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Sulfur-Directed Synthesis of Enantiopure Hydroxy 2-Sulfinyl Butadienes†

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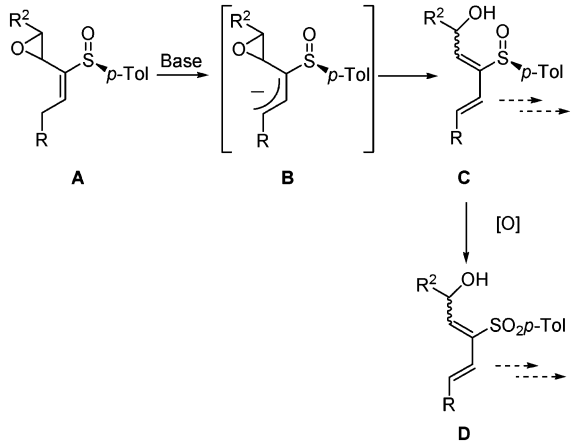
Received November 29, 2003

The treatment of sulfinyl chlorohydrins with KO-*t*-Bu in THF generates epoxy vinyl sulfoxides that undergo an efficient base-induced rearrangement to generate enantiopure hydroxy 2-sulfinyl dienes. This novel process takes place with high chemo- and stereoselectivity. The chirality at sulfur effectively controls the geometry of the trisubstituted alkene.

Introduction

Enantiopure 1,3-dienes are versatile substrates for enantioselective Diels−Alder cycloadditions, comparatively less developed than other asymmetric variants of the Diels−Alder protocol.[1] Within this field, enantiopure sulfinyl dienes have often displayed considerable synthetic usefulness due to a good control of facial selectivity followed by removal of the sulfur auxiliary.[2] 2-Sulfinyl butadienes were especially attractive targets since a vinyl sulfoxide would be generated after Diels−Alder cycloaddition and this should allow for a subsequent sulfur-directed asymmetric transformation.[3] Several years ago we developed short and general routes to enantiopure epoxy vinyl sulfoxides, **A** (Scheme 1).[4] We envisioned that these oxiranes could be adequate precursors to acyclic 2-sulfinyl butadienes with an additional oxygenated stereocenter, **C**, upon treatment with base. At the time, a related transformation was well-known for cyclic epoxy vinyl sulfones,[5] but our substrates had less acidic hydrogens and were acyclic systems and these facts rendered the viability and selectivity of the process questionable.

SCHEME 1



At this stage we expected that, if the proposed process were viable, the geometry of the disubstituted double bond should be under thermodynamic control, producing the *E* isomer. On the other hand, the more challenging stereochemical aspect of the process, namely the trisubstituted alkene, could be under control by the sulfinyl group that would dictate the configuration of the meta-

† Taken in part from the M.S. Theses of M.V.M. and M.V.B. and the Ph.D Theses of C.M. and M.T.

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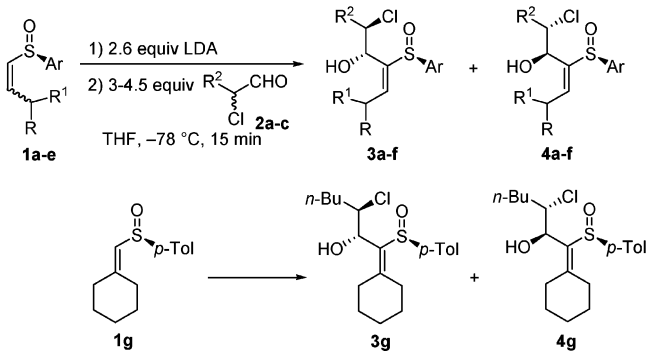
10.1021/jo035750g CCC: $27.50
Published on Web 02/13/2004

TABLE 1. Preparation of Sulfinyl Chlorohydrins



entry	substrate	Ar	R	R^1	aldehyde	R^2	3[a]	4[a]	yield,[b] %
1[4b]	**1a**	*p*-Tol	*n*-Pr	H	**2a**	*n*-Bu	**3a** (46)	**4a** (54)	74
2	**1b**	*p*-Tol	Me	H	**2b**	CH_2Ph	**3b** (48)	**4b** (52)	58
3	**1c**	*p*-Tol	*i*-Pr	H	**2b**	CH_2Ph	**3c** (58)	**4c** (42)	58
4	**1d**	*p*-Tol	Me	Me	**2a**	*n*-Bu	**3d** (52)	**4d** (48)	73
5	**1a**	*p*-Tol	*n*-Pr	H	**2c**	*i*-Pr	**3e** (56)	**4e** (44)	75
6	**1e**	1-Naphthyl-(2-OMe)	*n*-Pr	H	**2a**	*n*-Bu	**3f** (57)	**4f** (43)	72
7	**1g**	*p*-Tol			**2a**	*n*-Bu	**3g** (50)	**4g** (50)	81

[a] Diastereomeric ratios are shown in parentheses. [b] Combined yields of pure products after column chromatography.

lated intermediate **B**,[6] followed by epoxide cleavage by a well-defined stereochemical route.[7] In this report we describe in full our studies on the development of a novel strategy for the stereocontrolled preparation of acyclic 2-sulfinyl dienes **C**, as well as 2-sulfonyl dienes **D**,[8] bearing an additional allylic hydroxylated chiral center.[9]

Results

Preparation of Starting Materials. Table 1 shows the preparation of diastereomeric anti *E* chlorohydrins **3a**−**f** and **4a**−**f**, immediate precursors to vinyl oxiranes **A**;[4] these substrates are obtained by lithiation of the *E*/*Z* mixture of vinyl sulfoxides **1**, available in one step by the method of Craig,[10] and reaction with a variety of chloroaldehydes,[11] followed by a straightforward chromatographic separation in most cases.[12] The stereochemical assignment for chlorohydrins **3** and **4** is based on careful comparison of their ^{1}H and ^{13}C NMR data, as well as chromatographic behavior with the data of chlorohydrin **3a** of known structure established by X-ray crystallography.[4b] Chlorohydrins **3g** and **4g** with a tetrasubstituted alkene were obtained similarly from vinyl sulfoxide **1g**.

To test the scope of the methodology, the preparation of representative substrates of *Z* geometry was pursued by trying to apply the methodology entailing sulfinyl silyloxy mesylates previously developed,[4] and the results

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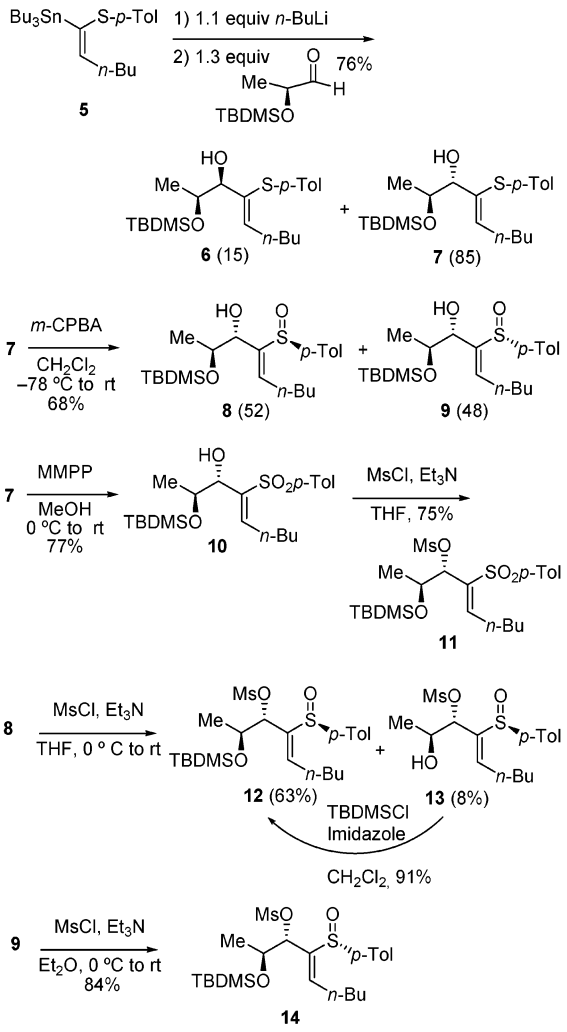
(12) Lithiation of *Z* vinyl sulfoxides with LDA yields *E* lithioderivatives without racemization; for details, see ref 9 of the following: Fernández de la Pradilla, R.; Manzano, P.; Montero, C.; Priego, J.; Martínez-Ripoll, M.; Martínez-Cruz, L. A. *J. Org. Chem.* **2003**, *68*, 7755−7767.

SCHEME 2



obtained are gathered in Scheme 2. Treatment of stannane **5**[13] with *n*-BuLi followed by condensation with TBDMS protected lactaldehyde[14] gave a mixture of syn and anti hydroxy vinyl sulfides **6** and **7**. Oxidation of the major anti product **7** with *m*-CPBA proceeded with an unusually low selectivity[15] to produce an equimolecular mixture of **8** and **9**. Alternatively, **7** was oxidized smoothly to *Z* vinyl sulfone **10**. Subsequent mesylation under standard conditions gave allylic mesylate **11** in good yield. Similarly, diastereomeric sulfoxides **8** and **9** were mesylated uneventfully to produce sulfinyl mesylates **12** and **14**.[16]

Synthesis of Hydroxy Sulfinyl Dienes from Sulfinyl Chlorohydrins. The initial stage of this investigation was carried out on pure vinyl oxirane **16a** (Table 2) that upon treatment with *n*-BuLi gave a hydroxy allene (structure not shown) presumably by sulfur−lithium exchange and subsequent elimination of the oxirane. The hindered base LDA gave just recovered starting material and NaH led to a complex mixture with just small amounts of the desired dienes. After considerable experimentation we found that the treatment of a cold (0 °C) THF solution of the vinyl oxirane with a suspension of KO-*t*-Bu in THF followed by slow warming to room temperature and stirring for 22 h gave a 42% isolated yield of *E*/*E* diene **21a** as a single isomer (Table 2, entry 8). To assess the influence of the chiral sulfur on the viability and selectivity of the process, diastereomeric epoxide **15a** was treated with KO-*t*-Bu similarly yielding, to our delight, *Z*/*E* diene **17a** as a single isomer in 62% yield (Table 2, entry 1). To simplify the experimental protocol a one-pot procedure from chlorohydrins **3a** and **4a** entailing sequential addition of two portions of 1.1 equiv of KO-*t*-Bu suspension in THF was explored with comparable results (Table 2, entries 2 and 9). A thorough analysis of the crude mixtures pointed out the formation of dimers **19a** and **22a**, both obtained as single isomers, respectively, derived from a highly stereoselective S_N2' displacement of the hydroxy diene on the vinyl oxirane still present in the reaction media. The stereochemical course of this secondary process was not investigated.

The structure and geometry of these dienes was derived from their ^{1}H and ^{13}C NMR spectra, as well as differential NOE data. Some typical features are a vicinal coupling of 15.6 Hz for the disubstituted alkene, and the different chemical shifts found for the vinyl proton H-6 (**17a**, 6.03 ppm; **21a**, 6.35 ppm) and for the allylic proton H-5 (**17a**, 4.90 ppm; **21a**, 4.52 ppm), consistent with the deshielding influence of a sulfinyl moiety for cis or syn protons, respectively. See the Supporting Information for additional details.

It was soon recognized that to ensure reproducibility, the reaction conditions had to be strictly anhydrous, and the THF suspension of KO-*t*-Bu had to be prepared and added carefully to the reaction vessel to ensure addition of the reagent was complete. Under these optimized conditions, once formation of the oxirane was complete (ca. 1 h), the desired dienes were obtained rapidly (15−30 min, Table 2, entries 2 and 9). In contrast, when the reaction conditions were not strictly anhydrous the process slowed substantially and, at long reaction times, significant amounts of diastereomeric dienes *ent*-**18a** (Table 2, entry 10) and more significantly inseparable mixtures of *E*/*E* dienes **18a** and *ent*-**21a** with just duplication of some signals in the ^{1}H and ^{13}C NMR spectra (Table 2, entries 3 and 5) were formed (it should be pointed out that the stereochemical assignments for "anomalous" products *ent*-**18a** and *ent*-**21a** are tentative and are based on the known configurational stability of allylic alcohols under mild basic conditions; see the Discussion section below for a rationalization of these observations).[17] The addition of 2 equiv of base once the oxirane had been formed to enhance the rate of the

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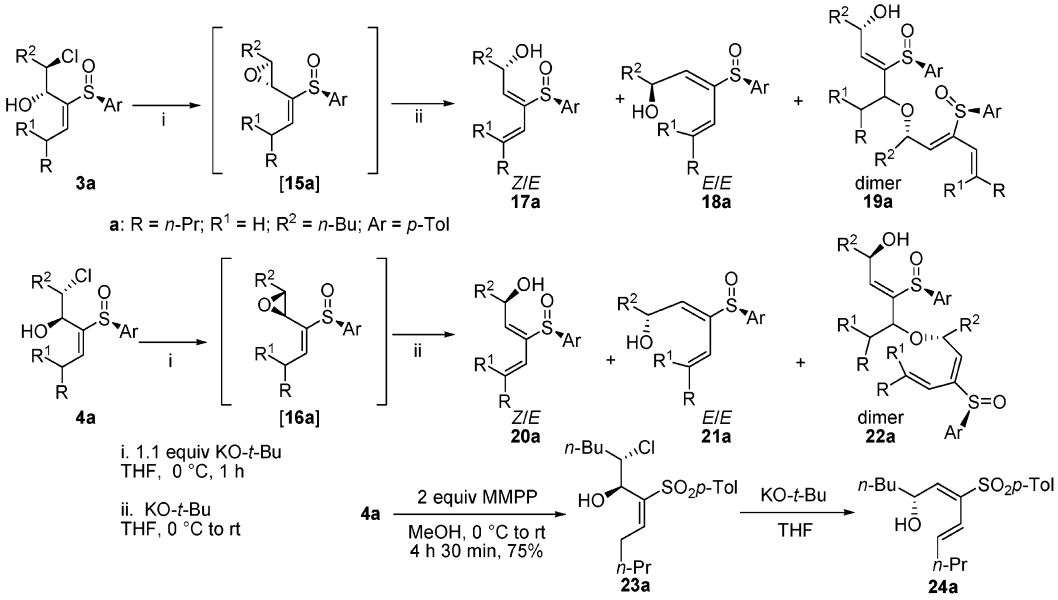
(15) It should be pointed out that the selectivity of the oxidation of anti sulfide **7** to sulfoxides **8** and **9** in CH_2Cl_2 is unusually low, compared with related allylic alcohols that do not have the additional oxygenated chiral center. See ref 13.

(16) Mesylation of **9** had to be carried out in ether; in THF a complex mixture of products was obtained, containing significant amounts of the corresponding diols.

(17) Interestingly, addition of solid KO-*t*-Bu to the THF solution of the chlorohydrin resulted largely in decomposition.

TABLE 2. Optimization of the Synthesis of Hydroxy Sulfinyl Dienes from Sulfinyl Chlorohydrins



entry	substrate	conditions	*Z*/*E*	*E*/*E*	dimer	yield,[a] %
1	**15a**	1.1 equiv of KO-*t*-Bu, THF, 0 °C, 90 min	**17a**			62
2	**3a**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 90 min	**17a** (91)		**19a** (9)	81
3	**3a**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C to rt, 15 h	**17a** (80)	**18a** (6):*ent*-**21a** (3)	**19a** (11)	60
4	**3a**	1.1 + 2.0 equiv of KO-*t*-Bu, THF, 0 °C to rt, 65 min	**17a** (40)	**18a** (40)	**19a** (20)	*b*
5	**3a**	3 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C to rt, 20 h	**17a** (57)	**18a** (22):*ent*-**21a** (12)	**19a** (9)	*b*
6[c]	**3a**	1.5 equiv of KO-*t*-Bu, THF, 0 °C, 10 min	**17a** (85)	**18a** (15)		*b*
7[c]	**3a**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 30 min	**17a** (30)	**18a** (70)		52
8	**16a**	1.1 equiv of KO-*t*-Bu, THF, 0 °C to rt, 22 h		**21a**		42
9	**4a**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 75 min		**21a** (88)	**22a** (12)	69
10	**4a**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 20 h		**21a** (83):*ent*-**18a** (2)	**22a** (15)	44
11	**4a**	1.0 + 2.0 equiv of KO-*t*-Bu, THF, 0 °C, 90 min		**21a** (80)	**22a** (20)	67
12[d]	**4a**	1.0 + 2.0 equiv of KO-*t*-Bu, THF, 0 °C, 65 min		**21a** (96)	**22a** (4)	63
13[c]	**4a**	1.0 equiv of KO-*t*-Bu, THF, 0 °C, 10 min		**21a** (81)	**22a** (19)	*b*
14	**23a**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 3 h		**24a**		25
15	**23a**	2.2 equiv of KO-*t*-Bu, THF, −78 °C to rt, 5 h		**24a**		53

[a] Combined yields of pure products after column chromatography. [b] The yield was not determined. [c] A 0.5 M solution of KO-*t*-Bu in THF was used. [d] The concentration of sulfinyl oxirane **16a** was reduced to half by addition of THF with regard to entry 11.

reaction and secure reproducibility gave rise to increased amounts of dimers and to substantial loss of geometric integrity for **15a** (Table 2, entries 4 and 11). To reduce the amount of dimer, the concentration of the oxirane was reduced by addition of THF prior to the second addition of 2 equiv of KO-*t*-Bu suspension (Table 2, entry 12).

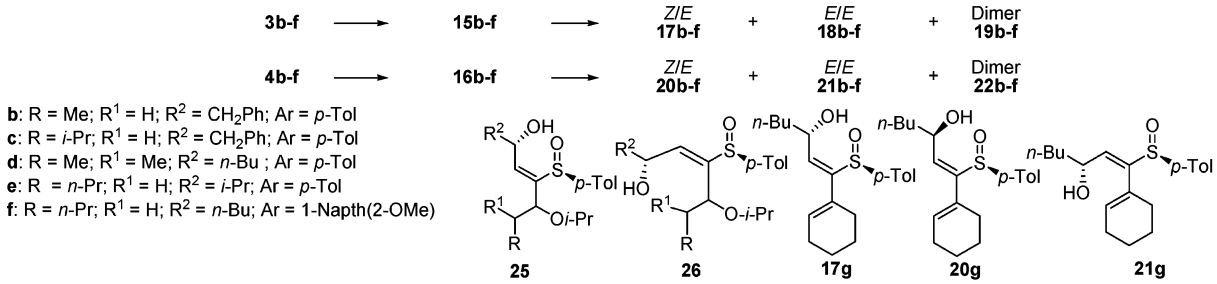
To further simplify the experimental protocol, the use of a freshly prepared 0.5 M THF solution of KO-*t*-Bu in anhydrous THF was tested. Thus, addition of just 1 equiv of KO-*t*-Bu solution to chlorohydrin **4a** or 1.5 equiv in the case of **3a** resulted in very fast reactions (Table 2, entries 6 and 13). These results suggest that the use of the THF solution of base could be the procedure of choice, even allowing for an effective, albeit low-yielding, route to *E*/*E* diene **18a** by addition of a second equivalent of KO-*t*-Bu solution in THF to the solution of *Z*/*E* diene **17a** (Table 2, entry 7).

To clarify the influence of the sulfinyl moiety on the process, the behavior of sulfonyl chlorohydrin **23a** was tested. Under standard conditions, *E*/*E* sulfonyl diene **24a** was obtained in low yield that was substantially improved by adding a THF suspension of 2.2 equiv of KO-*t*-Bu to a cold (−78 °C) solution of **23a** followed by slow warming of the mixture to room temperature over 5 h (Table 2, entries 14 and 15).

Scope of the Synthesis of Hydroxy Sulfinyl Dienes. Having established the viability of the methodology, we set out on exploring the scope of the process by starting from the chlorohydrins and carrying out sequential additions of 1.1 equiv of a suspension of KO-*t*-Bu in THF and the results obtained are shown in Table 3. Thus, benzyl-substituted chlorohydrins **3b** and **4b** led to dienes **17b** and **21b**, respectively, with good selectivity and in comparable yields to those found before (Table 3, entries 1 and 10). Therefore, it appears that the sulfinyl group is controlling not just the geometry of the alkene but also the regioselectivity of the deprotonation favoring allylic deprotonation on the intermediate vinyl oxiranes vs the competitive 1,2-benzylic deprotonation.[7c] Similarly, chlorohydrins **3c** and **4c**, bearing a bulkier substituent at the allylic center, gave rise to dienes **17c** and **21c** with identical chemo- and stereoselectivity (Table 3, entries 2 and 11).

Dimethyl-substituted chlorohydrins **3d** and **4d** led exclusively to the vinyl oxiranes **15d** and **16d** under these conditions (Table 3, entries 3 and 12), indicating that our methodology is not adequate to prepare 2-sulfinyl dienes

TABLE 3. Synthesis of Hydroxy Sulfinyl Dienes from Sulfinyl Chlorohydrins



entry	substrate	conditions	oxirane	*Z*/*E*	*E*/*E*	dimer	yield,[a] %
1	**3b**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 75 min		**17b** (88)		**19b** (12)	79
2	**3c**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 75 min		**17c** (87)		**19c** (13)	72
3	**3d**	3 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C to rt, 6 h	**15d** (100)	-			76
4	**15d**	3 equiv of NaH, THF, 0 °C to rot, 14 h	**15d** (100)	-			*b*
5	**3d**	3 × 1.1 of equiv KOH, *i*-PrOH:THF, 0 °C to rt, 16 h	**15d** (10)	**17d** (55)			56[c]
6[d]	**3e**	0.7 equiv of KO-*t*-Bu, THF, 0 °C, 25 min		**17e** (91)	**18e** (9)		62
7[d]	**3e**	1.0 + 1.8 equiv of KO-*t*-Bu, THF, 0 °C, 30 min		**17e** (50)	**18e** (50)		54
8	**15f**	1.0 + 2.5 equiv of KO-*t*-Bu, THF, rt, 16 h	**15f** (50)	**17f** (40)	**18f** (10)		96
9[d]	**3g**	1.0 + 0.5 equiv of KO-*t*-Bu, THF, 0 °C to rt, 75 min		**17g**			75
10	**4b**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 75 min			**21b** (86)	**22b** (14)	60
11	**4c**	2 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C, 4 h			**21c** (80)	**22c** (20)	66
12	**4d**	3 × 1.1 equiv of KO-*t*-Bu, THF, 0 °C to rt, 6 h	**16d** (100)				75
13	**4d**	3.2 equiv of KH, THF, 0 °C to rt, 22 h	**16d** (100)				*b*
14	**4d**	1.1 × 3 equiv of KOH, *i*-PrOH:THF, 0 °C to rt, 3 days					*e*
15	**4c**	4 equiv of KOH, *i*-PrOH:THF, 0 °C to rt, 4 h		**20c** (14)	**21c** (56)		61[f]
16	**4c**	4 equiv of KO-*t*-Bu, *t*-BuOH:THF, 0 °C to rt, 8 h	**16c** (28)	**20c** (14)	**21c** (58)		72
17[d]	**4e**	0.7 equiv of KO-*t*-Bu, THF, 0 °C, 5 min			**21e**		37[g]
18[d]	**16f**	1.0 + 0.5 equiv of KO-*t*-Bu, THF, rt, 3 h 30 min		**20f** (11)	**21f** (78)	**22f** (11)	78
19[d]	**4g**	3 × 1.0 equiv of KO-*t*-Bu THF, 0 °C to rt, 5 h		**20g** (8)	**21g** (92)		77

[a] Combined yields of pure products after column chromatography. [b] The yield was not determined. [c] About 35% ratio of **25d** was present in the crude mixture (^{1}H NMR); the yield refers to **25d** and diene **17d**. [d] Experiment carried out with a 0.5 M THF solution of KO-*t*-Bu. [e] The crude reaction mixture contained **26d** as the main product along with other minor products of unknown structure (^{1}H NMR). [f] About 30% ratio of **26c** was present in the crude mixture (^{1}H NMR). [g] Diene **21e** was obtained as an about 50:50 mixture with an uncharacterized compound.

disubstituted at C-4. Furthermore, these oxiranes were inert to NaH or even KH, respectively (Table 3, entries 4 and 13). We decided to test KOH in *i*-PrOH, conditions used by Maignan in a related context.[18] In this manner, chlorohydrin **3d** gave a 55:35:10 mixture of diene **17d**, S_N2' adduct **25d**, and oxirane **15d**. Under identical conditions, diastereomeric chlorohydrin **4d** led to a complex mixture that did not contain the desired diene and with formation of substantial amounts of the S_N2' adduct **26d** (Table 3, entries 5 and 14). It should be pointed out that again, these S_N2' adducts were isolated as single isomers of undetermined stereochemistry.

At this stage we decided to examine the influence of these protic conditions (KOH/*i*-PrOH) on the outcome of the process for a substrate that gave good results under standard conditions. Entry 15 shows that a considerable amount of S_N2' adduct **26c** was obtained, along with the expected diene **21c** and a significant amount of the *Z*/*E* diene **20c**. The use of KO-*t*-Bu in THF/*t*-BuOH to avoid formation of the S_N2' product gave some vinyl oxirane **16c** along with a comparable mixture of dienes **20c** and **21c** (Table 3, entry 16). These results suggest that the use of protic conditions suppresses the formation of the undesired dimers but at the expense of a noticeable erosion of the *E*/*Z* selectivity of the process.

To further extend the methodology, the behavior of chlorohydrin **3e** with a 0.5 M solution of KO-*t*-Bu in THF was explored with comparable results to those described in Table 2, giving rise to a small amount of *E*/*E* diene **18e**. Seeking a direct synthesis of **18e**, once formation of **17e** was complete, an excess of base was added to produce an equimolecular mixture of both dienes (Table 3, entries 6 and 7). Diastereomeric chlorohydrin **4e** gave the expected diene **21e** albeit in low yield (Table 3, entry 17).

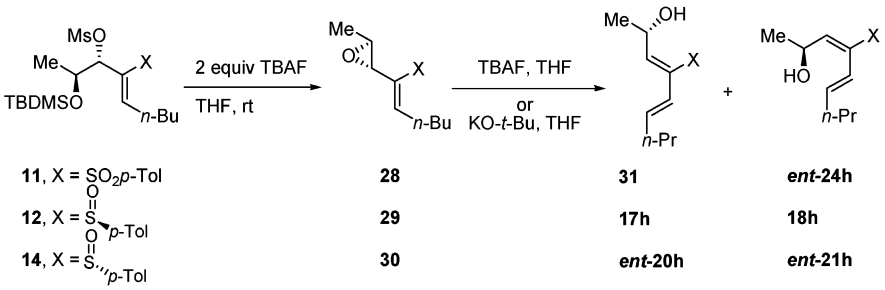
The influence of a 1-Naphthyl-(2-OMe) substituent on sulfur was then addressed and, under standard conditions, smooth formation of the vinyl oxiranes **15f** and **16f** was observed without significant amounts of dienes. Subsequent treatment of these oxiranes with an excess of base and at long reaction times gave a low conversion for diastereomer **15f** (Table 3, entry 8) and an 11:78 mixture of dienes **20f** and **21f** (Table 3, entry 18). Finally, chlorohydrins **3g** and **4g** with a tetrasubstituted alkene gave the expected dienes **17g** and **21g**, respectively, the latter obtained with a small amount of the *Z* isomer **20g** (entries 9 and 19).

To expand the scope of the methodology, standard procedures to carry out hydroxyl inversion on dienes **21** and **17** to yield diastereomeric dienes **18** and **20**, respectively, were examined with mixed success, and the results are shown in Scheme 3. The treatment of model diene **21a** with *p*-nitrobenzoic acid under Mitsunobu conditions,[19] followed by debenzoylation gave a good overall

(18) Bonfand, E.; Gosselin, P.; Maignan, C. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1667−1676.

(19) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020. For reviews, see: (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335−669. (c) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127−164.

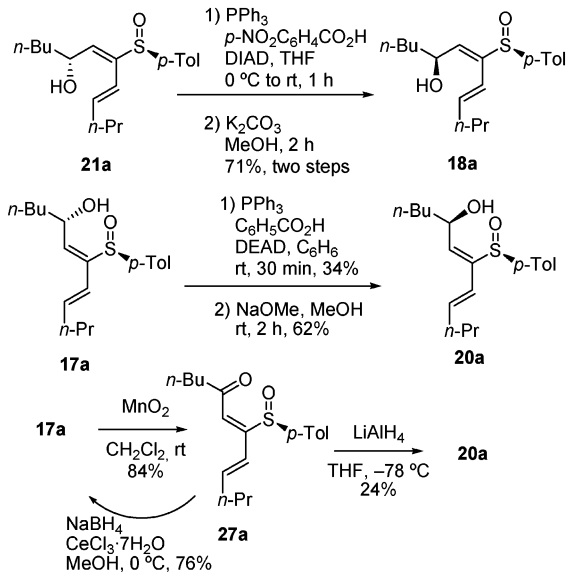
TABLE 4. Synthesis of Hydroxy Sulfinyl and Sulfonyl Dienes from *Z* Substrates



entry	substrate	conditions	oxirane	*Z*/*E*	*E*/*E*	yield,[a] %
1	**11**	2 equiv of TBAF, 4 h	**28** (29)	**31** (4)	*ent*-**24h** (67)	91
2	**12**	2 equiv of TBAF, 30 min	**29**			85
3	**29**	0.7 equiv KO-*t*-Bu, 15 min		**17h**		32
4	**12**	(1) 2 equiv of TBAF; (2) 1.7 equiv of KO-*t*-Bu, 4 h		**17h** (10)	**18h** (90)	69
5	**14**	2 equiv of TBAF, 30 min	**30**			72
6	**30**	1.4 equiv of KO-*t*-Bu, 3 h			*ent*-**21h**	70

[a] Combined yields of pure products after column chromatography.

SCHEME 3



yield of the target diene **18a** as a single isomer. A similar treatment on *Z*/*E* diene **17a** proved to be less selective and a ca. 50:25:25 mixture of *Z*/*E* and *E*/*E* (two diastereomers) benzoates was obtained. After chromatography, debenzoylation gave the desired *Z*/*E* diene **20a** in low overall yield; similarly, debenzoylation of the *E*/*E* benzoates gave a ca. 50:50 mixture of diastereomeric dienes **18a** and **21a**.[20] In an effort to improve the preparation of **20a** we explored briefly an oxidation−reduction sequence. Treatment of **17a** with activated MnO_2 gave an excellent yield of keto dienyl sulfoxide **27a**.[21] Interestingly, Luche reduction of **27a** gave exclusively **17a**, thus indicating that the geometry of **27a** is that shown and that the reduction of these keto dienyl sulfoxides may be controlled efficiently by the chiral sulfoxide.[22] Nonetheless, this was not the desired stereochemical outcome and therefore we examined a number of different reducing agents with little success.[23] Of this survey, $LiAlH_4$ gave a low yield of the desired dienol **20a** isolated from a fairly complex reaction mixture.

To extend the scope of the methodology, and to gain further insight into the stereochemical aspects of the initial hydrogen abstraction step to generate the transient allylmetal intermediate, the behavior of *Z* substrates **11**, **12**, and **14** was explored and the results are shown in Table 4. The treatment of sulfonyl mesylate **11** with TBAF gave a mixture of the expected vinyl oxirane **28** and *E*/*E* diene *ent*-**24h** as the major isomer and in good overall yield (Table 4, entry 1). In contrast, diastereomeric sulfinyl mesylates **12** and **14** under similar conditions led to good yields of the expected oxiranes **29** and **30** (Table 4, entries 2 and 5). These oxiranes were treated with a THF solution of KO-*t*-Bu with fairly different results to those found for the *E*-isomers. Indeed, **29** rapidly gave a low yield of the expected diene **17h** isolated from a rather complex reaction mixture (entry 3) and **30** gave a good yield of the expected *E*/*E* diene *ent*-**21h** but in a fairly slow reaction (entry 6). Finally, in an attempt at improving the yields of diene **17h**, mesylate **12** was treated with TBAF, followed by addition of KO-*t*-Bu to produce slowly a fair yield of a 10:90 mixture of **17h** and **18h**, presumably due to a surprisingly efficient isomerization of *Z*/*E* diene **17h** to *E*/*E* diene **18h** (Table 4, entry 4). At this point we do not fully understand these very different outcomes shown in entries 3 and 4.

The oxidation of our sulfinyl dienes to enantiopure hydroxy sulfonyl dienes was considered to be a simple and interesting application of the methodology and the results obtained are shown in Table 5. In this manner, *E*/*E* diene **21a** gave sulfonyl diene **24a**, with identical data to that found for material produced from sulfonyl chlorohydrin **23a**. Similarly, *Z*/*E* dienes **17a**, **17b**, and **17e** gave good yields of the expected sulfonyl dienes **32a**,

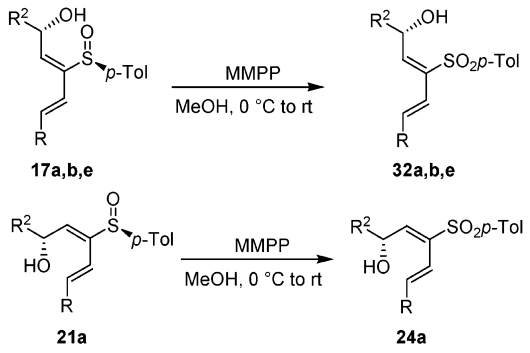
(20) Mitsunobu inversion with *p*-NO_2BzOH in THF gave slightly inferior results.

(21) This oxidation was initially attempted with PCC in CH_2Cl_2 to produce **27a** in 30−35% yield.

(22) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

(23) Reduction with DIBALH gave a complex mixture of products. See the Supporting Information.

TABLE 5. Synthesis of Hydroxy Sulfonyl Dienes by Oxidation



entry	substrate	R	R^2	conditions	product	yield,[a] %
1	**17a**	*n*-Pr	*n*-Bu	2.7 equiv, 9 h	**32a**	96
2	**17b**	Me	CH_2Ph	3.0 equiv, 21 h	**32b**	67
3	**17e**	*n*-Pr	*i*-Pr	1.2 equiv, 13 h	**32e**	71
4	**21a**	*n*-Pr	*n*-Bu	1.5 equiv, 100 min	**24a**	74

[a] Yields of pure products after column chromatography.

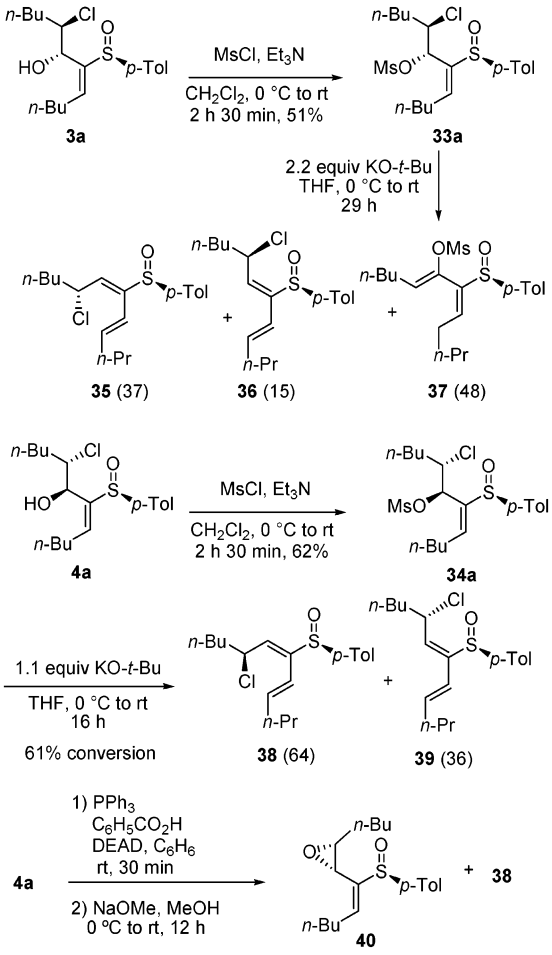
32b, and **32e** without any detectable loss of stereochemical integrity.

The use of a different leaving group for this elimination was briefly explored and we focused our efforts on mesylates **33a** and **34a**, prepared in good yield from chlorohydrins **3a** and **4a** by a standard procedure, and expected to be suitable precursors to enantiopure chloro sulfinyl dienes. Unfortunately, while the process was viable, these substrates were fairly unreactive and gave the dienes with low selectivity (Scheme 4).[24] Finally, the treatment of **4a** under Mitsunobu conditions gave a complex crude mixture that was debenzoylated with NaOMe to produce cis oxirane **40** and chlorodiene **38** isolated from a complex mixture. Unfortunately, all efforts to carry out the elimination of **40** to produce hydroxy dienes were fruitless and resulted in recovered starting material.

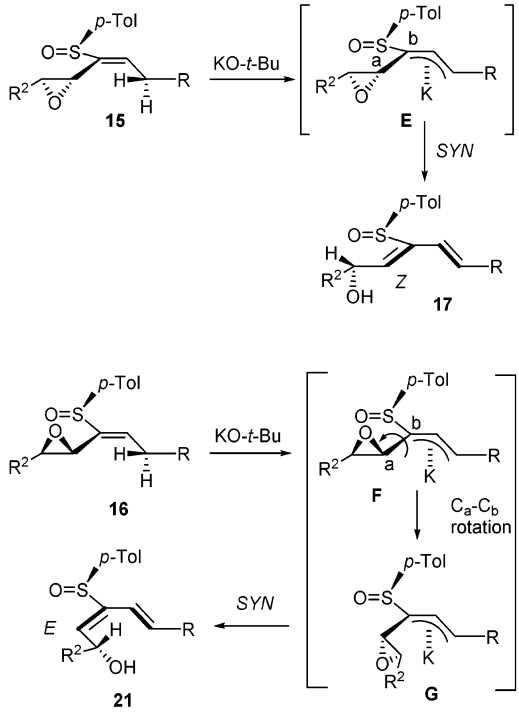
Discussion

The stereochemical outcome of this protocol may be rationalized tentatively in terms of a stepwise reaction course with a high degree of stereocontrol for each step. We believe that allylic deprotonation of oxiranes **15** and **16** leads to diastereomeric allylmetal species **E** and **F**, respectively (Scheme 5), for which the chiral sulfinyl functionality would place the metal in the α face of the molecule.[25] Assuming a syn *β*-elimination for oxirane cleavage,[7b] perhaps with coordination of the oxirane to the metal, **E** would lead to *Z*/*E* diene **17**. On the other hand, to attain the required syn geometry for oxirane elimination and to minimize steric interactions between the oxirane and the sulfinyl moiety, **F** would undergo a C_a-C_b bond rotation to produce **G** and that would dictate

SCHEME 4



SCHEME 5

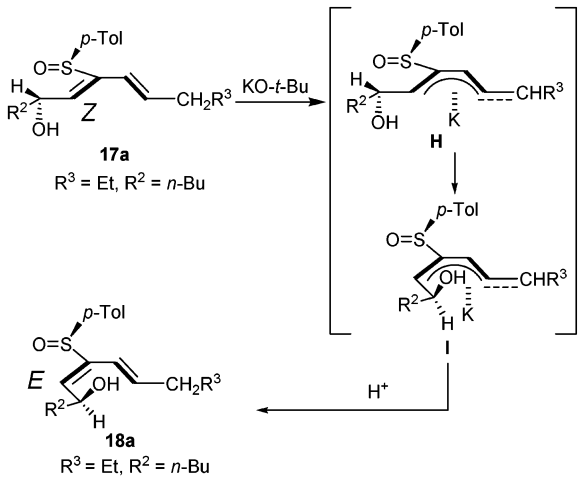


the *E* geometry of the trisubstituted alkene. Alternatively, when a sulfone moiety is present in the starting

(24) For the synthesis of chiral chlorodienols see: Yadav, J. S.; Barma, D. K.; Dutta, D. *Tetrahedron Lett.* **1997**, *38*, 4479−4482.

(25) This stereochemical arrangement is proposed in analogy with the transition state proposed by Haynes for the reaction between lithiated allyl sulfoxides and cyclic enones. See: Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411−5423.

SCHEME 6



oxirane, elimination leads exclusively to the *E*/*E* dienyl sulfone **24a**. When the process is not carried out under strictly anhydrous conditions, intermediates **E** and **F** (or **G**) (Scheme 5) may undergo protonation to some extent to produce allylic sulfoxides, prone to undergo a rapid and reversible sulfoxide−sulfenate rearrangement that could result in partial epimerization at sulfur.[26] It should be mentioned that an *E* alkene geometry for the starting material seems to be crucial for the yield and selectivity of the process (compare Tables 3 and 4). The unexpected and highly stereoselective S_N2' process that gives rise to dimeric structures **19** and **22** is noteworthy and suggests that the addition of oxygen-centered nucleophiles to our vinyl oxiranes could become a synthetically useful process.[27]

Finally, the isomerization found for some *Z*/*E* dienes to *E*/*E* dienes may be rationalized by allylic deprotonation on, for instance, hydroxy diene **17a** to generate a metalated dienylic species **H** that could favor isomerization to intermediate **I** that would undergo protonation affording *E*/*E* diene **18a**.

Conclusions

An expedient and stereocontrolled route to a variety of enantiopure hydroxy sulfinyl and sulfonyl dienes has been developed.[28] In this route, the geometry of the trisubstituted alkene is controlled by the absolute configuration at sulfur presumably due to sequential highly stereoselective metalation and β-elimination steps. We are currently addressing the application of these dienes in synthesis.[29]

(26) For reviews see: (a) Braverman, S. In *The Chemistry of Sulphones and Sulphoxides;* Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; New York, 1988; pp 717−757. (b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147−155. For a recent study see: (c) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1995**, *117*, 9077−9078.

(27) For a recent example of highly syn selective S_N2' additions of alcohols to cyclic vinyl oxiranes, see: Di Busolo, V.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett.* **2002**, *4*, 3695−3698.

(28) The optical purity of a representative hydroxy 2-sulfinyl diene was evaluated by formation of diastereomeric 2-methoxy-2-phenyl acetates and a careful ^{1}H NMR study. See the Supporting Information for details.

(29) For preliminary studies on the Diels−Alder reactivity of these sulfinyl and sulfonyl dienes, see: Fernández de la Pradilla, R.; Montero, C.; Viso, A. *Chem. Commun.* **1998**, 409−410.

Experimental Section

General Procedure for the Condensation between Vinyl Sulfoxides and α-Chloroaldehydes. A round-bottomed flask was charged with anhydrous THF (7 mL/mmol of sulfoxide) and 2.6 equiv of freshly distilled *i*-Pr_2NH then cooled to −78 °C. To the above solution was added 2.5 equiv of *n*-BuLi and the resulting LDA solution (ca. 0.4 M) was stirred at this temperature for 10 min. Then, a solution of 1.0 equiv of vinyl sulfoxide **1** in THF (3 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 the mixture was stirred for an additional 10 min at −78 °C, 3.5−4.5 equiv of freshly distilled chloroaldehyde in THF (0.9 mL/mmol of aldehyde) was added dropwise and the resulting colorless solution was stirred at this temperature for 15 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) then the layers were separated. The aqueous layer was extracted twice with EtOAc (6 mL/mmol). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography on silica gel with the appropriate mixture of eluents.

Synthesis of (−)-(2*S*,3*R*,*S*$_S$)-3-Chloro-1-cyclohexylidene-1-(*p*-tolylsulfinyl)heptan-2-ol (3g) and (−)-(2*R*,3*S*,*S*$_S$)-3-Chloro-1-cyclohexylidene-1-(*p*-tolylsulfinyl)heptan-2-ol (4g). From vinyl sulfoxide **1g** (235 mg, 1.00 mmol, 1.0 equiv), 2.5 equiv of LDA, and racemic 2-chlorohexanal (475 mg, 3.50 mmol, 3.5 equiv), following the general procedure, was obtained a 50:50 mixture of anti chlorohydrins **3g** and **4g**. Purification by chromatography (1−10% EtOAc−CH_2Cl_2) afforded 170 mg (0.46 mmol, 46%) of **3g** and 130 mg (0.35 mmol, 35%) of **4g** both as white solids that were recrystallized from EtOAc−hexane. Data for **3g**: mp 112−113 °C; R_f 0.55 (40% EtOAc−hexanes); $[\alpha]^{20}_D$ −172.8 (*c* 1.04); ^{1}H NMR (300 MHz) δ 0.83 (t, 3 H, J = 7.1 Hz), 1.10−1.26 (m, 3 H), 1.39 (m, 1 H), 1.50 (m, 1 H), 1.62−1.89 (m, 6 H), 2.06 (m, 1 H), 2.40 (s, 3 H), 2.44 (m, 2 H), 2.74 (m, 2 H), 3.62 (td, 1 H, J = 10.2, 2.6 Hz), 4.82 (d, 1 H, J = 9.8 Hz), 5.60 (br s, 1 H), 7.29 (d, 2 H, J = 8.5 Hz), 7.49 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 13.8, 21.3, 21.9, 26.0, 27.5, 27.7, 28.0, 32.3, 32.6, 33.5, 63.9, 77.3, 124.4 (2 C), 129.8 (2 C), 130.1, 139.2, 140.8, 155.7; IR (KBr) 3429, 2929, 2857, 1619, 1491, 1450, 1136, 1078, 1005, 804 cm^{-1}; MS (ES) 369 $[M + 1]^+$, 333 $[(M - Cl) + 1]^+$ (100%). Anal. Calcd for $C_{20}H_{29}ClO_2S$: C, 65.11; H, 7.92; Cl, 9.61; S, 8.69. Found: C, 65.31; H, 8.04; Cl, 9.76; S, 8.43. Data for **4g**: mp 120−122 °C; R_f 0.36 (40% EtOAc−hexane); $[\alpha]^{20}_D$ −271 (*c* 0.45); ^{1}H NMR (300 MHz) δ 0.89 (t, 3 H, J = 7.1 Hz), 1.20−1.80 (m, 12 H), 2.16 (m, 2 H), 2.37 (m, 2 H), 2.38 (s, 3 H), 4.31 (td, 1 H, J = 9.0, 2.7 Hz), 4.76 (br s, 1 H), 4.87 (dd, 1 H, J = 10.5, 9.0 Hz), 7.28 (d, 2 H, J = 8.3 Hz), 7.65 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (50 MHz) δ 14.0, 21.4, 22.3, 25.7, 26.9, 27.3, 28.0, 32.3, 32.4, 33.9, 65.7, 75.3, 126.5 (2 C), 130.0 (2 C), 131.4, 141.5, 142.4, 150.5; IR (KBr) 3411, 2926, 2855, 1627, 1450, 1080, 1031, 804 cm^{-1}; MS (ES) 369 $[M + 1]^+$, 333 $[(M - Cl) + 1]^+$ (100%). Anal. Calcd for $C_{20}H_{29}ClO_2S$: C, 65.11; H, 7.92; Cl, 9.61; S, 8.69. Found: C, 65.17; H, 7.70; Cl, 9.50; S, 8.85.

General Procedures for the Synthesis of Hydroxy Sulfinyl Dienes. **Procedure A:** A round-bottomed flask was charged with 1.0 equiv of chlorohydrin in THF (10 mL/mmol) under argon. The solution was cooled to 0 °C and, under strictly anhydrous conditions, a suspension of 1.1 equiv of KO-*t*-Bu (dried azeotropically twice with C_6H_6, finely ground, and stored in a desiccator prior to use) in THF (5 mL/mmol of chlorohydrin) was added rapidly via syringe. After 1 h, oxirane formation was complete (TLC) and 1.1 equiv of KO-*t*-Bu in THF (5 mL/mmol of chlorohydrin) was added similarly to produce a ca. 0.066 M solution of the oxirane. The reaction mixture was stirred and allowed to warm to room temperature until epoxide disappearance, monitored by TLC. The reaction was 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. Following this procedure the corresponding hydroxy dienes **17** and **21** were obtained along with small amounts (9−20%) of dimeric byproducts **19** and **22** whose structure was tentatively assigned as the S_N2' addition products derived from vinyl epoxides **15** or **16** and hydroxy dienes **17** or **21**. These products were obtained as single isomers at C-8 although their stereochemistry was not determined. **Procedure B:** After complete oxirane formation (procedure A), the reaction mixture was diluted with anhydrous THF (6.25 mL/mmol of chlorohydrin) and 2.0 equiv of KO-*t*-Bu in THF (10 mL/mmol of chlorohydrin) was added to give a ca. 0.033 M solution of oxirane in THF but with similar concentration of base as in procedure A. The products were isolated as described above. These experiments were designed to study the effect of oxirane concentration on the diene−dimer ratio. **Procedure C:** Following procedure A, from a solution of the chlorohydrin in THF (10−20 mL/mmol of chlorohydrin), and with addition of a freshly prepared 0.5 M solution of KO-*t*-Bu in THF. With this procedure we tried to minimize experimental errors upon addition of suspensions of base, particularly for small-scale experiments.

Synthesis of (+)-(3*S*,*S*$_S$)-(1*Z*)-1-Cyclohexenyl-1-(*p*-tolylsulfinyl)hept-1-en-3-ol (17g). From chlorohydrin **3g** (37 mg, 0.1 mmol, 1.0 equiv) in 2 mL of THF with two successive additions of KO-*t*-Bu (0.2 mL, 0.1 mmol, 1.0 equiv, and 0.1 mL, 0.05 mmol, 0.5 equiv after 1 h) according to the general procedure C (1 h + 15 min) was obtained diene **17g**. Purification by chromatography (10−30% EtOAc−hexanes) afforded 25 mg (0.075 mmol, 75%) of **17g** as a colorless oil. Data for **17g**: R_f 0.26 (30% EtOAc−hexanes); $[\alpha]^{20}_D$ +49.1 (*c* 1.00); ^{1}H NMR (300 MHz) δ 0.82 (t, 3 H, J = 7.0 Hz), 1.16−1.30 (m, 4 H), 1.42−1.64 (m, 6 H), 1.91 (m, 2 H), 2.04 (m, 2 H), 2.37 (s, 3 H), 4.87 (dt, 1 H, J = 8.3, 6.7 Hz), 5.97 (d, 1 H, J = 8.3 Hz), 5.98 (m, 1 H), 7.23 (d, 2 H, J = 8.2 Hz), 7.49 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (50 MHz) δ 13.9, 21.3, 21.5, 22.4, 22.5, 25.6, 27.4, 28.3, 37.0, 66.3, 124.7 (2 C), 129.6 (2 C), 130.6, 132.5, 138.3, 140.2, 140.6, 148.4; IR (film) 3379, 3034, 2929, 2858, 1595, 1493, 1447, 1435, 1378, 1304, 1269, 1207, 1179, 1136, 1081, 1027, 1012, 921, 888, 842, 810 cm^{-1}; MS (ES) 333 [M + 1]$^+$, 315 [(M − 18) + 1]$^+$(100%). Anal. Calcd for $C_{20}H_{28}O_2S$: C, 72.24; H, 8.49; S, 9.64. Found: C, 72.53; H, 8.62; S, 9.50.

Synthesis of (+)-(3*R*,*S*$_S$)-(1*E*)-1-Cyclohexenyl-1-(*p*-tolylsulfinyl)hept-1-en-3-ol (21g) and (3*R*,*S*$_S$)-(1*Z*)-1-Cyclohexenyl-1-(*p*-tolylsulfinyl)hept-1-en-3-ol, (20g). From chlorohydrin **4g** (31 mg, 0.08 mmol, 1.0 equiv) in 2 mL of THF with three successive additions of KO-*t*-Bu (0.16 mL, 0.08 mmol, 1.0 equiv, and 0.08 mL, 0.04 mmol, 0.5 equiv after 1 and 3 h) according to the general procedure C (1 h + 3 h +1 h) was obtained a 92:8 mixture of **21g** and **20g**. Purification by chromatography (10−30% EtOAc−hexanes) afforded 2 mg (0.005 mmol, 6%) of **20g** and 20 mg (0.060 mmol, 71%) of **21g** both as a colorless oils. Data for **21g**: R_f 0.26 (50% EtOAc−hexanes); $[\alpha]^{20}_D$ +186.1 (*c* 1.13); ^{1}H NMR (300 MHz) δ 0.87 (t, 3 H, J = 7.0 Hz), 1.22−1.56 (m, 8 H), 1.64 (m, 2 H), 1.76 (m, 1 H), 1.80 (m, 1 H), 1.98 (m, 2 H), 2.36 (s, 3 H), 4.32 (ap q, 1 H, J = 7.2 Hz), 5.40 (m, 1 H), 6.24 (d, 1 H, J = 8.8 Hz), 7.21 (d, 2 H, J = 8.1 Hz), 7.42 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (50 MHz) δ 14.0, 21.4 (2 C), 22.4, 22.6, 25.3, 27.4, 29.9, 37.0, 68.9, 125.6 (2 C), 129.3, 129.4 (2 C), 131.8, 132.1, 139.9, 141.6, 149.1; IR (film) 3391, 2929, 2858, 1595, 1492, 1435, 1378, 1303, 1207, 1177, 1119, 1082, 1038, 1014, 921, 808 cm^{-1}; MS (ES) 333 [M + 1]$^+$, 315 [(M − 18) + 1]$^+$(100%). Anal. Calcd for $C_{20}H_{28}O_2S$: C, 72.24; H, 8.49; S, 9.64. Found: C, 72.02; H, 8.63; S, 9.83. Data for **20g**: R_f 0.32 (50% EtOAc−hexanes); ^{1}H NMR (300 MHz) δ 0.91 (t, 3 H, J = 7.1 Hz), 1.20−1.90 (m, 12 H), 1.95 (m, 2 H), 2.38 (s, 3 H), 3.30 (br s, 1 H), 4.97 (m, 1 H), 5.76 (ddd, 1 H, J = 7.3, 3.7, 1.5 Hz), 6.03 (d, 1 H, J = 7.3 Hz), 7.25 (d, 2 H, J = 8.1 Hz), 7.50 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (75 MHz) δ 14.0, 21.4, 22.5, 22.6, 25.4, 27.7, 29.2, 29.7, 37.0, 66.1, 124.7, 125.9 (2 C), 129.6 (2 C), 130.3, 131.8, 139.6, 141.4, 146.9; IR (film) 3390, 2929, 2858, 1595, 1492, 1447, 1378, 1270, 1081, 1036, 807 cm^{-1}; MS (ES) 665 [2M + 1], 355 [M + Na]$^+$, 333 [M + 1]$^+$ (100%).

General Procedure for Oxidation of Sulfoxides with MMPP. To a cold (0 °C) solution of sulfoxide in MeOH (10 mL/mmol) was added 1.5−3.0 equiv of magnesium monoperoxyphthalate hexahydrate (MMPP). The mixture was stirred from 0 °C to room temperature, monitored by TLC until completion and then quenched with a saturated solution of $NaHCO_3$ (4 mL/mmol). After removal of MeOH under reduced pressure, the mixture was diluted with EtOAc (5 mL/mmol), the layers were separated, and the aqueous phase was extracted with EtOAc (3 times, 4 mL/mmol). The combined organic layers were washed with a saturated solution of NaCl (1 mL/mmol), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product that was purified by gradient column chromatography with EtOAc−hexanes mixtures.

Synthesis of (+)-(5*S*)-(6*Z*,8*E*)-7-(*p*-Tolylsulfonyl)dodeca-6,8-dien-5-ol (32a). From sulfinyl diene **17a** (26 mg, 0.080 mmol, 1.0 equiv) in MeOH (1.5 mL) and MMPP (130 mg, 0.220 mmol, 2.7 equiv), according to the general procedure (9 h), after chromatography (5−10% EtOAc−hexane), was obtained sulfonyl diene **32a** (26 mg, 0.077 mmol, 96%) as a colorless oil. Data for **32a**: R_f 0.19 (20% EtOAc−hexanes); $[\alpha]^{20}_D$ +26.0 (*c* 0.15); ^{1}H NMR (200 MHz) δ 0.81 (t, 3 H, J = 7.3 Hz), 0.84 (t, 3 H, J = 6.9 Hz), 1.23−1.65 (m, 8 H), 2.01 (qd, 2 H, J = 6.7, 1.1 Hz), 2.40 (s, 3 H), 2.50 (br s, 1 H), 5.11 (m, 1 H), 5.85 (dt, 1 H, J = 15.3, 6.6 Hz), 6.08 (dd, 1 H, J = 15.5, 0.6 Hz), 6.11 (d, 1 H, J = 8.6 Hz), 7.29 (d, 2 H, J = 8.5 Hz), 7.71 (d, 2 H, J = 8.3 Hz); ^{13}C NMR (50 MHz) δ 13.5, 13.9, 21.5, 21.9, 22.5, 27.3, 34.8, 36.6, 66.7, 123.9, 127.5 (2 C), 129.7 (2 C), 137.7 (2 C), 141.2, 142.1, 144.4; IR (film) 3460, 2960, 2930, 2880, 1460, 1320, 1300, 1150, 1080, 1030, 960, 810, 680 cm^{-1}; MS (EI) 336 [M]$^+$, 319, 279, 181, 157, 139 (100%), 109, 97, 95, 91, 85, 67, 57. Anal. Calcd for $C_{19}H_{28}O_3S$: C, 67.82; H, 8.39; S, 9.53. Found: C, 68.04; H, 8.17; S, 9.77.

Acknowledgment. This research was supported by DGICYT (BQU2001-0582 and BQU2003-02921) and CAM (08.5/0028/2003 2). We thank JANSSEN-CILAG for generous additional support. We thank CAM and MEC for doctoral fellowships to C.M. and M.T. We are grateful to Professor S. Valverde for encouragement and support.

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

JO035750G