Sulfoxide-Controlled S_N2' Displacements between Cyanocuprates and Epoxy Vinyl Sulfoxides[1]

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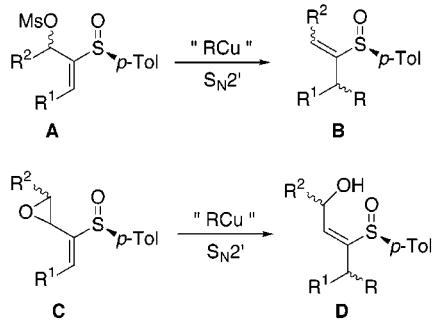
Received March 28, 2000

Two short and convergent routes have been devised for the preparation of enantiomerically pure acyclic epoxy vinyl sulfoxides. These substrates undergo highly regio- and stereoselective S_N2' displacements with lithium cyanocuprates to give α′-alkylated, γ-oxygenated *Z* α,β-unsaturated sulfoxides in moderate to good yields and with good to excellent diastereoselectivities. The absolute configuration of the newly formed carbon−carbon bond is primarily controlled by the chiral sulfur atom, which in a nonreinforcing situation can override the intrinsic anti tendency of the vinyl oxirane moiety and forces the cuprate to undergo syn addition. The hydroxy vinyl sulfoxide functionality of the resulting adducts should allow for subsequent asymmetric transformations thus enhancing the synthetic usefulness of this methodology.

The asymmetric construction of carbon−carbon bonds in acyclic systems remains a challenging area in organic synthesis.[2] Within this field, the S_N2' cleavage of alkenyl oxiranes by organocopper reagents[3] is a valuable methodology primarily due to the high degree of regio- and stereocontrol observed.[4] Previously, we have demonstrated that copper-mediated S_N2' displacements of acyclic allylic mesylates **A**, activated with a chiral sulfoxide, proceed with high asymmetric induction and *Z*−*E* selectivity to produce enantiomerically pure trisubstituted vinyl sulfoxides **B** (Scheme 1).[5] As an extension of this work we envisioned that the related enantiomerically pure epoxy vinyl sulfoxides **C** could be useful substrates for effecting allylic displacements with organocopper reagents to produce densely functionalized allylic alcohols **D** which maintain the versatile vinyl sulfoxide functionality thus allowing for additional enantioselective manipulations.[6e−g] Moreover, a variety of additional substrate-directed transformations were readily envisaged for the

Scheme 1



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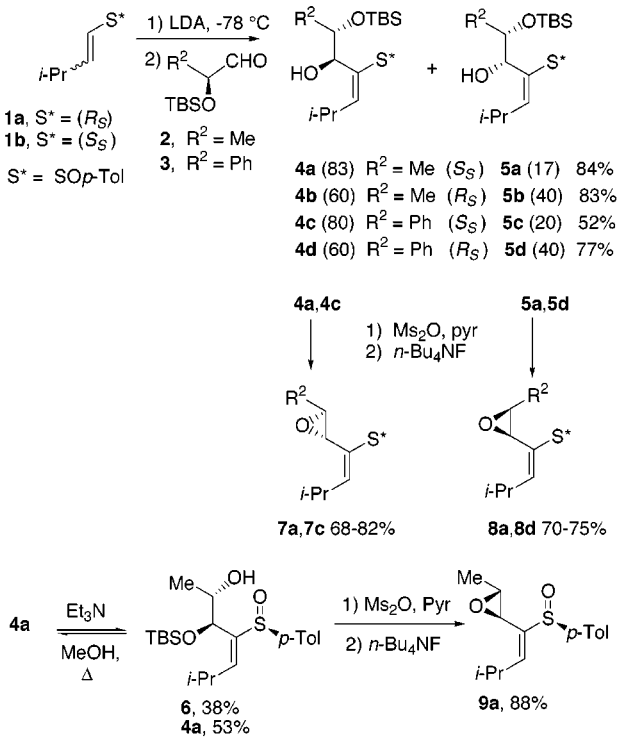
10.1021/jo000468k CCC: $19.00
Published on Web 09/07/2000

related enantiopure hydroxy vinyl sulfones,[7] readily accessible in a straightforward manner by oxidation at sulfur. In this paper, we present a full account of our research on the preparation of enantiomerically pure acyclic epoxy vinyl sulfoxides and their highly regio- and stereoselective S_N2' displacements with cyanocuprates. In contrast with our previous work,[5] the chiral sulfoxide appears to be the predominant element of *anti*−*syn* stereocontrol.

Preparation of Substrates

After evaluating several routes to sulfinyl oxiranes **C**,[8] we envisaged an approach based on the condensation of enantiomerically pure lithio vinyl sulfoxides with α-functionalized aldehydes and a straightforward functionalization of the resulting adducts to effect epoxide formation.[9] While it is known that this condensation takes place with low diastereoselectivity with nonchiral aldehydes, an increase in the steric size of the aldehyde results in the stereoselective formation of sulfinyl allylic alcohols in up to 70% de.[9f] Recently, in our studies directed toward the formal synthesis of the plant growth promoter Brassinolide, we described the first example of double diastereoselection in the condensation of simple enantiomeric lithiated vinyl sulfoxides with a chiral nonracemic steroidal aldehyde.[10] Unfortunately, in this example the reaction proceeded with moderate diastereoselectivity (20 and 60% de for the mismatched and matched pairs respectively). However, we hoped that the use of *O*-protected α-alkoxy aldehydes or α-halo aldehydes could result in an enhanced selectivity and provide a further understanding of the factors that control the stereochemical outcome of the process when a chiral sulfoxide and different chiral α-branched aldehydes are involved.

Scheme 2



Scheme 2 gathers our efforts to prepare the desired oxiranes from enantiopure α-alkoxy aldehydes **2** and **3**[11,12] and enantiomeric vinyl sulfoxides **1a** and **1b**.[13] These condensations took place in fair to good yields (52−84%) but with modest diastereoselectivities (60:40 to 83:17) to produce diastereomeric alcohols **4** and **5** which were readily separated by chromatography on silica gel. Oxirane formation was then achieved smoothly (68−82%) by mesylation and fluoride-induced ring closure. The

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(11) Prepared in two steps from the commercially available enantiomerically pure ethyl esters (lactate and mandelate): Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180−5182.

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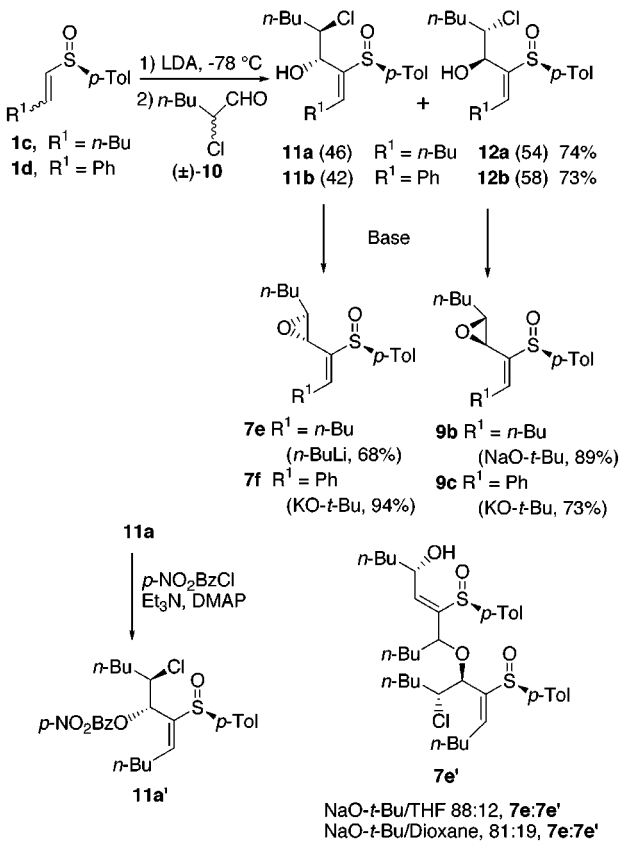
(13) Prepared in one step from commercially available enantiomerically pure (+)-menthyl (*R*)-*p*-toluensulfinate or (−)-menthyl (*S*)-*p*-toluensulfinate by the method of Craig: Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263−11304. Lithiation of *Z* vinyl sulfoxides yields *E* lithio derivatives; there are conflicting reports on the configurational stability at sulfur in this process, see: (a) Posner, G. H. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; ACS Symposium Series No. 185; American Chemical Society: Washington, DC, 1982; p 142. (b) See refs 9f and 9g.

Scheme 3



ability of silyl groups to migrate under basic conditions between adjacent hydroxyl groups[14] allowed for a simple entry to diastereomeric oxiranes such as **9a** by treatment of **4a** with Et_3N in refluxing methanol to produce **6** and subsequent ring closure as described above.

Scheme 3 shows a straightforward alternative approach to these oxiranes based on the condensation of lithiated vinyl sulfoxides with readily available racemic α-halo aldehydes.[15] Thus, metalation of enantiopure alkenyl sulfoxides **1c** and **1d**[13] and reaction with freshly distilled racemic 2-chlorohexanal, (±)-**10**,[16] afforded a ca. 50:50 mixture of diastereomeric anti chlorohydrins **11** and **12** with high selectivity. A very simple chromatographic separation followed by recrystallization gave good yields of these adducts (33−38% of each isomer),[17] along with small amounts of unreacted starting material (<10%, *E* isomer) and syn chlorohydrins (syn:anti ratio, ca. 92:8). The preparation of the desired oxiranes, **7** and **9**, was then explored. After considerable experimentation,[18] we focused our efforts on the use of a suspension of NaO-*t*-Bu in THF (0 °C, 30 min), which gave excellent results for **9b** but produced substantial amounts of dimeric byproduct **7e′** (ca. 10%), along with the desired oxirane, **7e**.[19] This unwanted reaction pathway could be suppressed by the use of 1.2 equiv of *n*-BuLi (−78 °C to room temperature, THF, 5 h). In contrast, phenyl-substituted chlorohydrins **11b** and **12b** led smoothly to the desired oxiranes **7f** and **9c**, even with a suspension of KO-*t*-Bu in THF (1.2 equiv, 0 °C, 30 min), provided the reaction conditions were carefully controlled.

The structures of sulfinyl diols **4**−**6**, chlorohydrins **11** and **12**, and oxiranes **7**−**9** were tentatively assigned by spectroscopic methods, primarily by ^{1}H and ^{13}C NMR. The geometry of our vinyl oxiranes conclusively followed from the vicinal coupling constants observed for the oxirane protons (1.8−2.4 Hz for trans isomers and 3.8−4.0 Hz for cis oxiranes).[20] This assignment, coupled with the known stereochemical course for oxirane formation, allowed for the unequivocal determination of an anti configuration for the precursors of trans oxiranes, **7** and **9**, derived from the alkoxy aldehyde route. It should be noted that diastereomeric oxiranes **7** and **9** display strikingly different chemical shifts for the oxirane protons (see Experimental Section) and a detailed comparison of these shifts for oxiranes obtained by either route allowed for firm structural assignments for chlorohydrins **11** and **12**.[21] These assignments were later secured by an X-ray diffraction analysis of the *p*-nitrobenzoate of **11a**, **11a′**.

The stereochemical outcome of these condensations is consistent with a predominant Cram addition of the vinyl

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(15) Enantiopure α-halo aldehydes are relatively difficult to prepare and particularly prone to undergo racemization under standard laboratory conditions. For the asymmetric synthesis of nonracemic α-fluoro aldehydes, see: (a) Davis, F. A.; Kasu, P. V.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546−7547. For the synthesis of related enantiomerically pure α-chloro and α-bromo aldehydes see: (b) Martín, V. S.; Palazón, J. M. *Tetrahedron Lett.* **1992**, 33, 2399−2402. For protocols to generate these intermediates in situ, see: (c) Bailey, P. L.; Briggs, A. D.; Jackson, R. F. W.; Pietruska, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3359−3363. (d) Wang, S.; Howe, G. P.; Mahal, R. S.; Procter, G. *Tetrahedron Lett.* **1992**, 33, 3351

(16) Prepared in one step by the method of Stevens: Stevens, C. L.; Farkans, E.; Gillis, B. J. *J. Am. Chem. Soc.* **1954**, *76*, 2695−2698.

(17) While at this early stage of the process access to both diastereomeric series (α and β epoxide) was in fact desirable, the possibility of preparing enantiopure α-halo aldehydes by selective reduction of the corresponding esters (DIBAL-H in toluene) and in situ condensation with lithiated alkenyl sulfoxides at low temperature was explored. Initial attempts performed on racemic α-chloro esters gave very low conversions (ca. 20%) to the desired chlorohydrins, presumably due to predominant protonation of the metalated sulfoxide by the acidic α-hydrogen under these conditions. An improved conversion (ca. 67%) was observed for racemic α-bromo esters. We believe that, after optimization, this experimentally challenging protocol could be a valuable alternative in some cases. Later, to improve the versatility of this route, the inversion of the allylic hydroxyls to generate syn chlorohydrins, potential precursors of cis oxiranes was explored. Under Mitsunobu conditions (Ph_3P, $C_6H_5CO_2H$, DIAD, benzene, rt) **11a** and **12a** gave clean S_N2 inversion albeit not synthetically useful due to a predominant nonselective S_N2' pathway for **12a** or to a low conversion (43%) for **11a**. A straightforward inversion of the mesylate derivative of **11a** with KO_2 (Corey, E. J.; Nicolau, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, *37*, 3183−3186) led to a complex mixture of products.

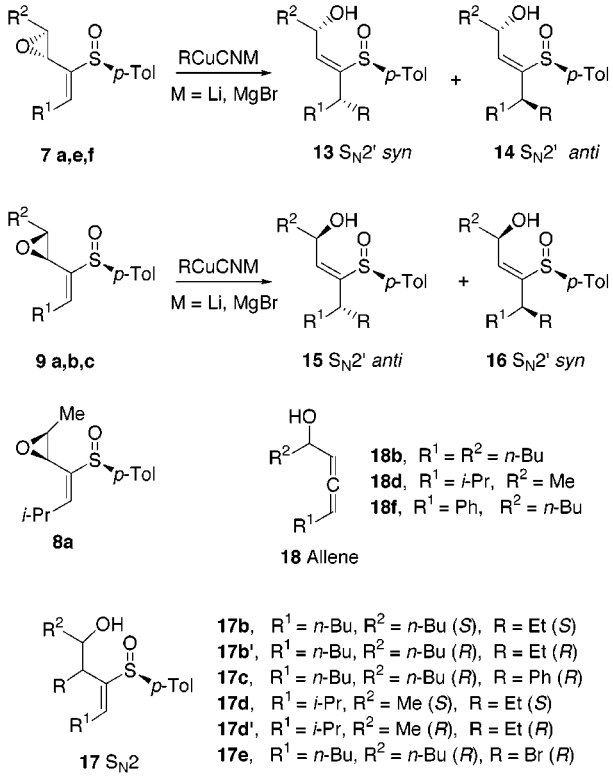
(18) The desired oxiranes **7e** and **9b** were obtained in fair yield by simply allowing the crude condensation mixture to warm to room temperature; however, separation of these diastereomers by chromatography was exceedingly difficult and therefore we settled for the use of pure chlorohydrins **11a** and **12a**. Our initial experiments entailed addition of solid NaO-*t*-Bu to a cold (0 °C) solution of **12a** in THF. These conditions, particularly upon scale-up, gave very erratic results with low yields of oxirane **9b** and complex reaction mixtures containing up to 50% of 1-*p*-tolylsulfinyl-2-hexene, presumably produced by fragmentation of **12a**. The use of solid KO-*t*-Bu gave even more complex reaction mixtures. Fortunately, we found that the use of a preformed suspension of NaO-*t*-Bu in THF gave reproducible results.

(19) Interestingly, this dimer was obtained as a single diastereomer derived from the stereoselective S_N2' addition of chlorohydrin **11a** to vinyl epoxide **7e**. The configuration at C-8 has not been determined.

(20) These are standard values for vicinal coupling constants in oxiranes. See ref 6h for data of a variety of sulfinyl oxiranes.

(21) Chlorohydrins **11** had a higher chromatographic mobility than diastereomers **12**; this is in agreement with previous findings for β-hydroxy sulfoxides. See ref 5. See also: (a) Brunet, E.; García Ruano, J. L.; Martínez, M. C.; Rodríguez, J. H. *Tetrahedron* **1984**, *40*, 2023−2034. (b) Rayner, C. M.; Westwell, A. D. *Tetrahedron Lett.* **1992**, *33*, 2409−2412. In an early attempt to secure the relative configuration of these chlorohydrins, the free radical dehalogenation of **11a** and **12a** was explored (Bu_3SnH, AIBN, toluene, 100 °C, 4 h), hoping to obtain sulfinyl alcohols closely related to those described in ref 5. Surprisingly, good yields of the corresponding enantiomeric sulfonyl chlorohydrins were obtained.

Scheme 4



anion to the less hindered face of the carbonyl[22] and may be rationalized in terms of a chelate chairlike transition state,[9f] where the aldehyde adopts a Felkin−Ahn rotational conformation,[10] with matched and mismatched pairs for alkoxy aldehydes. In contrast, chloro aldehydes do not display any measurable double diastereoselection upon reaction with lithiated vinyl sulfoxides.

Cuprate S_N2' Displacements on Epoxy Vinyl Sulfoxides

Our initial task was to establish the viability of the proposed copper-mediated S_N2' displacements on our sulfinyl oxiranes. After several preliminary attempts with Gilman's reagent ($Me_2CuLi{\cdot}LiI$, −78 °C to room temperature) and substrates **7e** and **9b** (Scheme 4) which led mainly to diastereomeric mixtures of allene **18b**,[23] we focused our efforts on the use of cyanocuprates,[24] and the results obtained are presented in Scheme 4 and Table 1. Thus, the reaction between oxirane **7e** and MeCuCNLi (6 equiv, Et_2O, −78 °C to room temperature, 2 h) gave a good yield of an 85:15 mixture of S_N2' products **13a** and **14a** with complete *Z* selectivity (Table 1, entry 1). In contrast, under identical reaction conditions, diastereomeric sulfinyl epoxide **9b** produced a 4:96 mixture of S_N2' adducts **16a** and **15a** in excellent yield (Table 1, entry 4). The major products of these displacements, **13a** and **15a** had remarkably similar spectral features (see below), and this suggested that a different syn/anti reaction pathway was operative for each diastereomeric oxirane.

Encouraged by these results, we carried on with the study to evaluate the scope of the methodology with respect to the use of different cyanocuprates and to the range of substituents on the vinyl oxiranes. In this manner, while EtCuCNLi gave a very high syn selectivity with **7e** in a very clean reaction (Table 1, entry 2), the use of EtCuCNMgBr afforded lower yields of S_N2' products due to competitive formation of variable amounts of allene **18b** and regioisomeric adducts **17b** and **17b′** (Table 1, entries 3 and 5), especially when the cyanocuprate was generated from commercial EtMgBr. Nonetheless, these processes took place in fair yields and, remarkably, with anti selectivity for both diastereomeric oxiranes (5:95 for **9b** and 27:73 for **7e**, opposite to the finding for EtCuCNLi, compare Table 1 entries 2 and 3).

The use of aryl copper species was also explored for oxirane **9b**, and not surprisingly,[25] a predominant S_N2 pathway was found for PhCuCNLi (Table 1, entry 6) which gave anti adduct **15c**. In an effort to improve the regiochemical outcome of the process we tested a Lewis acid modified aryl copper reagent, $PhCu{\cdot}LiBr{\cdot}BF_3$,[4c] which gave a clean S_N2' process but just moderately anti selective (20:80), along with substantial amounts of starting material and bromohydrin **17e**.[26]

The effect of a bulky isopropyl group on the vinyl moiety of our oxiranes was examined with excellent results for the reactions between substrates **7a** and **9a** and *n*-BuCuCNLi (Table 1, entries 8 and 13). On the other hand, the use of EtCuCNMgBr with **7a** and **9a** (Table 1, entries 9 and 14) afforded mainly S_N2 products **17d** and **17d′**[27] and allene **18d**; however, the S_N2' pathway showed also an anti selectivity as described above.

Entry 10 shows that the geometry of the oxirane does not have a significant effect on the stereochemical outcome of the process.[28] Finally, phenyl substituted vinyl sulfoxide **7f** gave a smooth syn 1,4 displacement with *n*-BuCuCNLi (91:9), further improved (96:4) by lowering the reaction temperature to −100 °C. Diastereomeric oxirane **9c** gave a clean anti displacement with MeCuCNLi but accompanied by a substantial amount of allene **18f**, which became the major product when the "higher order" reagent $Me_2CuLi{\cdot}LiCN$ was used, along with a decrease in anti selectivity (Table 1, entries 16 and 17). In contrast, *n*-BuCuCNLi gave a high yielding anti displacement with **9c** (Table 1, entry 17).

(22) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, 99, 1191−1223. Moderate diastereoselectivities have been obtained (dr = 77:23−88:12) in favor of anti chlorohydrins (Cram addition mode) in the condensation between standard nucleophiles and α-chloro aldehydes, see: (c) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *43*, 9005−9018.

(23) For a discussion of a related allene formation, see: (a) Fernández de la Pradilla, R.; Rubio, M. B.; Marino, J. P.; Viso, A. *Tetrahedron Lett.* **1992**, *33*, 4985−4988. See also: (b) Delouvrié, B.; Lacôte, E.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 3565−3568. (c) Satoh, T.; Kuramochi, Y.; Inoue, Y. *Tetrahedron Lett.* **1999**, *40*, 8815−8818.

(24) (a) Initial attempts in THF resulted in recovery of starting material. (b) Cyanocuprates have been the subject of a long standing controversy regarding structure and reactivity aspects. For a recent discussion, see: Krause, N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 79−80.

(25) Organocopper reagents with sp^2-hybridized ligands often show a decreased regioselectivity in these processes. See: Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898−4913.

(26) In sharp contrast, diastereomeric epoxide **7e** showed a different behavior under identical reaction conditions with aryl copper species (PhCuCNLi and $PhCuLiBr{\cdot}BF_3$). The crude reaction mixtures contained important amounts of starting material and complex mixtures of *Z*/*E* and syn/anti S_N2' adducts.

(27) The unusually large amount of S_N2 products and allene byproduct obtained in this experiment may be due to the fact that commercial EtMgBr was used.

(28) Due to the different geometry of the oxirane, the syn−anti stereochemistry of the S_N2' adduct is opposite to the stereochemical course.

Table 1. Reaction of Epoxy Vinyl Sulfoxides with Cuprates

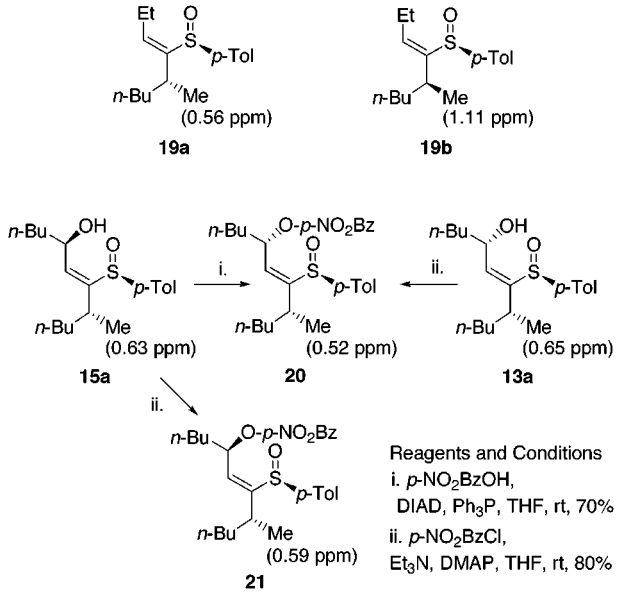
entry	substrate	R^2	R^1	RCu[a]	syn S_N2'	anti S_N2'	yield (%)[b]
1	**7e**	*n*-Bu	*n*-Bu	MeCuCNLi	**13a** (85)	**14a** (15)	69
2	**7e**	*n*-Bu	*n*-Bu	EtCuCNLi	**13b** (100)	**14b** (0)	82
3	**7e**	*n*-Bu	*n*-Bu	EtCuCNMgBr	**13b** (27)	**14b** (73)	56[c]
4	**9b**	*n*-Bu	*n*-Bu	MeCuCNLi	**16a** (4)	**15a** (96)	93
5	**9b**	*n*-Bu	*n*-Bu	EtCuCNMgBr	**16b** (5)	**15b** (95)	64[d]
6	**9b**	*n*-Bu	*n*-Bu	PhCuCNLi	**16c** (0)	**15c** (100)	*e*
7	**9b**	*n*-Bu	*n*-Bu	PhCu·LiBr·BF_3	**16c** (20)	**15c** (80)	*f*
8	**7a**	Me	*i*-Pr	*n*-BuCuCNLi	**13c** (88)	**14c** (12)	68
9	**7a**	Me	*i*-Pr	EtCuCNMgBr	**13d** (25)	**14d** (75)	*g*
10	**8a**	Me	*i*-Pr	MeCuCNLi	**14e** (7)	**13e** (93)[h]	70
11	**7f**	*n*-Bu	Ph	*n*-BuCuCNLi	**13f** (91)	**14f** (9)	82
12	**7f**	*n*-Bu	Ph	*n*-BuCuCNLi	**13f** (96)	**14f** (4)	*i*
13	**9a**	Me	*i*-Pr	*n*-BuCuCNLi	**16d** (0)	**15d** (100)	75
14	**9a**	Me	*i*-Pr	EtCuCNMgBr	**16e** (0)	**15e** (100)	*j*
15	**9c**	*n*-Bu	Ph	MeCuCNLi	**16f** (0)	**15f** (100)	*k*
16	**9c**	*n*-Bu	Ph	$Me_2CuCNLi_2$	**16f** (37)	**15f** (63)	*l*
17	**9c**	*n*-Bu	Ph	*n*-BuCuCNLi	**15c** (0)	**16c** (100)[m]	87

[a] Cyanocuprates were prepared from CuCN and the corresponding RLi or RMgBr. All experiments were carried out with an excess of the organocuprate (6−9 equiv) in Et_2O from −78 °C to room temperature unless otherwise stated. [b] Unoptimized combined yields of pure S_N2' products. Product ratios were measured by integration of well-separated absorptions of the ^1H NMR spectra of the crude reaction mixtures. [c] A 10% ratio of **17b** and a 25% ratio of **18b** were also observed in the ^1H NMR spectrum of the reaction mixture. [d] An 8% ratio of **17b′** and an 11% ratio of **18b** were also observed in the ^1H NMR spectrum of the reaction mixture. [e] A 30:70 mixture of **15c** and **17c** was obtained. The yield was not determined. [f] BF_3·Et_2O was added at −78 °C to a preformed solution of the organocuprate; 13% ratio of bromohydrin **17e** and 19% ratio of starting material were also detected in the ^1H NMR spectrum of the reaction mixture. The yield was not determined. [g] A 30% ratio of **17d** and a 40% ratio of **18d** were also observed in the ^1H NMR spectrum of the reaction mixture. Combined yield 54%. [h] Due to the different geometry of the starting material, **13e** is the anti S_N2' product. [i] The reaction was carried out at −100 °C. The yield was not determined. [j] A 50% ratio of **17d′** was also observed in the ^1H NMR spectrum of the reaction mixture. Combined yield 76%. [k] A 41% ratio of **18f** was also observed in the ^1H NMR spectrum of the reaction mixture. [l] A 67% ratio of **18f** was also also observed in the ^1H NMR spectrum of the reaction mixture. The yield was not determined. [m] In this particular case **16c** is the anti S_N2' product.

The general structure of these S_N2' adducts **13**−**16** was established readily from their ^1H and ^{13}C NMR spectral absorptions, including differential NOE experiments. The *Z* stereochemistry of the trisubstituted double bond derives from the chemical shifts found for the proton attached to the allylic hydroxyl group (H-5 for **15a**, 5.10 ppm) particularly deshielded due to the effect of the sulfinyl moiety relative to related *E* isomers prepared in our laboratories.[5] Furthermore, in the case of **15a**, a 1.1% NOE enhancement was found for the ortho ArH protons upon irradiation of H-5. The relative stereochemistry of the newly created carbon−carbon bond and the sulfoxide group was deduced by comparison of the spectral characteristics of these adducts with those of related compounds of known structure (Scheme 5).[5] A particularly distinctive feature found was that the methyl group attached to the allylic position appeared substantially more shielded in diastereomers **15a** and **13a** (0.63 and 0.65 ppm) than in **14a** and **16a** (1.09 and 1.04 ppm). This is in agreement with the shifts of 0.56 and 1.11 ppm observed for **19a** and **19b**.[5]

These spectroscopic evidences suggested that a different anti−syn stereochemical pathway was operative for each diastereomeric epoxide **7e** and **9b**. To confirm this hypothesis, we prepared the *p*-nitrobenzoates of alcohols **13a** and **15a**, **20** and **21**, respectively, under standard conditions (*p*-NO_2BzCl, Et_3N, cat DMAP, CH_2Cl_2). On the other hand, the treatment of **15a** with *p*-nitrobenzoic acid under Mitsunobu conditions (*p*-NO_2BzOH, DIAD, Ph_3P, THF),[29] led to a good yield of *p*-nitrobenzoate **20**, of identical physical and spectroscopic data to that obtained from **13a** as described above.[30] The structure of the other S_N2' products was assessed by comparison of key spectral absorptions with those of these series.

Scheme 5

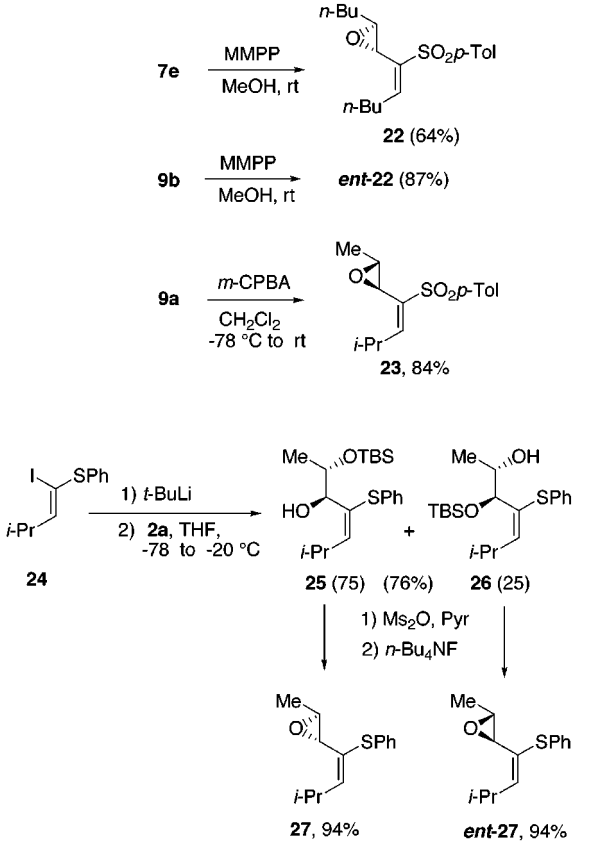


S_N2' Cuprate Displacements on Epoxy Vinyl Sulfides and Sulfones

At this stage we considered that varying the oxidation state on sulfur to sulfone and sulfide would extend the scope of the methodology and provide some insight on the stereochemical outcome of these processes.[31,32] Enantiomerically pure sulfonyl oxiranes **22**, ***ent*-22**, and **23** were obtained in good yields by oxidation of the corre-

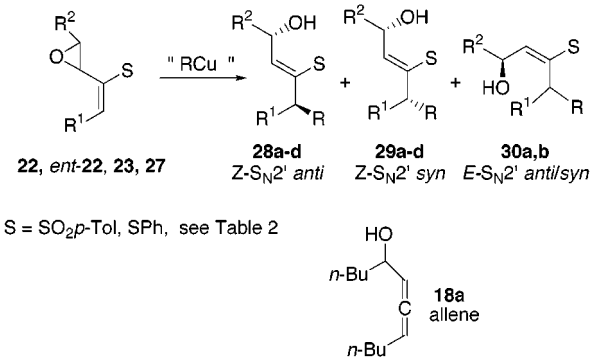
(29) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020. For reviews, see: (a) Hughes, D. L. *Org. React.* **1992**, *42*, 335−669. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127−164. The choice of solvent proved to be critical; polar solvents such as DME or DMF afforded unreacted starting material and in benzene a 20% ratio of the desired product was obtained along with an 80% ratio of a product (2:1 mixture of isomers) of undetermined structure.

Scheme 6



sponding sulfoxides **7e**, **9b**, and **9a** with MMPP or *m*-CPBA (Scheme 6). On the other hand, iodo vinyl sulfide **24**[33] was treated with *tert*-butyllithium, and the resulting vinyllithium reagent was condensed with silylated lactaldehyde **2a** to give a 75:25 mixture of anti adducts **25** and **26**.[34] Subsequent mesylation and fluoride-induced oxirane formation gave enantiomeric alkenyl sulfides **27** and ***ent*-27**.

Scheme 7

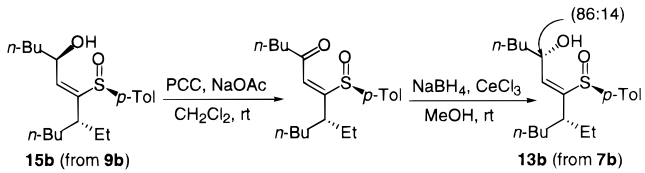


Scheme 7 and Table 2 gather our survey on these displacements. The reaction of sulfonyl oxirane **22** with MeLi gave a complex mixture of *E* and *Z* S_N2' products with low syn−anti stereoselectivity (Table 2, entry 1). A significant improvement in diastereoselection was observed when MeCu·$AlMe_3$ was used (Table 2, entry 2) but unfortunately, although a single *Z*-S_N2' isomer **28a** was obtained, a 33% ratio of allene **18b** was also present in the reaction mixture. On the other hand, lithium alkyl cyanocuprates displayed good *Z* selectivity but with poor anti stereochemistry (Table 2, entries 3 and 5). The use of a Grignard derived cyanocuprate (Table 2, entry 4) resulted in excellent *Z* anti selectivity but at the expense of a 27% ratio of *E* S_N2' product **30b**, obtained as a single diastereomer. Finally sulfide **27** gave a poorly anti selective displacement with *n*-BuCuCNLi but with complete *Z* stereocontrol. These preliminary studies have established the viability of these processes though some optimization is still needed.

The general structure of these S_N2' products (**28**−**30**) was derived from their spectral features, as described above. However, the elucidation of the relative stereochemistry at the allylic centers required some chemical correlations shown in Scheme 8. Thus, deoxygenation of **15d** ($TiCl_4$/Zn) gave sulfide ***ent*-28d′**,[35] and oxidation of **15a** and **15d** gave vinyl sulfones ***ent*-28a** and ***ent*-28c**, respectively. Similarly, oxidation of a 60:40 mixture of **14b** and **13b** gave a 60:40 mixture of sulfones ***ent*-28b** and ***ent*-29b**.

Results and Discussion

The *Z*-selectivity found for these cuprate displacements may be understood in terms of addition to the more stable *s*-trans reactive conformations of the vinyl oxiranes, dictated by competing allylic 1,2 and 1,3 strains, with the latter interaction being more severe (Scheme 9).[36] In turn, it is likely that the s-trans conformation proposed



(30) These assignments are further supported by the following chemical correlation: oxidation of *Z* anti adduct **15b** (for the oxidation of *E* γ-hydroxy α,β-unsaturated sulfoxides, see Guerrero de la Rosa, V.; Ordóñez, M.; Alcudia, F.; LLera, J. M. *Tetrahedron Lett.* **1995**, *36*, 4889−4892) gave a sulfinyl enone that was reduced with Luche's reagent (Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459) to produce *Z* syn adduct **13b** with good stereoselectivity (**13b**:**15b**, 86:14). These results suggest that, after optimization, syn adducts should be available by either syn displacement on oxiranes **7** or anti displacement on oxiranes **9** followed by oxidation−reduction or Mitsunobu protocols. Data for the sulfinyl enone: ^{1}H NMR (200 MHz) δ 0.62−1.75 (m, 21 H), 2.30 (m, 1 H), 2.43 (s, 3 H), 2.85 (m, 2 H), 6.26 (s, 1 H), 7.34 (d, 2 H, *J* = 8.4 Hz), 7.83 (d, 2 H, *J* = 8.4 Hz).

(31) For examples of S_N2' processes on acyclic vinyl sulfones, see: (a) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095−6106. (b) See also ref **5a**.

(32) For examples of S_N2' displacements on cyclic vinyl sulfones, see: (a) Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112−2114. (b) Pan, Y.; Hardinger, S. A.; Fuchs, P. L. *Synth. Commun.* **1989**, *19*, 403−416. (c) Pan, Y.; Hutchinson, D. K.; Nautz, M. H.; Fuchs, P. L. *Tetrahedron* **1989**, 45, 467−478. (d) Bäckvall, J. E.; Juntunen, S. K. *J. Org. Chem.* **1988**, *53*, 2398−2400. (e) Braish, T.; Saddler, J. C.; Fuchs P. L. *J. Org. Chem.* **1988**, *53*, 3647−3658. (f) Hardinger, S. A.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 2739−2749. (g) Arjona O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906−3916. (h) See ref 4i.

(33) Iodo vinyl sulfide **24** was prepared from (phenylthio)acetylene (Magriotis, P. A.; Brown J. T. *Org. Synth.* **1993**, *72*, 252−264) using the procedure described: (a) Alexakis, A.; Cahiez, G.; Normant, J. F.; Villieras, J. *Bull. Soc. Chim. Fr.* **1977**, 693−698. (b) Vermeer, P.; de Graaf, C.; Meijer, J. *Recl. Trav. Chim. Pays-Bas* **1974**, 93, 24−25.

(34) The unusual amount of silicon migration product **26** obtained in this experiment is likely due to the fact that the reaction mixture was allowed to warm to −20 °C prior to quenching; this procedure was not optimized.

(35) Although a definitive conclusion cannot be reached due to the difference in the aryl sulfide substituent (*p*-tolyl vs phenyl) the allylic proton of the deoxygenation product ***ent*-28d′** had identical chemical shift to the allylic proton of the major isomer of the cuprate addition **28d**.

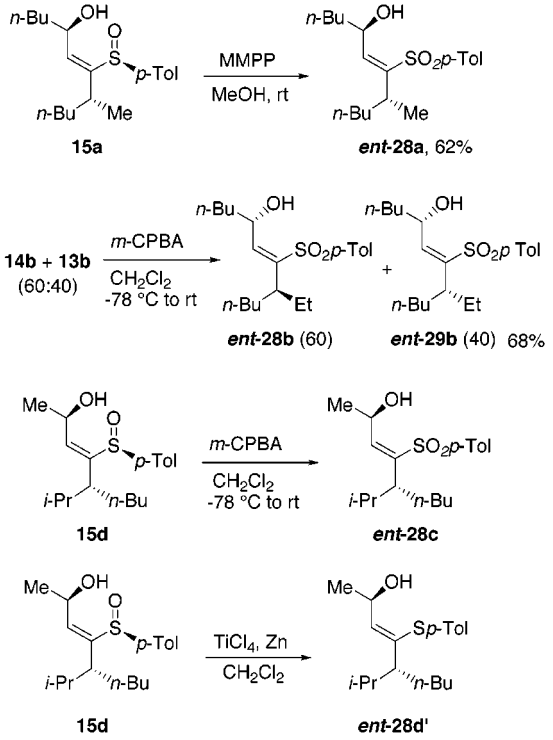
(36) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

Table 2. Reaction of Organocuprates with Epoxy Vinyl Sulfones and Sulfides

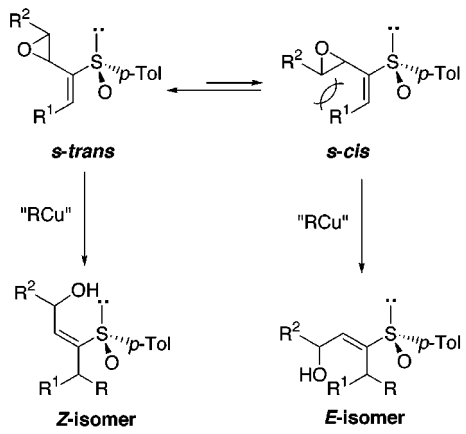
entry	substrate	R^2	R^1	S	RCu[a]	*Z* anti S_N2'	*Z* syn S_N2'	*E* S_N2'	allene[b]
1	**22**	*n*-Bu	*n*-Bu	SO_2-*p*-Tol	MeLi	**28a** (30)	**29a** (30)	**30a** (40)	
2[c]	**22**	*n*-Bu	*n*-Bu	SO_2-*p*-Tol	MeCu·$AlMe_3$	**28a** (67)	**29a** (0)		**18b** (33)
3	**22**	*n*-Bu	*n*-Bu	SO_2-*p*-Tol	MeCuCNLi	**28a** (63)	**29a** (37)		
4[d]	***ent*-22**	*n*-Bu	*n*-Bu	SO_2-*p*-Tol	EtCuCNMgBr	**28b** (63)	**29b** (0)	**30b** (27)	**18b** (10)
5[d]	**23**	Me	*i*-Pr	SO_2-*p*-Tol	*n*-BuCuCNLi	**28c** (70)	**29c** (30)		
6	**27**	Me	*i*-Pr	SPh	*n*-BuCuCNLi	**28d** (60)	**29d** (40)		

[a] Cyanocuprates were prepared from CuCN and the corresponding RLi or RMgBr; MeCu was prepared from CuI and MeLi. All experiments were carried out with an excess of the organocuprate or alkyllithium (6−9 equiv) in Et_2O at −78 °C unless otherwise noted. [b] Product ratios were measured by integration of the ^1H NMR spectra of the crude reaction mixtures. [c] The reaction was carried out in THF and $AlMe_3$ was added at −78 °C to a performed solution of the organocopper reagent. [d] For S_N2' products obtained from ***ent*-22** and **23**, the relative configuration of the allylic carbons in the displacement products is equal (anti/syn) but opposite to the one shown in Scheme 7.

Scheme 8

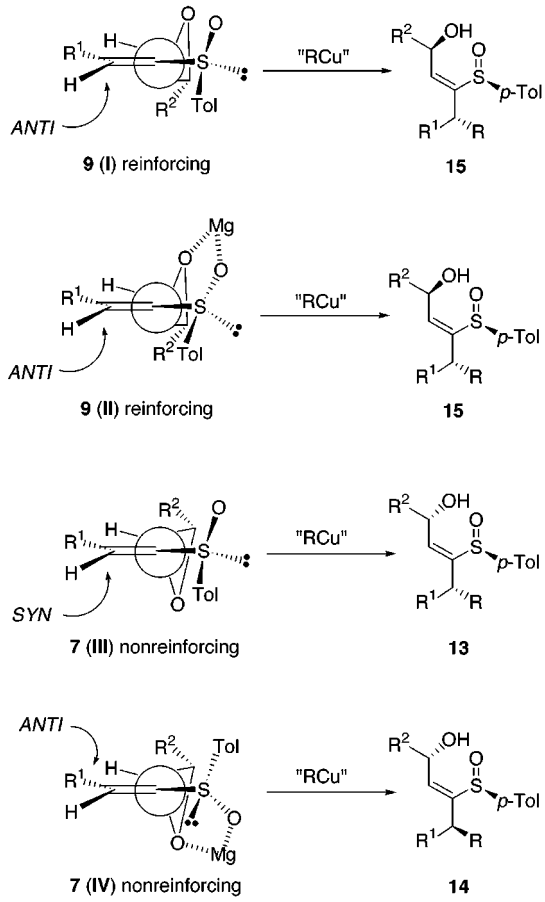


Scheme 9



for the vinyl oxirane functionality will influence the conformational distribution about the C−S bond of the vinyl sulfoxide moiety, in favor of a C=C/lone pair anti conformation.[37]

Scheme 10



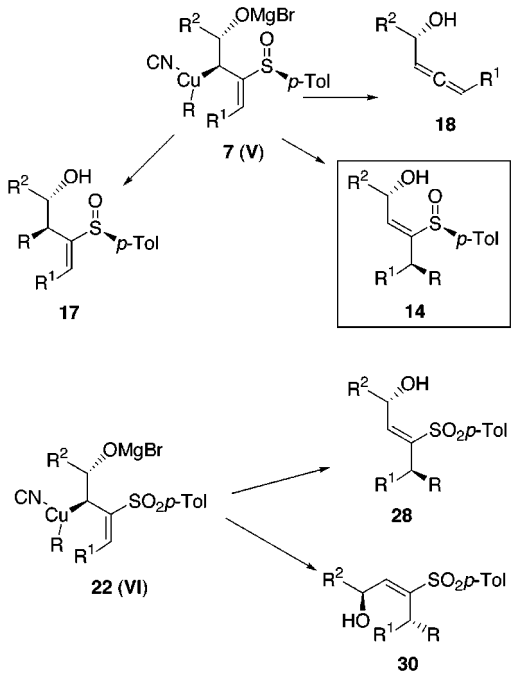
Most S_N2' displacements involving cuprates and vinyl oxiranes take place with high anti facial selectivity,[4a] and this preference has been rationalized in terms of orbital symmetry.[38] Our results may be accounted for in terms of a reinforcing vs nonreinforcing scenario,[39] involving the chiral sulfoxide and the vinyl oxirane moieties. For lithium cyanocuprates, diastereomers **9** afforded products consistent with direct addition of the copper reagent anti to the oxirane and sulfinyl oxygens on conformation **I** (Scheme 10), followed by reductive elimination. Alternatively, the remarkable reversal of facial selectivity found for vinyl oxiranes **7** suggests a nonreinforcing situation in which the sulfinyl group can override the intrinsic anti stereochemical bias of the process to produce 1,4 syn

(37) For a computational treatment of the conformations of α,β-unsaturated sulfoxides, see: Tiezte, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952−7958, and references therein.

(38) For mechanistic proposals, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, 25, 3063−3066. (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422−426.

(39) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

Scheme 11



adducts via conformation **III**.[40] On the other hand, magnesium cyanocuprates display good or modest anti selectivities upon reaction with diastereomers **9** and **7**, respectively; this is consistent with cuprate addition anti to both oxygens on chelated conformations **II** and **IV** with the latter being destabilized by steric interactions between the bulky *p*-tolyl group and the oxirane carbon.

An alternative rationalization for the results found for Grignard-derived cyanocuprates and diastereomers **7** is shown in Scheme 11. It is tempting to speculate about a more significant participation of S_N2 intermediate **V**, relative to when lithium cyanocuprates are used, followed by a suprafacial [1,3] shift and reductive elimination to produce **14**; alternatively, minor products **17** and **18** would derive from **V** by reductive elimination or β-elimination of the sulfinyl group, respectively. This picture also accommodates the exclusive obtention of *Z* S_N2' isomers by admitting some degree of chelation between the sulfinyl oxygen and magnesium, as well as the loss of geometric control observed when sulfones, with a diminished chelating ability, are used.[41,42]

Conclusions

Enantiomerically pure lithiated alkenyl sulfoxides undergo selective condensations with α-alkoxy and α-chloro aldehydes. These adducts are readily transformed into a variety of diastereomeric epoxy vinyl sulfoxides that undergo highly regio- and stereoselective anti or syn S_N2' displacements with lithium alkyl cyanocuprates in accord with a reinforcing/nonreinforcing scenario with the sulfoxide being the predominant element for stereocontrol. This reversal of selectivity under identical reaction conditions is unprecedented and underlines the extremely powerful stereocontrolling character of the readily available and synthetically useful sulfinyl functionality. In addition, the resulting γ-hydroxy α,β-unsaturated sulfoxides are ideally suited for further substrate-directed operations.

Experimental Section

Materials And Methods. All reactions were carried out under a positive pressure of dry argon, using freshly distilled solvents under anhydrous conditions. Reagents and solvents were handled by using standard syringe techniques. Hexane, toluene, CH_2Cl_2, Et_3N, pyridine, and *i*-Pr_2NH were distilled from CaH_2; THF and Et_2O were from sodium and benzophenone. Crude products were purified by flash chromatography on Merck 230−400 mesh silica gel with distilled solvents. Analytical TLC was carried out on Merck (Kieselgel 60F-254) silica gel plates with detection by UV light, iodine, acidic vanillin solution, 10% phosphomolybdic acid solution in ethanol, or acidic ceric ammonium molybdate solution. Commercial methyllithium (low halide solution in ether), *n*-butyllithium (solution in hexane), and phenyllithium (solution in cyclohexane) were purchased from Aldrich and titrated prior to use. Ethylmagnesium bromide was prepared from ethyl bromide and magnesium and titrated prior to use. Copper cyanide, copper iodide, and copper bromide dimethyl sulfide were purchased from Aldrich. Copper cyanide was heated at 90−100 °C in vacuo for 2 h and stored in a desiccator. Cuprate displacements were carried out in a 0.03−0.17 mmol scale. PPh_3 (hexane), *p*-NO_2BzCl (ether), and *p*-NO_2BzOH (benzene) were recently recrystallized prior to use. ^1H and ^{13}C NMR spectra were recorded at 200, 300, 360, or 500 MHz using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextuplet), m (multiplet), ap (apparent), br (broad). Melting points are uncorrected. Optical rotations were measured at 20 °C using a sodium lamp and in $CHCl_3$ solution. The vinyl sulfoxides,[13] chloroaldehyde,[16] lactaldehyde,[11] and mandelaldehyde[11] used in this study were prepared by literature methods.

General Procedure for the Condensation between Vinyl Sulfoxides and α-Functionalized Aldehydes. A round-bottomed flask was charged with anhydrous THF (7 mL/mmol of sulfoxide) and 1.6−2.6 equiv of freshly distilled *i*-Pr_2NH, and cooled to −78 °C. To the above solution was added 1.5−2.5 equiv respectively of *n*-BuLi, and the resulting LDA solution (ca. 0.2−0.4 M) was stirred at this temperature for 10 min. Then, a solution of 1 equiv of vinyl sulfoxide **1** in THF (2−10 mL/mmol) previously dried over 4 Å sieves was added dropwise slowly (ca. 8 min/mmol of sulfoxide) to produce a reddish or yellow solution. After an additional 10 min of stirring at −78 °C, 1.1−3.5 equiv of freshly chromatographed or distilled aldehyde in THF (0.6−1.2 mL/mmol of aldehyde) was added dropwise, and the resulting pale yellow solution was stirred at this temperature for 15−30 min. The reaction mixture was quenched at this temperature with a saturated solution of NH_4Cl (4 mL/mmol) and diluted with EtOAc (3 mL/mmol), and the layers were separated. The aqueous layer was extracted twice with EtOAc (6 mL/mmol). The combined organic extracts were concentrated under reduced pressure to give a crude product which was purified by column chromatography on silica gel using the appropriate mixture of eluents.

Synthesis of (+)-(2*S*,3*S*,S_S)-(4*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-4-(*p*-tolylsulfinyl)hept-4-en-3-ol (4a)

(40) Examples of syn S_N2' displacements involving organocopper reagents and vinyl oxiranes are scarce and generally involve special substrates or organocopper reagents. See: (a) Hudlicky, T.; Tian, X.; Königsberger, K.; Rouden, J. *J. Org. Chem.* **1994**, *59*, 4037−4039. (b) Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, *56*, 5496−5498. (c) Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, *52*, 1106−1113. (d) See ref 25. (e) Ziegler, F. E.; Cady, M. A. *J. Org. Chem.* **1981**, *46*, 122−128. For a related syn S_N2' displacement on a cyclic epoxy vinyl sulfone with MeLi, see refs 32a and 32e.

(41) For leading references on sulfonyl participation in chelated intermediates, see: (a) Yakura, T.; Tanaka, K.; Iwamoto, M.; Nameki, M.; Ikeda, M. *Synlett* **1999**, 1313−1315. (b) Marcantoni, E.; Cingolani, S.; Bartoli, G.; Bosco, M.; Sambri, L *J. Org. Chem.* **1998**, *63*, 3624−3630.

(42) We thank one of the reviewers for pointing out the rationalizations shown in Scheme 10.

and (+)-(2*S*,3*R*,*S*$_S$)-(4*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-4-(*p*-tolylsulfinyl)hept-4-en-3-ol (5a). From a *Z*/*E* mixture of vinyl sulfoxide **1a** (230 mg, 1.10 mmol, 1 equiv) in 11 mL of THF, 1.6 equiv of LDA in 18 mL of THF and with (2*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]propanal **2** (230 mg, 1.22 mmol, 1.1 equiv) in 1.5 mL of THF following the general procedure an 83:17 mixture of diastereomeric alcohols **4a** and **5a** was obtained. Separation by chromatography (30% EtOAc−hexane) afforded 307 mg (0.77 mmol, 70%) of **4a** and 63 mg (0.16 mmol, 14%) of **5a** as yellow oils. Data for **4a**: R_f = 0.46 (30% EtOAc−hexane); $[\alpha]^{20}_D$ = +45.4 (*c* = 0.68); ^{1}H NMR (360 MHz) δ −0.01 (s, 3 H), −0.07 (s, 3 H), 0.83 (s, 9 H), 1.03 (d, 6 H, *J* = 6.6 Hz), 1.06 (d, 3 H, *J* = 6.5 Hz), 2.36 (s, 3 H), 2.88 (d, 1 H, *J* = 5.8 Hz), 3.06 (m, 1 H), 3.66 (quint, 1 H, *J* = 6.0 Hz), 4.14 (ap t, 1 H, *J* = 5.0 Hz), 6.06 (d, 1 H, *J* = 10.5 Hz), 7.45 (d, 2 H, *J* = 7.9 Hz), 7.49 (d, 2 H, *J* = 7.9 Hz); ^{13}C NMR (50 MHz) δ −4.7, −4.7, 17.9, 18.5, 21.3, 22.2, 22.5, 25.7, 28.2, 70.8, 73.7, 125.8, 129.8, 140.5, 140.6, 141.7, 143.7. Data for **5a**: R_f = 0.57 (30% EtOAc−hexane); $[\alpha]^{20}_D$ = +25.2 (*c* = 0.94); ^{1}H NMR (360 MHz) δ 0.09 (s, 6 H), 0.90 (s, 9 H), 0.95 (d, 3 H, *J* = 6.3 Hz), 1.09 (d, 6 H, *J* = 6.6 Hz), 2.39 (s, 3 H), 2.76 (d, 1 H, *J* = 2.8 Hz), 2.83 (m, 1 H), 3.88 (quint, 1 H, *J* = 6.3 Hz), 4.20 (dd, 1 H, *J* = 7.7, 2.7 Hz), 6.42 (d, 1 H, *J* = 10.7 Hz), 7.29 (d, 2 H, *J* = 8.1 Hz), 7.47 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR (50 MHz) δ -4.7, 17.7, 18.0, 21.3, 22.1, 22.4, 25.5, 28.6, 69.8, 73.4, 125.1, 129.3, 140.2, 140.7, 141.3, 143.7, 147.4.

Synthesis of (+)-(2*S*,3*S*,*S*$_S$)-(4*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-4-(*p*-tolylsulfinyl)hept-4-en-2-ol (6). To a stirred solution of allylic alcohol **4a** (210 mg, 0.53 mmol, 1 equiv) in 8 mL of MeOH at room temperature was added Et_3N (0.025 mL, 0.18 mmol, 0.35 equiv). The reaction mixture was heated at reflux for 1 h and allowed to cool to room temperature. A saturated solution of NH_4Cl was added, and the layers were separated. The aqueous layer was extracted three times with 25 mL of EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and reduced to a residual oil. The mixture of alcohols was separated by column chromatography (30% EtOAc−hexane) to afford 80 mg (0.20 mmol, 38%) of **6** as a white solid and 112 mg (0.28 mmol, 53%) of starting material. Data for **6**: R_f = 0.36 (30% EtOAc−hexane); mp 103−106 °C; $[\alpha]^{20}_D$ = +94.1 (*c* = 0.29); ^{1}H NMR (360 MHz) δ −0.06 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 9 H), 1.01 (d, 3 H, *J* = 6.2 Hz), 1.05 (d, 3 H, *J* = 6.6 Hz), 1.06 (d, 3 H, *J* = 6.6 Hz), 1.78 (d, 1 H, *J* = 4.5 Hz), 2.37 (s, 3 H), 2.90 (m, 1 H), 3.01 (m, 1 H), 4.32 (d, 1 H, *J* = 7.1 Hz), 6.38 (d, 1 H, *J* = 10.8 Hz), 7.25 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR (90 MHz) δ −5.3, −4.7, 18.0, 19.4, 21.4, 22.1, 22.5, 25.7, 28.1, 69.3, 74.6, 125.7, 129.9, 140.7, 142.0 (2 C), 143.2.

Synthesis of (+)-(5*R*,6*S*,*S*$_S$)-(7*E*)-5-Chloro-7-(*p*-tolylsulfinyl)dodec-7-en-6-ol (11a) and (−)-(5*S*,6*R*,*S*$_S$)-(7*E*)-5-Chloro-7-(*p*-tolylsulfinyl)dodec-7-en-6-ol (12a). From a *Z*/*E* mixture of vinyl sulfoxide **1c** (896 mg, 4.03 mmol, 1 equiv) in 10 mL of THF with 2.5 equiv of LDA in 28 mL of THF and with racemic 2-chlorohexanal (1780 mg, 13.12 mmol, 3.25 equiv) in 8 mL of THF, following the general procedure, a 46:54 mixture of anti chlorohydrins **11a** and **12a** was obtained. Chromatographic separation (5−50% EtOAc−hexane) afforded 496 mg (1.39 mmol, 34%) of **11a** and 582 mg (1.63 mmol, 40%) of **12a** as yellow oils which were recrystallized from Et_2O−hexane to give white solids. Two minor isomers (syn chlorohydrins) were detected in the chromatographic fraction containing **12a**. The estimated global syn:anti ratio was approximately 8:92. Data for **11a**: R_f = 0.38 (30% EtOAc−hexane); mp 96−97 °C; $[\alpha]^{20}_D$ = +13.6 (*c* = 0.60); ^{1}H NMR (300 MHz) δ 0.84 (t, 3 H, *J* = 7.1 Hz), 0.92 (t, 3 H, *J* = 7.2 Hz), 1.10−1.60 (m, 9 H), 2.01 (m, 1 H), 2.32 (m, 2 H), 2.40 (s, 3 H), 3.53 (ddd, 1 H, *J* = 10.8, 8.4, 2.5 Hz), 4.53 (d, 1 H, *J* = 6.5 Hz), 4.68 (dd, 1 H, *J* = 8.4, 6.5 Hz), 6.59 (t, 1 H, *J* = 7.4 Hz), 7.29 (d, 2 H, *J* = 8.1 Hz), 7.52 (d, 2 H, *J* = 8.3 Hz); ^{13}C NMR (50 MHz) δ 13.9 (2 C), 21.4, 21.8, 22.4, 27.9, 28.8, 30.8, 32.7, 64.2, 76.0, 124.7 (2 C), 129.8 (2 C), 139.1, 139.6, 141.4, 143.2. Data for **12a**: R_f = 0.20 (30% EtOAc−hexane); mp 98−100 °C; $[\alpha]^{20}_D$ = −22.2 (*c* = 0.46); ^{1}H NMR (300 MHz) δ 0.87 (t, 3 H, *J* = 7.1 Hz), 0.87 (t, 3 H, *J* = 7.2 Hz), 1.20−1.68 (m, 9 H), 1.99 (m, 1 H), 2.30−2.37 (m, 2 H), 2.39 (s, 3 H), 3.66 (d, 1 H, *J* = 7.3 Hz), 3.97 (ddd, 1 H, *J* = 10.6, 9.6, 2.4 Hz), 4.57 (t, 1 H, *J* = 7.8 Hz), 6.08 (t, 1 H, *J* = 7.6 Hz), 7.29 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 2 H, *J* = 8.3 Hz); ^{13}C NMR (50 MHz) δ 13.8, 13.9, 21.4, 22.1, 22.4, 28.1, 28.7, 30.9, 33.1, 64.2, 73.8, 125.9 (2 C), 130.0 (2 C), 138.9, 140.1, 142.1, 142.3. Partial data for syn chlorohydrin: ^{1}H NMR (300 MHz) δ 2.90 (m, 1 H), 3.55 (m, 1 H), 4.38 (m, 1 H), 6.67 (t, 1 H, *J* = 7.5 Hz). Partial data of syn chlorohydrin: ^{1}H NMR (300 MHz) δ 2.60 (m, 1 H), 3.55 (m, 1 H), 4.52 (m, 1 H), 6.45 (t, 1 H, *J* = 7.5 Hz).

General Procedure for the Synthesis of Epoxy Vinyl Sulfoxides from Alcohols 4−6. (a) General Procedure for Mesylation. To a vigorously stirred cold (0 °C) solution of 1 equiv of allylic alcohol in pyridine (20 mL/mmol) was added 3 equiv of Ms_2O. The reaction mixture was stirred and warmed to room temperature over 3 h after which time it was poured into an ice-cold saturated solution of $NaHCO_3$ and diluted with CH_2Cl_2 (100 mL/mmol). The aqueous phase was extracted with CH_2Cl_2 (2 times, 20 mL/mmol), and the combined organic layers were washed sequentially with 10% aqueous HCl (4 times, 20 mL/mmol), water (2 times, 15 mL/mmol), and a saturated solution of NaCl (20 mL/mmol). Drying over anhydrous $MgSO_4$, filtration, and evaporation of the solvents under reduced pressure afforded a crude product which was used shortly thereafter for the epoxide formation without further purification. Formation of the mesylates was checked by IR and ^{1}H NMR. In some cases, the crude mesylate was purified by column chromatography to give pure product. **(b) General Procedure for Epoxide Formation from Mesylates.** To a solution of the mesylate derivative in THF (10 mL/mmol) at room temperature was added 1.5 equiv of *n*-Bu_4NF (1.0 M solution in THF), and the reaction mixture immediately turned dark brown. After 5 min the reaction mixture was quenched with a saturated NH_4Cl solution (4 mL/mmol), and the layers were separated. The aqueous layer was extracted with EtOAc (3 times, 4 mL/mmol), and the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude yellow oil residue was purified by column chromatography to give the pure epoxide.

Synthesis of the Mesylate of (+)-(2*S*,3*S*,*S*$_S$)-(4*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-4-(*p*-tolylsulfinyl)-hept-4-en-3-ol (4a′). From alcohol **4a** (370 mg, 0.93 mmol, 1 equiv) in 19 mL of pyridine and Ms_2O (490 mg, 2.82 mmol, 3 equiv), following the general procedure for mesylation, a crude product was obtained which was purified by column chromatography (30% EtOAc−hexane) to afford 330 mg (0.69 mmol, 75%) of the pure mesylate **4a′** as a yellow oil. Data for **4a′**: R_f = 0.40 (30% EtOAc−hexane); ^{1}H NMR (360 MHz) δ 0.002 (s, 3 H), 0.03 (s, 3 H), 0.84 (s, 9 H), 1.04 (d, 3 H, *J* = 6.4 Hz), 1.08 (d, 6 H, *J* = 6.8 Hz), 2.37 (s, 3 H), 2.61 (s, 3 H), 3.02 (m, 1 H), 3.86 (quint, 1 H, *J* = 5.6 Hz), 5.00 (d, 1 H, *J* = 5.4 Hz), 6.40 (d, 1 H, *J* = 11.0 Hz), 7.29 (d, 2 H, *J* = 8.2 Hz), 7.52 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR (90 MHz) δ −5.1, −4.6, 18.0, 19.3, 21.3, 22.0, 25.8, 28.4, 38.2, 70.1, 80.4, 125.3, 129.9, 138.3, 140.1, 141.8 146.6.

Synthesis of (+)-(2*S*,3*R*,*S*$_S$)-(4*E*)-2,3-Epoxy-6-methyl-4-(*p*-tolylsulfinyl)hept-4-ene (7a). From mesylate **4a′**, (177 mg, 0.37 mmol, 1 equiv) in 4 mL of THF and *n*-Bu_4NF (0.56 mL, 0.56 mmol, 1.5 equiv), following the general procedure for epoxide formation, a crude product was obtained which was purified by column chromatography (30% EtOAc−hexane) to afford 89 mg (0.34 mmol, 92%) of pure epoxide **7a** as a pale yellow oil. Data for **7a**: R_f = 0.38 (30% EtOAc−hexane); $[\alpha]^{20}_D$ = +166.8 (*c* = 1.46); ^{1}H NMR (300 MHz) δ 1.09 (d, 6 H, *J* = 6.6 Hz), 1.28 (d, 3 H, *J* = 5.1 Hz), 2.39 (s, 3 H), 2.84 (m, 1 H), 3.08 (d, 1 H, *J* = 2.2 Hz), 3.12 (qd, 1 H, *J* = 5.1, 2.2 Hz), 6.39 (d, 1 H, *J* = 10.2 Hz), 7.28 (d, 2 H, *J* = 8.2 Hz), 7.56 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR (75 MHz) δ 17.3, 21.4, 22.5, 27.9, 54.4, 55.2 125.4, 125.5, 129.1, 129.2, 141.4, 142.4; IR (film) 2961, 2869, 1596, 1464, 1083, 1052, 811 cm^{-1}.

Synthesis of Epoxy Vinyl Sulfoxides from Chlorohydrins 11 and 12. (A) Synthesis of (+)-(5*S*,6*R*,*S*$_S$)-(7*E*)-5,6-Epoxy-7-(*p*-tolylsulfinyl)dodec-7-ene (7e). To a cold (−78 °C) solution of chlorohydrin **11a** (100 mg, 0.28 mmol, 1 equiv) in 8 mL of THF, *n*-BuLi (0.30 mL, 0.42 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred and allowed

to warm to room temperature for 5 h, the reaction was quenched with 2 mL of a saturated solution of NH_4Cl and diluted with 4 mL of EtOAc, and the layers were separated. The organic layer was washed with 4 mL of a saturated solution of NaCl, and the aqueous layer was extracted with 4 mL of EtOAc (3 times). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressured to give a crude product which was purified by column chromatography on silica gel (CH_2Cl_2) to afford 61 mg (0.19 mmol, 68%) of **7e** as a colorless oil. Data for **7e**: R_f = 0.45 (5% EtOAc−CH_2Cl_2); $[\alpha]^{20}_D = +13.7$ ($c = 2.41$); ^{1}H NMR (300 MHz) δ 0.87 (t, 3 H, J = 7.7 Hz), 0.90 (t, 3 H, J = 7.3 Hz), 1.24−1.51 (m, 10 H), 2.31 (m, 2 H), 2.37 (s, 3 H), 3.04 (td, 1 H, J = 5.4, 2.3 Hz), 3.10 (br s, 1 H), 6.53 (td, 1 H, J = 7.8, 1.2 Hz), 7.25 (d, 2 H, J = 8.0 Hz), 7.56 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (50 MHz) δ 13.8 (2 C), 21.4, 22.3, 22.5, 27.8 (2 C), 31.0, 31.5, 53.6, 59.2, 125.5 (2 C), 129.8 (2 C), 135.9, 140.8, 141.0, 141.5.

(B) With NaO-*t*-Bu or KO-*t*-Bu. General Procedure. A round-bottomed flask was charged with 1 equiv of chlorohydrin in THF (20 mL/mmol). The solution was cooled to 0 °C and under strictly anhydrous conditions, a suspension of 1.2 equiv of KO-*t*-Bu or NaO-*t*-Bu (azeotropically dried with benzene) in THF (5 mL/mmol) was added dropwise via syringe. The reaction was stirred at this temperature for 30 min, quenched with a saturated solution of NH_4Cl (20 mL/mmol), and diluted with EtOAc (10 mL/mmol), and the layers were separated. The aqueous layer was extracted twice with EtOAc (10 mL/mmol), and the combined organic extracts were washed twice with a saturated solution of NaCl (20 mL/mmol), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography on silica gel.

Synthesis of (+)-(5*R*,6*S*,*S*$_S$)-(7*E*)-5,6-Epoxy-7-(*p*-tolylsulfinyl)dodec-7-ene (9b). From chlorohydrin **12a** (50 mg, 0.14 mmol, 1 equiv) in 8 mL of THF with NaO-*t*-Bu (16 mg, 0.16 mmol, 1.2 equiv) in 3 mL of THF according to the general procedure **9e** was obtained. Purification by chromatography (5−20% EtOAc−hexane) afforded 40 mg (0.12 mmol, 89%) of epoxide **9b** as a colorless oil. Data for **9b**: R_f = 0.36 (30% EtOAc−hexane); $[\alpha]^{20}_D = +54.4$ ($c = 1.43$); ^{1}H NMR (300 MHz) δ 0.80 (t, 3 H, J = 6.9 Hz), 0.91 (t, 3 H, J = 7.2 Hz), 1.08−1.52 (m, 10 H), 2.38 (m, 2 H), 2.38 (s, 3 H), 2.49 (td, 1 H, J = 5.6, 2.3 Hz), 3.21 (d, 1 H, J = 1.8 Hz), 6.59 (td, 1 H, J = 7.7, 0.9 Hz), 7.26 (d, 2 H, J = 8.0 Hz), 7.48 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (50 MHz) δ 13.8 (2 C), 21.4, 22.3 (2 C), 27.5, 27.7, 31.1, 31.5, 53.3, 58.3, 125.8 (2 C), 129.9 (2 C), 139.1, 139.6, 140.3, 141.7; IR (film) 2900, 1650, 1600, 1490, 1460, 1380, 1090, 1050, 1010, 810 cm^{-1}.

Synthesis of Epoxy Vinyl Sulfones by Oxidation of Epoxy Vinyl Sulfoxides. General Procedure for Oxidation of Sulfoxides to Sulfones with MMPP. Monoperoxyphthalic acid, magnesium salt hexahydrate (MMPP), (1.5 equiv) was added to a cold solution (0 °C) of sulfoxide (1 equiv) in MeOH (10 mL/mmol). The mixture was stirred, allowed to warm to room temperature, and monitored by TLC until starting material disappearance. The solvent was removed under reduced pressure, the residue was dissolved in EtOAc, and a 5% aqueous solution of $NaHCO_3$ (5 mL/mmol) was added. The aqueous layer was extracted with EtOAc (5 mL/mmol), and the combined organic extracts were washed with a saturated solution of NaCl (4 mL/mmol), dried over $MgSO_4$, and concentrated under reduced pressure to give a crude product which was purified by chromatography on silica gel.

Synthesis of (+)-(5*S*,6*R*)-(7*E*)-5,6-Epoxy-7-(*p*-tolylsulfonyl)dodec-7-ene (22). From epoxy sulfoxide **7e** (12 mg, 0.037 mmol, 1 equiv) in 0.5 mL of methanol and MMPP (27.8 mg, 0.056 mmol, 1.5 equiv) following the general procedure for oxidation with MMPP (4 h) epoxy sulfone **22** was obtained. Purification by chromatography (5−10% EtOAc−hexane) afforded 8 mg (0.024 mmol, 64%) of **22** as a colorless oil. Data for **22**: R_f = 0.52 (30% EtOAc−hexane); $[\alpha]^{20}_D = +17.4$ (c = 0.70); ^{1}H NMR (300 MHz) δ 0.86 (t, 3 H, J = 7.0 Hz), 0.90 (t, 3 H, J = 7.2 Hz), 1.24−1.48 (m, 10 H), 2.38 (m, 2 H), 2.41 (s, 3 H), 2.74 (td, 1 H, J = 5.5, 2.3 Hz), 3.28 (m, 1 H), 7.02 (td, 1 H, J = 7.8, 0.7 Hz), 7.30 (d, 2 H, J = 8.0 Hz), 7.72 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (50 MHz) δ 13.8, 13.9, 21.6, 22.4 (2 C), 27.7 (2 C), 30.7, 31.5, 53.1, 59.1, 127.9 (2 C), 129.7 (2 C), 137.4, 137.5, 144.2, 145.9.

Synthesis of (−)-(2*S*,3*S*)-(4*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-4-(phenylsulfenyl)hept-4-en-3-ol (25) and (+)-(2*S*,3*S*)-(4*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-4-(phenylsulfenyl)hept-4-en-2-ol (26). To a cold (−78 °C) solution of vinyl idodide **24** (204 mg, 0.67 mmol, 1 equiv) in 7 mL of THF was added *t*-butyllithium (0.78 mL, 1.30 mmol, 1.95 equiv, 1.7 M in hexanes) dropwise. The resulting dark brown solution was stirred for 5 min, and a solution of (2*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propanal (**2**) (125 mg, 0.67 mmol, 1 equiv) in 0.5 mL of THF was then added dropwise. After an additional 30 min of stirring, the reaction was allowed to warm to −20 °C at which time 25 mL of water was added. The aqueous phase was extracted with EtOAc (25 mL) two times, and the combined organic layers were washed with 25 mL of a saturated solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced presure to give a crude product which was purified by column chromatography on silica gel to afford 140 mg (0.38 mmol, 57%) of **25** and 47 mg (0.13 mmol, 19%) of **26**. Data for **25**: R_f = 0.31 (5% EtOAc−hexane); $[\alpha]^{20}_D = -50.7$ ($c = 1.61$); ^{1}H NMR (360 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 0.97 (d, 3 H, J = 6.6 Hz), 1.01 (d, 3 H, J = 6.6 Hz), 1.14 (d, 3 H, J = 6.2 Hz), 2.49 (d, 1 H, J = 7.4 Hz), 2.88 (m, 1 H), 3.97 (m, 1 H), 4.42 (dd, 1 H, J = 7.4, 5.3 Hz), 5.75 (d, 1 H, J = 10.2 Hz), 7.29−7.15 (m, 3 H), 7.38 (d, 2 H, J = 8.0 Hz); ^{13}C NMR (90 MHz) δ −4.7, −4.5, 18.0, 19.3, 22.7, 25.8, 28.5, 70.9, 74.8, 126.1, 128.9, 129.4, 131.1, 133.4, 148.9. Data for **26**: R_f = 0.20 (5% EtOAc−hexane); $[\alpha]^{20}_D = +48.1$ ($c = 0.74$); ^{1}H NMR (360 MHz) δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.92 (s, 9 H), 0.93 (d, 6 H, J = 6.6 Hz), 1.26 (d, 3 H, J = 6.2 Hz), 1.79 (br s, 1 H), 2.77 (m, 1 H), 3.90 (m, 1 H), 4.41 (d, 1 H, J = 6.8 Hz), 5.25 (d, 1 H, J = 10.5 Hz), 7.31 (m, 3 H), 7.44 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (90 MHz) δ -4.9, −4.6, 18.2, 19.0, 22.5, 23.0, 25.8, 28.5, 69.7, 75.8, 127.4, 129.1, 132.8, 134.8, 135.0, 141.1.

Synthesis of the Mesylate of (2*S*,3*S*)-(4*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-4-(phenylsulfenyl)hept-4-en-3-ol (25′). From alcohol **25** (140 mg, 0.38 mmol, 1 equiv) in 7.5 mL of pyridine and Ms_2O (198 mg, 1.14 mmol, 3 equiv) following the general procedure of mesylation a crude product **25′** was obtained which was used with no further purification. Data for **25′**: R_f = 0.54 (20% EtOAc−hexane); ^{1}H NMR (300 MHz) δ 0.09 (s, 3 H), 0.11 (s, 3 H), 1.02 (d, 3 H, J = 6.5 Hz), 1.04 (d, 3 H, J = 6.5 Hz), 1.30 (d, 3 H, J = 7.3 Hz), 2.64 (s, 3 H), 2.91 (m, 1 H), 4.25 (m, 1 H), 5.28 (d, 1 H, J = 6.9 Hz), 5.89 (d, 1 H, J = 10.3 Hz), 7.22−7.32 (m, 3 H), 7.43 (d, 2 H, J = 8.1 Hz); IR (film): 2957, 2859, 1471, 1360, 1254, 1175, 1115, 932, 831 cm^{-1}.

Synthesis of (−)-(2*S*,3*R*)-(4*E*)-2,3-Epoxy-6-methyl-4-(phenylsulfenyl)-4-heptene (27). From the crude mesylate derivative **25′** in 4 mL of THF and with *n*-Bu_4NF (0.56 mL, 0.56 mmol, 1.5 equiv) following the general procedure for epoxide formation, a crude product was obtained which was purified by column chromatography (20% EtOAc−hexane) to afford 84 mg (0.36 mmol, 94% two steps) of pure epoxide **27** as a colorless oil. Data for **27**: R_f = 0.63 (20% EtOAc−hexane); $[\alpha]^{20}_D = -37.8$ ($c = 1.09$); ^{1}H NMR (360 MHz) δ 1.07 (d, 6 H, J = 6.6 Hz), 1.22 (d, 3 H, J = 5.2 Hz), 2.98 (m, 1 H), 3.09 (dq, 1 H, J = 5.2, 2.2 Hz), 3.47 (d, 1 H, J = 2.0 Hz), 6.06 (d, 1 H, J = 10.2 Hz), 7.15−7.29 (m, 5 H); ^{13}C NMR (90 MHz) δ 17.2, 22.7, 22.3, 28.8, 54.9, 57.2, 126.0, 127.1, 128.6, 128.8, 136.6, 151.9.

General Procedure for S_N2' Addition of Organocuprate Reagents to Vinyl Epoxides. A round-bottomed flask was charged with 6−9 equiv of CuCN or CuI in Et_2O (50 mL/mmol) under argon. The resulting suspension was cooled to the appropriate temperature (0 °C or −20 °C), and the organolithium or Grignard reagent was added dropwise and vigorously stirred for 15 min. Upon formation of the organocuprate reagent, this suspension was cooled to −78 °C, a solution of vinyl epoxide in Et_2O (26 mL/mmol) was added dropwise, and the reaction mixture was slowly allowed to

warm for 30 min. After this time the cold bath was removed, and the reaction mixture was monitored by TLC until disappearance of starting material. Then, the reaction was quenched with a saturated solution of $Na_2S_2O_4$ solution, and the layers were separated. The aqueous layer was extracted twice with EtOAc (5 mL/mmol), and the combined organic extracts were washed twice with a saturated solution of NaCl (5 mL/mmol). After drying over $MgSO_4$ and concentration under reduced pressure, the crude product was purified by column chromatography on silica gel using the appropriate mixture of solvents as eluents. When the reaction was performed with Gilman cuprates (Me_2CuLi) or under not strictly anhydrous conditions, hydroxy allenes byproducts (as mixtures of diastereomers) were obtained as major components of the reaction mixture. Formation of these compounds was also observed when cyanocuprates were prepared from Grignard reagents, especially when commercial EtMgBr was used. Finally, the isolation of these compounds was difficult in some cases (R^1 = alkyl) due to its high volatility.

Synthesis of 6,7-Dodecadien-5-ol (mixture of diastereomers) (18b). Following the general procedure, from **7e** (18 mg, 0.056 mmol, 1 equiv) with 6 equiv of $Me_2CuLi{\cdot}LiI$ preformed at 0 °C, allene **18b** (75:25 mixture of diastereomers) was obtained as the major component of a mixture with traces of S_N2' addition products after 1 h 30 min. Chromatographic purification (5−30% EtOAc−hexane) afforded pure products. Data for allene **18b** (major isomer): R_f = 0.47 (CH_2Cl_2); ^{1}H NMR (200 MHz) δ 0.83−0.93 (m, 6 H), 1.29−1.49 (m, 8 H), 1.50−1.62 (m, 2 H), 1.95−2.05 (m, 2 H), 2.30 (m, 1 H), 4.11 (qd, 1 H, J = 6.1, 2.3 Hz), 5.20 (tt, 1 H, J = 6.0, 3.0 Hz), 5.27 (qd, 1 H, J = 6.5, 2.2 Hz); ^{13}C NMR (50 MHz) δ 13.8, 14.0, 22.1, 22.6, 27.6, 28.5, 31.3, 37.3, 69.9, 94.4, 95.9, 202.0. Data for allene **18b** (minor isomer): R_f = 0.40 (CH_2Cl_2); ^{1}H NMR (200 MHz) δ 0.83−0.93 (m, 6 H), 1.29−1.49 (m, 8 H), 1.50−1.62 (m, 2 H), 1.95−2.05 (m, 2 H), 2.30 (m, 1 H), 4.11 (qd, 1 H, J = 6.1, 2.3 Hz), 5.20 (tt, 1 H, J = 6.0, 3.0 Hz), 5.27 (qd, 1 H, J = 6.5, 2.2 Hz); ^{13}C NMR (50 MHz) δ 13.8, 14.0, 22.1, 22.6, 27.6, 28.4, 31.3, 37.2, 70.3, 94.1, 95.7, 202.3.

Synthesis of (−)-(5*S*,8*R*,*S*$_S$)-(6*Z*)-8-Methyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (13a) and (5*S*,8*S*,*S*$_S$)-(6*Z*)-8-Methyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (14a). Following the general procedure, from **7e** (43 mg, 0.133 mmol, 1 equiv) with 6 equiv of MeCuCNLi preformed at 0 °C, a not readily separable 85:15 mixture of S_N2' addition products **13a** and **14a** was obtained after 2 h. Chromatographic purification (5−30% EtOAc−hexane) afforded 31 mg (0.092 mmol, 69% combined) of products as a white solid. Data for **13a** (from an 85:15 mixture of **13a** and **14a**): R_f = 0.25 (30% EtOAc−hexane); $[\alpha]^{20}_D$ = −114.3 (c = 1.75); ^{1}H NMR (300 MHz) δ 0.65 (d, 3 H, J = 7.0 Hz), 0.87 (t, 3 H, J = 6.9 Hz), 0.95 (t, 3 H, J = 7.1 Hz), 1.22−1.80 (m, 12 H), 2.20 (br s, 1 H), 2.40 (s, 3 H), 2.53 (sext, 1 H, J = 6.9 Hz), 5.06 (td, 1 H, J = 8.5, 6.7 Hz), 5.88 (d, 1 H, J = 8.8 Hz), 7.28 (d, 2 H, J = 8.1 Hz), 7.59 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (75 MHz) δ 14.0 (2 C), 21.3, 22.2, 22.5, 22.7, 27.4, 29.3, 29.6, 38.0, 38.1, 67.6, 124.7 (2 C), 129.6 (2 C), 136.7, 139.4, 140.6, 153.4; IR (CCl_4) 3360, 2960, 2930, 2860, 1600, 1490, 1460, 1380, 1080, 1015, 790 cm^{-1}. Partial data for **14a** (from an 85:15 mixture of **13a** and **14a**): ^{1}H NMR (300 MHz) δ 1.09 (d, 3 H, J = 6.9 Hz), 5.87 (d, 2 H, J = 8.7 Hz).

Synthesis of (−)-(5*S*,8*R*,*S*$_S$)-(6*Z*)-8-Methyl-7-(*p*-tolylsulfinyl)-dodec-6-en-5-ol (13b). Following the general procedure, from **7e** (10 mg, 0.031 mmol, 1 equiv) with 6 equiv of EtCuCNLi (prepared from CuCN and EtLi) preformed at −20 °C, S_N2' addition product **13b** was obtained after 1 h 30 min as a single isomer. Chromatographic purification (5−30% EtOAc−hexane) afforded 9 mg (0.025 mmol, 82%) of **13b** as a colorless oil. Data for **13b**: R_f = 0.24 (20% EtOAc−hexane); $[\alpha]^{20}_D$ = −73.8 (c = 0.83); ^{1}H NMR (300 MHz) δ 0.37 (t, 3 H, J = 7.3 Hz), 0.83 (t, 3 H, J = 6.9 Hz), 0.91 (t, 3 H, J = 7.0 Hz), 0.99 (m, 2 H), 1.14−1.80 (m, 12 H), 2.28 (quint, 1 H, J = 6.8 Hz), 2.37 (s, 3 H), 5.05 (td, 1 H, J = 8.8, 6.7 Hz), 5.78 (d, 1 H, J = 8.7 Hz), 7.25 (d, 2 H, J = 8.0 Hz), 7.56 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 11.0, 14.0, 21.3, 22.5, 22.8, 27.5, 27.8, 29.0, 35.6, 36.8, 38.0, 67.6, 124.9 (2 C), 129.6 (2 C), 136.6, 139.3, 140.8, 151.5.

Synthesis of (−)-(2*S*,5*R*,*S*$_S$)-(3*Z*)-5-Isopropyl-4-(*p*-tolylsulfinyl)non-3-en-2-ol (13c) and (2*S*,5*S*,*S*$_S$)-(3*Z*)-5-Isopropyl-4-(*p*-tolylsulfinyl)non-3-en-2-ol (14c). Following the general procedure, from **7a** (40 mg, 0.151 mmol, 1 equiv) with 9 equiv of *n*-BuCuCNLi preformed at 0 °C, an 88:12 separable mixture of S_N2' addition products **13c** and **14c**, was obtained. Chromatographic separation afforded 33 mg (0.102 mmol, 68%, combined) of **13c** and **14c** as colorless oils. Data for **13c**: R_f = 0.45 (50% EtOAc−hexane); $[\alpha]^{20}_D$ = −28.1 (c = 1.26); ^{1}H NMR (300 MHz) δ 0.57 (d, 3 H, J = 7.2 Hz), 0.81 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.8 Hz), 1.01−1.30 (m, 6H), 1.43 (d, 3 H, J = 6.2 Hz), 1.82 (m, 1 H), 2.15 (m, 1 H), 2.36 (s, 3 H), 2.57 (br s, 3 H), 5.35 (dq, 1 H, J = 8.8. 6.2 Hz), 5.80 (d, 1 H, J = 8.8 Hz), 7.25 (d, 2 H, J = 8.2 Hz), 7.56 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (75 MHz) δ 13.8, 18.2, 20.9, 21.3, 22.6, 24.7, 28.6, 31.0, 32.7, 41.4, 64.03, 124.9, 129.5, 138.1, 140.6, 141.0, 149.0. Data for **14c**: R_f = 0.25 (50% EtOAc−hexane); ^{1}H NMR (360 MHz) δ 0.61 (t, 3 H, J = 7.3 Hz), 0.86 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.8 Hz), 0.90−1.15 (m, 6 H), 1.41 (d, 3 H, J = 6.3 Hz), 1.82 (m, 1 H), 2.12 (m, 1 H), 2.39 (s, 3 H), 2.51 (br s, 1 H), 5.40 (m, 1 H), 5.89 (d, 1 H, J = 8.7 Hz), 7.28 (d, 2 H, J = 8.2 Hz), 7.43 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (90 MHz) δ 13.8, 18.1, 21.2, 21.3, 22.6, 23.0, 28.4, 29.0, 32.2, 41.3, 63.2, 125.0, 129.6, 129.7, 138.7, 139.2, 141.2, 148.3.

Synthesis of (−)-(5*S*,8*R*,*S*$_S$)-(6*Z*)-8-Phenyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (13f) and (−)-(5*S*,8*S*,*S*$_S$)-(6*Z*)-8-Phenyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (14f). Following the general procedure, from **7f** (53 mg, 0.155 mmol, 1 equiv) with 9 equiv of *n*-BuCuCNLi preformed at −20 °C, a not readily separable 91:9 mixture of S_N2' addition products **13f** and **14f** was obtained after 1.25 h. Chromatographic purification (5−30% EtOAc−hexane) afforded 51 mg (0.128 mmol, 82% combined) of pure mixture of products as a colorless oil. Separation of these isomers required preparative TLC using 50% Et_2O−hexane as eluent. When the addition was performed at −100 °C a 96:4 mixture of S_N2' products **13f**,**14f** was obtained. The yield was not determined. Data for **13f**: R_f = 0.45 (65% Et_2O−hexane); $[\alpha]^{20}_D$ = −22.8 (c = 1.14); ^{1}H NMR (300 MHz) δ 0.61 (t, 3 H, J = 7.1 Hz), 0.81−1.70 (m, 15 H), 2.20 (br s, 1 H), 2.38 (s, 3 H), 3.66 (dd, 1H, J = 9.4, 5.9 Hz), 4.96 (ap q, 1 H, J = 8.5 Hz), 5.89 (d, 1 H, J = 8.7 Hz), 7.12−7.23 (m, 5 H), 7.27 (d, 2 H, J = 8.1 Hz), 7.58 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 13.6, 13.9, 21.2, 22.1, 22.4, 27.2, 29.5, 35.4, 37.7, 41.3, 67.5, 124.9 (2 C), 126.2, 127.8 (2 C), 128.3 (2 C), 129.6 (2 C), 138.6, 139.3, 140.9, 142.9, 151.2. Data for **14f**: R_f = 0.48 (65% Et_2O−hexane); $[\alpha]^{20}_D$ = −75.6 (c = 0.26); ^{1}H NMR (300 MHz) δ 0.80 (t, 3 H, J = 7.0 Hz), 0.92, (t, 3 H, J = 7.0 Hz), 1.10−1.85 (m, 12 H), 2.00 (br s, 1 H), 2.28 (s, 3 H), 3.65 (dd, 1 H, J = 8.6, 6.8 Hz), 5.05 (m, 1 H), 6.06 (d, 1 H, J = 8.7 Hz), 6.68−6.72 (m, 2 H), 6.97−7.00 (m, 3 H), 7.03 (d, 2 H, J = 8.1 Hz), 7.30 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 13.9, 14.0, 21.2, 22.5 (2 C), 27.4, 29.7, 36.8, 37.8, 41.5, 67.6, 124.8 (2 C), 125.8, 127.5 (2 C), 128.0 (2 C), 129.4 (2 C), 138.1, 138.8, 140.5, 142.3, 150.6.

Synthesis of (−)-(5*R*,8*R*,*S*$_S$)-(6*Z*)-8-Methyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (15a) and (5*R*,8*S*,*S*$_S$)-(6*Z*)-8-Methyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (16a). Following the general procedure, from **9b** (45 mg, 0.140 mmol, 1 equiv) with 6 equiv of MeCuCNLi preformed at 0 °C, a separable 96:4 mixture of S_N2' addition products **15a** and **16a** was obtained after 1.5 h. Chromatographic purification (5−30% EtOAc−hexane) afforded 42 mg (0.125 mmol) of **15a** and approximately 2 mg (0.006 mmol) of **16a** (93% combined) as colorless oils. Data for **15a**: R_f = 0.37 (30% EtOAc−hexane); $[\alpha]^{20}_D$ = −107.0 (c =1.33); ^{1}H NMR (300 MHz) δ 0.63 (d, 3 H, J = 6.8 Hz), 0.82 (t, 3 H, J = 6.7 Hz), 0.93 (t, 3 H, J = 7.0 Hz), 1.16−1.72 (m, 12 H), 2.37 (s, 3 H), 2.33−2.42 (sext, 1 H, J = 6.7 Hz), 2.60 (s, 1 H), 5.10 (td, 1 H, J = 8.2, 4.7 Hz), 5.97 (d, 3 H, J = 8.4 Hz), 7.26 (d, 2 H, J = 8.0 Hz), 7.46 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (50 MHz) δ 14.0, 21.3, 22.5 (2 C), 22.6, 27.6, 29.4, 30.0, 36.9, 37.8, 66.8, 125.0 (2 C), 129.8 (2 C), 138.3, 139.1, 141.1, 151.3. Partial data for **16a**: R_f = 0.10 (30% EtOAc−hexane); ^{1}H NMR (300 MHz): δ 0.65 (t, 3 H, J = 7.2 Hz), 0.75−1.09 (m, 6 H), 1.04 (d, 3 H, J = 6.8 Hz), 1.23−1.80 (m, 9 H), 2.33 (sext, 1 H,

J = 6.8 Hz), 2.38 (s, 3 H), 2.66 (br s, 1 H), 5.10 (m, 1 H), 5.96 (d, 1 H, J = 8.4 Hz), 7.27 (d, 2 H, J = 8.1 Hz), 7.46 (d, 2 H, J = 8.2 Hz).

Synthesis of (−)-(5*R*,8*R*,*S*$_S$)-(6*Z*)-8-Ethyl-7-(*p*-tolylsulfinyl)-dodec-6-en-5-ol (15b), (5*R*,8*S*,*S*$_S$)-(6*Z*)-8-Ethyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (16b), and (5*R*,6*R*,S$_S$)-(7*E*)-6-Ethyl-7-(*p*-tolylsulfinyl)dodec-7-en-5-ol (17b′). Following the general procedure, from **9b** (42 mg, 0.130 mmol, 1 equiv) with 6 equiv of EtCuCNMgBr preformed at −20 °C, an 81:8:11 mixture of S_N2', S_N2 addition products and allene byproduct (**15b**,**16b**):**17b′**:**18b** was obtained after 2 h. Chromatographic separation (CH_2Cl_2-15% EtOAc−CH_2Cl_2) afforded 29 mg (0.083 mmol, 64%, combined) of **15b**,**16b** as a separable 95:5 mixture of isomers. Data for **15b**: R_f = 0.12 (5% EtOAc−CH_2Cl_2); $[\alpha]^{20}_D$ = −50.5 (c = 1.39); ^{1}H NMR (300 MHz) δ 0.39 (t, 3 H, J = 7.4 Hz), 0.80 (t, 3 H, J = 6.8 Hz), 0.92 (t, 3 H, J = 7.0 Hz), 1.00 (quint, 2 H, J = 7.3 Hz), 1.17−1.73 (m, 12 H), 2.16 (sext, 1 H, J = 6.8 Hz), 2.37 (s, 3 H), 2.85 (d, 1 H, J = 3.3 Hz), 5.10 (m, 1 H), 5.90 (d, 1 H, J = 8.3 Hz), 7.25 (d, 2 H, J = 8.7 Hz), 7.47 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 10.9, 14.0, 21.3, 22.7, 27.6, 28.0, 29.1, 35.4, 37.0, 66.7, 125.3 (2 C), 129.7 (2 C), 138.3, 139.0, 141.3, 149.1. Partial data for **16b**: R_f = 0.12 (5% EtOAc−CH_2Cl_2); ^{1}H NMR (300 MHz) δ 0.60 (t, 3 H, J = 6.7 Hz), 5.10 (m, 1 H), 5.78 (d, 1 H, J = 8.3 Hz). Partial data for **17b′**: ^{1}H NMR (200 MHz) δ 6.37 (t, 1 H, J = 7.3 Hz).

Synthesis of (−)-(2*R*,5*R*,*S*$_S$)-(3*Z*)-5-Isopropyl-4-(*p*-tolylsulfinyl)non-3-en-2-ol (15d). Following the general procedure, from **9a** (24 mg, 0.091 mmol, 1 equiv) with 9 equiv of *n*-BuCuCNLi preformed at 0 °C, S_N2' addition product **15d** was obtained as a single isomer. Chromatographic purification (30% EtOAc−hexane) afforded 22 mg of **15d** (0.068 mmol, 75%) as a colorless oil. Data for **15d**: R_f = 0.23 (30% EtOAc−hexane); $[\alpha]^{20}_D$ = −120.9 (c = 0.34); ^{1}H NMR (300 MHz) δ 0.35 (m, 2 H), 0.60 (t, 3 H, J = 7.2 Hz), 0.84 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.8 Hz), 1.12−1.05 (m, 4 H), 1.40 (d, 3 H, J = 6.3 Hz), 1.82 (m, 1 H), 2.13 (m, 1 H), 2.39 (s, 3 H), 3.06 (d, 1 H, J = 2.9 Hz), 5.40 (m, 1 H), 5.88 (d, 1 H, J = 8.8 Hz), 7.28 (d, 2 H, J = 8.2 Hz), 7.42 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (75 MHz) δ 13.9, 18.2, 21.2, 21.3, 22.6, 23.3, 28.6, 29.3, 32.3, 41.5, 63.2, 125.0, 129.6, 139.3, 141.0, 147.6.

Synthesis of (−)-(5*R*,8*R*,*S*$_S$)-(6*Z*)-8-Phenyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (16c). Following the general procedure, from **9c** (57 mg, 0.167 mmol, 1 equiv) with 9 equiv of *n*-BuCuCNLi preformed at −20 °C, S_N2' addition product **16c** was obtained as a single isomer after 1 h 30 min. Chromatographic purification (5−20% EtOAc−hexane) afforded 58 mg (0.146 mmol, 87%) of **9e** as a colorless oil. Data for **16c**: R_f = 0.25 (30% EtOAc−hexane); $[\alpha]^{20}_D$ = −8.3 (c = 1.26); ^{1}H NMR (300 MHz) δ 0.62 (t, 3 H, J = 7.2 Hz), 0.77−1.77 (m, 15 H), 2.39 (s, 3 H), 2.62 (br s, 1 H), 3.54 (dd, 1 H, J = 9.4, 5.6 Hz), 5.02 (m, 1 H), 6.01 (d, 1 H, J = 8.5 Hz), 7.09−7−24 (m, 5 H), 7.27 (d, 2 H, J = 8.1 Hz), 7.50 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (75 MHz) δ 13.7, 14.0, 21.3, 22.1, 22.6, 27.6, 29.5, 36.0, 36.6, 41.2, 66.7, 125.1 (2 C), 216.2, 127.8 (2 C), 128.1, 128.3 (2 C), 129.7 (2 C), 140.2, 141.3, 142.6, 148.7.

Synthesis of the *p*-Nitrobenzoate of (−)-(5*R*,8*R*,*S*$_S$)-(6*Z*)-8-methyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (21). From **15a** (9 mg, 0.026 mmol, 1 equiv), Et_3N (5.6 μL, 0.04 mmol, 1.5 equiv), DMAP, and *p*-nitrobenzoyl chloride (6.4 mg, 0.034 mmol, 1.3 equiv) in 0.2 mL of CH_2Cl_2, following the general procedure (24 h), a crude product was obtained. Subsequent purification by column chromatography (10% EtOAc−hexane) afford 9.25 mg (0.019 mmol, 73%) of **21** as a yellow oil which was crystallized from Et_2O−hexane to produce a white solid. Data for **21**: R_f = 0.40 (30% EtOAc−hexane); mp 105−109 °C; $[\alpha]^{20}_D$ = −91.2 (c = 0.59); ^{1}H NMR (200 MHz) δ 0.59 (d, 3 H, J = 6.8 Hz), 0.72 (t, 3 H, J = 6.7 Hz), 0.92 (t, 3 H, J = 6.7 Hz), 1.06−1.49 (m, 10 H), 1.80 (m, 1 H), 1.95 (m, 1 H), 2.37 (s, 3 H), 2.57 (q, 1 H, J = 6.9 Hz), 5.90 (d, 1 H, J = 9.2 Hz), 6.44 (m, 1 H), 7.26 (d, 2 H, J = 8.2 Hz), 7.45 (d, 2 H, J = 8.2 Hz), 8.24 (ap q, 4 H, J = 6.3 Hz); ^{13}C NMR (50 MHz) δ 13.9, 14.1, 21.4, 22.5, 22.7, 27.4, 29.2, 29.3, 29.7, 34.6, 38.0, 71.3, 123.5 (2 C), 123.6 (2 C), 124.6 (2 C), 129.8 (2 C), 130.8, 135.6, 139.3, 141.0, 150.6, 155.3, 163.7.

Synthesis of the *p*-Nitrobenzoate of (−)-(5*S*,8*R*,*S*$_S$)-(6*Z*)-8-Methyl-7-(*p*-tolylsulfinyl)dodec-6-en-5-ol (20). From a not readily separable 85:15 mixture of alcohols **13a** and **14a** (12 mg, 0.034 mmol, 1 equiv), Et_3N (11 μL, 0.085 mmol, 2.5 equiv), DMAP (2 crystals), and *p*-nitrobenzoyl chloride (13 mg, 0.068 mmol, 2 equiv), in 0.3 mL of CH_2Cl_2, following the general procedure (30 min), a separable 85:15 mixture of *p*-nitrobenzoates was obtained. Chromatographic separation (5−30% EtOAc−hexane) afforded 12 mg (0.027 mmol, 80%) of **20** as a white solid. Product **20′** was accidentally lost during purification. Data for **20**: R_f = 0.37 (15% EtOAc−hexane); $[\alpha]^{20}_D$ = −100.7 (c = 1.00); ^{1}H NMR (300 MHz) δ 0.52 (d, 3 H, J = 6.9 Hz), 0.86 (t, 3 H, J = 6.9 Hz), 0.94 (t, 3 H, J = 7.0 Hz), 1.21−2.05 (m, 12 H), 2.35 (s, 3 H), 2.50 (sext, 1 H, J = 6.9 Hz), 5.90 (d, 1 H, J = 9.0 Hz), 6.45 (dt, 1 H, J = 8.9, 6.7 Hz), 7.24 (d, 2 H, J = 8.2 Hz), 7.60 (d, 2 H, J = 8.2 Hz), 8.23 (d, 2 H, J = 8.9 Hz), 8.31 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (75 MHz) δ 13.9, 21.3, 22.2, 22.4, 22.7, 27.1, 29.4, 29.7, 35.0, 38.6, 73.0, 123.6 (2 C), 124.6 (2 C), 129.5 (2 C), 130.8 (2 C), 132.9, 135.6, 138.8, 140.8, 150.7, 154.4, 163.9.

Mitsunobu Protocol To Transform Alcohol 15a into *p*-Nitrobenzoate 20. To a cold solution (0 °C) of alcohol **15a** (5 mg, 0.015 mmol, 1 equiv) in 0.5 mL of THF was added recently recrystallized PPh_3 (19 mg, 0.075 mmol, 5 equiv), *p*-nitrobenzoic acid (12 mg, 0.075 mmol, 5 equiv), and diisopropyl azodicarboxylate (DIAD) (14.7 μL, 0.075 mmol, 5 equiv). The reaction mixture was stirred and allowed to warm to room temperature over ca. 1.5 h after which time it was diluted with 7 mL of Et_2O and the layers were separated. The organic phase was washed with 2 mL of a saturated solution of $NaHCO_3$ and 2 mL of a saturated solution of NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product which was purified by column chromatography to afford 5 mg (0.010 mmol, 70%) of *p*-nitrobenzoate **20** as a white solid.

Acknowledgment. This research was supported by NIH (CA 22237), DGICYT (AGF98-0805-CO2-02 and PB96-0822) and CAM (08.5/0046/1998). We thank the CAM for a doctoral fellowship to C.M. We are grateful to Professor B. Rodríguez and Dr. J. C. López (IQO, CSIC) for encouragement and support. We thank Dr. Jeff Kampf (Department of Chemistry, The University of Michigan) for the X-ray analysis of the *p*-nitrobenzoate of chlorohydrin **11a**.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000468K