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Radical Cyclization of Epoxy Vinyl- and Allylsulfones Promoted by Titanocene Chloride

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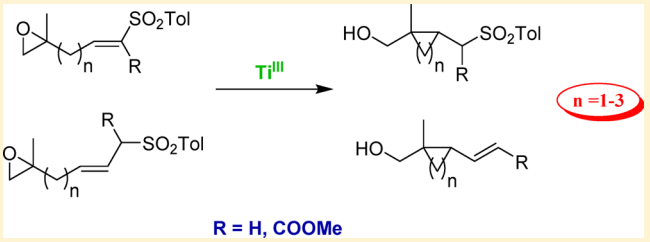
Supporting Information

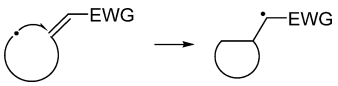
ABSTRACT: A titanocene-mediated intramolecular radical addition of different epoxy vinyl- and allylsulfones has been achieved. Five- and six-membered ring products were obtained in good to excellent yields in the presence of both 2.2 and 0.2 equiv of Cp_2TiCl. A novel double-activation strategy allowed us to achieve small-size rings such as cyclobutanes and cyclopropanes.



INTRODUCTION

Intramolecular additions of carbon radicals onto alkenes are very important reactions in organic synthesis. The efficiency of these reactions depends on their rate, which in turn is subject to the type of substituents on the radical and on the alkene. Thus, Michael-type radical conjugate additions, in which a nucleophilic radical is added to an alkene or an alkyne attached to an electron-withdrawing group (EWG), are among the most efficient radical cyclizations (Scheme 1).[1]

Scheme 1. Michael-Type Radical Conjugate Addition



In the early 1980s, several authors explored the synthetic utility of intramolecular free radical conjugate additions, and many novel ring systems and natural products have been obtained using this methodology.[1] However, very few examples of Michael-type radical cyclizations with a vinylsulfone as acceptor can be found in the literature.[2] Among these very few examples, it is worth mentioning the earlier work of Clive et al.,[2a,b] that introduced a new methodology for the synthesis of spiro-polycyclic compounds based on the intramolecular addition of a radical, generated with Bu_3SnH, to a vinylsulfone. Further examples of radical cyclization reactions onto vinylsulfones can be found in the review published by Srikanth and Castle.[3]

A few examples of titanocene-promoted radical cyclization reactions have been described in recent years,[4] but none of them involved a vinylsulfone as an acceptor group (Scheme 2).

Therefore, as a complement to our previous work addressing the intermolecular radical addition of epoxides to vinylsulfones promoted by titanocene,[5] it would be interesting to study the intramolecular radical coupling of epoxyvinyl- and allylsulfones mediated by Ti^{III} species.

RESULTS AND DISCUSSION

Here, we designed a study of the above-mentioned titanocene-promoted intramolecular addition, employing a series of epoxyvinyl- and allylsulfones as substrates, with the aim of developing a straightforward procedure for the synthesis of functionalized cyclic compounds. The results are discussed in different sections depending on the size of the cycle obtained.

5-*Exo*-*Trig* Cyclizations. First, we performed the titanocene-promoted cyclization of epoxysulfones **1** and **3a**/**b** (see Table 1), which have similar structures, in order to achieve a 5-*exo*-*trig* cyclization. All reactions were performed using either overstoichiometric or catalytic quantities of Cp_2TiCl. The results are summarized in Table 1.

All reactions provided the expected cyclization products in good to excellent yields, and for both sulfones better yields were achieved when the experiments were performed with an excess of the Ti^{III} reagent. All intramolecular additions afforded the cyclic products as an approximately 50% mixture of two diastereoisomers. A mechanism for the cyclization reaction of sulfone **1** is proposed in Scheme 3.

The reaction starts with the well-known homolytic cleavage of the C−O bond of the oxirane as a result of the Ti^{III} σ-coordination to the oxygen.[7] This epoxide opening regioselectively affords the β-alkoxy radical **A**, which further proceeds through the addition to the activated double bond to provide radical **B**. The radical cyclization proceeds with a higher rate than radical **A** reduction. In the next step, radical **B** reduces to the corresponding anion by a second equivalent of titanocene, yielding intermediate **C**, which after workup provides the isolated cyclization products **2a** and **2b**. In the catalytic reaction, titanocene is regenerated by the 2,4,6-trimethylsilylpyridinium chloride present in the reaction media.[8]

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Scheme 2. Titanocene-Promoted Radical Cyclizations

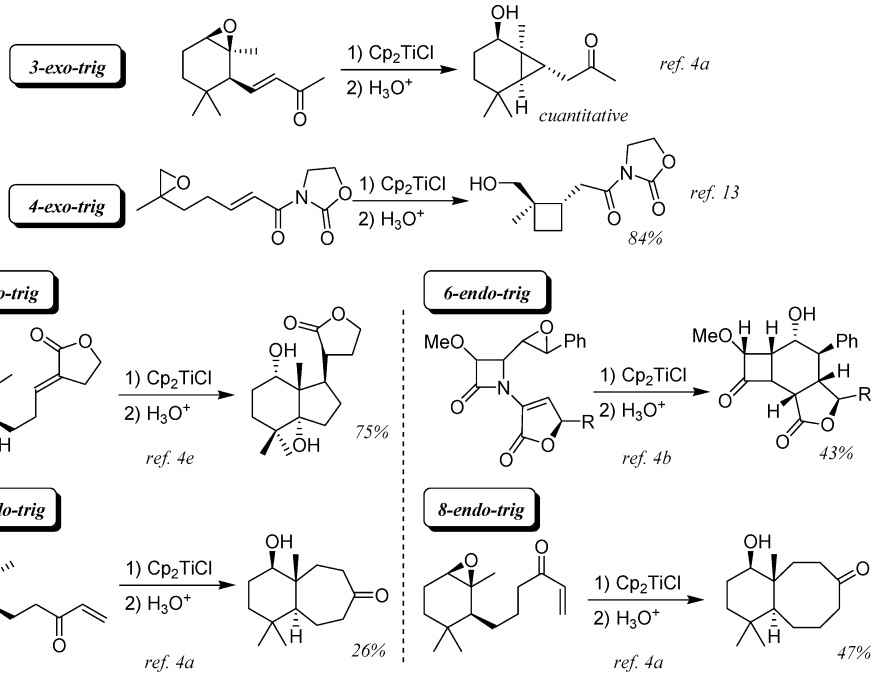
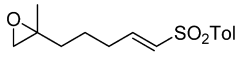
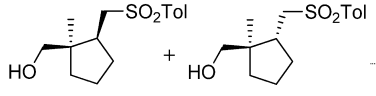
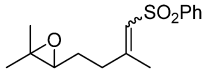
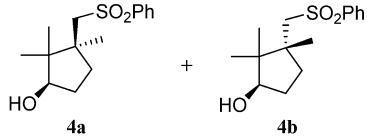


Table 1. Titanocene-Promoted 5-*Exo-Trig* cyclizations

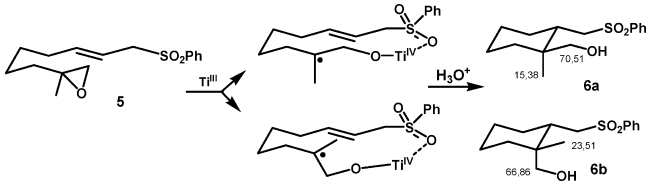
	Epoxy sulfone	Equiv of Cp_2TiCl	Products	Yield (%)
1		2.2		100% (53:47)[a]
2	**1**	0.2	**2a** + **2b**	72% (53:47)[a]
3		2.2		78% (53:47)[a]
4	**3a/b**	0.2	**4a** + **4b**	62% (50:50)[a]

[a]The ratio of diastereoisomers was determined in all cases by integration of signals in ^{1}H NMR spectra. Diastereoisomer assignation was achieved by comparison of the spectroscopic data of products with that of similar compounds previously described in the literature.[6]

For epoxy sulfones **4a/b**, however, the formation of 5-*exo-trig* cyclization products may not be so straightforward. Previously reported experimental data[9] show that the rate constant for cyclization reactions of 5-hexenyl radicals with an 5-alkyl substituent is much lower than the rate constant of those lacking this substitution. This kind of radical actually prefers the *6-endo-trig* cyclization to the 5-*exo-trig* type, and although mixtures of both are usually obtained, in most cases the ratio favors the first one by 65 to 35.[9] The fact that we obtained the 5-*exo* cyclization products, **4c/d**, not only in high yields but also as the only products clearly shows that the sulfonyl group attached to the double bond induces a very strong activating effect, completely overcoming the presence of the 5-methyl substituent.

6-*Exo-Trig*/6-*Endo-Trig* Cyclizations. We continued our research by studying the performance of two new epoxysulfones, **5** and **7** (see Table 2), which would provide six-membered cyclic products after 6-*exo* and 6-*endo* cyclizations, respectively. The reaction conditions and results are summarized in Table 2.

In the reactions performed with epoxyvinylsulfone **5** (entries 1 and 2 of Table 2), the desired 6-*endo* cyclization products were obtained in good yields when the reaction was performed with both 2.2 and 0.2 equiv of titanocene (III). As occurred in the reactions performed with sulfones **1** and **3a/b**, the products were obtained as a mixture of diastereoisomers, although in this case the *trans* product was clearly the major product isolated. A stereochemical model for formation of **6a** versus **6b** and assignation based on ^{13}C NMR methyl displacements is given in scheme below.



The intramolecular addition reaction with sulfone **7** was only performed in the presence of an overstoichiometric amount of

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Scheme 3. Cyclization Mechanism

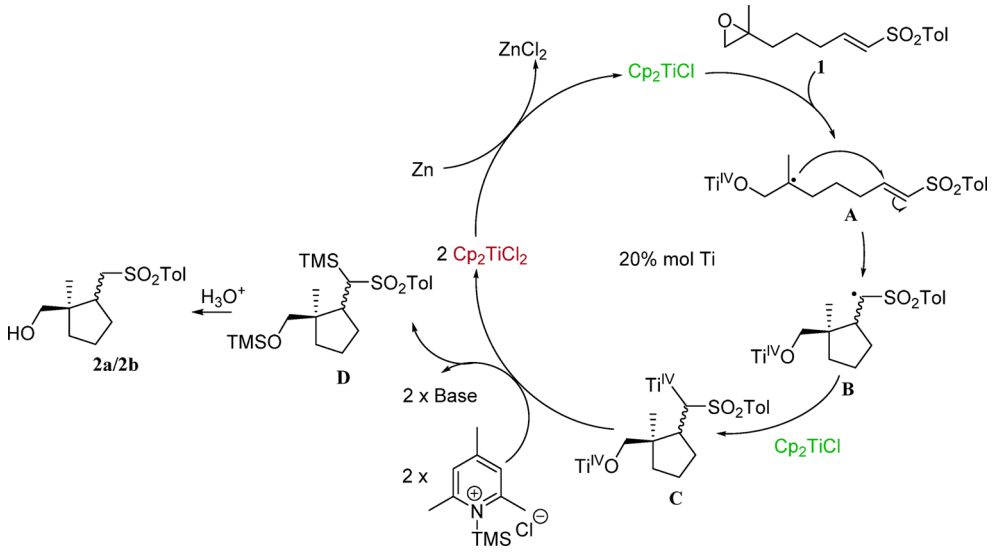
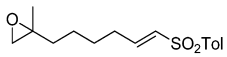
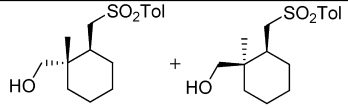
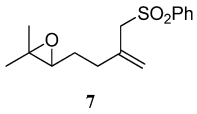
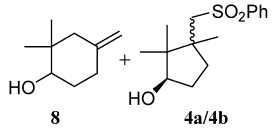
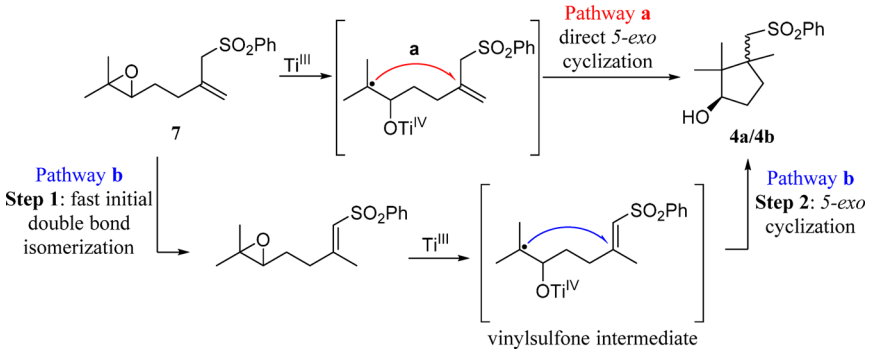


Table 2. Titanocene-Promoted 6-*Exo* and 6-*Endo* Cyclizations

	Epoxy sulfone	Equiv of Cp_2TiCl	Products	Yield (%)
1	 5	2.2	 6a + 6b	73% (67:33)
2		0.2		68% (67:33)
3	 7	2.2	 8 + 4a/4b	52% (35:65[a])

[a]The ratio of diastereoisomers (determined by integration of signals in ^{1}H NMR spectra) was 53:47, favoring the cis diastereroisomer **4a**.

Scheme 4. Possible Pathways for the Transformation of 7 into 4a/4b



titanocene dichloride reagent (2.2 equiv), and the reaction afforded as many as three cyclization products: the six-membered ring **8** and the five-membered rings **4a** and **4b** (Scheme 4). The unsaturated alcohol **8** was undoubtedly formed through a 6-*endo-trig* cyclization followed by the elimination of a sulfone group. However, two different pathways must be considered for the formation of hydroxysulfones **4a** and **4b** (Scheme 4): a direct 5-*exo-trig* cyclization or a two-step process in which an initial double-bond conjugation yields a vinylsulfone intermediate, which further proceeds through a 5-*exo-trig* cyclization.

The direct 5-*exo-trig* cyclization must be excluded. As we have reported previously,[9] cycling processes in which a 5-alkyl-substituted 5-hexenyl radical is involved show a preference for 6-*endo* cyclization.[4f] The two-step process more convincingly explains the formation of **4a**/**4b**, in which the more activated vinylsulfone intermediate could be formed readily, and quite rapidly, by any of the Lewis acids (i.e., titanocene chloride or zinc chloride) present in the reaction medium. Once this intermediate has been formed, the reaction proceeds through a 5-*exo* cyclization process that leads to **4a**/**4b**.

4-*Exo-Trig* Cyclization. Encouraged by the good results obtained, we decided to apply our method to the synthesis of four-membered cyclic hydroxy sulfones. Thus, epoxyvinylsulfone **9** was made to react with both 2.2 and 0.2 equiv of titanocene chloride. However, instead of the desired cyclic

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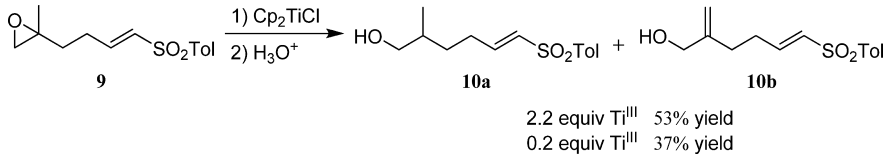
Scheme 5. Reaction of Epoxysulfone 9 with Ti^{III}



products, a mixture of the open-chained saturated (**10a**) and unsaturated (**10b**) hydroxyvinylsulfones was isolated in both reactions (see Scheme 5). Lowering the reaction temperature does not prevent elimination.

From this result it may concluded that for these model compounds the 4-*exo-trig* cyclization is slower than the hydrogen elimination process[10] and therefore does not occur. Activation of the sulfonyl group is insufficient for this to happen.

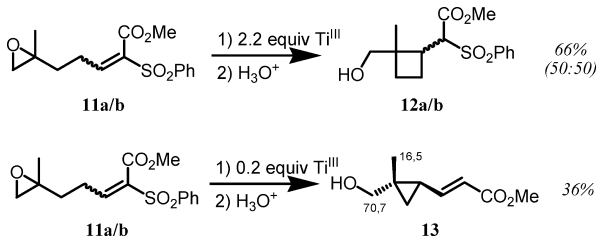
The synthesis of small-size rings, such as cyclopropanes or cyclobutanes, has always been a difficult task for chemists. Synthesizing these compounds using radical procedures involves the problem of reversibility. That is, the homolytic opening of the intermediate cyclic radicals (i.e., cyclopropylcarbinyl and cyclobutylcarbinyl) is in both cases faster than the cyclization of the initial radicals.[11] Several strategies have been applied in titanocene radical chemistry in order to achieve the synthesis of three- and four-membered ring cyclization products successfully.[12,4a,f,10a] In the past, both our group[4a] and that of Gansäuer[4f] have described the synthesis of cyclopropanes through a titanocene-mediated Michael-type intramolecular addition on α,β-unsaturated carbonyl compounds (see Scheme 6). In these examples, the reversibility of the cyclization reaction can be avoided by trapping the enolic intermediate radical with Ti^{III} complexes.

Scheme 6. Titanocene-Promoted Synthesis of Cyclopropanes

However, when attempting to synthesize cyclobutanes using this strategy, successful results were only obtained when additional strategies were also applied, such as the Thorpe–Ingold effect[12b] or the use of a template catalyst that binds both the radical and the radical acceptor, therefore favoring ring closure (Scheme 7).[13]

Based on the previous results described above for five- and six-membered rings, we decided to circumvent our cyclization rate problems through a novel strategy: the double activation of the β-carbon to the sulfone by the attachment of an ester moiety as an extra activating group. Accordingly, we performed the reactions on the double activated epoxysulfone **11a/b** with two different amoung of titanocene reagent: catalytic and overstoichiometric. Much to our surprise, different products were isolated, depending on the reaction procedure applied (see Scheme 8).

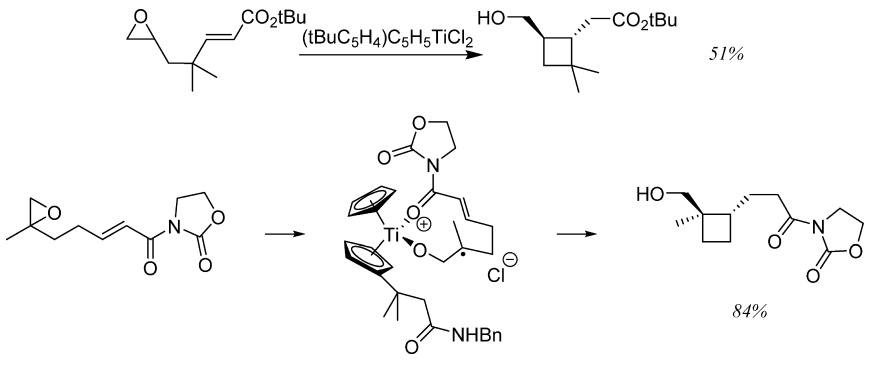
Scheme 8. Reaction of Epoxy Sulfone 11a/b with 2.2 and 0.2 equiv of Ti^{III}



The experiment in which an excess of titanocene chloride was added (Scheme 8, first row) afforded the desired cyclobutane as a mixture of isomers, **12a/b**, in 66% yield, meaning that our double-activation strategy had been successful. However, the experiment performed with a catalytic 20% of titanocene reagent (Scheme 8, second row) provided only the cyclopropane **13**, in a 36% yield. A likely mechanism to explain the formation of **13** requires double-bond isomerization toward the unconjugated position. The force responsible for preventing reversibility in the formation of cyclopropylcarbinyl radical **12B** from radical **12A** is the elimination of the sulfonyl radical, as depicted in Scheme 9.

Some authors have stated that allylsulfones are more thermodynamically stable than vinylsulfones.[14] In the late 1980s, Inomata et al.[15] performed a fairly exhaustive study of

Scheme 7. Gansäuer's Strategies for the Synthesis of Cyclobutanes with Ti^{III}



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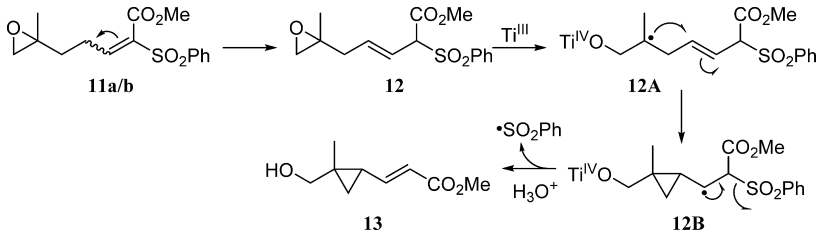
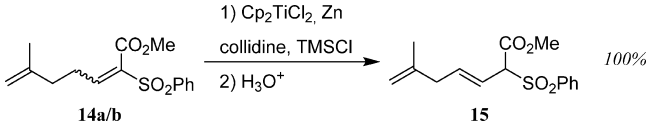
Scheme 9. Mechanism for the Formation of 13



the diazabicycloundecene-mediated conversion of vinylsulfones into allylsulfones, and isomerization to the allyl position proved to be general.

To confirm the above proposed mechanism we synthesized the corresponding alkene, **14a/b**, and proceeded to place it under the conditions in which the catalytic reaction had been performed. As shown in Scheme 10, this reaction afforded total isomerization of the double bond toward the $\beta-\gamma$ position. Further experiments revealed that among all species present in the reaction vessel 2,4,6-collidine was the only one responsible for this total isomerization, and hence, the mechanism proposed in Scheme 9 was confirmed. In addition, DBU also provided **15** in good yield, as described by Inomata.

Scheme 10. Study of the Double-Bond Isomerization



3-*Exo-Trig* Cyclization. The above reaction, although not initially intended for that purpose, provided us with a three-membered ring product through a three-step process: double-bond isomerization, 3-*exo-trig* cyclization, and sulfone elimination. Very few examples of the use of a process of fast elimination of a leaving group placed in the β-position of a cyclopropylcarbinyl radical for the synthesis of cyclopropanes can be found in the literature. To our knowledge, in the only examples described the authors used bromide or phenylthio leaving groups.[16] Therefore, the example described here presents a hitherto unprecedented successful 3-*exo* radical cyclization procedure.

As a next step, we decided to further study the scope of this cyclopropanation reaction for our usual epoxy monoactivated vinylsulfones. With this aim, we made epoxysulfone **16** react with Cp_2TiCl under the usual reaction conditions (see Scheme 11).

Unfortunately, the reaction of **16** with either 0.2 or 2.2 equiv of Ti^{III} provided only a mixture of the saturated and unsaturated alcohols **17a/b**, instead of the desired cyclization product. It may therefore be concluded that, for this epoxysulfone, as occurred with epoxy sulfone **9**, hydrogen elimination is faster than cyclization.

Nevertheless, as can be seen in Scheme 11, the second-activating-group strategy proved once more to be successful for the achievement of the desired intramolecular addition, providing the cyclopropane **13** in a more than satisfying 97% yield when catalytic conditions were applied. The low yield obtained in the reaction using overstoichiometric Ti(III) quantities could be explained by competitive hydrogen elimination, undertaken by Ti(III) in excess, from the methyl group of the radical initial to afford byproducts as complex mixtures of allyl alcohol−sulfonyl esters, which we have not been able to resolve.

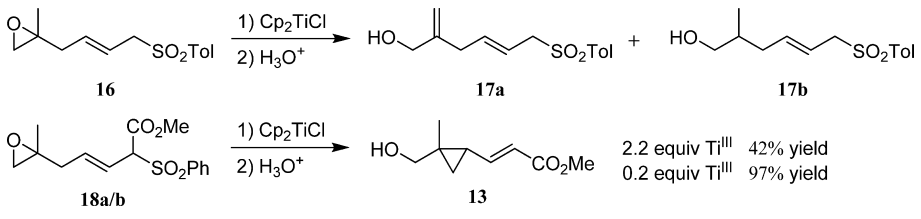
Tamdem Reaction. As a final point to our cyclization experiments, we decided to slightly modify the patterns followed by designing a two-molecule tandem cyclization experiment.

Based on the information acquired in the previously studied intra- and intermolecular addition experiments to vinyl- and allylsulfones, we believed that it might be interesting to perform a tandem reaction that combined both inter- and intramolecular consecutive additions, providing a cyclic extrafunctionalized product. To accomplish this, two molecules were selected. On one hand, we chose epoxy sulfone **16**, which provided us with the epoxide (radical precursor) and the allylsulfone, intended to be the secondary acceptor. On the other, phenyl vinylsulfone **19**, which afforded the best results in the intermolecular study,[5] was selected as the primary acceptor. The reaction was performed in the presence of 0.2 equiv of Ti^{III} reagent, and the results are depicted in Scheme 12.

Reaction of sulfones **16** and **19** promoted by titanocene chloride afforded cyclic hydroxy sulfone **20a/b** as a mixture of diastereoisomers in 51% yield. The reaction mechanism is depicted in Scheme 13.

The tertiary radical **16A**, formed after homolytic epoxide opening promoted by Ti^{III}, was added to the conjugated double bond of sulfone **19**, providing a new radical, **16B**, which after intramolecular addition to the allylic double bond afforded the five-membered ring followed by the elimination of a tosyl radical. The precise coordination of two addition processes with accurate kinetics (a fast intermolecular addition to the vinylsulfone and a slower intramolecular addition to the

Scheme 11. 3-*Exo-Trig* Cyclization Reactions



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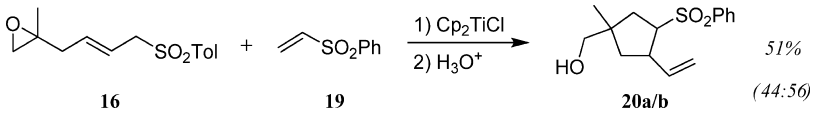
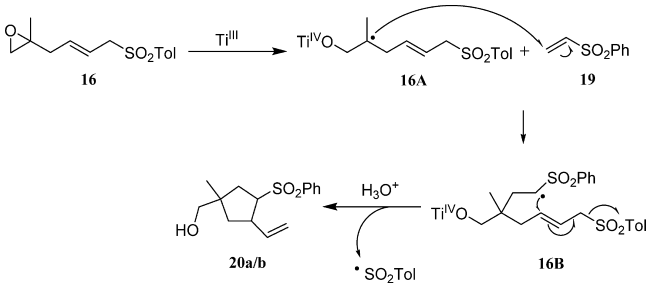
Scheme 12. Tandem Reaction



Scheme 13. Tandem Reaction Mechanism



allylsulfone, both processes faster than the reduction of the radicals by Ti^{III}) provided us with a five-membered ring with as many as three different functions in good yield.

■ CONCLUSIONS

A satisfying procedure for the achievement of several cyclic hydroxysulfones has been described. The titanocene-mediated intramolecular addition of different epoxy vinyl- and allylsulfones provided several 3- to 5-membered ring cyclic products in good to excellent yields. The reaction of 6,7-epoxyvinylsulfones with titanocene afforded the corresponding 5-*exo* cyclization products in very good yields as a result of the very strong activating effect exerted by the sulfone group on the *β*-carbon of the double bond. In turn, 7,8-epoxyvinylsulfones proceed through the desired 6-*exo* addition, affording the 6-membered ring products. An example of a 6-*endo* process favored by the elimination of a tosyl radical from an epoxy allylsulfone is described. This result once more confirms the strong activation effect performed by the sulfone. Also, a novel double activation procedure has been developed in order to achieve the synthesis of small-size rings, such as cyclobutanes and cyclopropanes, from the corresponding 5,6-epoxyvinylsulfonyl esters and 5,6-epoxy allylsulfonyl esters. Almost all reactions described here afforded products in good yields in the presence of both 2.2 and 0.2 equiv of Cp_2TiCl, although unfortunately, no remarkable diastereoselectivity was observed in any of the procedures. Finally, an accurate combination of two reactions with different addition rates allowed us to perform a two-molecule tandem addition which afforded a highly functionalized five-membered ring in good yield. The epoxy vinyl- and allylsulfones reported in this work were synthesized according to the multistep sequences depicted in Scheme 14.

■ EXPERIMENTAL SECTION

General Experimental Methods. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. ^1H NMR spectra were measured at either 200 or 400 MHz, and ^{13}C NMR spectra were measured at 50 or 100 MHz in $CDCl_3$ and referenced to solvent, except where otherwise indicated. HRMS mass spectrometry data were acquired in a hybrid quadrupole time-of-flight mass spectromer. Samples were dissolved in methanol, and electrospray was used for ionization. When required, all solvents and reagents were purified by standard techniques. Tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone and degassed before use. 1,2-Dimethoxyethane (DME) was purified by refluxing in sodium for 2 h before use. Sodium used for desiccation was renewed twice during this 2 h period and once more just before final distillation before use. All titanocene reactions were conducted under a positive pressure of argon by using standard benchtop techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques on Merck silica gel 60 (0.040−0.063 mm). Unless otherwise mentioned, yields reported are for chromatographically pure isolated products.

Titanocene Procedures. *General Procedure A (**GPA**).* A mixture of Cp_2TiCl_2 (2.20 mmol) and Zn (6.60 mmol) in strictly deoxygenated THF (11.0 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1.00 mmol) and the sulfone (1, 2, 5, or 10 mmol) were dissolved in strictly deoxygenated THF (10.0 mL). The green Ti^{III} solution was slowly added by cannula to the epoxide solution. After 30 min, an excess amount of saturated NaH_2PO_4 was added, and the mixture was stirred for 2 h. The mixture was filtered to remove insoluble titanium salts. The product was extracted with diethyl ether (Et_2O), and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography.

*General Procedure B (**GPB**).* A mixture of Cp_2TiCl_2 (2.20 mmol) and Zn (6.60 mmol) in strictly deoxygenated THF (11.0 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1.00 mmol) and the sulfone (1, 2, 5, or 10 mmol) were dissolved in strictly deoxygenated THF (10.0 mL). The epoxide solution was slowly added by cannula to the green Ti^{III} solution. After 1 h, an excess amount of saturated NaH_2PO_4 was added, and the mixture was stirred for 2 h. The mixture was filtered to remove insoluble titanium salts. The product was extracted with Et_2O, and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography.

*Catalytic Procedure (**CP**).* A mixture of Cp_2TiCl_2 (0.20 mmol) and Zn (8.00 mmol) in strictly deoxygenated THF (8.0 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1.00 mmol), 2,4,6-collidine (8.00 mmol), and the sulfone (1, 2, 5, or 10 mmol) were dissolved in strictly deoxygenated THF (0.8 mL). In a separate flask, chlorotrimethylsilane (TMSCl) (2.5 mmol) was strictly deoxygenated. Next, the epoxide solution and the TMSCl were slowly added at the same time by different cannulas to the green Ti^{III} solution. After 8 h, an excess amount of HCl 2 M was added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography.

*Compounds **2a** and **2b**.* Application of **GPB** to 100 mg of **1** followed by flash chromatography (Hex/AcOEt 65:35) afforded a 1:0.9 mixture of **2a** and **2b** in 100% yield (101 mg). Application of **CP** to 100 mg of **1** followed by flash chromatography (Hex/AcOEt 7:3) provided a 1:0.9 mixture of **2a*** and **2b**† in 72% yield (73 mg). IR: ν = 3520, 2955, 2877, 1723, 1599, 1456, 1301, 1152, 1048, 1087 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.74† (s, 3H), 0.94* (s, 3H), 1.2−2.4 (m, 16H), 2.41 (s, 6H), 2.85† (d, J = 9.8 Hz, 1H), 2.92* (d, J = 9.7 Hz, 1H), 3.04† (d, J = 10.6 Hz, 1H), 3.11* (d, J = 10.6 Hz, 1H), 3.34 (m, 4H), 7.32 (d, J = 7.8 Hz, 4H), 7.74 (d, J = 8.2 Hz, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.2† (CH_3), 21.8* (CH_3), 21.9† (CH_3), 22.3 ($2CH_2$), 23.2* (CH_3), 31.5† (CH_2), 31.7* (CH_2), 35.9† (CH_2), 36.1* (CH_2), 39.2† (CH), 43.3* (CH), 46.3 (2C), 58.1* (CH_2), 58.6† (CH_2), 67.1† (CH_2), 70.0* (CH_2), 128.1 (4CH), 130.0* (2CH),

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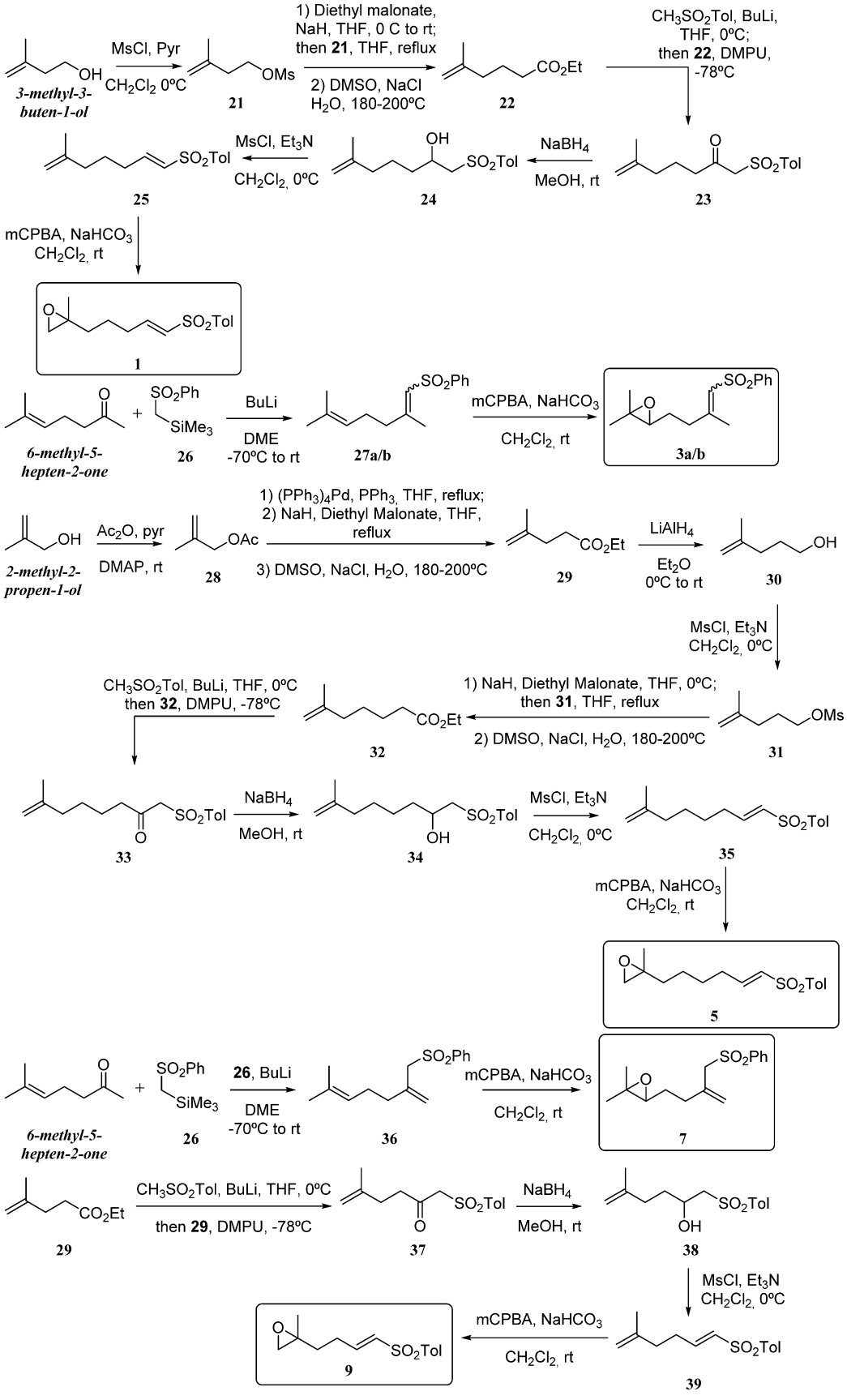
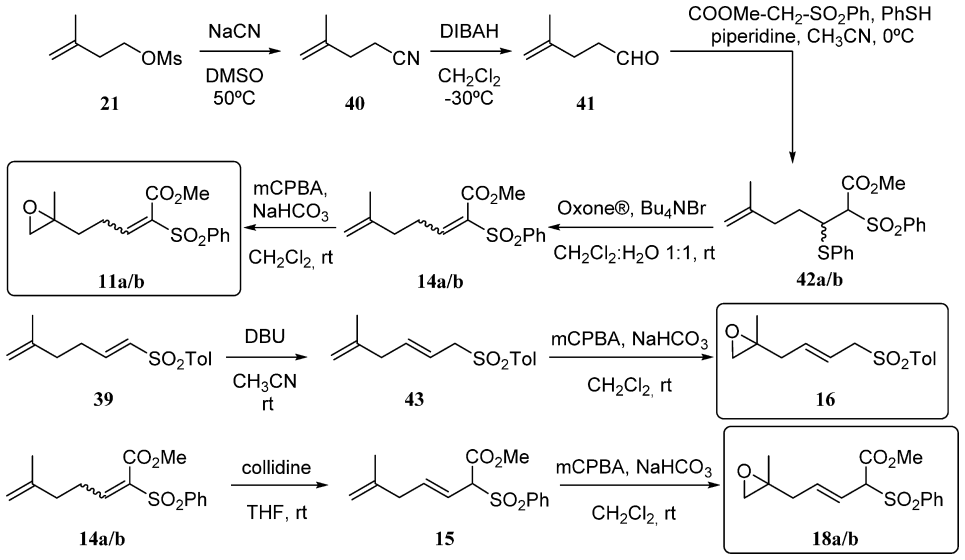
Scheme 14. Synthesis of Epoxy Vinyl- and Allylsulfones 1, 3a/b, 5, 7, 9, 11a/b, 16, and 18a/b



DOI: 10.1021/acs.joc.5b00206
J. Org. Chem. 2015, 80, 4378−4391

Scheme 14. continued



130.1† (2CH), 137.1† (C), 137.2* (C), 144.7* (C), 144.9† (C). HRMS (ESI) calcd for $C_{15}H_{22}O_3NaS$ 305.1182, found 305.1186.

*Compounds **4a** and **4b**.* Application of **GPB** to 100 mg of **3a/b** followed by flash chromatography (Hex/AcOEt 6:4) afforded a 1:0.9 mixture of **4a** and **4b** in 78% yield (79 mg). Application of **CP** to 100 mg of **3a/b** followed by flash chromatography (Hex/AcOEt 6:4) provided a 1:1 mixture of **4a*** and **4b**† in 62% yield (63 mg). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.73* (s, 3H), 0.74† (s, 3H), 0.84† (s, 3H), 0.88* (s, 3H), 1.23* (s, 3H), 1.32† (s, 3H), 1.4−2.2 (m, 10H), 3.01 (m, 3H), 3.34* (d, J = 14.2 Hz, 1H), 3.77* (dd, J_1 = 4.6 Hz, J_2 = 8.2 Hz, 1H), 3.94† (m, 1H), 7.55 (m, 6H), 7.89 (m, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.1† (CH_3), 17.4* (CH_3), 21.5† (CH_3), 21.8* (CH_3), 22.1† (CH_3), 23.6* (CH_3), 30.4† (CH_2), 31.6* (CH_2), 33.7† (CH_2), 34.4* (CH_2), 45.7† (C), 46.1* (C), 48.2† (C), 49.1* (C), 63.7† (CH_2), 64.2* (CH_2), 79.3† (CH), 80.9* (CH), 127.7 (4CH), 129.5 (4CH), 133.6 (2CH), 142.2 (2C). HRMS (ESI): calcd for $C_{15}H_{22}O_3NaS$ 305.1182, found 305.1174.

*Compounds **6a** and **6b**.* Application of **GPB** to 100 mg of **5** followed by flash chromatography (Hex/AcOEt 7:3) afforded **6a** (50 mg, 49%) followed by **6b** (25 mg, 24%). Application of **CP** to 100 mg of **5** followed by flash chromatography (Hex/AcOEt7:3) provided **6a** (47 mg, 46%) and **6b** (23 mg, 22%). **6a**. IR: ν = 3524, 2929, 2854, 1589, 1465, 1288, 1146 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.67 (s, 3H), 1.1−1.7 (m, 9H), 2.10 (m, 1H), 2.45 (s, 3H), 2.62 (dd, J_1 = 6.6 Hz, J_2 = 14.4 Hz, 1H), 3.12 (d, J = 12.0 Hz, 1H), 3.29 (dd, J_1 = 2.4 Hz, J_2 = 14.4 Hz, 1H), 3.47 (d, J = 11.2 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.4 (CH_3), 21.4 (CH_2), 21.9 (CH_3), 26.3 (CH_2), 30.3 (CH_2), 34.9 (CH_2), 35.1 (CH), 38.4 (C), 58.2 (CH_2), 70.5 (CH_2), 128.2 (2CH), 130.2 (2CH), 136.4 (C), 145.2 (C). **6b**. IR: ν = 3526, 2929, 2858, 1599, 1463, 1288, 1145 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 1.0−2.1 (m, 10H), 2.45 (s, 3H), 2.89 (dd, J_1 = 8.2 Hz, J_2 = 14.8 Hz, 1H), 3.35 (d, J = 11.4 Hz, 1H), 3.38 (dd, J_1 = 2.2 Hz, J_2 = 16.8 Hz, 1H), 3.54 (d, J = 11.4 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3 (CH_2), 21.9 (CH_3), 23.5 (CH_3), 24.5 (CH_2), 28.4 (CH_2), 34.4 (CH_2), 37.7 (C), 38.4 (CH), 57.6 (CH_2), 66.9 (CH_2), 128.2 (2CH), 130.1 (2CH), 136.8 (C), 144.9 (C). HRMS (ESI): calcd for $C_{16}H_{24}O_3NaS$ 319.1338, found 319.1349.

*Compound **8**.* Application of **GPB** to 211 mg of **7** followed by flash chromatography (Hex/AcOEt 9:1 to Hex/AcOEt 7:3) afforded **8** (19 mg, 18%) followed by a 1:0.9 mixture of **2*a*/2b** (35 mg, 34%). **8**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (s, 3H), 0.96 (s, 3H), 1.2−2.4 (m, 7H), 3.45 (dd, J_1 = 3.8 Hz, J_2 = 9.0 Hz, 1H), 4.59 (s, 1H), 4.68 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.4 (CH_3), 27.7 (CH_3), 31.3 (CH_2), 32.2 (CH_2), 37.0 (C), 46.4 (CH_2), 76.6 (CH), 109.5 (CH_2), 146.2 (C).

*Compounds **10a** and **10b**.* Application of **GPA** to 113 mg of **9** followed by flash chromatography (Hex/AcOEt 6:4) afforded a 1:0.95 mixture of **10a**† and **10b*** (60 mg, 53%). Application of **CP** to 120 mg of **9** followed by flash chromatography (Hex/AcOEt 6:4) provided a 1:1 mixture of **10a**† and **10b*** (44 mg, 37%). IR: ν = 3500, 3046, 2922, 2877, 1729, 1599, 1456, 1320, 1300, 1145, 1047, 814 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87† (d, J = 6.6 Hz, 3H), 1.0−2.2 (m, 11H), 2.41 (s, 6H), 3.42† (d, J = 5.8 Hz, 2H), 4.01* (s, 2H), 4.82* (s, 1H), 5.04* (s, 1H), 6.30 (m, 2H), 6.94 (m, 2H), 7.31 (d, J = 8.2 Hz, 4H), 7.72 (d, J = 8.2 Hz, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.5† (CH_3), 21.8 ($2CH_3$), 29.2* (CH_2), 29.7† (CH_2), 30.9* (CH_2), 31.2† (CH_2), 35.4† (CH), 65.9* (CH_2), 67.8† (CH_2), 111.2* (CH_2), 127.8 (4CH), 130.1 (4CH, C), 130.8† (CH), 131.3* (CH), 137.7† (C), 137.8* (C), 144.6† (C), 145.9* (CH), 146.7† (CH), 146.9* (C). **10a**. HRMS (ESI): calcd for $C_{14}H_{20}O_3NaS$ 291.1025, found 291.1016. **10b**. HRMS (ESI): calcd for $C_{14}H_{18}O_3NaS$ 289.0869, found 289.0870.

*Compounds **12a** and **12b**.* Application of **GPB** to 100 mg of **11a/b** followed by flash chromatography (Hex/AcOEt 7:3) afforded a **12a** (34 mg, 33%) followed by **12b** (34 mg, 33%). **12a** (less polar isomer). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.0−2.0 (m, 5H), 1.23 (s, 3H), 3.15 (m, 1H), 3.51 (s, 3H), 3.56 (d, J = 2.8 Hz, 2H), 4.17 (d, J = 10.6 Hz, 1H), 7.63 (m, 3H), 7.87 (m, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.9 (CH_3), 20.9 (CH_2), 26.8 (CH_2), 35.7 (CH), 43.8 (C), 52.9 (CH_3), 70.1 (CH_2), 71.9 (CH), 129.3 (4CH), 134.6 (CH), 137.5 (C), 165.6 (C). **12b** (more polar isomer). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (s, 3H), 1.2−2.2 (m, 5H), 2.84 (m, 1H), 3.16 (d, J = 11.2 Hz, 1H), 3.31 (d, J = 11.6 Hz, 1H), 3.58 (s, 3H), 4.08 (d, J = 12.0 Hz, 1H), 7.61 (m, 3H), 7.84 (m, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.7 (CH_3), 21.9 (CH_2), 28.1 (CH_2), 36.9 (CH), 44.2 (C), 53.3 (CH_3), 70.7 (CH_2), 72.9 (CH), 129.3 (4CH), 134.6 (CH), 137.9 (C), 167.7 (C). HRMS (ESI): calcd for $C_{15}H_{20}O_5NaS$ 335.0924, found 335.0918.

*Compound **13**.* Application of **CP** to 150 mg of **11a/b** followed by flash chromatography (Hex/AcOEt 8:2) provided **13** (30 mg, 36%). Application of **GPB** to 100 mg of **18a/b** followed by flash chromatography (Hex/AcOEt 7:3) afforded **13** (23 mg, 42%). Application of **CP** to 130 mg of **18a/b** followed by flash chromatography (Hex/AcOEt 7:3) provided **13** (67 mg, 97%). IR: ν = 3454, 2955, 2864, 1754, 1716, 1644, 1450, 1313, 1281, 1151, 1073 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.67 (t, J = 5.2 Hz, 1H), 0.83 (m, 1H), 1.04 (m, 1H), 1.19 (s, 3H), 2.36 (br s, 1H), 3.40 (d, J = 4.8 Hz, 2H), 3.68 (s, 3H), 5.90 (m, 1H), 6.68 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.5 (CH_3), 20.6 (CH_2), 25.1 (CH), 27.9 (C), 51.6 (CH_3), 70.7 (CH_2), 120.4 (CH), 150.2 (CH), 167.2 (C). HRMS (ESI): calcd for $C_9H_{14}O_3Na$ 193.0835, found 193.0840.

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Compound 15. Application of **CP** to 100 mg of **14a/b** provided a crude product identified as **15** (100 mg, 100%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.74 (s, 3H), 2.72 (d, J = 6.6 Hz, 2H), 3.72 (s, 3H), 4.52 (d, J = 9.4 Hz, 1H), 4.61 (s, 1H), 4.72 (s, 1H), 5.53 (s, 1H), 5.75 (m, 1H), 7.57 (m, 3H), 7.82 (m, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7 (CH_3), 41.2 (CH_2), 53.4 (CH_3), 74.3 (CH), 112.1 (CH_2), 118.7 (CH), 129.1 (2CH), 129.8 (2CH), 134.5 (CH), 137.1 (C), 139.9 (CH), 142.9 (C), 165.5 (C). HRMS (ESI): calcd for $C_{15}H_{18}O_4NaS$ 317.0818, found 317.0827.

Compounds 17a and 17b. Application of **GPB** to 100 mg of **16** followed by flash chromatography (Hex/AcOEt 7:3) afforded a 0.95:1 mixture of **17a**† and **17b*** (62 mg, 62%). Application of **CP** to 100 mg of **16** followed by flash chromatography (Hex/AcOEt 7:3) provided a 1:1 mixture of **17a**† and **17b*** (53 mg, 53%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.78* (d, J = 6.6 Hz, 3H), 1.6−2.4 (m, 5H), 2.42 (s, 6H), 2.75† (d, J = 6.2 Hz, 2H), 3.35 (d, J = 6.2 Hz, 4H), 3.73* (m, 2H), 3.94† (s, 2H), 4.71† (s, 1H), 4.99† (s, 1H), 5.52 (m, 4H), 7.31 (d, J = 8.2 Hz, 4H), 7.70 (d, J = 8.2 Hz, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.5* (CH_3), 21.8 ($2CH_3$), 35.7* (CH), 36.4* (CH_2), 36.6† (CH_2), 60.2* (CH_2), 60.4† (CH_2), 65.6* (CH_2), 67.6† (CH_2), 111.3† (CH_2), 117.7† (CH), 118.3* (CH), 128.6 (4CH), 129.92* (2CH), 129.96† (2CH), 135.7 (2C), 138.5* (CH), 139.9† (CH), 144.91† (C), 144.97* (C), 146.5† (C).

Compounds 20a and 20b. Application of **CP** to a mixture of 110 mg of **16** and 139 mg of **19** followed by flash chromatography (Hex/AcOEt 1:1) provided **20a** (10 mg, 9%) followed by an overall 33:67 mixture of **20a/b** (49 mg, 42%) (split in several fractions with different isomer ratios). **20a** (less polar isomer). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 3H), 1.38 (dd, J_1 = 9.7 Hz, J_2 = 13.2 Hz, 1H), 1.72 (dd, J_1 = 9.5 Hz, J_2 = 14.0 Hz, 1H), 1.75 (br s, 1H), 1.99 (dd, J_1 = 8.3 Hz, J_2 = 13.2 Hz, 1H), 2.19 (dd, J_1 = 7.8 Hz, J_2 = 13.8 Hz, 1H), 2.43 (br s, 1H), 3.13 (m, 1H), 3.45 (s, 2H), 4.82 (m, 2H), 5.56 (m, 1H), 7.53 (m, 2H), 7.62 (m, 1H), 7.87 (m, 2H. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (CH_3), 36.8 (CH_2), 43.1 (CH_2), 43.3 (C), 44.1 (CH), 68.7 (CH), 70.0 (CH_2), 115.2 (CH_2), 128.6 (2CH), 129.1 (2CH), 133.6 (CH), 138.7 (C), 139.1 (CH). HRMS (ESI): calcd for $C_{15}H_{21}O_3S$ 281.1206, found 281.1208. **20b** (more polar isomer). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01 (s, 3H), 1.0−2.3 (m, 6H), 3.44 (m, 1H), 3.49 (s, 2H), 5.04 (m, 2H), 6.21 (m, 1H), 7.55 (m, 3H), 7.86 (m, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.1 (CH_3), 37.1 (CH_2), 42.5 (CH_2), 43.3 (C), 45.8 (CH), 66.8 (CH), 71.1 (CH_2), 116.1 (CH_2), 128.6 (2CH), 129.2 (2CH), 133.7 (CH), 136.9 (CH), 140.1 (C).

Synthetic Procedures. *Compound 1*. To a 0 °C solution of 3-methyl-3-butenol (5.0 g, 58.0 mmol) in CH_2Cl_2 (20 mL) were added pyridine (9.4 mL, 116.1 mmol), and methanesulfonyl chloride (7.2 mL, 92.9 mmol). The resultant reaction mixture was stirred at 0 °C under an argon atmosphere for 1.5 h. After that time, water was added and the resultant mixture extracted with CH_2Cl_2. The combined organic layers were subsequently washed with a 2 M aqueous solution of HCl, a saturated aqueous solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Elimination of the solvent by careful distillation of the mixture with a Vigreux column afforded mesylate **21** (9.5 g, 100%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.78 (s, 3H), 2.46 (t, J = 7.2 Hz, 2H), 3.01 (s, 3H), 4.33 (t, J = 6.6 Hz, 2H), 4.79 (s, 1H), 4.88 (s, 1H). Diethyl malonate (13.2 mL, 86.9 mmol) was slowly added to a suspension of 50% NaH (3.9 g, 81.0 mmol) in THF (124.0 mL), under argon atmosphere and at 0 °C, and the mixture was stirred at room temperature until the complete formation of the anion (ca. 30 min). A solution of mesylate **21** (9.5 g, 57.9 mmol) in THF (19.0 mL) was then added dropwise and the new mixture refluxed for 12 h, when it was cooled to rt, quenched with a 2 M aqueous solution of HCl, and stirred for 10 min. The aqueous layer was extracted with Et_2O, the mixture of organic extracts was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure, yielding 23.0 g of a mixture of diethyl malonate and the diester intermediate, which was used without further purification in the next step. In that, the mixture (23.0 g) was dissolved in DMSO (150.0 mL), and anhydrous NaCl (17.7 g, 302.7 mmol) and water (5.4 mL, 302.7 mmol) were added. The reaction vessel was next stirred at 180−200 °C for 12 h. After this time, the mixture was cooled to rt, diluted in AcOEt, and subsequently washed several times with water and brine and dried over anhydrous Na_2SO_4. Solvent was then removed under reduced pressure to yield the monoester **22** (5.2 g, 57%). IR: ν = 2981, 2942, 1742, 1651, 1456, 1385, 1164, 1048, 898 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.0 Hz, 3H), 1.68 (s, 3H), 1.74 (m, 2H), 2.01 (t, J = 5.8 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 4.09 (q, J = 7.4 Hz, 2H), 4.65 (s, 1H), 4.69 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 22.4 (CH_3), 22.9 (CH_2), 33.9 (CH_2), 37.2 (CH_2), 60.4 (CH_2), 110.8 (CH_2), 144.9 (C), 173.8 (C). A 2 M solution of BuLi in cyclohexane (6.4 mL, 12.82 mmol) was added dropwise to a 0 °C solution of 4-(methylsulfonyl)toluene (1.09 g, 6.41 mmol) in anhydrous THF (23.0 mL), and the new mixture was stirred at this temperature for 30 min. After this time, it was cooled to −78 °C and a solution of ester **22** (1.00 g, 6.41 mmol) in DMPU (15.0 mL) was slowly added. This new mixture was stirred at −78 for 6 h, quenched with a saturated aqueous solution of NH_4Cl, and slowly allowed to reach rt. The aqueous phase was extracted with AcOEt, and the combined organic layers were subsequently washed with a 2 M aqueous solution of HCl, a saturated aqueous solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Finally, solvent was removed under reduced pressure and the residue was purified by flash chromatography over silica gel (Hex/AcOEt 9:1) to afford **22** (191 mg) followed by **23** (1.5 g, 82%). IR: ν = 2929, 1723, 1599, 1333, 1152 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 1.68 (m, 2H), 1.97 (t, J = 7.4 Hz, 2H), 2.43 (s, 3H), 2.66 (t, J = 7.4 Hz, 2H), 4.12 (s, 2H), 4.63 (s, 1H), 4.69 (s, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.1 (CH_2), 21.9 (CH_3), 22.4 (CH_3), 36.8 (CH_2), 43.9 (CH_2), 67.2 (CH_2), 11.0 (CH_2), 128.5 (2CH), 130.2 (2CH), 136.0 (C), 144.9 (C), 145.7 (C), 198.5 (C). HRMS (ESI): calcd for $C_{15}H_{20}O_3NaS$ 303.1025, found 303.1020. $NaBH_4$ (35 mg, 0.92 mmol) was added to a solution of keto sulfone **23** (216 mg, 077 mmol) in MeOH (3.8 mL), and the mixture was stirred under argon atmosphere at rt for 15 min. It was then quenched with acetone and stirred, and all solvents were removed at reduced pressure to yield a residue that was diluted in Et_2O and brine. The aqueous phase was extracted with Et_2O, the combined organic layers washed with brine and dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure, affording a residue identified as hydroxy sulfone **24** (211 mg, 97%). IR: ν = 3500, 2923, 1651, 1599, 1307, 1145, 1080 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (m, 4H), 1.61 (s, 3H), 1.91 (t, J = 6.6 Hz, 2H), 2.39 (s, 3H), 3.16 (m, 2H), 3.29 (br s, 1H), 4.09 (m, 1H), 4.55 (s, 1H), 4.61 (s, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 22.4 (CH_3), 23.0 (CH_2), 36.2 (CH_2), 37.5 (CH_2), 62.5 (CH_2), 65.9 (CH), 110.5 (CH_2), 128.1 (2CH), 130.3 (2CH), 136.5 (C), 145.3 (C), 145.4 (C). HRMS (ESI): calcd for $C_{15}H_{22}O_3NaS$ 305.1182, found 305.1167. To a solution of **24** (211 mg, 0.75 mmol) in CH_2Cl_2 (3.6 mL) at 0 °C were added Et_3N (248 μL, 1.79 mmol) and MsCl (69 μL, 0.89 mmol), and the new mixture was stirred at this temperature under argon atmosphere for 30 min. After this time, more Et_3N (207 μL, 1.50 mmol) was added and stirring maintained at 0 °C for 3 h, when the reaction was quenched by addition of an aqueous saturated solution of $NaHCO_3$ and stirred for a further 20 min. The aqueous phase was extracted with CH_2Cl_2, a the combined organic layers were washed with a 2 M aqueous solution of HCl, water, and brine and dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure to yield **25** (191 mg, 97%). IR: ν = 2974, 2929, 2858, 1638, 1592, 1450, 1320, 1145, 1093 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.59 (t, J = 7.4 Hz, 2H), 1.68 (s, 3H), 2.01 (t, J = 7.8 Hz, 2H), 2.22 (q, J = 7.4 Hz, 2H), 2.44 (s, 3H), 4.62 (s, 1H), 4.71 (s, 1H), 6.30 (d, J = 15.2 Hz, 1H), 6.94 (m, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.4 (CH_3), 25.6 (CH_2), 31.1 (CH_2), 37.1 (CH_2), 110.9 (CH_2), 127.8 (2CH), 130.1 (2CH), 131.1 (CH), 138.9 (C), 144.4 (C), 144.8 (C), 146.5 (CH). HRMS (ESI): calcd for $C_{15}H_{20}O_2NaS$ 287.1076, found 287.1085. A mixture of **25** (191 mg, 0.72 mmol), $NaHCO_3$ (73 mg, 0.87 mmol), and *m*-CPBA (137 mg, 0.79 mmol) in CH_2Cl_2 (3.6 mL) was stirred at rt for 90 min and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min, the aqueous layer was extracted with CH_2Cl_2, the

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combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/AcOEt 8:2) afforded epoxyvinylsulfone **1** (184 mg, 91%). IR: ν = 3513, 3046, 2936, 2877, 1716, 1632, 1599, 1463, 1320, 1152, 1087, 808 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.51 (m, 4H), 2.21 (m, 2H), 2.38 (s, 3H), 2.52 (s, 2H), 6.28 (d, J = 15.8 Hz, 1H), 6.89 (dt, J_1 = 6.8 Hz, J_2 = 15.2 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0 (CH_3), 21.8 (CH_3), 23.4 (CH_2), 31.4 (CH_2), 36.0 (CH_2), 53.9 (CH_2), 56.7 (C), 127.8 (2CH), 130.1 (2CH), 131.3 (CH), 137.8 (C), 144.5 (C), 145.9 (CH). HRMS (ESI): calcd for $C_{15}H_{20}O_3NaS$ 303.1025, found 303.1022.

*Compounds **3a/b**.* A 2 M solution of BuLi in cyclohexane (2.4 mL, 4.75 mmol) was added dropwise to a solution of the trimethylsilyl derivative **26**[17] (1.09 g, 6.41 mmol) in completely anhydrous and deoxygenated DME (23.0 mL) at −70 °C, and the resultant mixture was stirred under argon atmosphere at −70 °C for 30 min. At this point, a previously prepared deoxygenated solution of 6-methyl-5-hepten-2-one (300 mg, 2.38 mmol) in anhydrous DME (2.4 mL) was carefully added dropwise to the mixture, and once the addition was finished the reaction was allowed to reach rt (ca. 10 min) and then quenched with a saturated aqueous solution of NH_4Cl. The new mixture was then stirred for a further 15 min, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and solvent removed at reduced pressure. The crude product was purified by flash chromatography (Hex/AcOEt 9:1) to yield **27a***/**b**† (543 mg, 86%) as a mixture of E/Z isomers. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50 (s, 6H), 1.60 (s, 6H), 1.64† (s, 3H), 1.86* (s, 3H), 2.11 (m, 8H), 4.93* (m, 1H), 5.03† (m, 1H), 6.15 (s, 2H), 7.54 (m, 6H), 7.89 (m, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.9† (CH_3), 18.1* (CH_3), 25.7 ($2CH_2$), 25.8 ($4CH_3$), 40.6* (CH_2), 48.6† (CH_2), 122.3† (CH), 126.3* (CH), 126.9* (3CH), 127.2† (2CH), 127.3† (CH), 129.3 (4CH), 133.1* (CH), 133.2† (CH), 133.4 (2C), 142.7* (C), 143.9† (C), 157.7 (2C). A mixture of **27a**/**b** (932 mg, 3.53 mmol), $NaHCO_3$ (415 mg, 4.94 mmol), and *m*-CPBA (731 mg, 4.24 mmol) in CH_2Cl_2 (18.0 mL) was stirred at rt for 14 h and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/Et_2O 8:2) afforded epoxyvinylsulfones **3a***/**b**† (880 mg, 89%) as a mixture of E/Z isomers in which the E isomer (**3a**) was clearly favored. IR: ν = 3519, 2974, 2929, 1625, 1456, 1307, 1151, 1086 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.14* (s, 3H), 1.17* (s, 3H), 1.19† (s, 3H), 1.23† (s, 3H), 1.60 (m, 4H), 1.83† (s, 3H), 2.08* (s, 3H), 2.24 (m, 4H), 2.54* (t, J = 6.8 Hz, 1H), 2.67† (t, J = 6.0 Hz, 1H), 6.12† (s, 1H), 6.16* (s, 1H), 7.48 (m, 6H), 7.83 (m, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.0* (CH_3), 18.9 ($2CH_3$), 24.9 ($2CH_3$), 25.0† (CH_3), 26.8* (CH_2), 27.8† (CH_2), 29.6† (CH_2), 37.4* (CH_2), 58.7 (2C), 63.2* (CH), 63.7† (CH), 126.7* (CH), 126.9† (CH), 127.2 (4CH), 129.4 (4CH), 133.3 (2CH), 142.4 (2C), 156.7 (2C). HRMS (ESI): calcd for $C_{15}H_{20}O_3NaS$ 303.1025, found 303.1026.

*Compound **5**.* To a solution of 2-methyl-2-propen-1-ol (5.0 g, 69.3 mmol) in pyridine (11.2 mL, 138.6 mmol) were added Ac_2O (9.8 mL, 103.9 mmol) and a catalytic amount of DMAP. The mixture was stirred at rt for 1 h 15 min, quenched with water, and further stirred for another 30 min. The aqueous phase was extracted with Et_2O, and the combined organic layers were subsequently washed with a 2 M aqueous solution of HCl, a 5% aqueous solution of $NaHCO_3$ and brine and and dried over anhydrous Na_2SO_4. Elimination of the solvent by careful distillation of the mixture with a Vigreux column afforded allyl acetate **28** (6.5 g, 82%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 2.05 (s, 3H), 4.45 (s, 2H), 4.88 (s, 1H), 4.93 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.7 (CH_3), 21.1 (CH_3), 67.9 (CH_2), 113.1 (CH_2), 140.1 (C), 170.9 (C). To a flask with allyl acetate **28** (6.5 g, 57.0 mmol), in THF (88.0 mL) at 0 °C, were added triphenylphosphine (1.34 g, 5.13 mmol) and$Pd(PPh_3)_4$ (132 mg, 0.114 mmol), and this mixture was refluxed under argon atmosphere for 1 h. In the meantime, diethyl malonate (30.3 mL, 199.5 mmol) was slowly added to a suspension of 60% NaH (8.7 g, 182.4 mmol) in anhydrous THF (250 mL), under argon atmosphere at 0 °C, and the mixture was stirred at room temperature until complete formation of the anion (ca. 30 min). Once both solutions (Suzuki's reagent and malonate anion) were prepared, the malonate anion was slowly added over the Suzuki's reagent solution, avoiding both air and moisture, and the new mixture was refluxed for 24 h and then allowed to reach rt. In that moment, a 2 M aqueous solution of HCl was added, and the aqueous layer was extracted with AcOEt. The mixture of organic extracts was washed with an aqueous saturated solution of Na_2CO_3 and brine and dried over anhydrous Na_2SO_4, and the solvent was distilled away, yielding 40.5 g of a mixture of diethyl malonate and the diester intermediate, which was used without further purification in the next step. In that step, the mixture (40.5 g) was dissolved in DMSO (100.0 mL), and anhydrous NaCl (40.7 g, 696 mmol) and water (12.5 mL, 696 mmol) were added. The reaction vessel was next stirred at 180−200 °C for 48 h. After this time, the mixture was cooled to rt, diluted in AcOEt, subsequently washed several times with water and brine, and dried over anhydrous Na_2SO_4. Solvent was then carefully removed by distillation, and monoester **29** (8.1 g, 99%) was afforded. IR: ν = 2929, 2851, 1741, 1450, 1378, 1170, 1028, 891 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.4 Hz, 3H), 1.72 (s, 3H), 2.39 (m, 4H), 4.11 (q, J = 7.0 Hz, 2H), 4.66 (s, 1H), 4.72 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 22.7 (CH_3), 32.8 (CH_2), 32.9 (CH_2), 60.5 (CH_2), 110.5 (CH_2), 144.3 (C), 173.5 (C). A solution of **29** (3.0 g, 21.1 mmol) in dry Et_2O (21.0 mL) under argon atmosphere was stirred at 0 °C while a $LiAlH_4$ (1.6 g. 42.2 mmol) was added portionwise. The reaction was vigorously stirred at rt for 1 h 30 min. Then 1.54 mL of water was added dropwise, followed by 1.54 mL of a 15% aqueous solution of NaOH, 5 min stirring, another 2.5 mL of water, and a final 15 min stirring. The reaction was then filtered under reduced pressure through a fritted glass funnel, the solid washed with Et_2O, and the filtrate dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue obtained was identified as alcohol **30** (2.0 g, 95%). IR: ν = 3396, 2929, 2851, 1352 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (m, 3H), 1.74 (s, 3H), 2.09 (t, J = 8.2 Hz, 2H), 3.65 (t, J = 6.2 Hz, 2H), 4.72 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.6 (CH_3), 30.7 (CH_2), 34.3 (CH_2), 62.9 (CH_2), 110.4 (CH_2), 145.7 (C). HRMS (ESI): calcd for $C_6H_{13}O$ 101.0961, found 101.0955. To a 0 °C solution of **30** (1.4 g, 14.0 mmol) in CH_2Cl_2 (4.7 mL) were added Et_3N (3.9 mL, 28.0 mmol) and MsCl (1.8 mL, 22.4 mmol), and the new mixture was stirred at this temperature under argon atmosphere for 2 h 15 min when the reaction was quenched by addition of water and stirred for further 10 min. The aqueous phase was then extracted with Et_2O, the combined organic layers were washed with a 2 M aqueous solution of HCl, an aqueous saturated solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure to yield mesylate **31** (1.8 g, 74%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 1.87 (m, 2H), 2.12 (t, J = 7.8 Hz, 2H), 2.99 (s, 3H), 4.21 (t, J = 6.4 Hz, 2H), 4.70 (s, 1H), 4.76 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5 (CH_3), 27.1 (CH_2), 33.6 (CH_2), 37.5 (CH_3), 69.8 (CH_2), 111.3 (CH_2), 143.9 (C). HRMS (ESI): calcd for $C_7H_{14}O_3NaS$ 201.0556, found 201.0561. To a 0 °C suspension of 50% NaH (687 mg, 14.31 mmol) in THF (22.0 mL) under argon atmosphere was slowly diethyl malonate (2.3 mL, 15.3 mmol), and the mixture was stirred at room temperature until the complete formation of the anion (ca. 30 min). A solution of mesylate **31** (1.8 g, 10.2 mmol) in THF (3.4 mL) was then added dropwise and the new mixture refluxed for 12 h, when it was cooled to rt, quenched with a 2 M aqueous solution of HCl, and stirred for 10 min. The aqueous layer was extracted with Et_2O, the mixture of organic extracts was washed with water and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure, yielding 3.9 g of a mixture of diethyl malonate and the diester intermediate, which was used without further purification in the next step. In that step, the mixture (3.9 g) was dissolved in DMSO

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(28.7 mL) and anhydrous NaCl (3.4 g, 58.5 mmol) and water (1.0 mL, 57.96 mmol) were added. The reaction vessel was next stirred at 180−200 °C for 19 h. After this time, the mixture was cooled to rt, diluted in AcOEt, subsequently washed several times with water and brine, and dried over anhydrous Na_2SO_4. Solvent was then removed by careful distillation, yielding the monoester **32** (1.7 g, 98%). IR: ν = 3085, 2870, 1741, 1644, 1456, 1372, 1190, 1034 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.0 Hz, 3H), 1.3−1.7 (m, 4H), 1.67 (s, 3H), 1.99 (t, J = 7.0 Hz, 2H), 2.27 (t, J = 7.8 Hz, 2H), 4.09 (m, 2H), 4.63 (s, 1H), 4.66 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4 (CH_3), 22.5 (CH_3), 24.7 (CH_2), 27.2 (CH_2), 34.4 (CH_2), 37.6 (CH_2), 60.4 (CH_2), 110.2 (CH_2), 145.6 (C), 173.9 (C). A 2 M solution of BuLi in cyclohexane (6.5 mL, 11.76 mmol) was added dropwise to a 0 °C solution of 4-(methylsulfonyl)toluene (1.0 g, 5.88 mmol) in anhydrous THF (21.0 mL), and the new mixture was stirred at this temperature for 30 min. After this time, the mixture was cooled to −78 °C, and a solution of ester **32** (1.00 mg, 5.88 mmol) in DMPU (21.0 mL) was slowly added. This new mixture was stirred at −78 °C for 14 h, quenched with a saturated aqueous solution of NH_4Cl, and slowly allowed to reach rt. The aqueous phase was extracted with AcOEt, and the combined organic layers were subsequently washed with a 2 M aqueous solution of HCl, a saturated aqueous solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Finally, solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel (Hex/AcOEt 8:2 to Hex/AcOEt 7:3) to afford **32** (177 mg) followed by keto sulfone **33** (755 mg, 44%). IR: ν = 2929, 2864, 1729, 1657, 1599, 1333, 1151, 1086 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.2−1.4 (m, 4H), 1.67 (s, 3H), 1.97 (t, J = 7.0 Hz, 2H), 2.42 (s, 3H), 2.68 (t, J = 7.0 Hz, 2H), 4.11 (s, 2H), 4.63 (s, 1H), 4.67 (s, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 22.5 (CH_3), 22.9 (CH_2), 26.8 (CH_2), 37.6 (CH_2), 44.4 (CH_2), 67.2 (CH_2), 110.4 (CH_2), 128.5 (2CH), 130.2 (2CH), 135.9 (C), 145.6 (C), 145.7 (C), 198.6 (C). HRMS (ESI): calcd for $C_{16}H_{22}O_3NaS$ 317.1182, found 317.1178. $NaBH_4$ (44 mg, 1.16 mmol) was added to a solution of keto sulfone **33** (285 mg, 0.96 mmol) in MeOH (4.8 mL), and the mixture was stirred under argon atmosphere at rt for 4 h. It was then quenched with acetone and stirred, and all solvents were removed at reduced pressure, yielding a residue that was diluted in Et_2O and brine. The aqueous phase was extracted with Et_2O, the combined organic layers washed with brine, dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure, affording a residue identified as hydroxy sulfone **34** (275 mg, 96%). IR: ν = 3500, 2935, 2858, 1294, 1151 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.2−1.6 (m, 7H), 1.66 (s, 3H), 2.03 (m, 2H), 2.45 (s, 3H), 3.18 (m, 2H), 4.12 (m, 1H), 4.71 (s, 1H), 4.66 (s, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 22.5 (CH_3), 24.8 (CH_2), 27.4 (CH_2), 36.5 (CH_2), 37.8 (CH_2), 62.5 (CH_2), 66.1 (CH), 110.2 (CH_2), 128.2 (2CH), 130.3 (2CH), 136.4 (C), 145.4 (C), 145.9 (C). HRMS (ESI): calcd for $C_{16}H_{24}O_3NaS$ 319.1338, found 319.1339. To a 0 °C solution of **34** (275 mg, 0.93 mmol) in CH_2Cl_2 (4.4 mL) were added Et_3N (180 μL, 1.30 mmol) and MsCl (86 μL, 1.11 mmol), and the new mixture was stirred at this temperature under argon atmosphere for 30 min. After this time, more Et_3N (257 μL, 1.86 mmol) was added and stirring maintained at 0 °C for 3 h, when the reaction was quenched by addition of an aqueous saturated solution of $NaHCO_3$ and stirred for further 20 min. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers were washed with a 2 M aqueous solution of HCl, water and brine, and dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure to yield **35** (223 mg, 86%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 (m, 4H), 1.64 (s, 3H), 1.96 (t, J = 6.4 Hz, 2H), 2.21 (m, 2H), 2.39 (s, 3H), 4.60 (s, 1H), 4.66 (s, 1H), 6.28 (d, J = 14.4 Hz, 1H), 6.91 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.5 (CH_3), 27.1 (CH_2), 27.3 (CH_2), 31.5 (CH_2), 37.5 (CH_2), 110.4 (CH_2), 127.8 (2CH), 130.1 (2CH), 130.9 (CH), 137.9 (C), 144.4 (C), 145.5 (C), 146.7 (CH). HRMS (ESI): calcd for $C_{16}H_{22}O_2NaS$ 301.1233, found 301.1221. A mixture of **35** (400 mg, 1.44 mmol), $NaHCO_3$ (145 mg, 0.73 mmol), and *m*-CPBA (273 mg, 1.58 mmol) in CH_2Cl_2 (7.2 mL) was stirred at rt for 19 h, and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/AcOEt 8:2 to Hex/AcOEt 1:1) afforded epoxyvinylsulfone **5** (193 mg, 91%). IR: ν = 3513, 3052, 2929, 2864, 1729, 1638, 1599, 1450, 1326, 1145, 1093 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.44 (m, 6H), 2.21 (q, J = 7.0 Hz, 2H), 2.40 (s, 3H), 2.53 (s, 2H), 6.28 (d, J = 14.8 Hz, 1H), 6.91 (dt, J_1 = 6.6 Hz, J_2 = 14.0 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0 (CH_3), 21.8 (CH_3), 24.8 (CH_2), 27.8 (CH_2), 31.6 (CH_2), 36.5 (CH_2), 54.0 (CH_2), 56.9 (C), 127.8 (2CH), 130.1 (2CH), 131.1 (CH), 137.9 (C), 144.5 (C), 146.3 (CH). HRMS (ESI): calcd for $C_{16}H_{22}O_3NaS$ 317.1182; found 317.1176.

Compound ***7***. A 2 M solution of BuLi in cyclohexane (2.4 mL, 4.75 mmol) was added dropwise to a solution of the trimethylsilyl derivative **26**[17] (1.08 g, 4.75 mmol) in completely anhydrous and deoxygenated DME (23.7 mL) at −70 °C, and the resultant mixture was stirred under argon atmosphere at −70 °C for 30 min. At this point, a previously prepared deoxygenated solution of 6-methyl-5-hepten-2-one (300 mg, 2.38 mmol) in anhydrous DME (2.4 mL) was carefully added dropwise to the mixture, and once the addition was finished the reaction was allowed to reach rt for 48 h and then quenched with a saturated aqueous solution of NH_4Cl. The new mixture was then stirred for further 15 min, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and solvent was removed at reduced pressure. The crude product was purified by flash chromatography (Hex/AcOEt 9:1) to yield **36** (505 mg, 80%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 1.61 (s, 3H), 2.08 (m, 4H), 3.75 (s, 2H), 4.74 (s, 1H), 4.96 (m, 1H), 5.00 (s, 1H), 7.54 (m, 3H), 7.83 (m, 2H). A mixture of allylsulfone **36** (505 mg, 1.91 mmol), $NaHCO_3$ (225 mg, 2.68 mmol), and *m*-CPBA (396 mg, 2.29 mmol) in CH_2Cl_2 (9.6 mL) was stirred at rt for 12 h and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/Et_2O 8:2) afforded epoxy sulfone **7** (410 mg, 76%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (s, 3H); 1.25 (s, 3H), 1.67 (m, 2H), 2.30 (t, J = 7.4 Hz, 1H), 2.66 (m, 2H), 3.77 (s, 2H), 4.78 (s, 1H), 5.05 (s, 1H), 7.54 (m, 3H), 7.85 (m, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.9 (CH_3), 25.0 (CH_3), 27.1 (CH_2), 32.7 (CH_2), 58.5 (C), 63.1 (CH_2), 63.7 (CH), 120.4 (CH_2), 128.7 (2CH), 129.3 (2CH), 133.9 (CH), 136.7 (C), 138.5 (C).

Compound ***9***. A 2 M solution of BuLi in cyclohexane (6.5 mL, 13.03 mmol) was added dropwise to a 0 °C solution of 4-(methylsulfonyl)toluene (1.1 g, 7.04 mmol) in anhydrous THF (23.2 mL), and the new mixture was stirred at this temperature for 30 min. After this time, the mixture was cooled to −78 °C, and a solution of ester **29** (925 mg, 6.51 mmol) in DMPU (16.3 mL) was slowly added. This new mixture was stirred at −78 °C for 17 h, quenched with a saturated aqueous solution of NH_4Cl, and slowly allowed to reach rt. The aqueous phase was extracted with AcOEt, and the combined organic layers were subsequently washed with a 2 M aqueous solution of HCl, a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Finally, solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel (Hex/AcOEt 7:3 to Hex/AcOEt 1:1) to afford **29** (108 mg) followed by **37** (1.03 g, 59%). IR: ν = 2922, 1722, 1450, 1320, 1145, 1086 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.68 (s, 3H), 2.23 (t, J = 7.4 Hz, 2H), 2.42 (s, 3H), 2.81 (t, J = 7.4 Hz, 2H), 4.14 (s, 2H), 4.62 (s, 1H), 4.71 (s, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 22.8 (CH_3), 31.0 (CH_2), 42.7 (CH_2), 67.2 (CH_2), 110.9 (CH_2), 128.5 (2CH), 130.2 (2CH), 135.9 (C), 143.8 (C), 145.7 (C), 198.0 (C).

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HRMS (ESI): calcd for $C_{14}H_{18}O_3NaS$ 289.0869, found 289.0871. $NaBH_4$ (176 mg, 4.64 mmol) was added to a solution of keto sulfone **37** (1.03 g, 3.87 mmol) in MeOH (19.0 mL), and the mixture was stirred under argon atmosphere at rt for 45 min. It was then quenched with acetone and stirred, and all solvents were removed at reduced pressure, yielding a residue that was diluted in Et_2O and brine. The aqueous phase was extracted with Et_2O, the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure, affording a residue identified as hydroxy sulfone **38** (1.01 g, 97%). IR: ν = 3506, 2916, 2858, 1605, 1287, 1132, 1093 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50 (m, 2H), 1.59 (s, 3H), 1.98 (m, 2H), 2.36 (s, 3H), 3.14 (br s, 2H), 3.50 (br s, 1H), 4.06 (br s, 1H), 4.53 (s, 1H), 4.59 (s, 1H), 7.29 (d, J = 7.4 Hz, 2H), 7.73 (d, J = 7.0 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.6 (CH_3), 33.3 (CH_2), 34.6 (CH_2), 62.5 (CH_2), 65.9 (CH), 110.7 (CH_2), 128.1 (2CH), 130.2 (2CH), 136.6 (C), 144.8 (C), 145.3 (C). HRMS (ESI): calcd for $C_{14}H_{20}O_3NaS$ 291.1025, found 291.1024. To a solution of **38** (591 mg, 2.20 mmol) in CH_2Cl_2 (10.5 mL) at 0 °C were added Et_3N (427 μL, 3.09 mmol) and MsCl (205 μL, 2.64 mmol), and the new mixture was stirred at this temperature under argon atmosphere for 30 min. After this time, more Et_3N (610 μL, 4.41 mmol) was added and stirring maintained at 0 °C for 1 h 45 min, when the reaction was quenched by addition of an aqueous saturated solution of $NaHCO_3$ and stirred for further 20 min. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers were washed with a 2 M aqueous solution of HCl, water, and brine, and dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure to yield **39** (534 mg, 97%). IR: ν = 3078, 2929, 2864, 1651, 1599, 1456, 1320, 1151, 1086, 820 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.63 (s, 3H), 2.09 (t, J = 7.6 Hz, 2H), 2.29 (m, 2H), 2.36 (s, 3H), 4.60 (s, 1H), 4.68 (s, 1H), 6.28 (s, J = 15.2 Hz, 1H), 6.89 (m, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.5 (CH_3), 29.6 (CH_2), 36.7 (CH_2), 111.5 (CH_2), 127.8 (2CH), 130.1 (2CH), 131.1 (CH), 137.9 (C), 143.7 (C), 144.4 (C), 146.1 (CH). HRMS (ESI): calcd for $C_{14}H_{18}O_2NaS$ 273.0920, found 273.0917. A mixture of **39** (200 mg, 0.84 mmol), $NaHCO_3$ (81 mg, 0.96 mmol), and *m*-CPBA (152 mg, 0.88 mmol) in CH_2Cl_2 (4.0 mL) was stirred at rt for 2 h and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min and the aqueous layer extracted with CH_2Cl_2, the combined organic extracts washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/AcOEt 8:2) afforded epoxyvinylsulfone **9** (159 mg, 75%). IR: ν = 3052, 2929, 2864, 1638, 1592, 1456, 1313, 1287, 1158, 1086, 820 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.67 (m, 2H), 2.28 (m, 2H), 2.39 (s, 3H), 2.53 (s, 2H), 6.29 (d, J = 14.8 Hz, 1H), 6.89 (dt, J_1 = 6.6 Hz, J_2 = 14.8 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.1 (CH_3), 21.8 (CH_3), 27.2 (CH_2), 34.6 (CH_2), 53.9 (CH_2), 56.2 (C), 127.8 (2CH), 130.1 (2CH), 131.3 (CH), 137.7 (C), 144.6 (C), 145.5 (CH). HRMS (ESI): calcd for $C_{14}H_{18}O_3NaS$ 289.0869, found 289.0863.

Compounds ***11a/b***. To a solution of mesylate **21** in DMSO was added powdered NaCN, and the mixture was stirred at 50 °C for 30 h, quenched with water, and allowed to cool down to rt. The aqueous phase was extracted with Et_2O, the combined organic layers were washed several times with water and brine and dried over anhydrous Na_2SO_4, and solvent was carefully removed by distillation, which afforded **40** (2.0 g, 85%). IR: ν = 3084, 2940, 2247, 1651, 1441, 1384, 897 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.77 (s, 3H), 2.40 (m, 2H), 2.50 (m, 2H), 4.79 (s, 1H), 4.88 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7 (CH_3), 21.7 (CH_2), 33.0 (CH_2), 112.3 (CH_2), 119.2 (C), 141.6 (C). To a flask containing neat **40** (300 mg, 3.16 mmol) at −30 °C under argon atmosphere was added dropwise a 1 M solution of DIBAH in CH_2Cl_2 (3.5 mL). The reaction was stirred at this temperature for 2 h, when 3.1 mL of water was added and the stirred mixture allowed to reach room temperature. The reaction was then filtered through a fritted glass funnel, the solid washed with Et_2O, and the filtrate dried over anhydrous Na_2SO_4. In order to confirm by ^1H NMR that the reduction was successful, an aliquot of the mixture was withdrawn and solvent carefully evaporated without heating. Once the formation of **41** was so verified, the mixture of product and solvent was used in the next reaction assuming a 100% yield had been reached. All different procedures tried led either to evaporation and/or decomposition of aldehyde **41**. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.75 (s, 3H), 2.34 (m, 2H), 2.58 (m, 2H), 4.69 (s, 1H), 4.77 (s, 1H), 9.78 (s, 1H). Thiophenol (324 μL, 3.15 mmol) and piperidine (31 μL, 0.315 mmol) were added to a flask containing a 0 °C stirred solution of **41** (309 mg, 3.15 mmol) and methyl phenylsulfonyl acetate (608 mg, 2.84 mmol) in CH_3CN (6.3 mL), and the new mixture was stirred at the same temperature under argon atmosphere for 23 h. After this time, the mixture was dried under reduced pressure, and the residue was purified by flash chromatography over silica gel (Hex/AcOEt 9:1 to Hex/AcOEt 7:3) to afford **42a***/**b**† as a mixture of isomers (635 mg, 50% two steps). IR: ν = 3072, 2948, 2858, 1748, 1450, 1333, 1158, 1093, 904 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.67 (m, 4H), 1.75* (s, 3H), 1.80† (s, 3H), 2.37 (m, 4H), 3.40* (s, 3H), 3.61† (m, 1H), 3.66* (m, 1H), 3.70† (s, 3H), 4.18 (m, 2H), 4.73* (s, 1H), 4.77 (s, 2H), 4.81† (s, 1H), 7.2−7.8 (m, 20H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4† (CH_3), 22.7* (CH_3), 27.6† (CH_2), 29.3* (CH_2), 34.6† (CH_2), 35.6* (CH_2), 46.1† (CH), 47.5* (CH), 52.9* (CH_3), 53.1† (CH_3), 72.3† (CH), 76.1* (CH), 111.5* (CH_2), 111.9† (CH_2), 128.9 (2CH), 129.3 (8CH), 129.41 (2CH), 129.44 (2CH), 129.6 (2CH), 131.3† (C), 132.9 (2CH), 133.1* (C), 134.8 (2CH), 138.3 (2C), 144.4* (C), 144.6† (C), 164.6† (C), 165.8* (C). HRMS (ESI): calcd for $C_{21}H_{24}O_4NaS_2$ 427.1008, found 427.1001. To a solution of **42a/b** (2.3 g, 5.7 mmol) in a 1:1 CH_2Cl_2/water biphasic mixture (20.0 mL) were added Oxone (7.0 g, 11.4 mmol) and tetrabutylammonium bromide (175 mg, 1.13 mmol) , and the reaction was vigorously stirred for 5 days. The reaction was then filtered under reduced pressure through a fritted glass funnel, the solid washed with CH_2Cl_2, and the filtrate aqueous phase extracted with CH_2Cl_2. The mixture of organic extracts was washed with brine and dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel (Hex/AcOEt 7:3) to afford sulfonyl ester **14a***/**b**† as a mixture of isomers (1.4 g, 80%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.69* (s, 3H), 1.74† (s, 3H), 2.24 (t, J = 7.4 Hz, 4H), 2.76* (q, J = 7.4 Hz, 2H), 3.12† (q, J = 7.4 Hz, 2H), 3.65† (s, 3H), 3.68* (s, 3H), 4.68* (s, 1H), 4.72† (s, 1H), 4.76* (br s, 1H), 4.77† (br s, 1H), 7.49 (,m 8H), 7.92 (m, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4* (CH_3), 22.5† (CH_3), 27.2† (CH_2), 28.3* (CH_2), 36.2* (CH_2), 36.6† (CH_2), 52.6* (CH), 52.9† (CH), 111.8* (CH_2), 111.9† (CH_2), 128.3† (2CH), 128.6* (2CH), 129.0* (2CH), 129.1† (2CH), 133.6* (CH), 133.8† (CH), 134.9† (C), 135.8* (C), 140.3* (C), 141.3† (C), 143.7* (C), 143.8† (C), 156,5* (CH), 158.3† (CH), 162.1* (C), 162.7† (C). HRMS (ESI): calcd for $C_{15}H_{18}O_4NaS$ 317.0818, found 317.0824. A mixture of alkene **14a/b** (300 mg, 1.02 mmol), $NaHCO_3$ (146 mg, 1.73 mmol), and *m*-CPBA (264 mg, 1.53 mmol) in CH_2Cl_2 (10.0 mL) was stirred at rt for 3 h and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/AcOEt 7:3) afforded the mixture of isomers **11a***/**b**† (222 mg, 70%). IR: ν = 2968, 1741, 1456, 1326, 1151, 1086 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25* (s, 3H), 1.30† (s, 3H), 1.76† (m, 2H), 1.78* (m, 2H), 2.28† (m, 1H), 2.52† (d, J = 1.2 Hz, 2H), 2.55* (d, J = 4.2 Hz, 2H), 2.61* (d, J = 8.0 Hz, 1H), 2.69* (d, J = 7.4 Hz, 1H), 3.02† (m, 1H), 3.59† (s, 3H), 3.63* (s, 3H), 7.52 (m, 8H), 7.83 (m, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0* (CH_3), 21.3† (CH_3), 24.9† (CH_2), 26.1* (CH_2), 35.1* (CH_2), 35.5† (CH_2), 52.5* (CH_3), 52.9† (CH_3), 53.5† (CH_2), 53.6* (CH_2), 56.3* (C), 56.5† (C), 128.3† (2CH), 128.6* (2CH), 129.1 (4CH), 133.7* (CH), 133.8† (CH), 135.8* (C), 136.9† (C), 140.2* (C), 141.2† (C), 155.9* (CH), 157.6† (CH), 161.9* (C), 162.5† (C). HRMS (ESI): calcd for $C_{15}H_{19}O_5S$ 311.0937, found 311.0942.

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Compound **16**. DBU (490 μL, 3.28 mmol) was added to a solution of **39** (410 mg, 250 mmol) in CH_3CN (13.0 mL), and the mixture was stirred at rt. Reaction was followed by ^1H NMR. When the reaction was complete (24 h), solvent was removed under reduced pressure and residue diluted again with AcOEt. This new mixture was next washed with a 2 M aqueous solution of HCl, a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure, affording allylsulfone **43** as a mixture of *E*/*Z* isomers so enriched in isomer *E* that it is the only one herein described. IR: ν = 2929, 2851, 1722, 1599, 1300, 1151, 1093 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.58 (s, 3H), 2.40 (s, 3H), 2.65 (d, *J* = 6.4 Hz, 2H), 3.73 (d, *J* = 6.2 Hz, 2H), 4.51 (s, 1H), 4.66 (s, 1H), 5.48 (m, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 22.6 (CH_3), 41.1 (CH_2), 60.3 (CH_2), 111.6 (CH_2), 118.0 (CH_2), 128.7 (2CH), 129.9 (2CH), 135.7 (C), 138.9 (CH), 143.4 (C), 144.8 (C). HRMS (ESI): calcd for $C_{14}H_{18}O_2NaS$ 273.0920, found 273.0917. A mixture of **43** (424 mg, 1.70 mmol), $NaHCO_3$ (214 mg, 2.54 mmol), and *m*-CPBA (322 mg, 1.86 mmol) in CH_2Cl_2 (17.0 mL) was stirred at rt for 5 h and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/Et_2O 8:2) afforded epoxy sulfone **16** (337 mg, 75%) again as a mixture of *E*/*Z* isomers so enriched in isomer *E* that it is the only one described. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.09 (s, 3H), 2.16 (d, *J* = 5.2, 2H), 2.32 (s, 3H), 2.38 (s, 2H), 3.66 (d, *J* = 5.4 Hz, 2H), 5.41 (m, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.1 (CH_3), 21.7 (CH_3), 39.8 (CH_2), 53.0 (CH_2), 56.3 (C), 60.1 (CH_2), 119.9 (CH), 128.5 (2CH), 129.9 (2CH), 135.6 (C), 135.8 (CH), 144.8 (C). HRMS (ESI): calcd for $C_{14}H_{18}O_3NaS$ 289.0869, found 289.0861.

Compounds **18a/b**. To a stirred solution of **14a/b** (50 mg, 0.17 mmol) in deoxygenated THF (3 mL) was added collidine (166 mg, 1.36 mmol) and the mixture stirred at rt under argon atmosphere for 24 h, when it was quenched with a 2 M aqueous solution of HCl. The new mixture was further stirred for 15 min, the aqueous layer was extracted with Et_2O, the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield the isomerized product **15** (49 mg, 98%). A mixture of **15** (315 mg, 1.07 mmol), $NaHCO_3$ (198 mg, 2.36 mmol), and *m*-CPBA (370 mg, 2.14 mmol) in CH_2Cl_2 (10.0 mL) was stirred at rt for 12 h and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The new mixture was further stirred for 30 min, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel (Hex/AcOEt 8:2) afforded epoxy sulfone **18a/b** (337 mg, 75%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.26 (s, 3H), 2.33 (dd, J_1 = 2.0 Hz, J_2 = 6.0 Hz, 4H), 2.55 (s, 4H), 3.70 (s, 3H), 3.72 (s, 3H), 4.51 (d, *J* = 8.2 Hz, 2H), 5.67 (m, 4H), 7.54 (m, 6H), 7.84 (m, 4H. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4 ($2CH_3$), 39.9 ($2CH_2$), 53.1 (CH_2), 53.2 (CH_2), 53.4 (2CH), 56.3 (2C), 74.2 ($2CH_2$), 120.4 (CH), 120.6 (CH), 129.1 (2CH), 129.2 (2CH), 129.7 (2CH), 129.8 (2CH), 134.6 (2CH), 136.9 (CH), 137.0 (2C), 137.1 (CH), 165.3 (2C). HRMS (ESI): calcd for $C_{15}H_{18}O_5NaS$ 333.0767, found 333.0778.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds.This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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