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Asymmetric Claisen Rearrangements on Chiral Vinyl Sulfoxides

Roberto Fernández de la Pradilla,* Carlos Montero, Mariola Tortosa, and Alma Viso[a]

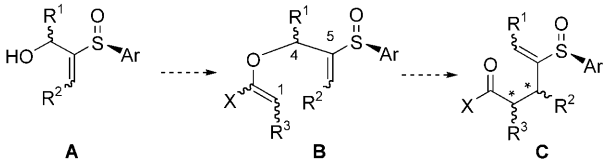
Abstract: Highly diastereoselective Claisen rearrangements of acyclic allyl vinyl ethers bearing a chiral sulfoxide at C-5 provide γ-δ-unsaturated aldehydes or ketones with up to two consecutive asymmetric centers in the molecule whilst preserving a useful vinyl sulfoxide. The reactivity of related vinyl sulfides and sulfones has also been examined in this work.

Keywords: diastereoselectivity · rearrangement · sulfides · sulfones · sulfoxides

Introduction

From its early discovery, the Claisen rearrangement has become one of the most efficient methods for the stereocontrolled synthesis of carbon–carbon bonds.[1] The search for new asymmetric Claisen protocols is a current problem in organic synthesis.[2] In fact, there is an important number of asymmetric Claisen rearrangements based on the transference of inner chirality from a substituent at C-4;[3] however, the number of examples that use an external chiral auxiliary or a Lewis acid as a source of stereocontrol is significantly lower.[4,1f] Most of the reported examples of diastereoselective Claisen rearrangements refer to allyl vinyl ethers with a chiral auxiliary on the vinylic fragment. In this context, high diastereoselectivities were observed in the Ireland–Claisen rearrangement of chiral acyclic α-alkoxy esters[5] and α-amino esters,[6] the asymmetric Carroll rearrangement of phosphorimidates[7] and β-hidrazono esters,[8] the Eschenmoser variant of chiral imidates[9] and β-amino amides,[10] and the Ficini–Claisen rearrangement with chiral ynamides.[11] However, compared to the vinylic part, the number of diastereoselective Claisen rearrangements bearing a chiral auxiliary on the allylic fragment has hardly been investigated.[12]

In the past years, we have been involved in devising new and efficient sulfur-based chirality transfer methodologies taking advantage of both the versatile reactivity and the remarkably chiral induction of vinyl sulfoxides in many different scenarios.[13,14] Within this context, we envisioned that vinyl sulfoxides **B** (Scheme 1) could be attractive scaffolds



Scheme 1. Proposed sulfinyl-mediated Claisen rearrangements.

for the asymmetric Claisen rearrangement. Considering the sigmatropic process as a formal intramolecular addition of an enol ether onto the α,β-unsaturated sulfoxide, an important facial diastereocontrol could be predicted. In addition, the moderate electron-withdrawing character of the sulfinyl group would increase the usual reactivity of allyl vinyl ethers, allowing for lower reaction temperatures. Aside from the above considerations, the use of chiral sulfur atoms in the Claisen rearrangement is scarcely documented[15] and the influence of a chiral auxiliary at C-5 has not been previously examined.

In this report, we describe in full our results[16] on the diastereoselective Claisen rearrangements of substrates **B**, readily available from α-hydroxy vinyl sulfoxides **A**, bearing a sulfinyl auxiliary at C-5 and a second chiral center at C-4. In addition, both (*Z*)- and (*E*)-vinyl sulfoxides (R^2) are accessible for **A**. The reinforcing/nonreinforcing combination of these three elements of stereocontrol could provide a diastereoselective Claisen rearrangement preserving the useful vinyl sulfoxide moiety in the final compound **C**.[17] To dissect the independent effect on the diastereoselectivity of each of the stereocenters (C-4 and sulfoxide), vinyl sulfides and

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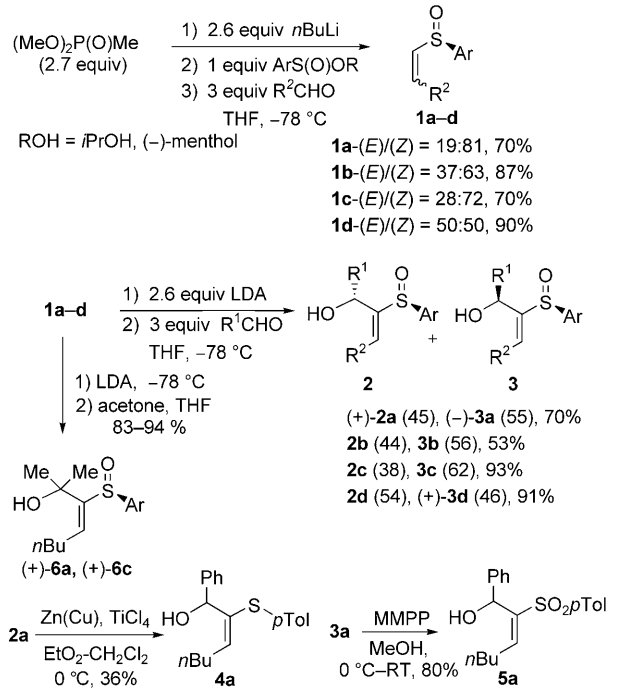
vinyl sulfones as well as 4,4-dimethyl vinyl sulfoxides related to **B** will be considered in this study. On the other hand, since stereoselectivity in the introduction of the vinyl ether of **B** is crucial for a high stereocontrol in the sigmatropic reaction, several methods have been used that allow for the examination of both Johnson–Claisen (**B**, X = OEt, R^3 = H, alkyl) and Claisen (**B**, X = H, $R^3 = CO_2Me$) variants. Finally, and within the Claisen alternative, the diastereoselective creation of two consecutive chiral centers has been addressed by using cyclohexanone-derived enol ethers.

Results and Discussion

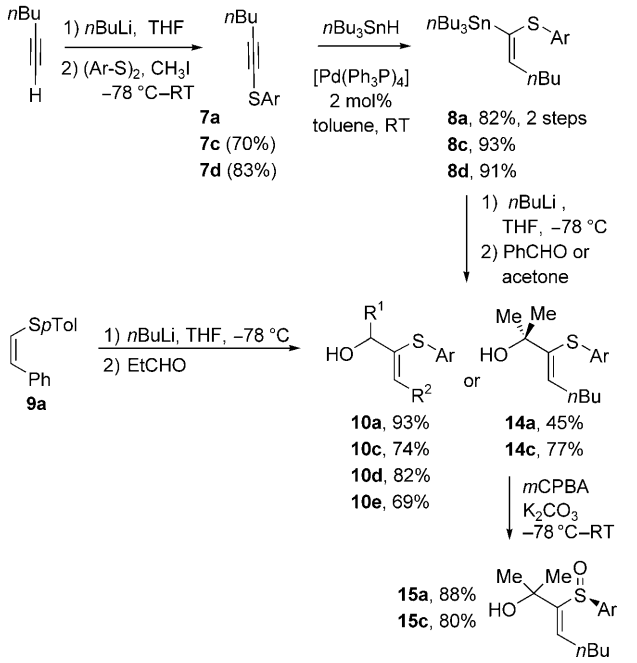
Synthesis of starting substrates: Racemic vinyl sulfoxides **1a–d** were prepared from isopropyl sulfinates as mixtures of *Z*/*E* isomers by following the method reported by Craig[18] (Scheme 2). For the synthesis of nonracemic vinyl sulfoxides,



Scheme 2. Synthesis of (*E*)-α-hydroxy vinyl sulfoxides, sufides, and sulfones. All compounds are racemic unless otherwise noted. **a**: Ar = *p*Tol, R^1 = Ph, R^2 = *n*Bu; **b**: Ar = *p*Tol, R^1 = Et, R^2 = Me; **c**: Ar = 1-Naphth, R^1 = Ph, R^2 = *n*Bu; **d**: Ar = 1-(2-MeO)Naphth, R^1 = Ph, R^2 = *n*Bu. LDA = lithium diisopropylamide; MMPP = magnesium bis(monoperoxyphthalate).

the same protocol was applied to enantiopure menthyl *p*-toluene-, 1-naphthalene-,[19] or 1-(2-methoxy)naphthalene[20] sulfinates. Low-temperature lithiation of the *Z*/*E* mixtures of **1a–d** produced a complete isomerization to the *E* double bond, which was followed by capture with benzaldehyde or propionaldehyde to provide mixtures of (*E*)-α-hydroxy vinyl sulfoxides **2a–d** and **3a–d** in good yields but with low selectivity. It should be pointed out that the absolute configuration of the allylic center in (*E*)-α-hydroxy vinyl sulfoxides has been successfully inverted in many cases by using Mitsunobu conditions.[21] A simple chromatography on silica gel allowed for the separation of **2a–c** and **3a–c**; however, a careful crystallization from EtOAc was required to isolate **3d** as a pure diastereomer. Similarly, capture of lithiated vinyl sulfoxides (Ar = *p*Tol, 1-Naphth) with acetone produced **6a** and **6c** in good yields as enantiopure materials. For the synthesis of vinyl sulfide **4a**, sulfoxide **2a** was deoxygenated with Zn(Cu)/$TiCl_4$[22] and sulfone **5a** was prepared by oxidation of **3a** with MMPP in good yield.

The synthesis of (*Z*)-α-hydroxy vinyl sulfides **10a,c–e** and sulfoxides **15a,c** is outlined in Scheme 3. Treatment of

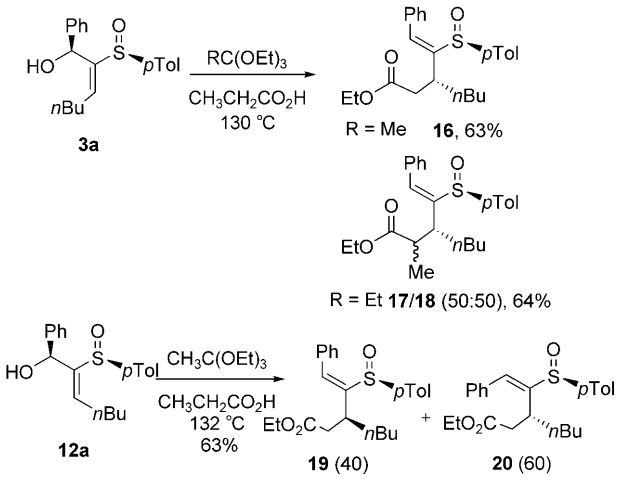


Scheme 3. Synthesis of (*Z*)-α-hydroxy vinyl sulfoxides, sulfides, and sulfones. All compounds are racemic unless otherwise noted. **a**: Ar = *p*Tol, R^1 = Ph, R^2 = *n*Bu; **c**: Ar = 1-Naphth, R^1 = Ph, R^2 = *n*Bu; **d**: Ar = 1-(2-MeO)Naphth, R^1 = Ph, R^2 = *n*Bu; **e**: Ar = *p*Tol, R^1 = Et, R^2 = Ph. *m*CPBA = *meta*-chloroperbenzoic acid.

1-hexyne with *n*BuLi followed by capture with diaryl disulfides afforded alkynyl sulfides **7a,c,d**.[23] At this point, we decided to prepare racemic compounds because their synthesis is slightly shorter than that of the optically pure materials and they were adequate substrates to study the diastereoselectivity of the process.[24] Then, *syn* Pd-catalyzed hydrostannylation provided vinyl stannanes **8a,c,d** in good yields.[25] Further transmetallation with *n*BuLi and addition to benzaldehyde or acetone provided α-hydroxy vinyl sulfides **10a,c,d** or **14a,c** as racemic materials. In addition, the synthesis of **10e** (R^2 = Ph) was accomplished by direct deprotonation of vinyl sulfide **9a** followed by addition of the lithium carbanion onto propionaldehyde.[14d] Finally, low-temperature oxidation of the (*Z*)-α-hydroxy vinyl sulfides **14a,c** with *m*CPBA provided (*Z*)-α-hydroxy vinyl sulfoxides **15a,c** in good yields without significant amounts of sulfur overoxida-

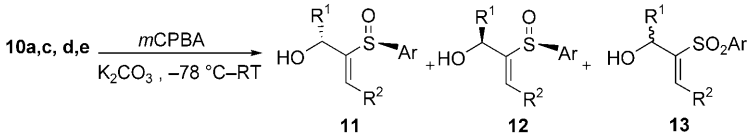
tion. Furthermore, the diastereoselectivity in the oxidation of α-hydroxy vinyl sulfides **10a**,**c**,**d** with *m*CPBA has been examined by using an array of solvents (Table 1). Polar solvents, such as acetone, chloroform, and methanol, diminished the diastereoselectivity (entries 1, 3, 5–8). In contrast, by using less polar solvents, such as Et_2O and CH_2Cl_2, a significant increase of diastereoselectivity to nearly 10:90 (**11**/**12**) was observed (entries 2 and 4). The above trend in stereoselectivity is compatible with coordination of the hydroxyl group and the peracidic reagent prior to the oxidation of sulfur. The relative configuration of (*Z*)- and (*E*)-α-hydroxy vinyl sulfoxides **2**, **3**, **11**, and **12** was established by the similarity of their data with related compounds previously assigned by X-ray analysis.[22]

Sulfinyl-mediated Johnson–Claisen rearrangement: The initial attempts for the sigmatropic rearrangement were focused on the Ireland–Claisen rearrangement of acetates



Scheme 4. Claisen–Johnson rearrangements from (*E*)- and (*Z*)-hydroxy vinyl sulfoxides. All compounds are racemic unless otherwise noted.

Table 1. Diastereoselective oxidation of (*Z*)-α-hydroxy vinyl sulfides **10** with *m*CPBA.



Entry	Compound	R^1	R^2	Ar	**11**	**12**	**13**	Solvent	Yield [%][a]
1	**10a**	Ph	*n*Bu	*p*Tol	38	62	–	acetone	91
2	**10a**	Ph	*n*Bu	*p*Tol	8	91	1	CH_2Cl_2	92
3[b,c]	**10a**	Ph	*n*Bu	*p*Tol	23	68	9	$CHCl_3$	nd[e]
4[d]	**10a**	Ph	*n*Bu	*p*Tol	8	92	–	Et_2O	nd [e]
5[d]	**10a**	Ph	*n*Bu	*p*Tol	11	66	23	MeOH	nd [e]
6[c]	**10c**	Ph	*n*Bu	1-Naphth	34	64	2	acetone	92
7[c]	**10d**	Ph	*n*Bu	1-(2-MeO)Naphth	26	60	14	acetone	93
8	**10e**	Et	Ph	*p*Tol	42	50	8	acetone	89

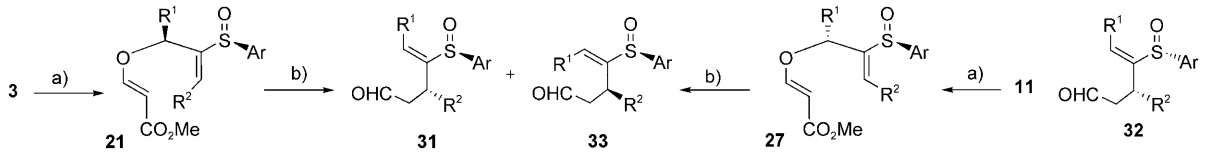
[a] Combined yield of isolated products. Ratios measured in the ^{1}H NMR spectra of the crude mixtures. [b] The reaction was carried out at −60 °C. [c] A small amount (≤8%) of starting material was also found in the crude. [d] Results for 85% conversion. [e] nd = not determined.

derived from **2b** and **3b**. However, after considerable fruitless experimentation,[26] we turned our attention to the Johnson–Claisen alternative for substrates (*E*)-**3a** and (*Z*)-**12a** (Scheme 4).[27] Thus, upon heating (*E*)-**3a** with triethyl orthoacetate and propionic acid, the ketene acetal formed in situ underwent a highly diastereoselective [3,3]-sigmatropic rearrangement producing (*Z*)-**16** in 63% yield. In contrast, when (*Z*)-**12a** was submitted to the above reaction conditions, a 40:60 mixture of (*Z*)-**19** and (*E*)-**20** was found. Pursuing the formation of an additional stereocenter in the final product, **3a** was treated with triethyl orthopropionate and propionic acid to furnish an equimolecular mixture of C-2 epimers **17** and **18**. The lack of *Z*/*E* selectivity in the formation of the ketene acetal and the epimerization of the final compounds under acidic conditions could explain the low selectivity found.

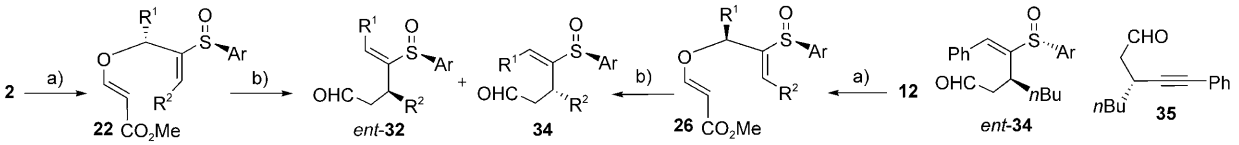
Sulfinyl-mediated Claisen rearrangement: At this point, we shifted our attention to the stereoselective formation of the vinyl ether moiety of substrates **B** (Scheme 1). The use of sulfinyl acrylates (X = H, $R^3 = CO_2Me$) seemed an attractive alternative and, therefore, we treated allylic alcohols **2**, **3**, **11**, and **12** with Et_3N and methyl propiolate (Table 2).[28] In most cases, these acrylates were prepared from diastereomerically pure alcohols except for **2d** and **12e** (see the Supporting Information for details). This procedure allowed for the exclusive isolation of compounds with *E* stereochemistry in the new acrylate moiety ($J(H_2,H_3) = 12.3$–12.5 Hz) and *E* (**21** and **22**) or *Z* (**26** and **27**) stereochemistry in the vinyl sulfoxide moiety (H_7 shifted $\delta = 0.30$–0.70 ppm downfield for *E* isomers **21** and **22**) (Table 2).

The first substrates examined were (*E*,*E*)-vinyl sulfinyl acrylates (+)-**21a** and (+)-**22a** (Table 2, entries 1 and 10). The sigmatropic rearrangement took place upon heating a solution of (+)-**21a** in DMF giving an excellent yield of aldehyde **31a** containing a (*Z*)-alkene as a single diastereomer. Surprisingly, a concurrent decarboxylation was observed under these conditions even in the absence of any additives. Upon prolonged heating (>3 h) small amounts of diastereomerization at sulfur was observed (**32a**). In contrast, (+)-**22a** gave a 73:27 mixture of (*Z*)- and (*E*)-vinyl sulfoxides *ent*-**32a** and **34a** along with small amounts (<5% ratio) of *ent*-**31a** derived from diastereomerization at sulfur and **35** obtained by sulfinyl elimination from **34a**. In spite of the diastereomeric nature of the final products, their optical purity was secured by ^{1}H NMR spectroscopic experiments by using (+)-Eu(tfc)$_3$ (tfc = tris[3-(trifluoromethylhydroxy-

Table 2. Sulfinyl-mediated Claisen rearrangements of (*E,E*)- and (*Z,E*)-vinyl sulfinyl acrylates.[a]



Entry	Compound	Conditions	R^1	R^2	Ar	**31** (*Z*)	**33** (*E*)	Yield [%][b]
1	(+)-**21a** (87%)	130°C, 1 h	Ph	*n*Bu	*p*Tol	100	0	79
2[c]	**21b** (67%)	134°C, 3 h	Et	Me	*p*Tol	100	0	78
3	**21c** (87%)	130°C, 75 min	Ph	*n*Bu	1-Naphth	100	0	79
4[d]	(+)-**21d** (85%)	120°C, 5 h	Ph	*n*Bu	1-(2-MeO)Naphth	97	3	79
5[e]	**21e**	134°C, 4 h	Et	Ph	*p*Tol	100	0	75
6[f]	**27a** (93%)	120°C, 3 h	Ph	*n*Bu	*p*Tol	8	92	74
7[f]	**27c** (78%)	120°C, 5 h	Ph	*n*Bu	1-Naphth	4	96	57
8	**27d** (88%)	110°C, 7 h	Ph	*n*Bu	1-(2-MeO)Naphth	0	100	77
9	**27e** (77%)	134°C, 11 h	Et	Ph	*p*Tol	28	72	69



Entry	Compound	Conditions	R^1	R^2	Ar	*ent*-**32** (*Z*)	34 (*E*)	Yield [%][b]
10[g]	(+)-**22a** (86%)	134°C, 3 h	Ph	*n*Bu	*p*Tol	73	27	79
11[g]	**22b** (72%)	134°C, 3 h	Et	Me	*p*Tol	74	26	76
12[g]	**22c** (71%)	138°C, 7 h	Ph	*n*Bu	1-Naphth	69	31	71
13[h]	**22d** (81%)	130°C, 7 h	Ph	*n*Bu	1-(2-MeO)Naphth	52	48	nd
14[i]	**26a** (95%)	126°C, 150 min	Ph	*n*Bu	*p*Tol	25	75	74
15[j]	**26c** (91%)	126°C, 4 h,	Ph	*n*Bu	1-Naphth	22	78	78
16[j]	**26d** (89%)	110°C, 4 h	Ph	*n*Bu	1-(2-MeO)Naphth	0	100	77
17[e]	**26e**	134°C, 11 h	Et	Ph	*p*Tol	24	76	84

[a] Reaction conditions: a) $HC{\equiv}CCO_2Me$, NEt_3, Et_2O/CH_2Cl_2, 0°C–RT; b) DMF, BHT. [b] Combined yield of isolated Claisen products. Ratios measured in the ^1H NMR spectra of the crude mixtures. All compounds are racemic unless otherwise noted. [c] A 5% ratio of **32b** was detected in the crude. [d] A 15% ratio of **32d** was detected in the crude. [e] **26e** and **21e** were obtained from an 85:15 of **12e** and **3e**. [f] Small amounts (<5% ratio) of *ent*-**34** and **35** were detected in the crude. All compounds are racemic unless otherwise noted. [f] Small amounts (nearly 5% ratio) of *ent*-**31** and **35** were detected in the crude. [g] A 19% ratio of *ent*-**31d** was detected in the crude. nd = not determined [h] Small amounts (≈5% ratio) of *ent*-**33** and **35** were detected in the crude. [i] A 13% ratio of **35** was detected in the crude. [j] A 3% ratio of *ent*-**33d** was also found in the crude.

methylene)-(+)-camphorate]) as a chiral shift reagent. The relative stereochemistry for the new stereocenter was established by comparison with related compounds previously assigned by X-ray analysis.[22] In addition, although a number of the compounds examined were racemic, we have maintained the *ent* nomenclature for a better understanding of the stereochemical relationship between the products. The same pattern of reactivity and selectivity was observed for other compounds within these series (**21b**,**e** and **22b**,**d**, entries 2,5 and 11,13). The influence of the Ar substituent on sulfur was explored with substrates **21c**,**d** and **22c**,**d** with the readily available 1-naphthyl and 1-(2-methoxy)naphthyl moieties. The introduction of a bulky 1-naphthyl group at sulfur did not modify the selectivity for **21c** (entry 3); however, a decrease in reactivity and selectivity was observed for **22c** (138°C, 7 h, 69:31, entry 12). In contrast, a substituted naphthyl group (Ar = 1-(2-MeO)Naphth) produced a decrease in selectivity for both diastereomers **21d** and **22d** (entries 4 and 13) allowing for the first time the detection of a small amount (3% ratio) of (*E*)-vinyl sulfoxide **33d** from **21d**, along with a 97% ratio of **31d** as the major product. Additionally, the longer heating periods required for these substrates provided a higher degree of diastereomerization at sulfur on the final compounds (15% ratio of **32d** from (+)-**21d** and 19% ratio of *ent*-**31d** from **22d**). The influence of a *tert*-butyl group on sulfur was also studied (not shown) but the rearrangement was not successful, probably due to elimination of the sulfinyl moiety on the acrylates, prior to the Claisen rearrangement.

The influence of the geometry of the vinyl sulfoxide was then addressed with compounds **27a**,**c**–**e** and **26a**,**c**–**e**. Similarly to the *E,E* series, a remarkable difference in selectivity was observed for each diastereomer. While **27a** provided a good yield of **31a** and **33a** (*Z*/*E* 8:92), **26a** (epimer of **27a** at C-4) led to a less selective mixture (*Z*/*E* 25:75) of *ent*-**32a** and **34a** (Table 2, entries 6 and 14). In both cases, it was noteworthy that **33a** and **34a** containing an (*E*)-vinyl sulfoxide were formed of as major isomers.[29] Compound **27e** (R^2 = Ph) showed lower reactivity and selectivity (entry 9) than **27a**, but similar to that found for its diastereomer **26e**

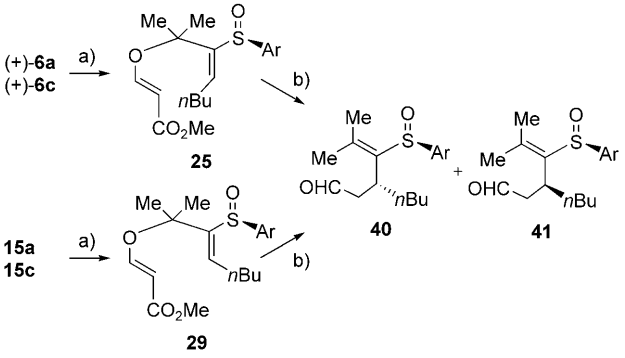
(entry 17). This was in contrast with the difference in selectivity observed for diastereomers **27a** and **26a**. Replacement of the *p*-tolyl for the 1-naphthyl group at the sulfoxide moiety in the *Z*,*E* series, produced a small but significant increase of selectivity for both diastereomers (**26c** and **27c**, entries 7 and 15). However, the most remarkable effect was induced by the introduction of the 1-(2-methoxy)naphthyl group as Ar. Gratifyingly, acrylates **27d** and **26d** gave aldehydes **33d** and **34d**, respectively, as single isomers containing an (*E*)-vinyl sulfoxide (entries 8 and 16). In contrast, the rearrangement of (*Z*)-*tert*-butylsulfinyl acrylates (not shown) led only to decomposition products.

Seeking to independently assess the level of stereocontrol of the allylic stereocenter (C-4), we prepared (*E*,*E*)- and (*Z*,*E*)-vinyl sulfenyl acrylates **23** and **28** from **4a** and **10a**, respectively, and methyl propiolate (Scheme 5). With the same purpose, (*E*,*E*)-vinyl sulfonyl acrylate **24a** was prepared by treating vinyl sulfonyl alcohol **5a** methyl propiolate and Et_3N. Additionally, sulfonyl acrylates **24b** and **30** were obtained by oxidation of (*E*,*E*)-vinyl sulfinyl acrylates **22b** and **26a**, respectively, with MMPP.

Following the same pattern of selectivity observed for sulfoxides, (*E*)-vinyl sulfide results in greater selectivity than its *Z* isomer (Scheme 5). Thus, upon heating (*E*,*E*)-vinyl sulfenyl acrylate **23** (134 °C, 75 min) a 93:7 mixture of (*Z*)-**36** and (*E*)-**37** was obtained in good yield. (*Z*,*E*)-Vinyl sulfenyl acrylate **28** furnished a moderately selective mixture in favor of the (*Z*)-sulfide **36**. This result was in contrast with the *E* selectivity observed for the corresponding sulfoxides (Table 2, entries 6 and 14).

Subsequently, (*E*,*E*)- and (*Z*,*E*)-vinyl sulfonyl acrylates were examined (Scheme 5). (*E*,*E*)-Sulfones **24a** and **24b** were slightly less selective than sulfide **23** giving 85:15 and 88:12 mixtures of aldehydes **38a**,**b** and **39a**,**b**, respectively. In contrast, submitting (*Z*)-vinyl sulfone **30** to the reaction conditions allowed for the isolation of aldehyde **39a** containing an *E* alkene as the single product. This result, along with those previously obtained for the related sulfide and sulfoxides, pointed out that steric hindrance at C-5 could cause a dramatic change in the *E*/*Z* selectivity of the Claisen rearrangement.

Finally, we examined the behavior of vinyl sulfinyl acrylates lacking the allylic chiral center (Scheme 6). Instead, a *gem*-dimethyl motif at C-4 in substrates **25a**,**c** and **29a**,**c** would allow to assess the independent stereocontrol exerted

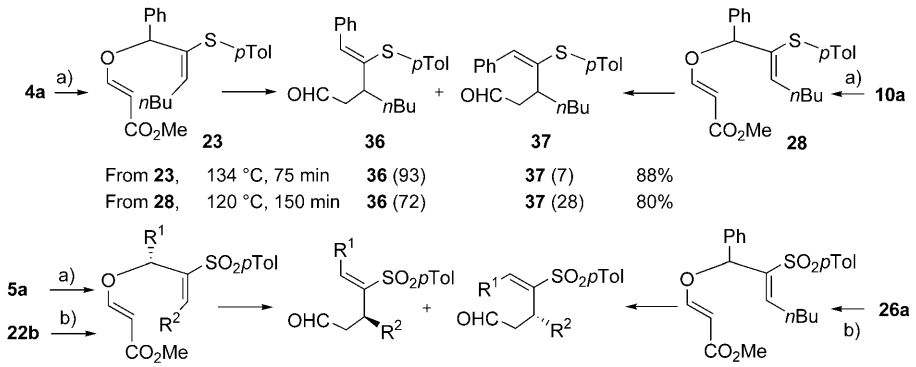


From (+)-**25a**, 134 °C, 3 h, Ar = *p*Tol	(–)-**40a** (86)	**41a** (14)	79%
From (+)-**25c**, 134 °C, 1 h, Ar = 1-Naphth	(+)-**40c** (99)	**41c** (1)	80%
From **29a**, 130 °C, 75 min, Ar = *p*Tol	**40a** (17)	**41a** (83)	80%
From **29c**, 134 °C, 1 h, Ar = 1-Naphth	**40c** (14)	**41c** (86)	78%

Scheme 6. Influence of the sulfinyl moiety. All compounds are racemic unless otherwise noted. a) HC≡CCO_2Me, NEt_3, Et_2O/CH_2Cl_2, 0 °C–RT; b) DMF, BHT. BHT = 2,6-di-*tert*-butyl-4-methylphenol.

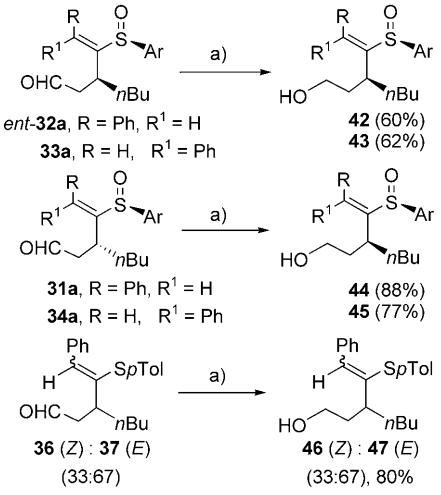
by the sulfinyl group in the Claisen rearrangement. Thus, heating in DMF (*E*,*E*)-vinyl sulfinyl acrylate (+)-**25a** (Ar = *p*Tol), afforded an 86:14 mixture of **40a** and **41a**; however, an increase in the size of the sulfinyl moiety ((+)-**25c**, Ar = 1-Naphth) resulted in the isolation of (+)-**40c** practically as a single isomer. On the contrary, this effect was not observed for the *Z*,*E* compounds **29a** and **29c** since upon the reaction conditions each of them furnished 17:83 and 14:86 mixtures of **40a**,**c** and **41a**,**c**, respectively. These results indicate that the sulfinyl moiety alone is capable of efficiently controlling the diastereoselectivity of the process.

Seeking to explore the reactivity of the compounds produced with the above methodology, we examined the reduction of vinyl sulfinyl and vinyl sulfenyl carbaldehydes. To our delight, reduction with $NaBH_4$ in EtOH proved to be a general method for the synthesis of these carbinols (Scheme 7). Thus, (*Z*)-and (*E*)-vinyl sulfinyl carbaldehydes *ent*-**32a** and **33a** gave good yields of γ-hydroxy vinyl sulfoxides **42** and **43**.

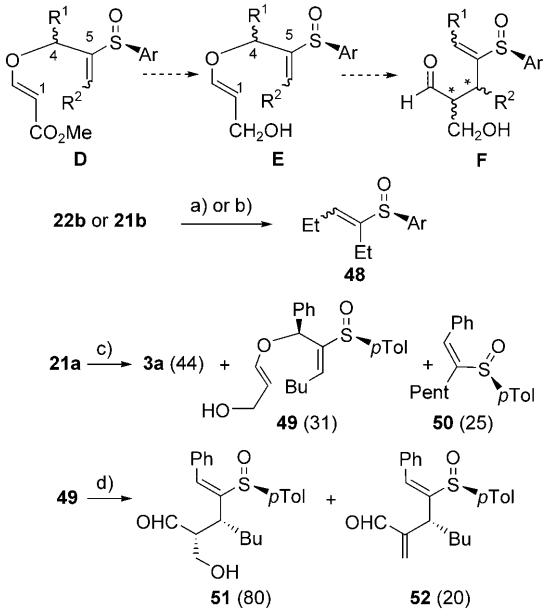


From **23**,	134 °C, 75 min	**36** (93)	**37** (7)	88%	
From **28**,	120 °C, 150 min	**36** (72)	**37** (28)	80%	
From **24a**,	136 °C, 8 h	**38a** (85)	**39a** (15)	67%	**a**, R^1 = Ph, R^2 = *n*Bu
From **24b**,	134 °C, 3 h	**38b** (88)	**39b** (12)	54%	**b**, R^1 = Et, R^2 = Me
From **30**,	136 °C, 4 h		**39a** (100)	71%	

Scheme 5. Influence of the allylic center in (*E*)- and (*Z*)-vinyl sulfides and sulfones. a) HC≡CCO_2Me, NEt_3, Et_2O/CH_2Cl_2, 0 °C–RT; b) MMPP, MeOH, 0 °C–RT.



Scheme 7. Reduction of (*Z*)- and (*E*)-sulfinyl and sulfenyl carbaldehydes. a) $NaBH_4$, EtOH, 0 °C.



Scheme 8. Attempts for the Claisen rearrangement on carbinols. a) $LiAlH_4$, −78 °C, THF; b) $NaBH_4$, LiI, THF, 0 °C–RT; c) DIBAL-H, CH_2Cl_2, −78 °C–RT; d) DMF, BHT, 120–122 °C, 1 h. DIBAL-H = diisobutylaluminum hydride.

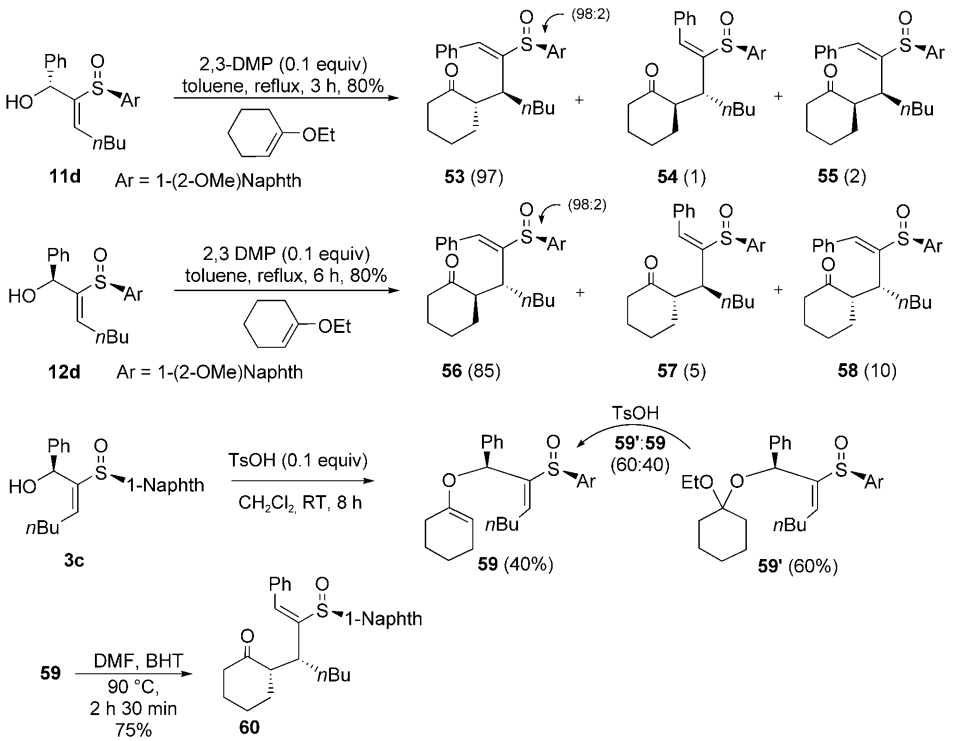
Likewise, diastereomeric **31a** and **34a** were easily reduced with $NaBH_4$ furnishing primary alcohols **44** and **45**, respectively, in good yields. Finally, the reactivity of vinyl sulfides was examined by using a 33:67 mixture of (*Z*)- and (*E*)-vinyl sulfenyl carbaldehydes **36** and **37** and an 80% yield of alcohols **46** and **47** was obtained keeping the same ratio.

Construction of two consecutive stereocenters: While the use of acrylates allowed for the straightforward stereocontrolled construction of the (*E*)-vinyl ether fragment, the concurrent decarboxylation represented a shortcoming of the method, since one of the chiral centers is lost in the final molecule. Consequently, we considered that reduction of acrylates **D** could afford allylic alcohols **E** that upon heating would give γ-δ unsaturated aldehydes **F** with an additional chiral center (Scheme 8).

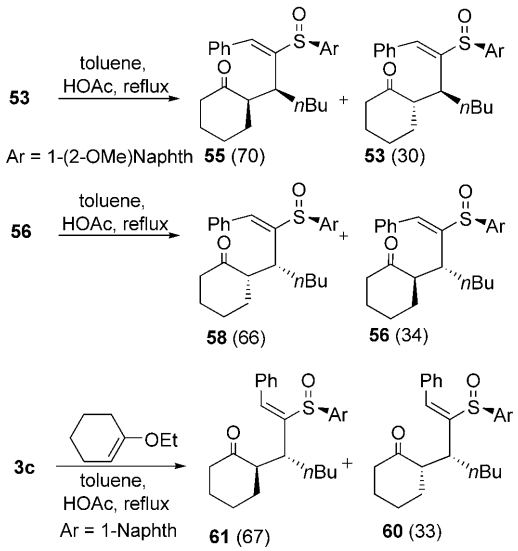
Unfortunately, attempts to reduce vinyl sulfinyl acrylates **21b** and **22b** by using $LiAlH_4$ or $NaBH_4$ only gave vinyl sulfoxide **48** through hydride S_N2' displacement. Alternatively, treatment of **21a** with DIBAL-H gave allylic alcohol **49** in 31% yield along with **3a** (44%) and vinyl sulfoxide **50** (25%). In spite of the discouraging results, we examined the reactivity of **49** under Claisen conditions. Thus, heating **49** at 120–122 °C in DMF provided an 80% yield of **51** as a single diastereomer along with a 20% yield of dehydration byproduct **52**.

In view of the difficulties found to prepare these allylic alcohols, we envisioned other substrates suitable for setting two consecutive stereocenters in the molecules. Therefore, to avoid the lack of stereocontrol in the generation of the vinyl ether, we focused our attention in the formal transetherification of 1-ethoxy-1-cyclohexene generated in two steps from cyclohexanone.[30] Initial Claisen attempts were carried out by using 2,3-dimethylphenol (2,3-DMP) for the preparation of the vinyl ether since its mildly acidic character could prevent further epimerizations in the final products.[31] Thus, refluxing in toluene a mixture of (*Z*)-**11d** and 1-ethoxy-1-cyclohexene in the presence of a catalytic amount of 2,3-DMP furnished a remarkably diastereoselective mixture of (*E*)-vinyl sulfinyl cyclohexanone **53** (97% ratio) along with small amounts of diastereomers **54** (1% ratio), **55** (2% ratio), and the sulfur epimer of **53** (<2% ratio, not shown). Similarly, (*Z*)-**12d** was submitted to the above conditions giving (*E*)-vinyl sulfinyl cyclohexanone **56** as the major product (85% ratio) with traces of diastereomerization at sulfur and small amounts of diastereomers **57** (5% ratio) and **58** (10% ratio). In both reactions, compounds **55** and **58** were probably formed from **53** and **56** by epimerization under acidic reaction conditions. This fact was secured by heating in toluene/HOAc pure samples of **53** and **56** to yield mixtures of **53**/**55** and **56**/**58**, respectively (Scheme 10).

In contrast, 2,3-DMP was too mild to effect the transetherification of **3c**. Alternatively, *p*TsOH (0.1 equiv) along with an excess of 1-ethoxy-1-cyclohexene was employed (Scheme 9). Under these conditions, a mixture of **59** and the intermediate ketal **59′** was produced. Recovered **59′** was again submitted to the reaction conditions yielding a 60:40 mixture of both compounds. Finally, pure **59** underwent a highly diastereoselective Claisen rearrangement furnishing (*Z*)-vinyl sulfinyl cyclohexanone **60** as a single isomer in 75% yield. To avoid epimerization at C-2, compound **59** had to be isolated prior to the Claisen rearrangement. When **59** was formed in situ by treatment of **3c** with acetic acid in refluxing toluene, a 33:67 mixture of C-2 epimers, **60** and **61**, was obtained (Scheme 10). This result, along with those obtained for the epimerization of **53** and **56** (Scheme 10), pointed out that epimerization at C-2 was influenced by the vinyl sulfoxide geometry. As shown in Scheme 10, treatment



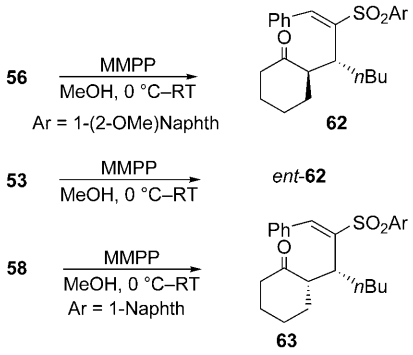
Scheme 9. Preparation of two consecutive chiral centers by Claisen rearrangement of cyclohexene derivatives. 2,3-DMP = 2,3-dimethylphenol; Ts = tosyl.



Scheme 10. Acid-promoted epimerization of sulfinyl cyclohexenones.

of (*E*)-**53** and (*E*)-**56** with AcOH in refluxing toluene gave *anti* products **55** and **58** as major isomers, while *syn* product **61** was preferentially obtained from (*Z*)-**60**. Importantly, these C-2 epimers (**55**/**53**, **58**/**56**, **60**/**61**) were easily separated by chromatography on silica gel. Consequently, the overall yield of **55**, **58**, and **61** could be potentially increased after several epimerization cycles.

The geometry of these trisubstituted alkenes was established by the chemical shift of the vinyl proton, nearly $\delta =$ 0.7 ppm higher for *E* isomers, which follows a similar trend to related compounds. The relative *syn*/*anti* stereochemistry of the new stereocenters was tentatively determined by analysis of the NOESY-1D spectroscopic data for each isomer.[32] To further secure the structural assignment of (*E*)-**56** and (*E*)-**53**, oxidation with MMPP was carried out. Thus, oxidation of **56** along with its epimer at sulfur (*ent*-**53**, not shown) gave a single sulfone **62** (Scheme 11). Subsequently, **53** underwent oxidation to *ent*-**62** verifying the *RR* or *SS* relative configuration of the adjacent stereocenters in (*E*)-**53** and (*E*)-**56**. On the other hand, oxidation of (*E*)-**58** allowed for the isolation of sulfone **63** pointing out an *RS* relative configuration of the stereocenters in (*E*)-**58**.



Scheme 11. Oxidation of sufinyl cyclohexenones.

Stereochemical pathway of the Claisen rearrangement: These results for the Claisen rearrangement of vinyl sulfinyl acrylates may be rationalized in terms of diastereomeric chairlike transition states derived of conformers **D**–**G** (Figure 1) with an (s)-*cis* C=C/S=O conformation around the C–S bond.[33] In the case of 5-*E* substrates ($R^4 = H$), **21** displays a reinforcing relationship of stereocontrolling elements with **D** accounting for the observed selectivity and providing **31** with complete selectivity, since **E** would have a severe 1,3-diaxial interaction between R^1 and R^2 and the bulky aryl group pointing toward the incoming vinyl ether residue. For nonreinforcing diastereomer **22**, the energy difference between **F** (1,3 diaxial interactions) and **G** (aryl

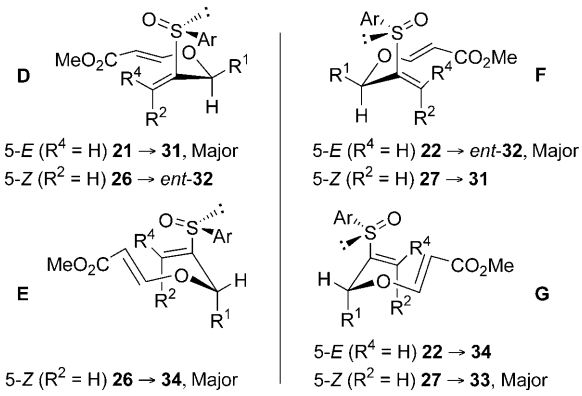


Figure 1. Proposed reactive conformers for sulfinyl-mediated Claisen rearrangements.

group facing the incoming vinyl ether) should be smaller than for **21** (**D** vs. **E**), with **F** being more stable.

The case of 5-*Z* isomers **26**–**28** ($R^2=H$) was predicted to follow an increased stereodirecting contribution by $A^{1,2}$ strain relative to 1,3-diaxial interactions (**E** vs. **D** and **G** vs. **F**). Nonetheless, sulfide **28** displayed moderate *Z* selectivity (72:28, Scheme 5). For diastereomer **26** ($R^2=H$), a nonreinforcing scenario was found, with conformer **E** being favored relative to **D**. Likewise, for **27** ($R^2=H$), **F** and **G** are operative with the latter being substantially more stable providing selectively **33**. The phenyl group in **27e** is probably responsible for a change in conformation around the C–S bond altering the energy differences for the transition states **F**/**G**. The more hindered 1-(2-OMe)Naphthyl moiety (**26**–**27d**) results in very high stereoselectivity producing exclusively the *E* rearrangement products **33** and **34**.

Conclusion

The first examples of Claisen rearrangements of substrates bearing a chiral sulfinyl functionality at C-5 have been described. The rearrangement takes place under mild conditions, preserving the configurational stability of the sulfinyl group, which could racemize at higher temperatures. A second chiral center at C-4 along with the *Z* or *E* stereochemistry in the starting vinyl sulfoxides provide a reinforcing/nonreinforcing combination of these elements of stereocontrol giving a remarkably diastereoselective Claisen rearrangement. Additionally, (*Z*,*E*)-vinyl sulfinyl and sulfonyl acrylates showed an unusual stereodirecting contribution by $A^{1,2}$ strain relative to 1,3-diaxial interactions. This methodology entails three to four steps for 5-*E* isomers or six to seven steps for 5-*Z* isomers from commercially available starting materials and allows for the creation of up to two asymmetric centers with regeneration of the valuable vinyl sulfoxide moiety in an expedient manner. Further applications to the synthesis of more complex molecules are currently being pursued in our laboratory.

Experimental Section

General: Reagents and solvents were handled by using standard syringe techniques. All reactions were carried out under an argon atmosphere. Hexane, toluene, and CH_2Cl_2 were distilled from CaH_2, and THF and Et_2O from sodium. Crude products were purified by flash chromatography on 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on silica-gel plates with detection either by using UV light, iodine, acidic vanillin solution, or a 10% solution of phosphomolybdic acid in ethanol. All reagents were commercial products. Throughout this section, the volume of solvents is reported in mL mmol^{-1} of starting material. The ^1H and ^{13}C NMR spectra were recorded at 200, 300, 400, or 500 MHz (^1H) using $CDCl_3$ as the solvent, and with the residual solvent signal as the internal reference ($CDCl_3$: 7.24 and 77.0 ppm) unless otherwise stated. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Melting points are uncorrected. Optical rotations were measured at 20 °C in $CHCl_3$ solution by using a sodium lamp. Low-resolution mass spectra were recorded by using the electronic impact (EI) technique with an ionization energy of 70eV or by using the atmospheric pressure chemical ionization (ACPI) or electrospray (ES) chemical ionization techniques in their positive or negative modes.

General procedure for Johnson–Claisen rearrangements: A kimble vial equipped with a stirring bar was charged with the corresponding hydroxy vinyl sulfoxide (1.0 equiv), the appropriate orthoester (25 equiv), and propionic acid (0.4 equiv). Argon was bubbled through the solution for 15 min by using a needle, and the vial was quickly stoppered. The vial was then immersed in a preheated oil bath (130–134 °C) and the reaction was monitored by TLC until the starting material disappeared (5–8 h). The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography using the appropriate mixture of solvents.

Synthesis of (±)-(3*R*,*S*$_S$)-(*Z*)-ethyl 3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)-pent-4-enoate (16): From alcohol **3a** (33 mg, 0.10 mmol) and $CH_3C(OEt)_3$ (0.50 mL, 2.50 mmol), by following the general procedure (130 °C, 8 h), ester **16** was obtained. Purification by chromatography (10–30% EtOAc/hexane) afforded **16** (25 mg, 0.063 mmol, 63%) as a colorless oil. $R_f=0.33$ (30% EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz): $\delta=0.53$ (m, 1H; *n*Bu), 0.61 (t, 3H, $J=7.1$ Hz; Me-*n*Bu), 0.73–0.96 (m, 3H), 1.22 (t, 3H, $J=7.1$ Hz; Me-EtO), 1.23–1.43 (m, 2H), 2.34 (s, 3H; Me-*p*Tol), 2.46 (dd, 1H, $J=15.2$, 8.5 Hz; H-2), 2.76 (dd, 1H, $J=15.3$, 5.0 Hz; H-2), 3.03 (m, 1H; H-3), 4.10 (qd, 2H, $J=7.1$, 1.0 Hz; CH_2O), 6.97 (s, 1H; H-5), 7.23 (d, 2H, $J=8.5$ Hz), 7.33–7.43 (m, 5H), 7.49–7.53 ppm (m, 2H); ^{13}C NMR (50 MHz): $\delta=13.8$ (Me-*n*Bu), 14.2 (Me-EtO), 21.3 (Me-*p*Tol), 22.2, 28.6, 32.8, 33.3, 42.5, 60.3, 124.4 (2C), 128.4, 128.6 (2C), 129.6 (4C), 134.5, 135.1, 139.5, 140.8, 149.0, 171.8 ppm; IR (film): $\tilde{\nu}=2929$, 2860, 1732, 1597, 1492, 1445, 1375, 1248, 1174, 1080, 1044, 920, 877, 809, 751 cm^{-1}; MS (APCI): *m*/*z* (%): 391 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{24}H_{30}O_3S$: C 72.32, H 7.59, S 8.05; found: C 72.06, H 7.80, S 8.29.

General procedure for the synthesis of sulfenyl, sulfinyl, and sulfonyl acrylates: To a solution of methyl propiolate in dry Et_2O (3.0 equiv, 15 mL mmol^{-1} of alcohol) at 0 °C, Et_3N (2.5 equiv) was added. The mixture was stirred for 20 min at this temperature and then a solution of the corresponding alcohol in CH_2Cl_2 (6 mL mmol^{-1} of alcohol) was added. The mixture was allowed to warm to RT and was monitored by TLC until the starting material disappeared (1–4 h). Then water (10 mL mmol^{-1} of alcohol) and EtOAc (5 mL mmol^{-1} of alcohol) were added and the layers were separated. The aqueous phase was extracted twice with EtOAc (5 mL mmol^{-1} of alcohol) and the combined organic extracts were washed with a saturated solution of NaCl, dried over $MgSO_4$, and filtered to give, after evaporation of the solvents, a crude product that was purified by chromatography on silica gel (7–10 g mmol^{-1} of alcohol) by using the appropriate mixture of solvents.

Synthesis of (+)-(*E*)-methyl 3-[(1*S*,*S*$_S$)-2-(*E*)-1-phenyl-2-(*p*-tolylsulfinyl)-hept-2-en-1-oxy]acrylate (21a): From alcohol **3a** (180 mg, 0.55 mmol), methyl propiolate (0.15 mL, 1.65 mmol), and Et_3N (0.19 mL, 1.37 mmol), by following the general procedure (3 h), acrylate **21a** was obtained. Pu-

rification by chromatography (0–10% EtOAc/CH_2Cl_2) afforded **21a** (200 mg, 0.48 mmol, 87%) as a pale-yellow oil. From racemic **3a**, by following the general procedure, (±)-**21a** was obtained as a white solid that was recrystallized from Et_2O/hexane. M.p. (±)74–75°C; R_f=0.15 (10% EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$=+55.0 (c=0.86 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.83 (t, 3H, J=7.2 Hz; Me-*n*Bu), 1.19–1.40 (m, 4H; *n*Bu), 2.19 (m, 1H; H-4′), 2.29 (m, 1H; H-4′), 2.30 (s, 3H; Me-*p*Tol), 3.66 (s, 3H; CO_2Me), 5.36 (d, 1H, J=12.3 Hz; H-2), 5.63 (s, 1H; H-1′), 6.71 (t, 1H, J=7.7 Hz; H-3′), 6.81 (d, 2H, J=8.3 Hz), 7.08–7.14 (m; 5H), 7.34 (d, 2H, J=8.2 Hz), 7.46 ppm (d, 1H, J=12.4 Hz; H-3); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 21.2 (Me-*p*Tol), 22.3 (C-6′), 28.9 (C-4′), 30.6 (C-5′), 51.1 (CO_2Me), 76.4 (C-1′), 99.1 (C-2), 125.1 (2C), 126.3 (2C), 128.0, 128.2 (2C), 129.7 (2C), 136.7, 138.9, 141.4, 141.7, 142.5, 160.8 (C-3), 167.7 ppm (CO_2Me); IR (CCl_4): $\tilde{\nu}$=3000, 2920, 2890, 2820, 1700, 1620, 1480, 1430, 1420, 1310, 1270, 1160, 1110, 1060, 1030, 750, 670 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 311, 171, 139 (100), 129, 115, 103, 91, 77, 65; elemental analysis calcd (%) for $C_{24}H_{28}O_4S$: C 69.87, H 6.84, S 7.77; found: C 71.12, H 7.06, S 7.45.

Synthesis of (+)-(*E*)-methyl 3-[(1*R*,*S*$_S$)-2-(*E*)-1-phenyl-2-(*p*-tolylsulfinyl)-hept-2-en-1-oxy]acrylate (22a): From alcohol **2a** (163 mg, 0.49 mmol), methyl propiolate (0.13 mL, 124 mg, 1.47 mmol), and Et_3N (0.17 mL, 123 mg, 1.22 mmol), by following the general procedure (3 h), acrylate **22a** was obtained. Purification by chromatography (1% EtOAc/CH_2Cl_2) afforded 173 mg (0.42 mmol, 86%) of **22a** as a pale-yellow oil. From racemic **2a**, following the general procedure, (±)-**22a** was obtained as a white solid that was recrystallized from Et_2O/hexane. M.p. (±) 80–81°C; R_f=0.25 (2×1% EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$=+68.4 (c=1.30 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.76 (t, 3H, J=7.0 Hz; Me-*n*Bu), 1.13–1.35 (m, 4H; *n*Bu), 2.13 (m, 2H; 2H-4′), 2.36 (s, 3H; Me-*p*Tol), 3.59 (s, 3H; CO_2Me), 4.95 (d, 1H, J=12.3 Hz; H-2), 5.59 (s, 1H; H-1′), 6.68 (t, 1H, J=7.7 Hz; H-3′), 6.73 (d, 1H, J=12.3 Hz; H-3), 7.22–7.33 (m, 7H), 7.46 ppm (d, 2H, J=8.3 Hz); ^{13}C NMR (75 MHz): δ=13.7 (Me-*n*Bu), 21.3 (Me-*p*Tol), 22.2 (C-6′), 28.5 (C-4′), 30.3 (C-5′), 51.0 (CO_2Me), 77.4 (C-1′), 98.3 (C-2), 125.1 (2C), 125.8 (2C), 127.9, 128.4 (2C), 129.9 (2C), 137.6, 139.2, 141.8, 142.8, 143.6, 160.6 (C-3), 167.4 ppm (CO_2Me); IR (CCl_4): $\tilde{\nu}$=3000, 2910, 2880, 2820, 1690, 1620, 1470, 1430, 1410, 1300, 1260, 1110, 1060, 1030, 920, 760, 670, 620 cm^{-1}; MS (APCI): *m*/*z* (%): 411 (100) $[M-1]^-$, 271, 171, 139; MS (EI, 70 eV): *m*/*z* (%): 311, 171, 139 (100), 129, 115, 105, 91, 77, 65; elemental analysis calcd (%) for $C_{24}H_{28}O_4S$: C 69.87, H 6.84, S 7.77; found: C 69.70, H 6.99, S 7.92.

Synthesis of (±)-(*E*)-methyl 3-[(1*S*,*S*$_S$)-2-(*Z*)-1-phenyl-2-(*p*-tolylsulfinyl)-hept-2-en-1-oxy]acrylate (26a): From alcohol **12a**[14d] (300 mg, 1.0 mmol), methyl propiolate (0.26 mL, 3.0 mmol), and Et_3N (0.35 mL, 2.5 mmol), by following the general procedure (2 h), acrylate **26a** was obtained. Purification by chromatography (0–15% EtOAc/CH_2Cl_2) afforded **26a** (395 mg, 0.95 mmol, 95%) as a colorless oil that was crystallized as a white solid from Et_2O/hexane. M.p. 55–57°C; R_f=0.50 (10% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.92 (t, 3H, J=7.1 Hz; Me-*n*Bu), 1.32–1.54 (m, 4H; *n*Bu), 2.28 (s, 3H; Me-*p*Tol), 2.49 (m, 1H; H-4′), 2.77 (ddt, 1H, J=14.5, 8.7, 7.2 Hz; H-4′), 3.64 (s, 3H; CO_2Me), 5.40 (d, 1H, J=12.4 Hz; H-2), 5.67 (s, 1H; H-1′), 6.33 (ddd, 1H, J=8.9, 6.8, 0.6 Hz; H-3′), 6.74 (m, 2H), 6.99–7.12 (m, 5H), 7.19 (d, 2H, J=8.2 Hz), 7.53 ppm (d, 1H, J=12.4 Hz; H-3); ^{13}C NMR (50 MHz): δ=13.8 (Me-*n*Bu), 21.2 (Me-*p*Tol), 22.3, 28.7, 31.2, 51.0 (CO_2Me), 76.1 (C-1′), 98.9 (C-2), 124.0 (2C), 126.6 (2C), 127.9, 128.2 (2C), 129.6 (2C), 137.6, 138.2, 140.7, 142.3, 142.8, 160.8 (C-3), 167.9 ppm (CO_2Me); IR (KBr): $\tilde{\nu}$=2900, 1690, 1590, 1465, 1430, 1410, 1300, 1200, 1100, 1010, 980, 905, 800, 780, 730, 670, 630 cm^{-1}; MS (APCI): *m*/*z* (%): 411 (100) $[M-1]^-$, 271, 171; elemental analysis calcd (%) for $C_{24}H_{28}O_4S$: C 69.87, H 6.84, S 7.77; found: C 70.08, H 7.00, S 7.56.

Synthesis of (±)-(*E*)-methyl 3-[(1*S*,*S*$_S$)-2-(*Z*)-1-phenyl-2-(*p*-tolylsulfinyl)-hept-2-en-1-oxy]acrylate (27a): From alcohol **11a**[14d] (188 mg, 0.57 mmol), methyl propiolate (0.15 mL, 1.71 mmol) and Et_3N (0.20 mL, 1.43 mmol), by following the general procedure (3 h, 30 min), acrylate **27a** was obtained. Purification by chromatography (0–15% EtOAc/CH_2Cl_2) afforded **27a** (218 mg, 0.53 mmol, 93%) as a white solid that was recrystallized from EtOAc/hexane. M.p. 68–69°C; R_f=0.50 (10% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.86 (t, 3H, J=7.1 Hz; Me-*n*Bu), 1.21–1.41 (m, 4H; 2CH_2-*n*Bu), 2.36 (s, 3H; Me-*p*Tol), 2.45 (m, 1H; H-4′), 2.67 (ddt, 1H, J=14.7, 8.7, 7.4 Hz; H-4′), 3.56 (s, 3H; CO_2Me), 4.83 (d, 1H, J=12.3 Hz; H-2), 5.81 (s, 1H; H-1′), 5.93 (dd, 1H, J=8.5, 6.8 Hz; H-3′), 6.87 (d, 1H, J=12.3 Hz; H-3), 7.19–7.34 (m, 7H), 7.45 ppm (d, 2H, J=8.3 Hz); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 21.3 (Me-*p*Tol), 22.2, 28.6, 30.9, 50.9 (CO_2Me), 75.9 (C-1′), 98.2 (C-2), 124.1 (2C), 126.3 (2C), 128.0, 128.6 (2C), 129.8 (2C), 137.8, 138.9, 141.1, 144.2, 144.8, 160.8 (C-3), 167.6 ppm (CO_2Me); IR (KBr): $\tilde{\nu}$=2900, 1680, 1610, 1420, 1195, 1155, 1105, 1050, 810, 760, 700 cm^{-1}; MS (APCI): *m*/*z* (%): 411 (100) $[M-1]^-$, 271, 257, 171; elemental analysis calcd (%) for $C_{24}H_{28}O_4S$: C 69.87, H 6.84, S 7.77; found: C 70.10, H 7.10, S 8.00.

Synthesis of (±)-(*E*)-methyl 3-[(*E*)-1-phenyl-2-(*p*-tolylsulfenyl)hept-2-en-1-oxy]acrylate (23): From alcohol **4a** (30 mg, 0.10 mmol), methyl propiolate (27 μL, 0.30 mmol), and Et_3N (35 μL, 0.25 mmol), by following the general procedure (1 h 30 min), acrylate **23** was obtained. Purification by chromatography (80% CH_2Cl_2/hexane) afforded **23** (32 mg, 0.081 mmol, 81%) as a colorless oil. R_f=0.44 (80% CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.88 (t, 3H, J=7.1 Hz; Me-*n*Bu), 1.25–1.41 (m, 4H; *n*Bu), 2.28 (m, 2H; H-4′), 2.30 (s, 3H; Me-*p*Tol), 3.67 (s, 3H; CO_2Me), 5.26 (d, 1H, J=12.4 Hz; H-2), 5.79 (s, 1H; H-1′), 5.82 (t, 1H, J=7.7 Hz; H-3′), 7.05 (d, 2H, J=8.2 Hz), 7.19 (d, 2H, J=8.2 Hz), 7.29–7.40 (m, 5H), 7.47 ppm (d, 1H, J=12.4 Hz; H-3); ^{13}C NMR (50 MHz): δ=13.9 (Me-*n*Bu), 21.0 (Me-*p*Tol), 22.4, 29.2, 31.4, 51.1 (CO_2Me), 82.1 (C-1′), 98.5 (C-2), 126.5 (2C), 128.2, 128.4 (2C), 129.8 (2C), 130.5, 132.4 (2C), 133.7, 137.5, 137.6, 138.6, 160.9 (C-3), 168.0 ppm (CO_2Me); IR (film): $\tilde{\nu}$=3021, 2955, 2859, 1716, 1644, 1492, 1435, 1328, 1283, 1190, 1132, 1049, 809, 736 cm^{-1}; MS (APCI): *m*/*z* (%): 397 $[M+1]^+$, 379, 295 (100), 171; elemental analysis calcd (%) for $C_{24}H_{28}O_3S$: C 72.69, H 7.12, S 8.09; found: C 72.85, H 6.91, S 8.33.

Synthesis of (±)-(*E*)-methyl 3-[(*Z*)-1-phenyl-2-(*p*-tolylsulfonyl)hept-2-en-1-oxy]acrylate (30): From acrylate **26a** (124 mg, 0.30 mmol) and MMPP (371 mg (80%), 0.60 mmol), by following the general procedure (12 h), sulfone **30** was obtained. Purification by chromatography (10–30% EtOAc/hexane) afforded **30** (105 mg, 0.24 mmol, 80%) as a white solid that was recrystallized from Et_2O/hexane. M.p. 68–69°C; R_f=0.35 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=0.80 (t, 3H, J=7.0 Hz; Me-*n*Bu), 1.18–1.25 (m, 4H, *n*Bu), 2.40 (s, 3H; Me-*p*Tol), 2.55 (m, 2H; H-4′), 3.64 (s, 3H; CO_2Me), 5.25 (d, 1H, J=12.5 Hz; H-2), 6.05 (s, 1H; H-1′), 6.06 (t, 1H, J=7.8 Hz; H-3′), 7.19–7.36 (m, 7H), 7.43 (d, 1H, J=12.4 Hz; H-3), 7.60 ppm (d, 2H, J=8.5 Hz); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 21.6 (Me-*p*Tol), 22.3, 28.5, 30.5, 51.1 (CO_2Me), 81.6 (C-1′), 99.4 (C-2), 127.2 (2C), 127.6 (2C), 128.8 (3C), 129.6 (2C), 136.5, 138.5, 140.8, 144.4, 148.6, 160.7, 167.6 ppm (CO_2Me); IR (KBr): $\tilde{\nu}$=2956, 2927, 1710, 1641, 1303, 1188, 1131, 729 cm^{-1}; MS (APCI): *m*/*z* (%): 429 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{24}H_{28}O_5S$: C 67.26, H 6.59, S 7.48; found: C 67.35, H 6.71, S 7.62.

General procedure for Claisen rearrangements: A kimble vial equipped with a stirring bar was charged with a solution of the corresponding acrylate and BHT (0.2 equiv) in DMF (10 mL mmol^{-1} of acrylate). Argon was bubbled through the solution for 15 min by using a needle, and the vial was quickly stoppered. The vial was then immersed in a preheated oil bath (110–138°C) and the reaction was monitored by TLC until the starting material disappeared (1–7 h). The solution was then allowed to cool and was diluted with water (10 mL mmol^{-1} of acrylate) and EtOAc (10 mL mmol^{-1} of acrylate). The layers were separated and the organic phase was washed with water (×3 10 mL mmol^{-1} of acrylate) and a saturated solution of NaCl, dried over $MgSO_4$, and filtered to give, after evaporation of the solvent, a crude product that was purified by chromatography on silica gel (6–12 g mmol^{-1} of acrylate) by using the appropriate mixture of solvents.

Sigmatropic rearrangement of 21a: Synthesis of (−)-(3*R*,*S*$_S$)-4-(*Z*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)pent-4-enal (31a): From acrylate **21a** (37 mg, 0.089 mmol), by following the general procedure (130°C, 60 min), aldehyde **31a** was obtained. Purification by chromatography (10–50% EtOAc/hexane) afforded (25 mg, 0.070 mmol, 79%) **31a** as a colorless oil. M.p. (±) 55–56°C; R_f=0.20 (30% EtOAc/hexane); $[\alpha]_D^{20}$=−360.5 (c=0.80 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.61 (t, 3H, J=7.2 Hz; Me-*n*Bu), 0.68–1.02 (m, 4H; 2CH_2-*n*Bu), 1.14–1.38 (m, 2H),

2.37 (s, 3H; Me-*p*Tol), 2.57 (ddd, 1H, J=16.3, 7.6, 2.4 Hz; H-2), 2.73 (ddd, 1H, J=16.3, 6.1, 2.2 Hz; H-2), 3.13 (m, 1H; H-3), 6.96 (s, 1H; H-5), 7.25 (d, 2H, J=8.3 Hz), 7.27–7.44 (m, 5H), 7.50 (d, 2H, J=8.1 Hz), 9.70 ppm (t, 1H, J=2.3 Hz; H-1); DNOE between H-5/H-2 (2.73 ppm): 2.6%, H-5/H-2 (2.57 ppm): 1.3%, H-3/H-1: 1.3%; ^{1}H NMR (C_6D_6, 300 MHz): δ=0.59 (t, 3H, J=7.1 Hz; Me-*n*Bu), 0.45–0.95 (m, 4H; *n*Bu), 1.00–1.25 (m, 2H; *n*Bu), 1.92 (s, 3H; Me-*p*Tol), 2.28 (ddd, 1H, J=16.5, 7.4, 2.1 Hz; H-2), 2.60 (ddd, 1H, J=16.4, 6.2, 2.1 Hz; H-2), 3.27 (m, 1H; H-3), 6.68 (s, 1H; H-5), 6.80 (d, 2H, J=8.0 Hz), 7.06–7.10 (m, 3H), 7.36 (d, 2H, J=7.3 Hz), 7.45 (d, 2H, J=8.3 Hz), 9.62 ppm (t, 1H, J=2.1 Hz; H-1); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 21.2 (Me-*p*Tol), 22.2, 28.8, 30.5, 34.5, 51.0 (C-2), 124.4 (2 C), 128.6 (2 C), 129.6 (2C), 129.7 (2C), 134.3, 135.7, 139.4, 141.0, 149.2, 201.9 ppm (*C*HO); IR (CCl_4): $\tilde{\nu}$=3000, 2980, 2920, 2880, 2820, 2680, 1700, 1580, 1470, 1420, 1370, 1150, 1060, 1020, 990, 890, 770, 730, 620, 600 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 215, 171, 140, 129, 117, 105, 91 (100), 77, 65, 55; elemental analysis calcd (%) for $C_{22}H_{26}O_2S$: C 75.54, H 7.39, S 9.04; found: C 75.72, H 7.18, S 8.83.

Sigmatropic rearrangement of 22a: Synthesis of (−)-(3*S*,S_S)-4-(*Z*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)pent-4-enal (*ent*-32a) and (+)-(3*R*,S_S)-4-(*E*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)pent-4-enal (34a): From acrylate **22a** (100 mg, 0.27 mmol), by following the general procedure (134 °C, 3 h), a 70:23:4:3 mixture of aldehydes *ent*-**32a**, **34a**, **35**, and *ent*-**31a** was obtained. Purification by chromatography afforded **35** (2 mg) and *ent*-**32a** (55 mg, 0.155 mmol, 57%), both as colorless oils, and **34a** (21 mg, 0.059 mmol, 22%) as a white solid (±) that was recrystallized from Et_2O/hexane, or as a colorless oil (+). In a previous experiment, from **22a** (54 mg, 0.130 mmol) at a higher temperature and with a longer reaction time (142 °C, 6 h) a 68:26:15:8 mixture of aldehydes *ent*-**32a**, **34a**, **35**, and *ent*-**31a** was obtained. Purification by chromatography afforded pure **35** (4 mg, 0.018 mmol, 14%), *ent*-**32a** (24 mg, 0.068 mmol, 52%), and a 65:15 mixture of **34a** and *ent*-**31a** (8 mg, 0.022 mmol, 17%). Separation of *ent*-**31a** and **34a** was achieved by preparative TLC (2% EtOAc/$CHCl_3$).

Data for ent-***32a***: R_f=0.45 (2×30% EtOAc/hexane); $[\alpha]_D^{20}$=−397.2 (c=1.50 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=0.87 (t, 3H, J=7.1 Hz; Me-*n*Bu), 1.27–1.37 (m, 4H; *n*Bu), 1.52–1.65 (m, 2H; *n*Bu), 1.93 (ddd, 1H, J=16.1, 6.4, 2.6 Hz; H-2), 2.16 (ddd, 1H, J=16.1, 7.8, 2.5 Hz; H-2), 2.35 (s, 3H; Me-*p*Tol), 3.25 (quint, 1H, J=7.1 Hz; H-3), 6.95 (s, 1H; H-5), 7.23 (d, 2H, J=7.9 Hz), 7.33–7.43 (m, 5H), 7.50 (d, 2H, J=7.9 Hz), 8.90 ppm (t, 1H, J=2.5 Hz; H-1); ^{1}H NMR (C_6D_6, 300 MHz): δ=0.90 (t, 3H, J=7.0 Hz; Me-*n*Bu), 1.25–1.49 (m, 7H; *n*Bu), 1.55–1.63 (m, 1H; *n*Bu), 1.74 (ddd, 1H, J=16.0, 7.1, 2.8 Hz; H-2), 1.89 (s, 3H; Me-*p*Tol), 1.92 (ddd, 1H, J=16.1, 7.4, 2.1 Hz, H-2), 3.38 (quint, 1H, J=6.8 Hz; H-3), 6.68 (s, 1H; H-5), 6.80 (d, 1H, J=8.4 Hz), 7.03–7.15 (m, 3H), 7.37–7.40 (m, 2H), 7.45 (d, 2H, J=8.3 Hz), 8.71 ppm (t, 1H, J=2.4 Hz; H-1); DNOE between H-5/H-2 (1.93 ppm): 3.1%, H-2/H-5: 3.9%, H-5/H-3: 0.8%, H-5/H-1: 0.4%; ^{13}C NMR (50 MHz): δ=13.9 (Me-*n*Bu), 21.3 (Me-*p*Tol), 22.6, 29.1, 29.9, 36.8, 49.4 (C-2), 142.2 (2C), 128.6 (2C), 129.6 (2C), 129.8 (2C), 132.4, 134.2, 135.7, 139.5, 141.1, 149.5, 200.1 ppm (*C*HO); IR (CCl_4): $\tilde{\nu}$=3000, 2980, 2920, 2880, 2820, 2680, 1700, 1580, 1470, 1420, 1370, 1280, 1150, 1060, 1020, 990, 900, 790, 730, 670, 600 cm^{-1}; MS (APCI): *m*/*z* (%): 355 (100) $[M+1]^+$, 260; MS (EI, 70 eV): *m*/*z* (%): 215, 171, 140, 129, 117, 105, 91 (100), 77, 65, 55, 41; elemental analysis calcd (%) for $C_{22}H_{26}O_2S$: C 74.54, H 7.39, S 9.04; found: C 74.77, H 7.07, S 9.40.

Data for ***34a***: M.p. (±) 65–66 °C; R_f=0.28 (2×30% EtOAc/hexane); $[\alpha]_D^{20}$=+29.3 (c=0.45 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.67 (t, 3H, J=6.9 Hz; Me-*n*Bu), 0.80–1.30 (m, 4H; *n*Bu), 1.26 (m, 2H; *n*Bu), 2.39 (s, 3H; Me-*p*Tol), 2.42 (dd, 2H, J=7.6, 1.5 Hz; H-2), 3.19 (quint, 1H, J=7.3 Hz; H-3), 7.27–7.79 (m, 7H), 7.53 (s, 1H; H-5), 7.59 (d, 2H, J=8.3 Hz), 9.25 ppm (t, 1H, J=1.5 Hz; H-1); DNOE between H-3/H-1: 2.6%, H-3/H-*p*Tol *ortho*: 1.3%, H-1/H-*p*Tol *ortho*: 1.9%, H-1/H-3: 3.0%, H-1/H-2: 1.9%; ^{13}C NMR (75 MHz): δ=13.7 (Me-*n*Bu), 21.4 (Me-*p*Tol), 22.3, 29.6, 32.7, 34.1, 47.7 (C-2), 125.9 (2C), 128.1, 128.5 (2C), 128.6 (2C), 129.9 (2C), 132.7, 135.1, 139.9, 142.1, 148.6, 200.3 ppm (*C*HO); IR (CCl_4): $\tilde{\nu}$=3000, 2920, 2890, 2820, 2680, 1700, 1580, 1470, 1430, 1360, 1240, 1060, 1030, 780, 740, 680, 600 cm^{-1}; MS (APCI): *m*/*z* (%): 355 (100) $[M+1]^+$, 256, 215, 178; elemental analysis calcd (%) for $C_{22}H_{26}O_2S$: C 74.54, H 7.39, S 9.04; found: C 74.23, H 7.52, S 9.27.

Data for ***35***: R_f=0.50 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.91 (t, 3H, J=7.2 Hz; Me-*n*Bu), 1.31–1.60 (m, 6H; *n*Bu), 2.58 (ddd, 1H, J=16.5, 6.3, 2.0 Hz; H-2), 2.66 (ddd, 1H, J=16.6, 7.6, 2.1 Hz; H-2), 3.07 (quint, 1H, J=7.4 Hz; H-3), 7.25–7.28 (m, 3H), 7.35–7.38 (m, 2H), 9.85 ppm (t, 1H, J=2.3 Hz; H-1); ^{13}C NMR (50 MHz) δ=14.0 (Me-*n*Bu), 22.4, 26.8, 29.4, 34.7, 48.6 (C-2), 91.1, 91.6, 127.9 (2C), 128.2 (2C), 131.5, 131.6 ppm; IR (CCl_4): $\tilde{\nu}$=3030, 2920, 2890, 2820, 2680, 1710, 1580, 1470, 1450, 1420, 1330, 1050, 1010, 670 cm^{-1}; MS (APCI): *m*/*z* (%): 256 (100) $[M+CH_3CN]^+$, 215, 171, 138, 105.

Data for ent-***31a***: Data for *ent*-**31a** is identical to that described above for **31a** except for the opposite optical rotation.

Sigmatropic rearrangement of 26a: Synthesis of (±)-(3*S*,S_S)-4-(*Z*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)pent-4-enal (*ent*-32a) and (±)-(3*R*,S_S)-4-(*E*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)pent-4-enal (34a): From acrylate **26a** (186 mg, 0.45 mmol), by following the general procedure (126 °C, 2 h), a 73:24:2:1 mixture of **34a**, *ent*-**32a**, *ent*-**33a**, and **35** was obtained. Purification by chromatography (5–30% EtOAc/hexane) afforded *ent*-**32a** (28 mg, 0.08 mmol, 18%) as a colorless oil and **34a** (90 mg, 0.025 mmol, 56%) as a colorless oil that was crystallized as a white solid from EtOAc/hexane.

Sigmatropic rearrangement of 27a: Synthesis of (±)-(3*R*,S_S)-4-(*Z*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)pent-4-enal (31a) and (±)-(3*S*,S_S)-4-(*E*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfinyl)pent-4-enal (33a): From acrylate **27a** (161 mg, 0.39 mmol), by following the general procedure (120 °C, 3 h), an 88:8:2:2 mixture of **33a**, **31a**, *ent*-**34a**, and **35** was obtained. Purification by chromatography (0–10% CH_2Cl_2) afforded **33a** (97 mg, 0.27 mmol, 69%) as a white solid that was recrystallized from Et_2O/hexane and **31a** (7 mg, 0.017 mmol, 5%) as a colorless oil.

Data for ***33a***: M.p. 72–73 °C; R_f=0.20 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.70 (t, 3H, J=6.8 Hz; Me-*n*Bu), 0.93–1.18 (m, 4H; *n*Bu), 1.28 (m, 1H; *n*Bu), 1.34–1.47 (m, 1H; *n*Bu), 2.12 (ddd, 1H, J=17.7, 8.1, 1.6 Hz; H-2), 2.21 (ddd, 1H, J=17.7, 6.0, 0.8 Hz; H-2), 2.40 (s, 3H; Me-*p*Tol), 3.43 (ddt, 1H, J=8.3, 6.0, 5.9 Hz; H-3), 7.28–7.40 (m, 7H), 7.61 (d, 2H, J=8.1 Hz), 7.61 (s, 1H; H-5), 9.30 ppm (s, 1H; H-1); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 21.5 (Me-*p*Tol), 22.3, 29.4, 32.4, 33.2, 48.4 (C-2), 126.4 (2C), 128.2, 128.59 (2C), 128.60 (2C), 130.1 (2C), 132.0, 134.9, 140.3, 142.5, 148.1, 200.1 ppm (*C*HO); IR (KBr): $\tilde{\nu}$=2927, 1718, 1493, 1455, 1079, 1040, 815, 767, 702, 623, 517 cm^{-1}; MS (ES): *m*/*z* (%): 409 (100), 377 $[M+Na]^+$, 355 $[M+1]^+$; elemental analysis calcd (%) for $C_{22}H_{26}O_2S$: C 74.54, H 7.39, S 9.05; found: C 74.27, H 7.12, S 9.07.

Sigmatropic rearrangement of 23: Synthesis of (±)-4-(*Z*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfenyl)pent-4-enal (36) and (±)-4-(*E*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfenyl)pent-4-enal (37): From acrylate **23** (20 mg, 0.05 mmol), by following the general procedure (134 °C, 1 h 15 min), a 93:7 mixture of aldehydes **36** and **37** was obtained. Purification by chromatography (2% EtOAc/hexane) afforded a mixture of **36** and **37** (5 mg, 0.015 mmol, 30%) and pure **36** (10 mg, 0.029 mmol, 58%) as a colorless oil.

Data for ***36***: R_f=0.12 (2% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.85 (t, 3H, J=6.9 Hz; Me-*n*Bu), 1.17–1.29 (m, 4H; *n*Bu), 1.46 (m, 1H; *n*Bu), 1.66 (m, 1H; *n*Bu), 2.27 (s, 3H; Me-*p*Tol), 2.47 (ddd, 1H, J=16.5, 6.5, 2.1 Hz; H-2), 2.70 (ddd, 1H, J=16.5, 7.3, 2.3 Hz; H-2), 2.87 (m, 1H; H-3), 6.82 (s, 1H; H-5), 7.03 (d, 2H, J=8.5 Hz), 7.17 (d, 2H, J=8.2 Hz), 7.20–7.31 (m, 3H), 7.56 (m, 2H), 9.59 ppm (t, 1H, J=2.1 Hz; H-1); ^{13}C NMR (50 MHz): δ=14.0 (Me-*n*Bu), 21.1 (Me-*p*Tol), 22.6, 29.1, 33.8, 41.8, 48.4 (C-2), 127.5, 128.0 (2C), 129.4 (2C), 129.8 (2C), 130.5, 130.7 (2C), 133.4, 136.1, 136.9, 137.3, 201.9 ppm (*C*HO); IR (film): $\tilde{\nu}$=3021, 2927, 2857, 2717, 1724, 1595, 1491, 1445, 808, 752, 694 cm^{-1}; MS (APCI): *m*/*z* (%): 339 (100) $[M+1]^+$, 321, 215, 173; elemental analysis calcd (%) for $C_{22}H_{26}OS$: C 78.06, H 7.74, S 9.47; found: C 78.32, H 7.92, S 9.75.

Synthesis of (±)-4-(*E*)-3-*n*-butyl-5-phenyl-4-(*p*-tolylsulfonyl)pent-4-enal (39a): From acrylate **30** (30 mg, 0.07 mmol), by following the general procedure (136 °C, 4 h), aldehyde **39a** was obtained. Purification by chromatography (10–30% EtOAc/hexane) afforded **39a** (21 mg, 0.05 mmol,

71%). R_f=0.33 (15% EtOAc/hexane ×3); ^{1}H NMR (300 MHz): δ=0.62 (t, 3H, J=7.0 Hz; Me-*n*Bu), 0.78–0.99 (m, 4H; *n*Bu), 1.28 (m, 1H; *n*Bu), 1.45 (m, 1H; *n*Bu), 2.42 (s, 3H; Me-*p*Tol), 2.61 (ddd, 1H, J=17.9, 7.3, 1.5 Hz; H-2), 2.86 (ddd, 1H, J=17.9, 6.8, 1.1 Hz; H-2), 3.50 (m, 1H; H-3), 7.26–7.40 (m, 7H), 7.80 (d, 2H, J=8.3 Hz), 7.88 (s, 1H; H-5), 9.43 ppm (t, 1H, J=1.2 Hz; H-1); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 21.6 (Me-*p*Tol), 22.2, 29.4, 32.9, 33.2, 48.1 (C-2), 128.3 (2C), 128.4 (2C), 128.6 (2C), 128.8, 129.8 (2C), 134.0, 137.6, 141.2, 144.4, 145.0, 200.2 ppm (*C*HO); IR (film): $\tilde{\nu}$=3021, 2927, 2857, 2717, 1724, 1595, 1491, 1445, 808, 752, 694 cm^{-1}; MS (APCI): *m*/*z* (%): 339 (100) $[M+1]^+$, 321, 215, 173; elemental analysis calcd (%) for $C_{22}H_{26}O_3S$: C 71.32, H 7.07, S 8.65; found: C 71.52, H 7.32, S 8.75.

Synthesis of (±)-(2*S*,1′*R*,*R*$_S$)-2-[(*E*)-1-*n*-butyl-3-phenyl-2-(2-methoxynaphthalen-1-ylsulfinyl)-2-propen-1-yl]cyclohexanone (53): A solution of sulfoxide **11d** (73 mg, 0.2 mmol), 1-ethoxy-1-cyclohexene (10 equiv), and 2,3-dimethylphenol (0.1 equiv, 2.4 mg, 0.02 mmol) in toluene (2 mL) was heated at 120°C for 3 h. Then the solvent was removed under reduced pressure and a 97:2:1 mixture of **53** (as a 98:2 mixture of *S* epimers), **55**, and **54** was obtained. Purification by chromatography (CH_2Cl_2) afforded a mixture of **54** and **55** (5 mg) and **53** (75 mg, 0.16 mmol, 80%) with traces of the epimer at sulfur as a white solid that was recrystallized from EtOAc/hexane. A second chromatography of the first fraction (50–60% Et_2O-hexane) gave **54** (1 mg) and **55** (1 mg). In a related experiment, with 1-ethoxy-1-cyclohexene (2.0 equiv) and 2,3-dimethylphenol (0.5 equiv), the mixture was heated at 120°C for 9 h affording an 85:15 mixture of **53** and its epimer at sulfur. M.p. 127–128°C; R_f=0.14 (40% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=0.57 (t, 3H, J=7.0 Hz; Me-*n*Bu), 0.57–0.66 (m, 1H), 0.80–1.10 (m, 6H), 1.21–1.37 (m, 3H), 1.57 (m, 1H), 1.66 (m, 2H), 1.91 (m, 1H), 2.23 (m, 1H), 3.10 (ddd, 1H, J=9.2, 8.1, 4.4 Hz; H-1′), 3.95 (s, 3H; OMe), 7.24 (m, 1H), 7.33–7.42 (m, 3H), 7.55–7.60 (m, 3H), 7.78 (d, 2H, J=11.0 Hz; H-5″), 7.80 (s, 1H; H-3′), 7.95 (dd, 1H, J=9.2, 2.0 Hz; H-4″), 8.66 ppm (d, 1H, J=8.8 Hz; H-8″); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 22.5, 25.1, 28.4, 29.5, 30.7, 32.2, 37.8, 41.6 (C-6), 53.6 (C-2), 56.6 (OMe), 113.5, 120.8 (C-1″), 122.8, 124.4, 127.2, 128.2 (2C), 128.3, 128.7, 128.8 (2C), 129.2, 131.8, 132.7, 134.7, 136.8, 144.3, 158.9 (C-2″), 211.2 ppm (CO); IR (KBr): $\tilde{\nu}$=2933, 2862, 1705, 1621, 1593, 1507, 1467, 1272, 1249, 1151, 1055, 819, 719 cm^{-1}; MS (APCI): *m*/*z* (%): 475 (100) $[M+1]^+$, 346, 310, 269; elemental analysis calcd (%) for $C_{30}H_{34}O_3S$: C 75.90, H 7.21, S 7.26; found: C 75.60, H 7.60, S 7.44.

Synthesis of (±)-(2*R*,1′*R*,*R*$_S$)-2-[(*E*)-1-*n*-butyl-3-phenyl-2-(2-methoxynaphthalen-1-ylsulfinyl)-2-propen-1-yl]cyclohexanone (55): A kimble vial was charged with a solution of ketone **53** (15 mg, 0.032 mmol) and acetic acid (1.0 equiv, 2 μL, 0.032 mmol) in toluene (0.3 mL). The mixture was heated at 120°C for 6 h and then cooled to RT. A saturated solution of K_2CO_3 (0.5 mL) and H_2O (0.5 mL) was added and the mixture was diluted with EtOAc. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a 70:30 mixture of **55** and **53**. Purification by chromatography (20–40% EtOAc/hexane) afforded ketone **53** (4 mg, 0.008 mmol, 25%) and the title ketone **55** (10 mg, 0.021 mmol, 66%), both as white solids that were recrystallized from EtOAc/hexane. M.p. 141–143°C; R_f=0.25 (40% EtOAc/hexane); ^{1}H NMR (C_6D_6, 300 MHz, 60°C): δ=0.50 (m, 3H; Me-*n*Bu), 0.60–0.98 (m, 4H), 1.13–1.42 (m, 6H), 1.68 (td, 1H, J=12.3, 5.6 Hz), 1.93 (m, 1H), 2.01–2.15 (m, 3H), 3.33 (m, 1H; H-1′), 3.45 (s, 3H; OMe), 6.73 (d, 1H, J=9.3 Hz), 7.02 (d, 1H, J=7.7 Hz), 7.09–7.15 (m, 4H), 7.26 (d, 1H, J=7.6 Hz), 7.35 (ddd, 1H, J=8.5, 7.0, 1.5 Hz), 7.52 (d, 2H, J=8.8 Hz), 8.31 (s, 1H; H-3′), 9.41 ppm (d, 1H, J=8.5 Hz; H-8″); ^{13}C NMR (50 MHz): δ=13.7 (Me-*n*Bu), 22.4, 24.8, 29.2, 29.4, 31.2, 33.7, 38.0, 42.9, 55.5, 56.8, 112.8, 120.4, 123.1, 124.6, 127.5, 128.0 (2C), 128.4, 128.8 (2C), 129.5, 132.8, 133.4, 134.9, 136.3, 144.2, 158.0, 212.2 ppm (CO); IR (KBr): $\tilde{\nu}$=2932, 2857, 1706, 1621, 1593, 1506, 1466, 1430, 1333, 1272, 1248, 1150, 1135, 1051, 1024, 819, 772, 748, 718, 697 cm^{-1}; MS (APCI): *m*/*z* (%): 971 $[2M+Na]^+$, 475 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{30}H_{34}O_3S$: C 75.90, H 7.21, S 7.26; found: C 75.74, H 7.46, S 7.52.

Synthesis of (±)-(2*S*,1′*R*,*S*$_S$)-2-[(*Z*)-1-*n*-butyl-2-(naphthalen-1-ylsulfinyl)-3-phenyl-2-propen-1-yl]cyclohexanone (60) and (±)-(2*R*,1′*R*,*S*$_S$)-2-[(*Z*)-1-*n*-butyl-2-(naphthalen-1-ylsulfinyl)-3-phenyl-2-propen-1-yl]cyclohexanone (61): A kimble vial was charged with a solution of sulfoxide **3c** (20 mg, 0.050 mmol), 1-ethoxy-1-cyclohexene (4 equiv, 25 mg, 0.2 mmol) and acetic acid (0.5 equiv, 2 μL, 0.025 mmol) in of toluene (0.5 mL). The mixture was heated at 90°C for 14 h and then at 120°C for 8 h. The solvent was removed under reduced pressure to give a 33:67 mixture of **60** and **61**. Purification by chromatography afforded ketone **60** (4 mg, 0.009 mmol, 18%) and ketone **61** (9 mg, 0.020 mmol, 40%), both as white solids that were recrystallized from EtOAc/hexane.

*Data for **60***: M.p. 178–179°C; R_f=0.34 (10% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=−0.54 (m, 1H; H-2 *n*Bu), −0.32 (m, 1H; H-2 *n*Bu), 0.13 (t, 3H, J=7.3 Hz; Me-*n*Bu), 0.46 (sext, 2H, J=7.5 Hz), 0.81–0.88 (m, 1H), 0.93–1.24 (m, 2H), 1.61–2.02 (m, 4H), 2.10–2.16 (m, 1H), 2.22–2.40 (m, 2H), 2.50 (m, 1H), 2.77 (dt, 1H, J=8.8, 4.1 Hz; H-1′), 7.00 (d, 1H, J=8.4 Hz), 7.08 (s, 1H; H-3′), 7.14 (ddd, 1H, J=8.4, 7.0, 1.3 Hz), 7.38–7.45 (m, 2H), 7.49–7.54 (m, 2H), 7.64–7.69 (m, 3H), 7.82 (d, 1H, J=8.3 Hz), 7.90 (d, 1H, J=8.2 Hz), 8.17 ppm (dd, 1H, J=7.2, 1.1 Hz; H-8″); NOESY-1D between H-1′/H-8″: 7.0%, H-1′/H-1 *n*Bu: 4.1%, H-2/H-3′: 3.6%, H-3′/H-2: 3.8%, H-3′/H-1 *n*Bu: 5.1%, H-3′/Ph: 5.1%; ^{13}C NMR (50 MHz): δ=13.4 (Me-*n*Bu), 22.3 (C-3 *n*Bu), 24.8, 28.0 (C-2 *n*Bu), 28.5, 33.0 (C-1 *n*Bu), 33.2, 35.9 (C-1′), 42.8 (C-6), 57.8 (C-2), 122.8, 124.3, 125.4, 126.3 (2C), 126.5, 128.6 (4C), 129.3, 129.4, 131.1, 133.4, 135.0, 137.2 (C-3′), 138.1, 146.8, 212.8 ppm (CO); IR (KBr): $\tilde{\nu}$=2930, 2855, 1709, 1447, 1038, 806, 774, 751, 699 cm^{-1}; MS (APCI): *m*/*z* (%): 445 (100) $[M+1]^+$, 269, 171; elemental analysis calcd (%) for $C_{29}H_{32}O_2S$: C 78.34, H 7.24, S 7.21; found: C 78.51, H 7.10, S 7.52.

*Data for **61***: M.p. 103–105°C; R_f=0.20 (5% EtOAc/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=−0.37 (m, 1H; H-2 *n*Bu), −0.14 (m, 1H; H-2 *n*Bu), 0.20 (t, 3H, J=7.3 Hz; Me-*n*Bu), 0.42–0.60 (m, 2H; H-3 *n*Bu), 1.06 (m, 2H; H-1 *n*Bu), 1.37 (qd, 1H, J=12.6, 3.5 Hz), 1.50–1.73 (m, 2H), 1.88 (m, 1H), 1.99–2.14 (m, 2H), 2.25–2.43 (m, 2H), 2.90 (ddd, 1H, J=12.8, 5.3, 2.2 Hz; H-2), 3.20 (td, 1H, J=7.2, 2.2 Hz; H-1′), 6.89 (s, 1H; H-3′), 6.97 (d, 1H, J=8.3 Hz), 7.14 (ddd, 1H, J=8.2, 6.8, 1.1 Hz), 7.38–7.44 (m, 2H), 7.45–7.55 (m, 2H), 7.65–7.70 (m, 3H), 7.83 (d, 1H, J=8.2 Hz), 7.91 (d, 1H, J=8.2 Hz), 8.14 ppm (dd, 1H, J=7.2, 1.1 Hz; H-8″); NOESY-1D: between H-1′/H-2: 5.2%, H-1′/H-8″: 4.3%, H-1′/H-1 *n*Bu: 3.5%, H-2/H-1′: 5.4%, H-3′/H-1 *n*Bu: 7.9%, H-3′/Ph: 4.8%; ^{13}C NMR (50 MHz)-HSQC: δ=13.6 (Me-*n*Bu), 22.0 (C-3 *n*Bu), 25.0, 26.4, 27.1, 27.5 (C-1 *n*Bu), 28.3 (C-2 *n*Bu), 34.5 (C-1′), 42.2 (C-6), 55.1 (C-2), 122.8, 124.3 (C-8″), 125.5, 126.2, 126.3, 128.6, 128.7 (3C), 128.9, 129.5 (2C), 131.1, 133.4, 134.9, 136.5 (C-3′), 137.7, 145.1, 210.7 ppm (CO); IR (KBr): ν=3050, 2929, 2855, 1705, 1443, 1042 cm^{-1}; MS (APCI): *m*/*z* (%): 445 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{29}H_{32}O_2S$: C 78.34, H 7.24, S 7.21; found: C 78.51, H 7.10, S 7.52.

Synthesis of (±)-(2*S*,1′*R*,*S*$_S$)-2-[(*Z*)-1-*n*-butyl-2-(naphtalen-1-ylsulfinyl)-3-phenyl-2-propen-1-yl]cyclohexanone (60): From sulfoxide **59** (12 mg, 0.024 mmol), by following the general procedure (90°C, 2 h 30 min), ketone **60** was obtained. Purification by chromatography (CH_2Cl_2) afforded **60** (8 mg, 0.018 mmol, 75%) as a white solid that was recrystallized from EtOAc/hexane.

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