogenic centers in the starting material are 4*S*,(S)*R*.

To determine if the sulfinyl group played a role in the control of both the stereoselectivity and reactivity of these reactions, we explored the same process on hydroxy sulfonyl derivative (2*E*,4*S*)-**5** and the TBS-protected analogue (2*E*,4*S*)-**6**. In the presence of TMSCl and TMEDA, Me_2CuLi, generated from MeLi and CuI, reacted with free hydroxy sulfone **5** at −30 °C, leading to a mixture of *anti*-(3*S*,4*S*)-**16** and *syn*-(3*R*, 4*S*)-**17** in an anti:syn 81:19 diastereomeric ratio, after NH_4OH hydrolytic treatment. These 1,4-conjugate addition compounds were isolated as the OTMS-protected derivatives in a 40% yield (Scheme 4).

Under similar conditions, TBDMS-protected hydroxy sulfonyl pentenoate **6** reacted smoothly at −30 °C to room temperature to give adducts **18** and **19**, together with the silyl ketene acetals **20** and **21** as a mixture of *E* and *Z* isomers (Scheme 4). After chromatographic purification, the 70:30 mixture of **18** and **19** was isolated in a 20% yield. The mixture of products **20** and **21** was obtained in a 15% yield. Similar results were obtained when the organocuprate was generated from $CuBr{\cdot}SMe_2$ and MeLi under analogous conditions. In this case, the reaction of **6** with lithium dimethylcuprate, in the presence of TMSCl and HMPA, took place at −78 °C to room temperature in 5 h, to give an 83:17 mixture of (3*S*,4*S*)-**18** and (*3R*,4*S*)-**19** in a 67% isolated yield. The facial diastereoselectivity slightly increased, probably because of the lower temperature.

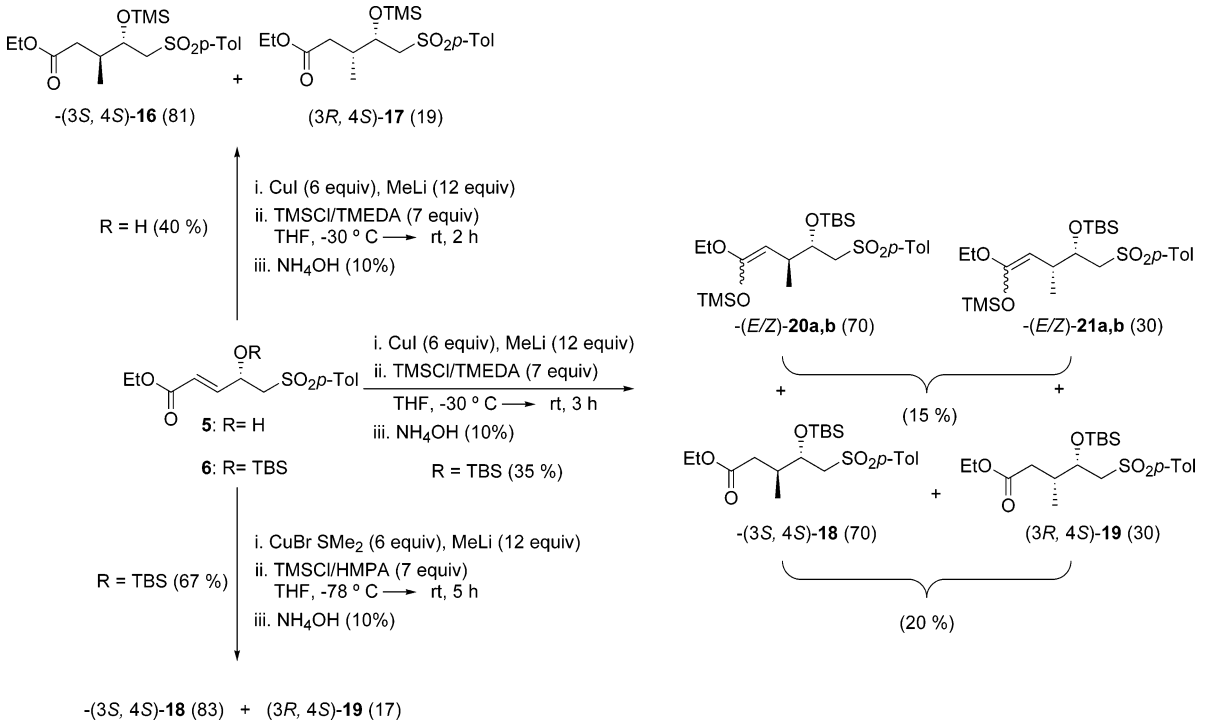
It should be noted that the role of TMSCl and TMEDA or HMPA is not only to increase the reaction rate but also to direct the π-facial diastereoselection in favor of the anti addition products. The favored anti diastereoselectivity observed in these cases, starting from the free OH derivative **5** or the OTBS-protected analogue **6**, suggests the initial transformation of the OH of **5** into an OTMS group, whose evolution is similar to that of the OTBS-protected analogue.

(21) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 241557. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: (+44) 123-336033; e-mail: depositcdc.cam.ac.uk.)

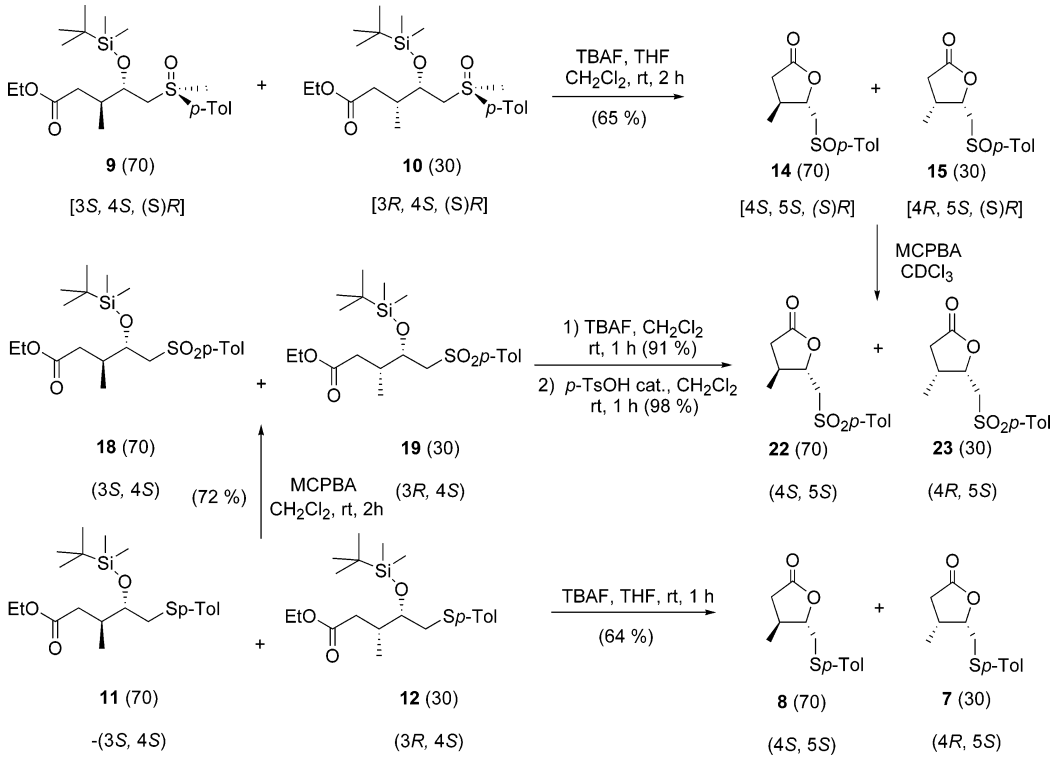
(22) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Oxford, U.K., 1980.

(23) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, *25*, 2327−2330. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224−1226. (c) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027−2029.

SCHEME 4. Reactions of γ-Hydroxy (or TBDMSO)-δ-*p*-tolylsulfonyl Pentenoates 5 and 6 with Me_2CuLi/TMSCl/TMEDA or HMPA, Followed by NH_4OH Hydrolysis



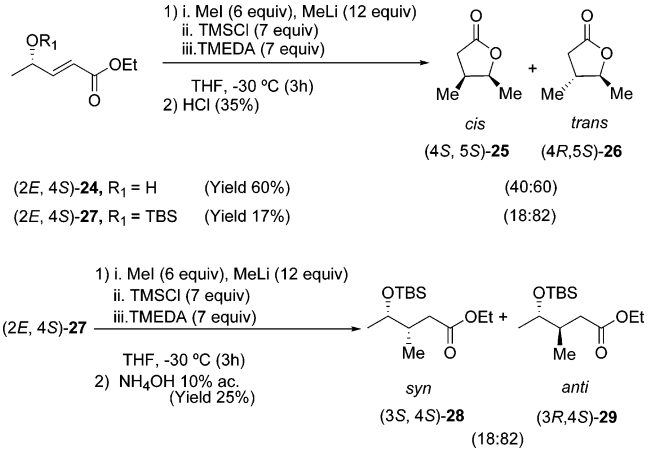
SCHEME 5. Chemical Correlation of Compounds 7−12, 14, 15, 18, and 19



The absolute configurations of all the products obtained in these reactions were established by chemical correlation (Scheme 5) on the basis of the known 4*S* configuration of the hydroxylic carbon of compounds **1**, **2**, **5**, and **6**, the *R* configuration of the sulfoxide in the starting pentenoates **1** and **2**, and the 3*S*,4*S*,(S)*R* configuration of lactone **14**, which was unambiguously determined by X-ray diffraction.

Thus, the treatment of the 70:30 mixture of compounds **9** and **10** with TBAF afforded, after cleavage of the protected carbinol, the sulfinyl lactones **14** and **15** in the same ratio. The NMR spectra of the compounds **14** and **15** that resulted from this reaction were identical to the spectra of **14** and **15** formed directly from the addition of Me_2CuLi to pentenoate **2** in the presence of TMSCl (Scheme 2) after acidic hydrolysis. MCPBA oxidation of

SCHEME 6. Reactions of Ethyl γ-Hydroxy (or TBDMSO) Pentenoates with $LiMe_2Cu$/TMSCl/TMEDA



14 and **15** (70:30 mixture) gave rise to **22** and **23** (70:30), which were also formed by successive TBAF and acidic treatment of the acyclic *tert*-butyl dimethyl silyloxy-protected sulfones **18** and **19**. The correlation of thioethers **11** and **12** with these acyclic sulfones **18** and **19** was achieved by MCPBA oxidation. The formation of a mixture of epimers in the same 70:30 ratio of the starting addition products **11** and **12** allowed us to confirm the configurations of the stereogenic centers C-3 and C-4, which must be identical in each couple of epimers. Finally, lactonization of thioethers **11** and **12** (70:30) to **8** and **7** (70:30) occurred by simple treatment of TBAF.

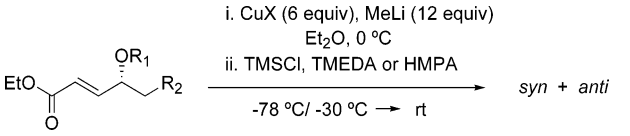
We finally decided to study the role of ethyl (2*E*,4*S*)-4-hydroxy-2-pentenoate **24**,[22] which lacks the sulfur function, in the control of these conjugate additions with Me_2CuLi to establish the weight of the oxygenated function relative to that of the sulfoxide or sulfone.

Upon treatment with an excess of Me_2CuLi (6 equiv) in the presence of TMSCl and TMEDA, compound **24** gave a mixture of lactones **25** and **26** after HCl hydrolysis (3 h, 60% yield, cis:trans 40:60). The OTBDMS-protected derivative **27** afforded, under a similar treatment, an 18:82 mixture of both lactones **25** and **26**, but in only 17% isolated yield after 3 h. If the hydrolysis of the mixture is carried out with NH_4OH, the syn:anti 1,4-addition products **28** and **29** were isolated in a 25% yield and 18:82 ratio.

A comparison of the different results, which are summarized in Table 2, shows that the anti:syn diastereoselectivity observed for these conjugate additions is mainly controlled by the oxygenated function. The anti diastereomer is always the major component of the resulting mixture in the presence of TMSCl and TMEDA or HMPA, starting from hydroxy sulfoxides **1** and **2**, hydroxy sulfones **5** and **6**, or the sulfur-lacking derivatives **24** and **27**. A substantial increase of the diastereoselectivity is observed when comparing the results of compound **24** (free OH, no sulfur function, entry 1) with those of sulfoxide- and sulfone-bearing derivatives **1** and **5** (entries 3 and 5). Thus, it is evident these functions play a significant role in the diastereoselectivity control.

When comparing the results obtained on the OTBS-protected derivatives, we observed no differences in the

TABLE 2. Comparison of Me_2CuLi Addition to Pentenoates 1, 2, 5, 6, 24, and 27



entry	substrate	R_1	R_2	yield (%)	syn:anti
1	**24**	H	H	60	40:60
2	**27**	TBDMS	H	25	18:82
3	**1**	H	(*R*)SO*p*-Tol	46	18:82
4	**2**	TBDMS	(*R*)SO*p*-Tol	57−80	30:70
5	**5**	H	SO_2*p*-Tol	40	19:81
6	**6**	TBDMS	SO_2*p*-Tol	67	17:83[a]

[a] HMPA instead of TMEDA was added at −78 °C.

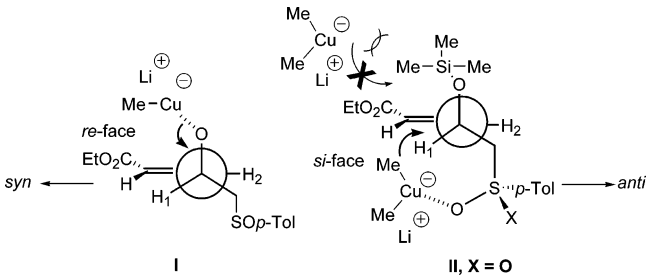


FIGURE 2. Reactive species leading to the major diastereomers.

diastereoselectivityfor **27** (without the sulfur function), **2**, and **6** (entries 2, 4, and 6) with a sulfoxide or sulfone in their structures, suggesting that only the bulky OTBDMS group is essential in this diastereocontrol. Significantly better yields are obtained from the OTBDMS derivatives having a SO*p*-Tol (entry 4) or SO_2*p*-Tol group (entry 6). A cooperative effect of the sulfur functions must be operating in these cases, thus increasing the reactivity.

A rationalization of the different behavior as well as the observed π-facial diastereoselectivity is not easy. Previous work has shown a strong dependence of the diastereoselectivity of conjugate additions of organometallic reagents to γ-alkoxy-α,β-unsaturated compounds on the structures of both the Michael type acceptors and reagents. Even when Gilman's reagents are used, opposite π-facial diastereoselectivities have been observed by changing from dimethallyl cuprate,[23] which gave the syn addition diastereomer as the major product, to dibutyl cuprate, which yielded the anti epimer.[24] In our reactions with lithium dimethyl cuprate, when no activating agents are added to the reaction medium, the *cis*-lactone **7**, proceeding from the syn addition diastereomer, was formed from the free OH sulfoxide **1**, whereas when TMSCl is present, all reactions are anti-diastereoselective. The former result can be explained on the basis of a modified Felkin−Anh model, assuming the evolution of the conformation represented as I in Figure 2, through the association of the reagent with the oxygen function of compound **1**, giving rise to the favored attack by the re-face. When TMSCl is added to reaction medium, the in situ formation of the OTMS-protected derivative of **1**

(24) Ziegler, F.; Giligan, P. J. *J. Org. Chem*. **1981**, *46*, 3874−3880.

or **5** justifies the major formation of the anti epimer as a consequence of the lithium dimethyl cuprate attack favored from the less-hindered face (si-face) of the intermediate II. A similar evolution should occur when the OTBDMS-protected derivatives **2** and **6** react. The role of the sulfoxide or sulfone, to increase the final yield and reactivity, could be a consequence of an association of the organocuprate with the basic sulfinyl oxygen, which can assist with the transfer of the methyl group from the si-face of the pentenoate. The conformation represented in II for the sulfinyl moiety (*R* absolute configuration) is favored because the bulky *p*-tolyl substituent is located in an antiperiplanar disposition with respect to the hydroxy pentenoate chain. The lack of reactivity observed for the 4*R*,(S)*R* epimers **3** and **4** must be a consequence of a disfavored disposition of the *p*-tolyl group in the reactive associated species that must assist in the organometallic transfer. In the case of sulfones, assistance by the sulfonyl oxygen is also possible (Figure 2, II; X = O)

Summary

In conclusion, the relative configuration of a 4-hydroxy-5-sulfinyl moiety situated at the (2*E*)-2-pentenoate chain is defining the reactivity of the conjugated system with Me_2CuLi. Compounds **1** and **2**, bearing the 4*S*,(S)*R* configuration, gave the conjugate addition products upon reaction with Me_2CuLi, whereas the epimeric analogues 4*R*,(S)*R* did not react. The presence of the oxygenated function in combination with the sulfoxide or sulfone is also enhancing the reactivity of the OTBDMS-protected analogues. In both cases, the π-facial diastereoselectivity is mainly governed by the configuration of the oxygenated function, as a similar diastereoselectivity is observed for all the reactions of sulfur-bearing derivatives **1**, **2**, **5**, and **6** and for those of the sulfur-function-lacking analogues **24** and **27**. The syn diastereomer is favored when the conjugate addition occurs from the free hydroxy derivatives with Me_2CuLi (syn:anti (70:30)), whereas when TMSCl and TMEDA (or HMPA) were added to the reaction medium of free hydroxy systems **1** and **5**, or to the OTBDMS-protected compounds **2** and **6**, the diastereofacial selectivity is inverted, the anti addition product then being the favored one under these conditions.

Experimental Section

General Procedure of Me_2CuLi Additions. A flame-dried flask was loaded with CuI (60 mg, 0.43 mmol, 6 equiv) in an argon atmosphere, evacuated with an oil pump, and heated until the CuI showed a yellowish color. After the mixture reached room temperature, diethyl ether (0.2 M, 1.6 mL) was added under argon, and the suspension was cooled to −5 °C, followed by a dropwise addition of methyllithium solution (1.6 M in Et_2O, 532 μL, 0.85 mmol, 12 equiv). The resulting colorless clear solution containing the Me_2CuLi was stirred for another 30 min at −5 °C, and cooled to the specified temperature indicated in each case. Me_2CuLi could be also prepared from $CuBr{\cdot}SMe_2$ following the same procedure indicated above. A solution of the α,β-unsaturated ester (0.07 mmol, 1 equiv) in ethyl ether (0.4 mL) was then added dropwise. An immediate color change from colorless to intense yellow-orange was observed. After the reaction mixture was kept at this temperature for the time described for each product, the crude mixture was quenched by addition of MeOH (3 mL) followed by an aqueous saturated NH_4Cl solution (10 mL/mmol of cuprate). The mixture was diluted with diethyl ether.

Hydrolysis with NH_4OH, Method A. A 10% aqueous NH_4OH solution (ca. 25 mL/mmol starting product) was added to the resulting crude mixture, and after shaking vigorously until both phases were homogeneous, we separated the aqueous phase and extracted it with ethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. NMR spectroscopy of this crude was used to determine the diastereomeric ratio. Flash chromatography with the indicated eluents in each case furnished the 1,4-addition products in the yield specified for each product.

Hydrolysis with HCl, Method B. An aqueous solution of HCl (10%) was added (10 mL) to the resulting crude mixture. An immediate color change from blue to deep red was observed as the same time as the pH decreased to near 1. The aqueous phase was separated and extracted with ethyl ether (3 × 10 mL). The combined organic layers were then washed with a saturated NaCl solution (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. NMR spectroscopy of this crude was used to determine the diastereomeric ratio. Flash chromatography with the indicated eluents in each case furnished the cyclized 1,4-addition products in a yield specified for each product.

General Procedure of Me_2CuLi Additions in the Presence of TMSCl and TMEDA or HMPA, Method C. A 0.2 M solution of Me_2CuLi (0.98 mmol) in ether (0.8 mL), obtained as indicated above, was cooled (temperature indicated for each product), and freshly distilled TMSCl (144 μL, 1.41 mmol, 7 equiv), TMEDA or HMPA (1.41 mmol, 7 equiv, as indicated in each case), and a 0.2 M solution of the α,β-unsaturated ester (0.163 mmol, 1 equiv) in ether (0.8 mL) were added. An immediate color change from a colorless clear solution to a pale yellowish suspension was observed. The reaction mixture was allowed to stand at this temperature for the time indicated in each case, and was quenched by addition of MeOH (2 mL), followed by a saturated aqueous NH_4Cl solution (10 mL/mmol of cuprate). The mixture was diluted with ether, and a 10% NH_4OH solution (ca. 25 mL/mmol of starting product) was added. The aqueous phase was separated and extracted with ethyl ether (3 × 10 mL). The combined organic layers were worked up as above.

4-Methyl-5-(*p*-tolylsulfenyl)dihydrofuran-2-one (4*R*,5*S*)-7 and (4*S*,5*S*)-8. Compounds **7** and **8** were obtained from **1** following methods B and C (hydrolytic treatment with HCl instead of NH_4OH). Method B: from 40 mg (0.14 mmol) of **1** was isolated a 22% yield (7 mg, yellowish oil) of **7** and **8** as a 79:21 mixure. Reaction time 18 h, from 0 °C to room temperature. Method C: from 46 mg (0.16 mmol) of **1** in the presence of TMSCl and TMEDA was isolated a 46% yield (18 mg, yellowish oil) of **7** and **8** as a 18:82 mixture. Reaction time 15 min at −78 °C; TLC and flash chromatography (eluent hexane/AcOEt, 1:3). (4*R*,5*S*)-**7** (major diastereomer of a 79:21 mixture of **7** and **8**): ^{1}H NMR (300 MHz) δ 1.05 (d, J_d = 7.2 Hz, 3H), 2.14−2.80 (AB part of ABX, J_{AB} = 14.2, J_{AX} = 8.1, J_{BX} = 5.9 Hz, $\Delta\nu$ = 139.5 Hz, 2H), 2.33 (s, 3H), 2.65−2.77 (m, X part of ABX system, 1H), 2.94−3.30 (AB part of A′B′X′ system, J_{AB} = 13.5, J_{AX} = 8.1, J_{BX} = 6.1 Hz, $\Delta\nu$ = 80.3 Hz, 2H), 4.51 (dt, X part of A′B′X′ system, J_d = 8.1 Hz, J_t = 5.5 Hz, 1H), 7.09−7.35 (AA′BB′ system, J_{AB} = 8.3 Hz, $\Delta\nu$ = 60.5 Hz, 4H); ^{13}C NMR (75 MHz) δ 13.8, 21.0, 32.3, 34.3, 37.6, 80.8, 130.0, 130.9, 131.2, 137.4, 176.0; MS (EI) (79:21 mixture of **7** and **8**) *m/z* (%) (4*R*:4*S*, 79:21) 65 (9), 71 (25), 77 (11), 83 (21), 91 (24), 99 (40), 123 (11), 124 (15), 137 (100), 138 (25), 236 (M^+, 63); HRMS (EI) calcd for $C_{13}H_{16}O_2S$ [M^+] 236.0871, found 236.0862. (4*S*,5*S*)-**8** (major diastereomer of a 18:82 mixture of **7** and **8**): $[\alpha]^{20}_D$ +23 (*c* = 0.33, HCl_3); ^{1}H NMR (300 MHz) δ 1.21 (d, J_d = 6.8 Hz, 3H), 2.19−2.82 (AB part of ABX system, J_{AB} = 17.4, J_{AX} = 8.7, J_{BX} = 7.9 Hz, $\Delta\nu$ = 166.1 Hz, 2H), 2.33 (s, 3H), 2.39−2.55 (ddd, X part of ABX system, J_{AX} = 8.5, J_{BX} = 6.7, $J_{XX'}$ =

6.3 Hz, 1H), 3.07−3.28 (AB part of A′B′X′ system, $J_{A'B'} = 14.1$, $J_{A'X'} = 6.5$, $J_{B'X'} = 5.5$ Hz, $\Delta\nu = 71.6$ Hz, 2H), 4.17 (td, X part of A′B′X′ system, $J_{A'X'} = 6.5$, $J_{XX'} = 6.5$ Hz, 1H), 7.14−7.37 (AA′BB′ system, $J_{AB} = 8.3$ Hz, 4H, $\Delta\nu = 94.7$ Hz); ^{13}C NMR (75 MHz) δ 18.4, 21.0, 34.7, 36.6, 38.3, 84.9, 130.0, 130.7, 131.2, 137.2, 175.8; MS (EI) (18:82 mixture of **7** and **8**) *m/z* (%) 65 (11), 71 (26), 77 (10), 83 (21), 91 (24), 99 (42), 123 (12), 124 (15), 137 (100), 236 (M^+, 77); HRMS (EI) calcd for $C_{13}H_{16}O_2S$ [M^+] 236.0871, found 236.0863.

Ethyl 4-(*tert*-Butyldimethylsilyloxy)-3-methyl-5-(*p*-tolylsulfinyl)pentanoate [3*S*,4*S*,S(*R*)]-9 and [3*R*,4*S*,S(*R*)]-10. Compounds **9** and **10** were obtained from **2** (50 mg, 0.13 mmol), following method C (TMSCl was used as additive, neither TMEDA nor HMPA was added in this case), in a 50% yield (29 mg, yellowish oil) as a 70:30 mixture. Reaction time 24 h at −30 °C to room temperature; TLC and flash chromatography (eluent hexane/AcOEt, 1:3). A mixture of thioethers **11** and **12** (70:30), [30% isolated yield (17 mg, yellowish oil)], and compound **13** [19% yield (9 mg, yellowish oil)] was also isolated from the resulting mixture. [3*S*,4*S*,S(*R*)]-**9** (major diastereomer of a 70:30 mixture of **9** and **10**): ^{1}H NMR (300 MHz) δ 0.16 (s, 3H), 0.25 (s, 3H), 0.93 (d, $J_d = 6.7$ Hz, 3H), 0.95 (s, 9H), 1.23 (t, $J_d = 7.2$ Hz, 3H), 1.98−2.34 (AB part of ABX system, $J_{AB} = 16.6$, $J_{AX} = 10.7$, $J_{BX} = 5.5$ Hz, $\Delta\nu = 78.7$ Hz, 2H), 2.19−2.33 (m, X part of ABX system, 1H), 2.41 (s, 3H), 2.50−2.78 (AB part of A′B′X′ system, $J_{A'B'} = 13.5$, $J_{A'X'} = 8.9$, $J_{B'X'} = 4.2$ Hz, $\Delta\nu = 17.8$ Hz, 2H), 4.11 (q, $J_q = 7.2$ Hz, 2H), 4.23 (ddd, X part of A′B′X′ system, $J_{A'X'} = 8.5$, $J_{B'X'} = 4.2$, $J_{XX'} = 3.5$ Hz, 1H), 7.27−7.53 (AA′BB′ system, $J_{AB} = 8.0$ Hz, $\Delta\nu = 55.1$ Hz, 4H). [3*R*,4*S*,S(*R*)]-**10** (minor diastereomer of a 70:30 mixture of **9** and **10**): ^{1}H NMR (300 MHz) δ 0.15 (s, 3H), 0.23 (s, 3H), 0.93 (d, $J_d = 7.1$ Hz, 3H), 0.94 (s, 9H), 1.23 (t, $J_d = 7.3$ Hz, 3H), 1.85−1.95 (A part of ABX system, $J_{AB} = 14.9$, $J_{AX} = 10.5$ Hz, 1H), 2.19−2.35 (2m, B and X parts of ABX system, 2H), 2.41 (s, 3H), 2.50−2.78 (AB part of A′B′X′ system, $J_{A'B'} = 12.6$, $J_{A'X'} = 9.4$, $J_{B'X'} = 2.4$ Hz, $\Delta\nu = 51.9$ Hz, 2H), 4.11 (q, $J_q = 7.2$ Hz, 2H), 4.17−4.27 (m, X part of A′B′X′ system, 1H), 7.27−7.53 (AA′BB′ system, $J_{AB} = 8.0$ Hz, $\Delta\nu = 55.1$ Hz, 4H); ^{13}C NMR (75 MHz) (70:30 mixture of **9** and **10**) δ −4.0, −3.9, −3.7, −3.6, 14.2, 14.5, 15.3, 18.2, 21.4, 25.8, 25.9, 35.9, 36.1, 36.4, 37.3, 60.3, 60.5, 63.1, 63.6, 69.3, 69.5, 123.7, 130.0, 141.3, 141.6, 172.4, 172.8; MS (EI) (70:30 mixture of **9** and **10**) *m/z* (%) 57 (12), 59 (11), 73 (38), 75 (42), 91 (9), 101 (11), 123 (27), 137 (11), 139 (36), 355 (100), 356 (26), 397 [$(M - 15)^+$, 3]; HRMS (EI) calcd for $C_{21}H_{35}O_3SSi$ [$M^+ - CH_3$] 397.1869, found 397.1853. Anal. Calcd for $C_{21}H_{35}O_3SSi$: C, 61.12; H, 8.79; S, 7.77. Found: C, 61.10; H, 8.42; S, 7.75.

Ethyl 4-(*tert*-Butyldimethylsilyloxy)-3-methyl-5-(*p*-tolylsulfenyl)pentanoate (3*S*,4*S*)-11 and (3*R*,4*S*)-12. A 77:23 mixture of **11** and **12** was also obtained from **2** (50 mg, 0.13 mmol), following method C (TMEDA was used as additive), in a 60% yield (34 mg, yellowish oil). (3*S*,4*S*)-**11** (major diasteromer of a 70:30 mixture of **11** and **12**): ^{1}H NMR (300 MHz) δ 0.01 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.90 (d, $J_d = 6.9$ Hz, 3H), 1.25 (t, $J_d = 7.2$ Hz, 3H), 2.02−2.46 (AB part of ABX system, $J_{AB} = 16.6$, $J_{AX} = 10.8$, $J_{BX} = 6.0$ Hz, $\Delta\nu = 86.4$ Hz, 2H), 2.31 (s, 3H), 2.39 (ddd, X part of ABX system, $J_{AX} = 11.5$, $J_{BX} = 6.3$, $J_{XX'} = 2.8$ Hz, 1H), 2.86−2.98 (AB part of A′B′X′ system, $J_{A'B'} = 10.7$, $J_{A'X'} = 6.2$, $J_{B'X'} = 6.0$ Hz, $\Delta\nu = 10.8$ Hz, 2H), 3.69 (ddd, X part of A′B′X′ system, $J_{A'X'} = 6.3$, $J_{B'X'} = 6.0$, $J_{XX'} = 3.2$ Hz, 1H), 4.11 (q, $J_q = 7.2$ Hz, 2H), 7.04−7.26 (AA′BB′ system, $J_{AB} = 8.0$ Hz, $\Delta\nu = 49.4$ Hz, 4H). (3*R*,4*S*)-**12** (minor diasteromer of a 70:30 mixture of **11** and **12**): ^{1}H NMR (300 MHz) δ 0.00 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.87 (d, $J_d = 5.9$ Hz, 3H), 1.23 (t, $J_d = 7.3$ Hz, 3H), 2.02−2.46 (AB part of ABX system, $J_{AB} = 14.3$, $J_{AX} = 6.3$, $J_{BX} = 5.5$ Hz, $\Delta\nu = 91.1$ Hz, 2H), 2.31 (s, 3H), 2.33−2.48 (m, X part of ABX, 1H), 2.86−2.98 (AB part of A′B′X′ system, $J_{A'B'} = 13.4$, $J_{B'X'} = 7.1$, $J_{A'X'} = 7.1$ Hz, $\Delta\nu = 18.2$ Hz, 2H), 3.69 (ddd, 1H, X part of A′B′X′, system $J_{A'X'} = 6.5$, $J_{B'X'} = 6.5$, $J_{X'X} = 2.2$ Hz), 4.11 (q, $J_q = 7.2$ Hz, 2H), 7.04−7.29 (AA′BB′ system, $J_{AB} = 8.0$ Hz, $\Delta\nu = 51.6$ Hz, 4H); ^{13}C NMR (75 MHz) (70:30 mixture of **11** and **12**) δ −4.0, −3.5, −3.4, 13.2, 14.2, 16.6, 18.0, 21.0, 25.8, 34.2, 34.3, 36.1, 38.1, 38.5, 38.9, 60.2, 60.4, 73.5, 74.5, 129.7, 130.2, 132.8, 136.1, 136.2, 173.2, 176.1; MS (FAB+) (70:30 mixture of **11** and **12**) *m/z* (%) 57 (10), 73 (24), 75 (47), 91 (19), 101 (10), 123 (35), 138 (16), 304 (11), 350 (25), 366 (100), 408 {[(M + 1) − 17]$^+$, 4}; HRMS (FAB+) calcd for $C_{21}H_{35}O_3SSi$ [(M + 1) − OH]$^+$ 395.2076, found 395.2099.

(−)-[2*E*,3(*R*)]-Ethyl 4-(*tert*-Butyldimethylsilyloxy)-5-(*p*-tolylsulfenyl)-2-pentanoate 13: $[\alpha]^{20}_D$ −16 ($c = 0.9$, $CHCl_3$); ^{1}H NMR (300 MHz) δ −0.01 (s, 3H), 0.02 (s, 3H), 0.97 (s, 9H), 1.29 (t, $J_t = 7.1$ Hz, 3H), 2.31 (s, 3H), 2.90−3.01 (AB part of ABX system, $J_{AB} = 13.5$, $J_{AX} = 6.7$, $J_{BX} = 6.0$ Hz, $\Delta\nu = 31.3$ Hz, 2H), 4.21 (q, $J_q = 7.1$ Hz, 2H), 4.36 (dddd, X part of ABXYZ system, $J_{AX} = 6.7$, $J_{BX} = 6.0$, $J_{XZ} = 4.7$, $J_{YX} = 1.8$ Hz, 1H), 6.01 (dd, $J_{YZ} = 15.4$, $J_{YX} = 1.8$ Hz, 1H), 7.01 (dd, $J_{YZ} = 15.4$, $J_{ZX} = 4.8$ Hz, 1H), 7.06−7.29 (AA′BB′ system, $J_{AB} = 7.5$ Hz, $\Delta\nu = 53.1$ Hz, 4H); ^{13}C NMR (75 MHz) δ −3.6, −3.4, 14.3, 18.1, 21.0, 25.7, 41.7, 60.4, 70.9, 119.1, 129.7, 130.2, 130.4, 136.5, 142.4, 167.0; MS (EI) *m/z* (%) 57 (21), 73 (100), 75 (46), 91 (13), 103 (14), 123 (25), 137 (69), 149 (11), 243 (29), 323 (83), 380 (M^+, 1); HRMS (EI) calcd for $C_{20}H_{32}O_3SSi$ [M^+] 380.1841, found 380.1832.

4-Methyl-5-[(*p*-tolylsulfinyl)methyl]dihydrofuran-2-one (+)-[4*S*,5*S*,S(*R*)]-14. Compound **14** was obtained from **2** (50 mg, 0.13 mmol), following method C (TMEDA was used as additive and hydrolytic treatment was performed with HCl). Reaction time 24 h at −30 °C to room temperature. A **7/8/14/15** mixture in a 15:35:35:15 ratio was formed. A first flash column chromatography (eluent hexane/AcOEt, 1:2) furnished a 70:30 mixture of [4*S*,5S,S(*R*)]-**14** and (+)-[4*R*,5S,(S)*R*]-**15** in a 49% yield and a 70:30 diastereomeric mixture of lactones **7** and **8** in an 11% yield. A second chromatographic separation allowed for the isolation of diastereomerically pure **14** in a 32% yield (11 mg, yellowish needles) and **15** (14% yield as a yellowish oil, 6 mg). (+)-[4*S*, 5S, S(*R*)]-**14**: mp 134−136 °C (hexane/Et_2O); $[\alpha]^{20}_D$ +216 ($c = 1.0$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.18 (d, $J_d = 7.1$ Hz, 3H), 2.23−2.38 (2m, A and X part of ABX system, 2H), 2.61−2.78 (m, part B of ABX system, 1H), 2.43 (s, 3), 2.81−3.05 (AB part of A′B′X′ system, $J_{A'B'} = 13.3$, $J_{A'X'} = 9.7$, $J_{B'X'} = 2.6$ Hz, $\Delta\nu = 41.4$ Hz, 2H), 4.60 (ddd, X part of A′B′X′ system, 1H, $J_{X'A'} = 9.8$, $J_{XX'} = 7.5$, $J_{X'B'} = 2.6$ Hz, 1H), 7.31−7.58 (AA′BB′ system, $J_{AB} = 8.1$ Hz, $\Delta\nu = 61.4$ Hz, 4H); ^{13}C NMR (75 MHz) δ 16.6, 21.4, 36.4, 36.6, 62.7, 80.0, 123.7, 130.2, 140.6, 142.0, 175.0; MS (EI) *m/z* (%) 65 (16), 69 (19), 91 (24), 92 (13), 99 (40), 113 (21), 139 (100), 140 (48), 236 (6), 252 (M^+, 7); HRMS (EI) calcd for $C_{13}H_{16}O_3S$ [M^+] 252.0820, found 252.0816. (+)-[4*R*,5*S*,S(*R*)]-**15**: $[\alpha]^{20}_D$ +168 ($c = 0.5$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.99 (d, $J_d = 7.1$ Hz, 3H), 2.20−2.86 (AB part of ABX system, $J_{AB} = 16.7$, $J_{AX} = 7.6$, $J_{BX} = 3.1$ Hz, $\Delta\nu = 179.8$ Hz, 2H), 2.65−2.77 (m, X part of ABX system, 1H), 2.43 (s, 3H), 2.79−2.92 (AB part of A′B′X′ system, $J_{A'B'} = 13.4$, $J_{A'X'} = 8.1$, $J_{B'X'} = 5.0$ Hz, $\Delta\nu = 12.9$ Hz, 2H), 5.07 (ddd, X part of A′B′X′ system, $J_{X'A'} = 8.1$, $J_{XX'} = 5.9$, $J_{B'X'} = 5.0$ Hz, 1H), 7.30−7.61 (AA′BB′ system, $J_{AB} = 8.1$ Hz, $\Delta\nu = 60.7$ Hz, 4H); ^{13}C NMR (75 MHz) δ 14.3, 21.4, 33.1, 37.2, 59.8, 76.5, 123.7, 130.3, 140.7, 142.1, 175.3; MS (EI) *m/z* (%) 65 (13), 69 (14), 91 (20), 92 (11), 113 (26), 137 (13), 139 (100), 140 (32), 236 (7), 252 (M^+, 9); HRMS (EI) calcd for [M^+] $C_{13}H_{16}O_3S$ 252.0820, found 252.0817.

Ethyl 3-Methyl-5-(*p*-tolylsulfonyl)-4-trimethylsilyloxy-2-pentanoate (3*S*,4*S*)-16 and (3*R*,4*S*)-17. Compounds **16** and **17** were obtained from **5** (22 mg, 0.07 mmol), following method C (TMEDA was used as additive), in 40% yield (12 mg, yellowish oil) as an 81:19 mixture of **16** and **17**. Reaction time 2 h at −30 °C to room temperature; TLC and flash chromatography (eluent hexane/AcOEt, 1:1). (3*S*, 4*S*)-**16** (major diastereomer of a 81:19 mixture of **16** and **17**): $[\alpha]^{20}_D$ +12 ($c = 1.2$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.06 (s, 9H), 0.95 (d, $J_d = 6.9$ Hz, 3H), 1.25 (t, $J_t = 7.1$ Hz, 3H), 1.98−2.32 (AB part of ABX system, $J_{AB} = 16.4$, $J_{AX} = 10.7$, $J_{BX} = 5.0$ Hz, $\Delta\nu = 64.0$ Hz, 2H), 2.21−2.38 (m, X part of ABX system, 1H), 2.45 (s, 3H), 3.03−3.29 (AB part of A′B′X′ system, $J_{A'B'} = 14.1$, $J_{A'X'} =$

5.8, $J_{B'X'}$ = 4.9 Hz, $\Delta\nu$ = 22.4 Hz, 2H), 4.11 (q, J_q = 7.1 Hz, 2H), 4.23 (ddd, X part of A′B′X′ system, $J_{A'X'}$ = 5.8, $J_{B'X'}$ = 4.9, $J_{XX'}$ = 2.6 Hz, 1H), 7.30−7.80 (AA′BB′ system, J_{AB} = 8.1 Hz, $\Delta\nu$ = 129.1 Hz, 4H). (3*R*,4*S*)-**17** (minor diastereomer of an 81:19 mixture of **16** and **17**): ^{1}H NMR (300 MHz) δ 0.00 (s, 9H, Me_3Si), 0.85 (d, J_d = 5.7 Hz, 3H, Me-CH-), 1.25 (t, J_t = 7.1 Hz, 3H, EtO-), 1.97−2.35 (2m, 3H, $2H_2$ and H_3), 2.45 (s, 3H, *p*-$TolSO_2$), 3.10−3.26 (m, 2H, $-CH_2-SO_2$*p*-Tol), 4.12 (q, J_q = 7.1 Hz, 2H, EtO), 4.18−4.25 (m, X part of A′B′X′ system, 1H, −CH−OTBDMS), 7.30−7.80 (AA′BB′ system, J_{AB} = 8.1 Hz, $\Delta\nu$ = 129.1 Hz, 4H, *p*-$TolSO_2$); ^{13}C NMR (75 MHz) (81:19 mixture of **16** and **17**) δ 0.16, 14.1, 14.2, 15.6, 21.6, 35.8, 36.0, 36.5, 60.0, 60.4, 60.5, 69.5, 70.0, 127.7, 127.8, 129.9, 130.0, 137.5, 137.6, 144.6, 172.5, 172.6; MS (FAB+) (81:19 mixture of **16** and **17**) *m/z* (%) 55 (8), 69 (14), 73 (48), 75 (42), 89 (20), 91 (27), 93 (25), 103 (15), 105 (11), 107 (24), 115 (11), 120 (12), 123 (12), 137 (11), 136 (58), 137 (50), 139 (50), 149 (23), 152 (11), 154 (65), 155 (28), 213 (11), 297 (21), 371 (91), 383 (47), 429 [$(M + 1)^+$, 100]; HRMS (FAB+) calcd for $C_{21}H_{37}O_5SSi$ $[M + 1]^+$ 429.2131, found 429.2138.

Ethyl 4-(*tert*-Butyldimethylsilyloxy)-3-methyl-5-(*p*-tolylsulfonyl)-2-pentenoate (3*S*,4*S*)-18 and (3*R*,4*S*)-19. Compounds **18** and **19** were obtained from **6** (50 mg, 0.12 mmol) and $CuBr{\cdot}SMe_2$ (150 mg, 0.73 mmol) following method C (HMPA was used as additive), in a 67% yield (35 mg, yellowish oil) as an 83:17 mixture of **18** and **19**. Reaction time 5 h at −78 °C to room temperature; TLC and flash chromatography (eluent hexane/AcOEt, 1:1). Compounds **18** and **19** were also obtained from **6** (40 mg, 0.10 mmol) following method C (TMEDA was used as additive), in a 20% yield (8 mg, yellowish oil) as a 70:30 mixture of **18** and **19**. Reaction time 5 h at −30 °C to room temperature; TLC and flash chromatography (eluent hexane/AcOEt, 1:1). A mixture of silyl enol ethers **20** and **21** was also formed in the same diastereoisomeric ratio (70:30, each one as a 1:1 mixture of *E* and *Z* isomers) in a 15% yield (7 mg, yellowish oil). A second column chromatography of this mixture allowed for the separation of a 70:30 mixture of **20a** and **21a** (each one as pure *Z* or *E* isomer, configuration not assigned) as well as a pure **20b** (*E* or *Z*, not assigned) and pure **21b** (*E* or *Z* configuration not assigned). (3*S*,4*S*)-**18** (major diastereomer of a 70:30 mixture of **18** and **19**): ^{1}H NMR (300 MHz) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 0.95 (d, J_d = 6.9 Hz, 3H), 1.25 (t, J_d = 7.1 Hz, 3H), 1.98−2.32 (AB part of ABX system, J_{AB} = 16.4, J_{AX} = 10.7, J_{BX} = 5.0, Hz, $\Delta\nu$ = 64.0 Hz, 2H), 2.21−2.38 (m, X part of ABX system, 1H), 2.45 (s, 3H), 3.03−3.29 (AB part of A′B′X′ system, $J_{A'B'}$ = 14.1, $J_{A'X'}$ = 5.8, $J_{B'X'}$ = 4.9, Hz, $\Delta\nu$ = 43.4 Hz, 2H), 4.11 (q, J_q = 7.1 Hz, 2H), 4.23 (ddd, X part of A′B′X′ system, $J_{A'X'}$ = 5.8, $J_{B'X'}$ = 4.9, $J_{X'X}$ = 2.6 Hz, 1H), 7.31−7.79 (AA′BB′ system, J_{AB} = 8.1 Hz, $\Delta\nu$ = 133.2 Hz, 4H). (3*R*,4*S*)-**19** (minor diastereomer of a 70:30 mixture of **18** and **19**): ^{1}H NMR (300 MHz) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 0.85 (d, J_d = 5.7 Hz, 3H), 1.25 (t, J_t = 7.1 Hz, 3H), 1.97−2.50 (AB part of ABX system, J_{AB} = 15.0, J_{AX} = 8.0, J_{BX} = 5.5 Hz, $\Delta\nu$ = 127.3 Hz, 2H), 2.21−2.38 (m, X part of ABX system, 1H), 2.45 (s, 3H), 3.01−3.33 (AB part of A′B′X′ system, $J_{A'B'}$ = 14.4, $J_{A'X'}$ = 6.7, $J_{B'X'}$ = 4.4 Hz, $\Delta\nu$ = 65.9 Hz, 2H), 4.12 (q, J_q = 7.1 Hz, 2H), 4.18−4.25 (m, 1H, X part of A′B′X′ system), 7.36−7.83 (AA′BB′ system, J_{AB} = 8.1 Hz, $\Delta\nu$ = 127.3 Hz, 4H); ^{13}C NMR (75 MHz) δ −4.8, 13.4, 14.2, 15.9, 17.9, 21.6, 25.7, 35.4, 35.8, 36.0, 37.3, 60.0, 60.4, 68.9, 69.6, 127.8, 129.9, 137.3, 144.6, 172.5; MS (FAB+) *m/z* (%) 55 (8), 69 (14), 73 (48), 75 (42), 89 (20), 91 (27), 93 (25), 103 (15), 105 (11), 107 (24), 115 (11), 120 (12), 123 (12), 137 (11), 136 (58), 137 (50), 139 (50), 149 (23), 152 (11), 154 (65), 155 (28), 213 (11), 297 (21), 371 (91), 383 (47), 429 [$(M + 1)^+$, 100]; HMRS (FAB+) calcd for $C_{21}H_{37}O_5SSi$ $[M + 1]^+$ 429.2131, found 429.2138.

1-[2′-(*tert*-Butyldimethylsilyloxy)-5′-ethoxy-3′-methyl-5′-(trimethylsiloxy)-4-pentenyl]-*p*-tolyl sulfones (2*S*,3*S*,4*Z*/*E*)-20a,b and (2*S*,3*R*,4*Z*/*E*)-21a,b. (2*S*, 3*S*, 4*Z*/*E*)-**20a** (major diastereomer of a 70:30 mixture of **20a** and **21a**): yellowish oil; ^{1}H NMR (300 MHz) δ 0.08 (s, 9H), 0.09 (s, 3H), 0.86 (s, 9H), 1.12 (d, J_d= 6.9 Hz, 3H), 1.30 (t, J_t = 7.3 Hz, 3H), 2.14−2.27 (dqd, J_d = 9.1, J_q = 6.3, J_d = 3.8 Hz, 1H), 2.45 (s, 3H), 3.10−3.33 (AB part of ABX system, J_{AB} = 13.9, J_{AX} = 6.4, J_{BX} = 4.5 Hz, $\Delta\nu$ = 47.1 Hz, 2H), 4.09−4.36 (2m, X part of ABX systems, 2H), 4.20 (q, J_q = 7.1 Hz, 2H), 7.35−7.80 (AA′BB′ system, J_{AB} = 8.5 Hz, $\Delta\nu$ = 132.3 Hz, 4H). (2*S*, 3*R*, 4*Z*/*E*)-**21a** (minor diastereomer of a 70:30 mixture of **20a** and **21a**): ^{1}H NMR (300 MHz) δ −0.69 (s, 3H), −0.05 (s, 3H), 0.08 (s, 9H), 0.83 (s, 9H), 1.12 (d, J_d = 6.9 Hz, 3H), 1.30 (t, J_t = 7.1 Hz, 3H), 2.14−2.27 (m, 1H), 2.46 (s, 3H), 3.08−3.46 (AB part of ABX system, J_{AB} = 14.3, J_{AX} = 7.9, J_{BX} = 4.2 Hz, $\Delta\nu$ = 88.1 Hz, 2H), 4.09−4.36 (2m, X part of ABX system, 2H), 4.20 (q, J_q = 7.1 Hz, 2H), 7.35−7.80 (AA′BB′ system, J_{AB} = 8.0 Hz, $\Delta\nu$ = 127.3 Hz, 4H); MS (EI) (70:30 mixture of **20a** and **21a**) *m/z* (%) 55 (20), 57 (32), 59 (35), 69 (52), 73 (67), 75 (42), 83 (11), 91 (56), 95 (23), 101 (35), 103 (36), 138 (60), 143 (11), 149 (100), 154 (19), 212 (47), 215 (14), 313 (38), 325 (28), 371 (M^+ − 129: -*t*-Bu, -Me_3Si-, 77), 372 (19), 496 (88), 497 (22). (2*S*,3*S*,4*Z*/*E*)-**20b**: ^{1}H NMR (300 MHz) δ 0.08 (s, 9H), 0.14 (s, 3H), 0.16 (s, 3H), 0.88 (s, 9H), 0.98 (d, J_d = 6.5 Hz, 3H), 1.26 (t, J_t = 7.1 Hz, 3H), 2.25−2.36 (m, 1H), 2.45 (s, 3H), 3.08−3.46 (AB part of ABX system, J_{AB} = 14.3, J_{AX} = 7.1, J_{BX} = 3.6 Hz, $\Delta\nu$ = 33.8 Hz, 2H), 4.11 (q, J_q = 7.1 Hz, 2H), 4.18 (dq, J_d = 7.1, J_q = 2.2 Hz, 1H), 4.67 (ddd, X part of ABX system, J_d = 7.0, J_{AX} = 6.9, J_{BX} = 3.2 Hz, 1H), 7.35−7.83 (AA′BB′ system, J_{AB} = 8.1 Hz, $\Delta\nu$ = 127.8 Hz, 4H); MS (EI) *m/z* (%) 55 (11), 57 (18), 59 (31), 69 (42), 73 (67), 75 (61), 91 (50), 95 (22), 101 (35), 103 (34), 138 (64), 149 (100), 154 (19), 213 (50), 215 (13), 313 (35), 325 (36), 371 [(M − 129: -*t*-Bu, -$Me_3Si)^+$, 95], 372 (24), 496 (57), 497 (14). (2*S*,3*R*,4*Z*/*E*)-**21b**: ^{1}H−NMR (300 MHz) δ −0.07 (s, 3H), 0.05 (s, 3H), 0.08 (s, 9H), 0.82 (s, 9H), 0.91 (d, J_d = 6.7 Hz, 3H), 1.28 (t, J_t = 7.3 Hz, 3H), 2.34−2.51 (m, 1H), 2.47 (s, 3H), 3.10−3.50 (AB part of ABX system, J_{AB} = 14.6, J_{AX} = 9.3, J_{BX} = 2.6 Hz, $\Delta\nu$ = 81.6 Hz, 2H), 4.12 (q, J_q = 7.1 Hz, 2H), 4.22 (dq, J_d = 6.7, J_q = 1.2 Hz, 1H), 4.67 (ddd, X part of ABX system, J_{AX} = 9.1, J_{BX} = 2.6, J_d = 1.4 Hz, 1H), 7.38−7.90 (AA′BB′ system, J_{AB} = 7.9 Hz, $\Delta\nu$ = 148.3 Hz, 4H); MS (EI) *m/z* (%) 55 (10), 57 (18), 59 (32), 69 (38), 73 (69), 75 (64), 91 (48), 95 (19), 101 (30), 103 (28), 138 (62), 149 (100), 154 (14), 213 (48), 215 (15), 313 (23), 325 (25), 371 [(M − 129: -*t*-Bu, -Me_3Si-)$^+$, 72], 372 (17), 496 (62), 497 (18).

4-Methyl-5-(*p*-tolylsulfonyl)dihydrofuran-2-one (4*S*,5*S*)-22 and (4*R*,5*S*)-23. A 70:30 diastereomeric mixture of sulfonyl butanolides **22** and **23** was easily accessible, in an 89% two-step overall yield. To a solution of a 70:30 mixture of (3*S*,4*S*)-**18** and (4*R*,5*S*)-**19** (27 mg, 0.08 mmol) in THF at 0 °C was added TBAF (1.2 equiv). After the solution was stirred for 1 h at room temperature, the THF was eliminated in vacuo. Purification by flash column chromatography (hexane/AcOEt, 1:1) provided a 70:30 mixture of γ-hydroxypentenoates obtained in a 91% yield. This mixture (12 mg, 0.04 mmol, 1 equiv) was dissolved in THF (1 mL), and treated with a catalytic amount of *p*-TsOH (0.05 equiv) at 0 °C. After 1 h, the reaction mixture was washed with water, dried over $MgSO_4$, and filtered. The crude reaction mixture showed a 70:30 mixture of butanolides **22** and **23**. Purification by column chromatography in a 1:1 hexane/AcOEt mixture provided a 90:10 mixture of butanolides **22** and **23** in a 98% yield (10 mg, white solid). (4*S*,5*S*)-**22**: mp 134−136 °C (hexane/Et_2O); $[\alpha]^{20}_D$ (90:10 mixture of **22** and **23**) +30 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) (only the major diastereoisomer **22** is described) δ 1.04 (d, J_d = 7.3 Hz, 3H), 2.46 (s, 3H), 2.66−2.72 (2m, 3H), 3.33−3.52 (AB part of A′B′X′ system, J_{AB} = 14.5, J_{AX} = 7.1, J_{BX} = 5.5 Hz, $\Delta\nu$ = 32.0 Hz, 2H), 4.92 (td, J_t = 7.1, J_d = 5.5 Hz, 1H), 7.34−7.85 (AA′BB′ system, J_{AB} = 7.9 Hz, $\Delta\nu$ = 131.9 Hz, 4H); ^{13}C NMR (75 MHz) δ 14.2, 21.7, 33.1, 37.1, 56.6, 77.4, 128.2, 130.1, 145.4, 148.30, 172.7; MS (EI) *m/z* (%) 55 (16), 59 (17), 65 (29), 68 (11), 69 (27), 71 (15), 72 (11), 90 (14), 91 (100), 92 (36), 97 (24), 112 (11), 113 (26), 138 (22), 139 (12), 155 (36), 156 (14), 268 (M^+, 24); HRMS (EI) calcd for $C_{13}H_{16}O_4S$ [M^+] 268.0769, found 268.0762.

Ethyl 4-(*tert*-Butyldimethylsilyloxy)-3-methylpentanoate (3*S*,4*S*)-28 and (3*R*,4*S*)-29. Starting from (2*E*,4S)-**27** (150 mg, 0.57 mmol), following method C (TMEDA was used as additive), addition at −30 °C to room temperature for 3 h, using TLC and flash chromatography (eluent hexane/AcOEt, 40:1), we isolated an 18:82 mixture of **28** and **29** in a 25% yield (39 mg, yellowish oil). (3*S*,4*S*)-**29** (only the major diastereoisomer **29** is described): $[\alpha]^{D}_{20}$ (18:82 mixture of **28** and **29**) +10 (c = 0.4, $CHCl_3$); ^{1}H−NMR (300 MHz) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.94 (d, J_d = 6.4 Hz, 3H), 1.08 (d, J_d = 6.1 Hz, 3H), 1.25 (t, J_t = 7.1 Hz), 1.88−2.03 (m, X part of ABX system, 1H), 1.96−2.53 (AB part of ABX system, J_{AB} = 14.1, J_{AX} = 9.3, J_{BX} = 3.8 Hz, $\Delta\nu$ = 133.6 Hz, 2H), 3.65 (m, 1H), 4.12 (q, J_q = 7.1 Hz); ^{13}C−NMR (75 MHz) δ −3.8 (−SiMe), −3.4 (−SiMe), 14.2 (CH_3, EtO), 16.0 (CH_3), 18.0, 20.6, 25.8 (3C), 37.1, 37.6, 60.1, 71.4, 173.7; MS (18:82 mixture of **28** and **29**) (GM) *m/z* (%) 67 (12), 69 (12), 73 (40), 75 (62), 99 (25), 103 (43), 127 (34), 159 (17), 171 (67), 172 (9), 189 (36), 217 [(M − 57)$^+$, 100], 218 (19), 229 (22), 259 [(M − 15)$^+$, 6].

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Supporting Information Available: NMR spectra for compounds **1**−**12**, **14**, **15**, **18**, **19**, **22**, **23**, **28**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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