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Sulfur-Directed Enantioselective Synthesis of Functionalized Dihydropyrans

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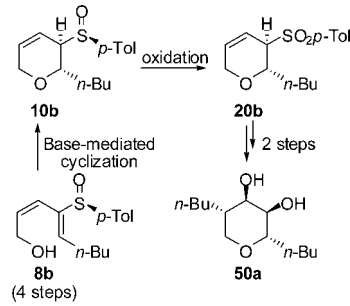

The highly selective base-promoted cyclization of enantiopure sulfinyl dienols affords allylic sulfinyl dihydropyrans. The scope of this methodology, including the preparation of seven-membered rings, has been studied in depth. The reactivity of our sulfinyl dihydropyrans toward oxidation, imination, and dihydroxylation has been explored, and thus several routes to densely functionalized pyran derivatives have been outlined. The reactivity of allylic dihydropyranyl sulfones and sulfoximines in S_N2' processes with organocuprates has been examined. The displacement products were obtained with good regio- and stereoselectivity and fair to good yields. The reactivity of these products to dihydroxylation opens new possibilities to access enantiopure polyhydroxylated tetrahydropyrans that could be of interest for the synthesis of natural products.

Introduction

Dihydro- and tetrahydropyrans are key building blocks of many natural and bioactive products that exhibit a broad variety of biological activities and can be isolated from numerous sources.[1] These bioactive compounds often present multisubstituted heterocyclic rings with a defined stereochemistry, and so the development of new methods to access enantiopure dihydro- and tetrahydropyrans has remained a current challenge for synthetic organic chemistry.[2]

Several years ago, while studying the synthesis of hydroxy sulfinyl dienes from epoxy vinyl sulfoxides, we observed that vinyl oxiranes **A** (Scheme 1) displayed an undesired S_N2' reactivity with complex secondary alcohols existing in the reaction media to produce adducts **B**.[3] Although at that time the stereochemical reaction pathway was not investigated, the

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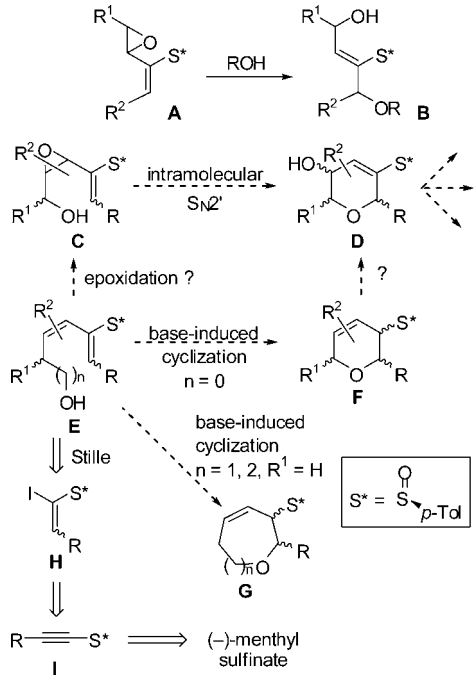
SCHEME 1. Proposed Sulfinyl-Mediated Synthesis of Dihydropyrans



fact that only one isomer was formed was significant and indicated that the process occurred with high selectivity. In connection with our interest in the design of sulfoxide-based synthetic procedures, especially those that allow for multiple chirality-transfer operations,[4] and with our involvement in the synthesis of functionalized tetrahydrofurans,[5] we envisioned that an intramolecular variant of this process entailing the cyclization of *cis*-hydroxy oxiranes **C** to hydroxy dihydropyrans **D** could be a viable process. If successful, we perceived that dihydropyrans **D** had a useful array of functionality for synthetic purposes either at sulfoxide or sulfone oxidation states.[6]

Alternatively, dienyl sulfoxides **E** were also identified as suitable precursors of dihydropyrans **F** and oxepines **G** with a stereochemically labile allylic sulfoxide functionality, upon treatment with base.[7,8] Dienols **E** are available by Stille coupling between vinyl stannanes and stereodefined *Z*- or *E*-iodo alkenyl sulfoxides **H**, which are prepared from alkynyl sulfoxides **I** by stereocontrolled hydrostannylation and tin−halogen exchange. In this paper we describe in full our results on the efficient base-induced cyclization of hydroxy dienyl sulfoxides **E** to produce good to excellent yields of allylic sulfoxides **F** and **G**.[9] In addition, we have outlined a simple protocol for producing enantiopure sulfones related to **D** from intermediates **F** and have examined several potentially useful transformations of these compounds. Finally, we have addressed the allylic displacements of enantiopure sulfones and sulfoximines related to **F** with organocuprates. Interestingly, this work brings to light that each sulfur moiety −sulfoxide, sulfone, sulfoximine− exerts a particular control on the stereochemical outcome of the cyclizations and S_N2' displacements.

Results and Discussion

Preparation of Hydroxy Dienyl Sulfoxides. The required iodo alkenyl sulfoxides were prepared from menthyl *p*-toluene sulfinate in three steps as shown in Scheme 2. From commercially available alkynes **1a** and **1b**, alkynyl sulfoxides **2a** and **2b** were prepared following the literature procedure.[10] Palladium-catalyzed hydrostannylation of the alkynyl sulfoxides led to *E* vinyl stannanes **3a** and **3b** as major products along with small amounts of the regioisomeric products. The non-catalyzed hydrostannylation proceeded with lower yields due to the formation of variable mixtures of the expected *Z* vinyl stannanes **4a** and **4b** and their *E* isomers, and in the case of **2a**, also a considerable amount of an unexpected regioisomeric product (see Supporting Information). Because of the low solubility of substrate **2a** in hexane, the usual solvent for these reactions, toluene had to be used. This change of solvent might be the reason for the loss of regioselectivity observed in the

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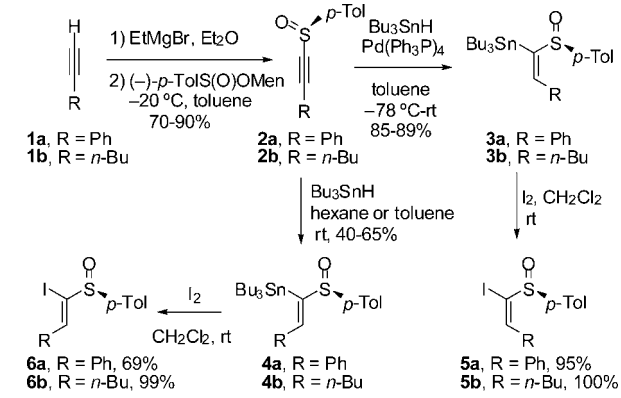
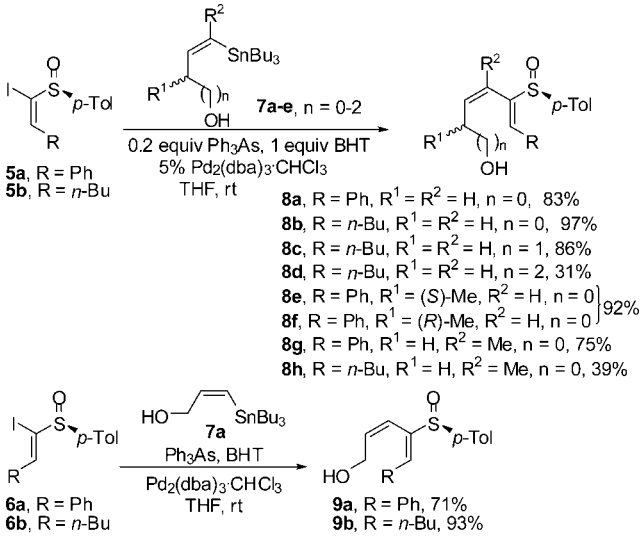
SCHEME 2. Synthesis of Iodo Vinyl Sulfoxides



SCHEME 3. Synthesis of Hydroxy Dienyl Sulfoxides



process. The rapid tin−iodine exchange afforded *E* iodo vinyl sulfoxides **5a** and **5b** from stannanes **3** and *Z* isomers **6a** and **6b** from intermediates **4**.[11]

The iodo vinyl sulfoxides were then subjected to Stille coupling conditions with a variety of known vinyl stannanes, available in one step from commercially available alkynols.[12] Thus, from *E* iodides **5a,b**, and using vinyl stannanes **7a**−**e**, *Z,Z* hydroxy dienyl sulfoxides **8a**−**h** were obtained (Scheme 3). In the case of *Z* iodo vinyl sulfoxides **6a,b**, the Stille coupling reaction was only carried out with stannane **7a**, to afford *Z,E* dienyl sulfoxides **9a,b**. All dienyl sulfoxides were obtained with moderate to excellent yields and were stable compounds. Diastereomeric dienes **8e** and **8f** were prepared from racemic stannane **7d** (R^1 = Me, R^2 = H, n = 0) and could be separated by chromatography. It should be pointed out that they could be obtained as single isomers using commercially available enantiopure alkynols to prepare stannanes **7d**.

Cyclization of *Z,Z* and *E,Z* Hydroxy Dienyl Sulfoxides. Substrate **8b** was selected as a representative example to pursue the monoepoxidation to produce the desired vinyl oxirane related to **C** (Scheme 1). After considerable experimentation, all attempts of electrophilic epoxidation on hydroxy dienyl sulfoxide **8b** led to complex reaction mixtures or to the oxidation of the sulfoxide to the sulfone. Therefore, we decided to examine the base-induced cyclization of dienols **8** and **9** to obtain **F**-type structures (Scheme 1). Table 1 summarizes the results obtained for the cyclization of *Z,Z* dienols **8a**−**h** to dihydropyrans **F**. We first examined the use of 2 equiv of LDA with diene **8b**, to afford 2,3-*trans* dihydropyran **10b** as a single isomer (Table 1, entry 1). Even though the addition of the base was carried out at low temperature, the product was not observed by TLC until the temperature reached 0 °C. With diene **8a**, under the same conditions dihydropyran **10a** was obtained, although a significant amount of enyne **12**, resulting from the base-promoted elimination of the sufinyl group, was obtained. Subsequently dihydropyran **10a** was obtained as a single isomer in excellent yield decreasing the amount of base and again starting the reaction at −78 °C (Table 1, entry 2). The use of NaH at low temperature also afforded enantiopure **10a** and **10b**, with good yields (Table 1, entries 3 and 4). Interestingly, these allylic sulfoxides **10a,b** were stable and could be purified on silica gel and stored for months, and no epimerization at sulfur was observed.

The influence of an additional stereogenic center was explored next under the optimized conditions. Diene **8e** displayed a similar behavior as the previous examples, affording allylic sulfoxide **10e** in good yield (Table 1, entry 5). Along with the major product a small amount of vinyl sulfoxide was isolated, resulting from the isomerization of the allylic double bond in the final product. In contrast, diastereomeric dienol **8f** did not react under these conditions, and NaH was necessary to promote cyclization (Table 1, entry 6). These results show that this methodology gives straightforward access to enantiomerically pure 2,6-*cis* and 2,6-*trans* dihydropyrans. The cyclization was compatible with additional substitution on the diene. From diene **8g** (R^2 = Me), using the original conditions (LDA, −78 °C to rt), a 70:30 mixture of dihydropyran **10g** and allylic alcohol **13g**, resulting from sulfoxide-sulfenate sigmatropic rearrangement of **10g**, was obtained. As a consequence, we considered that a hydride base would accelerate the cyclization and perhaps suppress the rearrangement. Using KH, the yield of **10g** was optimized (Table 1, entry 7), and though the same conditions were used for diene **8h**, the product was obtained only in moderate yield (Table 1, entry 8). Even though dihydropyrans **10f**−**h** were obtained as single isomers, they were unstable on silica gel or upon standing in CH_2Cl_2 solution. Epimerization at sulfur was observed affording equilibrated mixtures of allylic sulfoxides, 70:30 for **10f**, and 50:50 for both **10g** and **10h**.

Scheme 4 shows the model proposed to rationalize the formation of dihydropyrans **10** from *Z,Z* dienes **8** that assumes an *S-cis* eclipsed conformation C═C/S−:[13] and takes into consideration the model proposed by Iwata for the addition of oxygenated nucleophiles to cyclic vinyl sulfoxides under basic conditions.[8b,c] Coordination of the sulfinyl oxygen and the alkoxide with the metal would direct the attack to the α face of the diene, forming an intermediate **J** that after protonation

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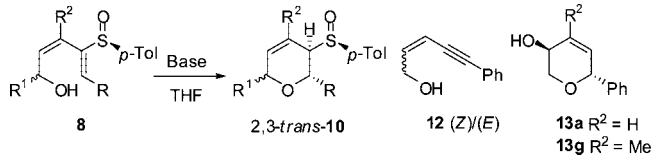
TABLE 1. Base-Induced Cyclization of *Z,Z* Hydroxy Dienyl Sulfoxides

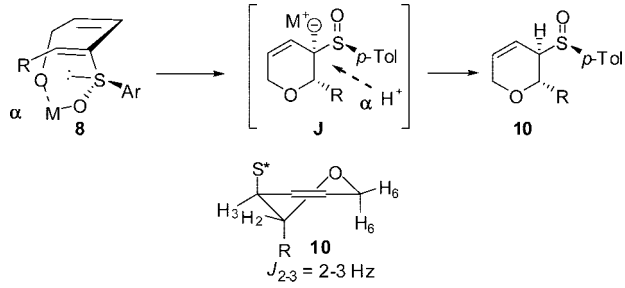


8 2,3-*trans*-**10** **12** (*Z*)/(*E*) **13a** R^2 = H **13g** R^2 = Me

entry	R	R^2	R^1	**8**	conditions	**10** (yield %)
1	*n*-Bu	H	H	**8b**	2 equiv LDA, −78 °C to rt, 4 h	**10b** (94)
2	Ph	H	H	**8a**	1.1 equiv LDA, −78 °C to rt, 4 h	**10a** (84)[a]
3	Ph	H	H	**8a**	1.1 equiv NaH, −30 °C to rt, 20 h	**10a** (72)
4	*n*-Bu	H	H	**8b**	1.3 equiv NaH, −30 °C to rt, 3 h	**10b** (82)
5	Ph	H	(*S*)-Me	**8e**	1.1 equiv LDA, −78 °C to rt, 2 h	**10e** (70)[b]
6	Ph	H	(*R*)-Me	**8f**	1.3 equiv NaH, −30 °C to rt, 3 h	**10f** (100)
7	Ph	Me	H	**8g**	1.1 equiv KH, −30 °C to rt, 1 h 30 min	**10g** (87)
8	*n*-Bu	Me	H	**8h**	1.3 equiv KH, −30 °C to rt, 1 h 45 min	**10h** (58)
9	*n*-Bu	H	H	**8b**	1.1 equiv DBU, 0 °C to rt, 5 days	**10b** (50)[c]

[a] ^{1}H NMR of the crude reaction showed a 93:7 ratio of **10a** and *Z*-**12**. [b] 17% of the corresponding vinyl sulfoxide was obtained. [c] 50% of **8b** recovered. Reaction carried out in CH_2Cl_2.

SCHEME 4. Rationalization of Cyclization Results



from the same face of the molecule, would lead to 2,3-*trans* dihydropyran **10**.

To generalize the process and study the effect of nonionic bases on the stereochemistry of the cyclization, we examined the use of other conditions. Initial experiments with substrate **8b** using DBU in THF, afforded the expected product **10b** with very low yield, a result that could be slightly improved by changing the solvent to CH_2Cl_2 and increasing the reaction time (Table 1, entry 9).

We next examined phosphazene BEMP, in the same conditions used for DBU, obtaining dihydropyran **10b** with a considerable amount of 3,6-*cis* alcohol **14b** in good yield (Table 2, entry 1). When the stoichiometry of the base was decreased and with shorter reaction times (Table 2, entry 2), a small amount of 2,3-*cis* dihydropyran **11b** was isolated accounting for the rapid formation of 3,6-*cis* alcohol **14b**. In the case of substrate **8a**, with an aromatic substituent, again both 2,3-*trans* **10a** and 2,3-*cis* **11a** isomers were isolated along with alcohol **14a** (Table 2, entry 3).[14]

Seeking to improve the amount of 2,3-*cis* **11**, we used a stronger phosphazene base such as P_2-^{t}Bu at −78 °C. These new conditions increased the yield of cyclization for aromatic substrate **8a** (Table 2, entry 4) and reduced the amount of alcohol **14a**. In the case of **8b**, shorter reaction times and a nonaqueous workup, to prevent an eventual epimerization of the 2,3-*cis* dihydropyran, gave a higher yield of isomer **11b**, along with some *trans* isomer **10b** and a small amount of alcohol **14b** (Table 2, entry 5). Finally, the use of P_2-^{t}Bu or P_4-^{t}Bu in different solvents (toluene, CH_2Cl_2) did not improve the previous findings. From these results, it is tempting to speculate that, with the strongly basic phosphazenes that allow for the use of low temperatures and short times, the 2,3-*cis* dihydropyrans **11** might be the kinetic products, with the *trans* isomers **10** being obtained under thermodynamic control by epimerization α to sulfur. Alternatively, both isomers would arise from attack of the alkoxide to the α face of the diene, leading to products with the same configuration at C-2, identical to the findings for LDA and hydrides. Subsequent protonation with inversion or retention would afford the *cis* and *trans* products **11** and **10**.[15] The *cis* alcohols **14** formed in the reaction would originate from the facile sigmatropic rearrangement of the less stable 2,3-*cis* sulfinyl dihydropyrans **11** under those conditions. The considerable complexity of these examples, leading to three products in most cases precluded a more detailed study of the process, particularly addressing the possibility of *cis* isomers **11** undergoing epimerization to *trans* products **10**.

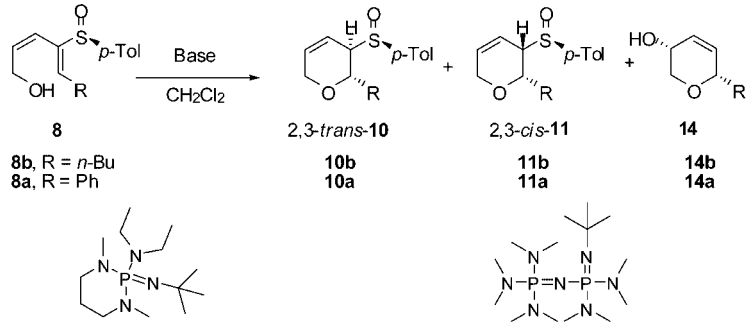
At this stage, the cyclization of isomeric *Z,E* dienes **9a** and **9b** was explored, observing in both cases lower reactivities and selectivities (Scheme 5). The use of LDA at low temperature failed to promote the cyclization and the optimal conditions required the use of KH for **9a** and NaH for **9b**. Treatment of **9a** with KH provided a diastereomeric 2,3-*trans* product **16a** and a small amount of vinyl sulfoxide. In contrast, treatment of **9b** with NaH afforded 2,3-*cis* sulfinyl dihydropyran **15b** and a small amount of **10b** with variable selectivities (from 96:4 to 68:12). Whereas **9b** followed the stereochemical course previously observed for *Z,Z* dienes (attack to the α face and protonation from the same face) to give 2,3-*cis* products, a different scenario was found for **9a**. We speculate that the expected 2,3-*cis* product **15a** could not be formed due to strong steric interaction of the substituents in adjacent positions.

To broaden the scope of the methodology toward 7- and 8-membered oxacycles, we focused our attention on substrates **8c** and **8d**. While conditions previously successful for *Z,Z* substrates (LDA, BEMP) led to recovery of starting material for substrate **8c**, the desired cyclic product 2,3-*trans* **17c** was obtained with hydride bases (Table 3, entries 1 and 2) as a single isomer albeit in low yields. These yields were increased using

(14) 2,3-*cis* and 2,3-*trans* stereochemistry was easily assigned by analysis of coupling constants and NOESY-1D experiments (see Supporting Information).

(15) It should be mentioned that we made several attempts to trap the intermediate anion formed in the reaction under different conditions (see Supporting Information). Unfortunately, all efforts to capture the anion with MeI were unsuccessful, but we were able to obtain dihydropyrans **10b** and **11b** partially deuterated at C-3 with NaH and quenching with CD_3OD.

TABLE 2. Phosphazene-Induced Cyclization of *Z,Z* Hydroxy Dienyl Sulfoxides



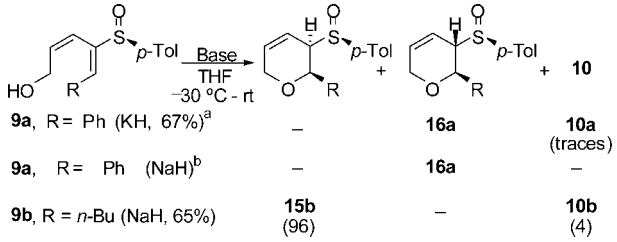
BEMP: 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine

P$_2$-^{t}Bu: 1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-$-2^5,4^5$-catenadi(phosphazene)

entry	dienol	conditions	**10**[a] ratio %	**11**[a] ratio %	**14**[a] ratio %	combined yield %
1	**8b**	1.3 equiv BEMP, 0 °C to rt, 4 days	**10b** (40)		**14b** (60)	100
2	**8b**	0.5 equiv BEMP, 0 °C to rt, 2 h	**10b** (55)	**11b** (15)	**14b** (30)	61[b]
3	**8a**	1.3 equiv BEMP, 0 °C to rt, 40 min	**10a** (41)	**11a** (46)	**14a** (13)	99
4	**8a**	1.1 equiv P$_2$-^{t}Bu, −78 °C, 1 h	**10a** (40)	**11a** (56)	**14a** (4)	100
5	**8b**	1.1 equiv P$_2$-^{t}Bu, −78 °C, 5 min	**10b** (22)	**11b** (58)	**14b** (20) [c]	86

[a] Ratio measured in ^{1}H NMR of the crude product. [b] 37% of **8b** recovered. [c] Nonaqueous workup. The cold reaction mixture was filtered through a short pad of silica gel.

SCHEME 5. Base-Induced Cyclization of *Z,E* Hydroxy Dienyl Sulfoxides



[a] 10% of vinyl sulfoxide was obtained. [b] A ca. 1:1 mixture of **16a** and **9a**, 50% was isolated, along with ca. 50% of alcohole ***ent*-13a**.

phosphazene P$_2$-^{t}Bu, but the product was obtained as a mixture of *trans-cis* diastereoisomers **17c**−**18c** (Table 3, entries 3 and 4). Unfortunately, none of the conditions examined for dienol **8d** allowed for the formation of the eight-membered ring.

Reactivity and Chemical Correlations of Sulfinyl and Sulfonyl Dihydropyrans. To study some aspects of the reactivity of these allylic sulfoxides, we examined their behavior under oxidation and dihydroxylation conditions and the results are summarized in Tables 4 and 5 and Scheme 6. In addition, a thorough study of the sigmatropic sulfoxide-sulfenate rearrangement was also carried out and the results of this study will be described in due time.

The oxidation of several substrates under standard conditions supports the stereochemical assignments carried out at the sulfoxide stage. Substrates **10** and **11** afforded enantiopure allylic sulfones **20** and **21**,[16] versatile synthetic intermediates, in good yields (Table 4, Scheme 6). Thus, whereas **10a** and **11a** gave diastereomeric allylic sulfones **20a** and **21a**, respectively (Table 4, entries 1 and 6), **10a** and **16a** led to enantiomeric products (Scheme 6). Similarly, upon oxidation **11b** and **15b** afforded **21b** and ***ent*-21b**, respectively. Furthermore, the oxidation of diastereomeric mixtures of **10g** and **10h** gave single isomers of sulfones **20g** and **20h**, respectively. Finally, the oxidation of a mixture of sulfoxides **17c** and **18c** led to a mixture of sulfones **22c** and **23c** with a similar ratio as the starting sulfoxide mixture.

At this stage we focused our efforts on carrying out exploratory experiments on the reactivity of our sulfinyl dihydropyrans to gain insight on the design of future synthetic applications. We first examined the Pummerer rearrangement of **10a** that led to a complex reaction mixture. A hydroboration−oxidation sequence was studied on the same substrate, and this led to a mixture of regioisomers, along with a considerable amount of sulfone products. The one-pot oxidation/epoxidation of sulfinyl dihydropyrans **10a** and **10b** was explored using *m*-CPBA under different conditions, but for both substrates, only sulfones **20a,b** were obtained. We briefly considered the possibility of forming the desired epoxide from the corresponding bromohydrin, but treatment of **10a** with NBS led to a complex mixture of unidentified products. The functionalization of the carbon−carbon double bond by an osmium-catalyzed dihydroxylation was considered a reasonable alternative, and the results obtained are gathered in Table 5.[17]

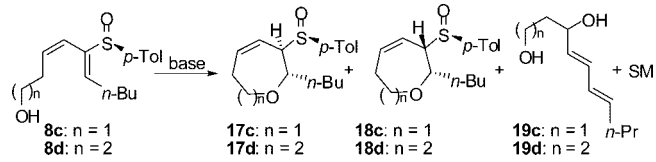
The dihydroxylation of diastereomeric mixtures of sulfoxides **10g**, substituted at position 4 and hence more conformationally restricted substrates, gave an excellent yield of sulfonyl diol **24g** (Table 5, entry 1). Encouraged by this result we examined the dihydroxylation of less hindered substrates **10a,b** that led to good yield of diols **24a,b** as single isomers. With substrate **10a** we studied the reaction in depth trying to control the overoxidation of the sulfoxide, but we were not able to obtain the sulfinyl diol with good chemoselectivity (see Supporting Information). The sulfinyl diol was oxidized with MMPP affording the expected sulfonyl diol **24a** as a single product, which could also be obtained by dihydroxylation of sulfone **20a** (not shown, see Supporting Information). All attempts to carry

(16) For reviews, see: (a) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107–124. (b) Pyne, S. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds; Thieme: Stuttgart, 1995; Vol. E21b, p 2068.

(17) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

(18) All attempts to obtain the related sulfinyl diol using OsO_4 under controlled conditions led to mixtures of starting material, allylic sulfone, sulfinyl diol, and sulfonyl diol **24**. For details see Supporting Information.

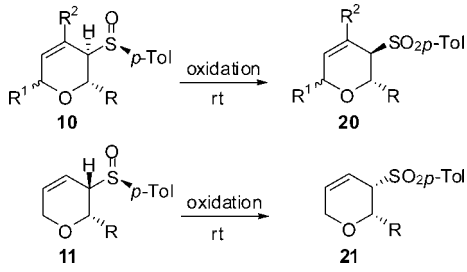
TABLE 3. Base-Induced Cyclizations to Obtain Seven-Membered Rings



entry	*n*	**8**	conditions	**17:18** ratio	yield %	**8c** yield %
1	1	**8c**	1.1 equiv NaH, THF, −30 °C to rt, 2 h 30 min	**17c**:**18c** (100:0)	29	59
2	1	**8c**	1.3 equiv KH, THF, −45 °C to rt, 3 h	**17c**:**18c** (100:0)	26	39[a]
3	1	**8c**	1.1 equiv P_2-^{t}Bu, CH_2Cl_2, −78 °C to rt, 2 h	**17c**:**18c** (81:19)	47	8[a]
4	1	**8c**	1.1 equiv P_2-^{t}Bu, CH_2Cl_2, −78 to −20 °C, 2 h	**17c**:**18c** (81:19)	65	18

[a] 16% of diol **19c** was recovered.

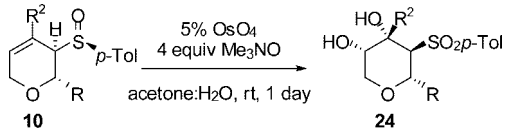
TABLE 4. Oxidation of Sulfinyl Dihydropyrans and Stereochemical Correlations



entry	**10/11**	R	R^1	R^2	conditions	**20/21** (yield %)
1	**10a**	Ph	H	H	MMPP, MeOH	**20a** (75)
2	**10b**	*n*-Bu	H	H	MMPP, MeOH	**20b** (86)
3	**10f**	Ph	(*R*)-Me	H	*m*-CPBA, CH_2Cl_2	**20f** (60)[a]
4	**10g**	Ph	H	Me	*m*-CPBA, CH_2Cl_2	**20g** (68)[b]
5	**10h**	*n*-Bu	H	Me	MMPP, MeOH	**20h** (88)[a]
6	**11a**	Ph	H	H	*m*-CPBA, CH_2Cl_2	**21a** (61)
7	**11b**	*n*-Bu	H	H	MMPP, MeOH	**21b** (31)[c]

[a] Starting material [70:30] mixture of epimers at sulfur. [b] Starting material [50:50] mixture of epimers at sulfur. [c] Allylic alcohol **14b** (58%) was also obtained. MMPP = magnesium bis(monoperoxyphthalate) hexahydrate, *m*-CPBA = *m*-chloroperbenzoic acid.

TABLE 5. Dihydroxylation of 2,3-*trans* Dihydropyrans 10



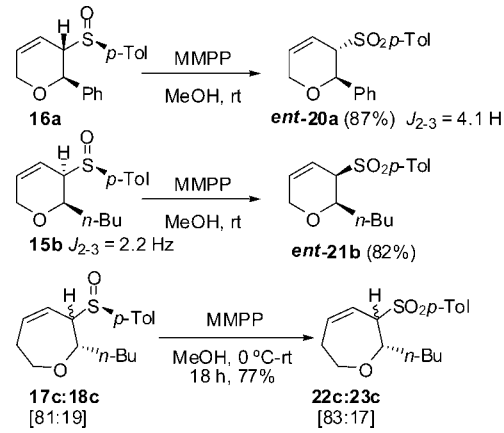
entry	**10**	R	R^2	**24** (yield %)
1	**10g**	Ph	Me	**24g** (86)[a]
2	**10a**	Ph	H	**24a** (70)
3	**10b**	*n*-Bu	H	**24b** (69)

[a] Starting material [50:50] mixture of epimers at sulfur.

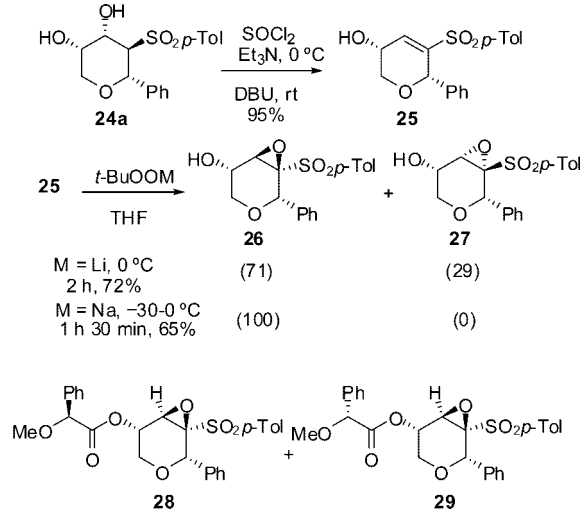
out the desulfonylation of **24b** failed, leading only to recovery of the starting sulfonyl diol.[19]

Sulfonyl diol **24a** was transformed smoothly to hydroxy vinyl sulfone **25** (Scheme 7), structurally related to our initial objective **D** (Scheme 1), according to the protocol of Rayner.[20] Next, the nucleophilic epoxidation of hydroxy vinyl sulfone **25** using metallated hydroperoxides was explored, and optimal results

SCHEME 6. Oxidation of Sulfinyl Dihydropyrans and Stereochemical Correlations



SCHEME 7. Reactivity of Hydroxy Sulfonyl Dihydropyrans



were obtained with *t*-BuOONa, which led to epoxy sulfone **26** as a single isomer. The absolute configuration of hydroxy sulfonyl oxirane **26** was determined by synthesis of (*S*)- and (*R*)-methoxyphenylacetates **28** and **29** (Scheme 7).[22]

Sulfonyl oxirane **26** could be cleaved with $MgBr_2$ to obtain bromopyranone **30** (Scheme 8), initially as a single isomer,

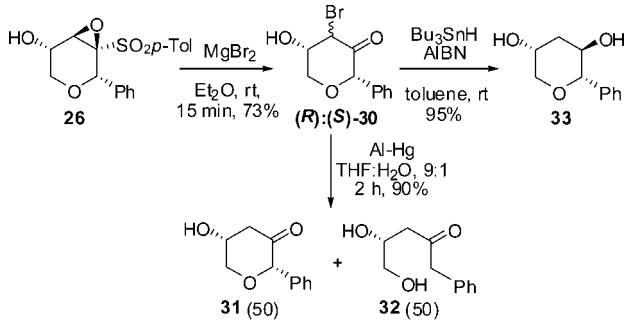
(19) (a) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547–10658. (b) Lee, G. H.; Youn, I. K.; Choi, E. B.; Lee, H. K.; Yon, G. H.; Yang, H. C.; Pak, C. S. *Curr. Org. Chem.* **2004**, *8*, 1263–1287. (c) Das, I.; Pathak, T. *Org. Lett.* **2006**, *8*, 1303–1306.

(20) Westwell, A. D.; Thornton-Pett, M.; Rayner, C. M. *J. Chem. Soc. Perkin Trans. 1* **1995**, 847–859.

(21) Briggs, A. D.; Jackson, R. F. W.; Brown, P. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4097–4102.

(22) (a) For details see Supporting Information. (b) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569–8577. For a review on the determination of absolute configuration by NMR, see: (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–118.

SCHEME 8. Reactivity of Hydroxy Sulfonyl Oxirane 26

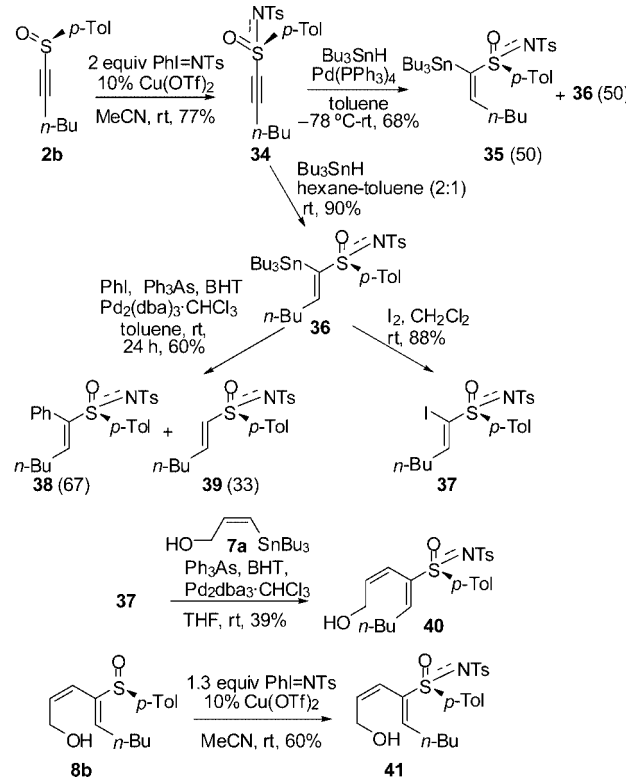


which underwent a rapid epimerization of the halogen bearing center.[23] An attempt to cleave the C−Br bond with Al−Hg led to an equimolar mixture of the desired product **31** and diol **32** derived from dehalogenation and concurrent ring cleavage. Treatment of the mixture with Bu_3SnH and AIBN resulted not only in the elimination of the bromine atom but also in a rapid and stereoselective reduction of the carbonyl group, obtaining diol **33** as a single isomer in excellent yield (Scheme 8).

At this stage we wanted to explore the reactivity of our dihydropyranyl allylic sulfones **20** and **21** in copper-mediated S_N2' processes. While this study was successful in some cases (see below), some important limitations prompted us to consider that the use of the related dihydropyranyl allylic sulfoximines could display an enhanced reactivity in those processes and, additionally, the chiral leaving group might influence the stereochemical outcome of the displacement.[24] Furthermore, examining the behavior of hydroxy dienyl sulfoximines related to our sulfinyl dienols **E** (Scheme 1) in this chemistry was considered to be an interesting extension of the methodology. Therefore we set out to explore briefly the preparation of hydroxy dienyl sulfoximines using similar chemistry to that used for the related sulfoxides.

Preparation of Hydroxy Dienyl Sulfoximines. Imination of sulfoxide **2b** as described by Malacria[25] led to alkynyl sulfoximine **34**, which was transformed into stannanes *E*-**35** and *Z*-**36** by hydrostannylation (Scheme 9). Interestingly, while the uncatalyzed hydrostannylation was completely selective and high-yielding, the Pd-catalyzed variant afforded an equimolar mixture of stannanes **35** and **36**. The behavior of stannane **36** as a coupling partner in the Stille reaction with iodobenzene was tested, to afford the expected product in moderate yield along with the product of protonolysis, **39**. It should be noted that this coupling is somewhat more efficient than when the related sulfinyl stannane is used. Alternatively, stannane **36** was smoothly transformed into vinyl iodide **37** that was coupled with hydroxy vinyl stannane **7a** in a Stille process to afford *Z*,*E* diene **40** in low yield. Since tin−halogen exchange of stannane **35** was low-yielding, we essayed the imination of readily available hydroxy sulfinyl diene **8b** to obtain *Z*,*Z* diene **41** in moderate yield. It should be mentioned that we have assumed that all of these iminations take place with complete retention of configuration at the sulfur atom, in analogy with the findings of Malacria.[25]

SCHEME 9. Synthesis of Hydroxy Dienyl Sulfoximines



Cyclization of Hydroxy Dienyl Sulfoximines. The cyclization of hydroxy sulfoximinoyl dienes **40** and **41** was then briefly examined in a parallel fashion as the related sulfoxides, and the results are shown in Table 6. Dienyl sulfoximine **41** gave dihydropyrans **42** and **43** in similar yields and selectivity with LDA or KH (Table 6, entries 1 and 2), whereas the use of NaH led to comparable selectivity but with lower yield. Because of availability problems with dienol **40**, we were able to try only the conditions with NaH, to obtain an equimolar mixture of allylic sulfoximines **42** and **43** that were difficult to separate by chromatography.

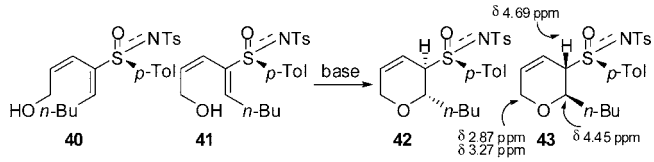
In analogy to the results obtained for sulfoxides, we expected that **42** and **43** would arise by alkoxide attack to the same face of the diene and protonation from opposite faces to form both *trans* and *cis* diastereoisomers, as we had previously observed at least in one case. The NOESY experiments for **42** and **43** were not conclusive, and therefore to confirm the stereochemistry initially assigned to these allylic sulfoximines, we explored the imination of the related sulfinyl dihydropyrans (Scheme 10). Since these allylic sulfoxides were perceived as potentially sensitive substrates, the behavior of substrate **10b** with each of the reagents for the imination was examined separately, and no epimerization or diastereomerization at sulfur was observed. The imination of **10b** led to 2,3-*trans* **42** that was identical to the minor product obtained in the cyclization of **41**. We then expected to obtain **43** from the imination of *cis* diastereoisomer **11b**, and surprisingly we obtained a new isomer 2,3-*cis* **44**. Similarly, the imination of the alternative *cis* isomer **15b** led to **45**, and again we were surprised to discover it had spectroscopic properties different from those of **43**. Therefore, we concluded that the only remaining possibility was that the absolute stereochemistry of **43** was a 2,3-*trans* system diastereomeric to **42**. The patterns found for the chemical shifts of **44** and **45**

(23) (a) de Reinach-Hirtzbach, F.; Durst, T. *Tetrahedron Lett.* **1976**, *17*, 3677–3680. (b) Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789–1797.

(24) (a) Gais, H.-J.; Mueller, H.; Bund, J.; Scommoda, M.; Brandt, J.; Raabe, G. *J. Am. Chem. Soc.* **1995**, *117*, 2453–2466. (b) Scommoda, M.; Gais, H.-J.; Bosshammer, S.; Raabe, G. *J. Org. Chem.* **1996**, *61*, 4379–4390. (c) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1–64.

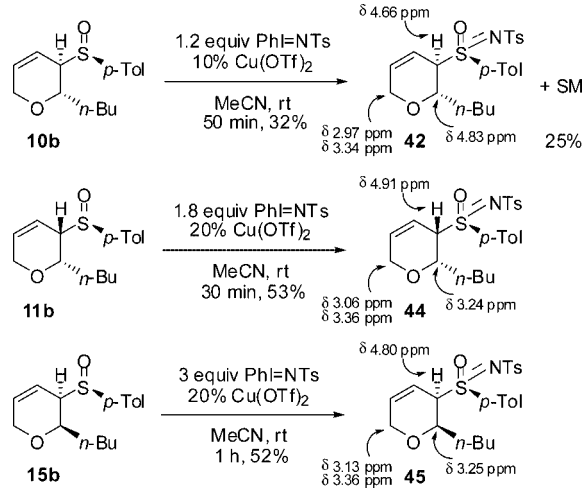
(25) (a) Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116–118. (b) Leca, D.; Song, K.; Amatore, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Eur. J.* **2004**, *10*, 906–916.

TABLE 6. Cyclization of Dienyl Sulfoximines

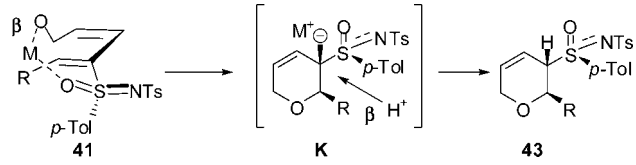


entry	substrate	conditions	**42**:**43** ratio	yield %
1	**41**	1.1 equiv LDA THF, −78 °C to rt, 3 h	20:80	68
2	**41**	1.3 equiv KH THF, −78 °C to rt, 1 h 30 min	15:85	68
3	**41**	1.3 equiv NaH THF, −78 °C to rt, 1 h 30 min	17:83	54
4	**40**	2.6 equiv NaH THF, −78 °C, 5 h	50:50	79

SCHEME 10. Imination of Sulfinyl Dihydropyrans



SCHEME 11. Rationalization of Cyclization Results for Dienyl Sulfoximine 41



were similar, in agreement with their *cis* relative configuration, enantiomeric except for the configuration at sulfur.

We believe the stereochemical outcome of this cyclization is the result of the low facial selectivity in the attack of the alkoxide intermediate to the diene and protonation from the same face of the attack in both cases. This could be caused by the different conformation adopted by the substrates to accommodate the chiral sulfoximine group to minimize possible interactions.[26] A tentative rationalization implies an *anti* arrangement of the *N*-tosyl group relative to the vinyl group, which places the oxygen atom above the plane of the diene, and attack of the nucleophile could be controlled by coordination of the alkoxide to the sulfoximine oxygen (Scheme 11). This alkoxide attack is also occurring on the less-hindered face of the diene. Thus, for dienol **41** a relatively weak coordination of the alkoxide with the sulfoximine oxygen from the less hindered β face would lead to a metallated allylic sulfoximine **K** that after protonation from the β face would deliver **43**.

The rationalization of results for *Z,E* isomer **40** would imply a less restricted conformation about the C−S bond that results in a nonselective attack of the alkoxide to the dienyl sulfoximine, producing an equimolar mixture of **42** and **43**. Though dienyl sulfoximines display a higher reactivity than the related sulfoxides, their selectivity in these processes is much lower, at least in the few examples examined; these results underline the synthetic usefulness of the sulfinyl functionality for this chemistry. Nonetheless, it should be pointed out that, after optimization of the cyclization of dienyl sulfoximines, in principle, both enantiomeric series of dihydropyrans could be accessed from the same precursor by adjusting the oxidation state at sulfur.

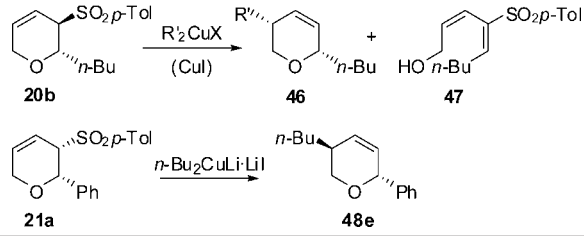
S_N2' Displacements of Allylic Sulfones and Sulfoximines. To explore the reactivity of our dihydropyranyl allylic sulfones, their behavior under different S_N2' displacement conditions was examined. When necessary, 3-tosylcyclohexene was used as a model substrate before trying the different processes on sulfone **20b**. The Lewis acid promoted reaction with silyl enol ethers was successfully carried out with $AlCl_3$, affording the expected ketone for the model system.[16a] Unfortunately substrate **20b** did not react with any of the Lewis acids tried ($EtAlCl_2$, $AlCl_3$, $BF_3 \cdot Et_2O$, $TiCl_4$). Allylation of **20b** with a variety of Lewis acids and allyl trimethylsilane was unsuccessful. Free radical processes with Bu_3SnH and AIBN afforded complex reaction mixtures, where small amounts of substitution products could be identified, but they could not be isolated cleanly. Several attempts of palladium-catalyzed substitution with malonate anion also failed to afford substituted products, leading to the recovery of sulfone **20b**. At this stage we focused our efforts on the S_N2' reaction of allylic sulfoxides, sulfones, and sulfoximines with organocuprates. The displacement on allylic sulfoxide **10b** (not shown) afforded only traces of the desired product, and mainly starting material was recovered. In contrast allylic sulfones displayed a reasonable, albeit somewhat capricious behavior and these results are gathered in Table 7. As expected, these displacements led to products of regioselective γ attack of the cuprate to the allylic sulfone.[27]

At the beginning, we carried out a small scale reaction of 2,3-*trans* **20b** and *n*-Bu_2CuLi to produce a good yield of 3,6-*cis* **46a**. However, the use of *n*-butyllithium to generate the cuprate gave results difficult to reproduce, and when the scale was increased, *Z,E* sulfonyl diene **47**, presumably derived from ring cleavage of **20b**, was obtained as the major product (Table 7, entries 1 and 2). The *Z,E* stereochemistry of **47** was confirmed

(26) (a) Jackson, R. F. W.; Briggs, A. D.; Brown, P. A.; Clegg, W.; Elsegood, M. R. J.; Frampton, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1673–1682. (b) Briggs, A. D.; Clegg, W.; Elsegood, M. R. J.; Frampton, C. S.; Jackson, R. F. W. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1998**, *54*, 1335–1341.

(27) (a) Julia, M.; Righini-Tapif, A.; Verpeaux, J.-N. *Tetrahedron* **1983**, *39*, 3283–3287. (b) Julia, M.; Verpeaux, J.-N. *Tetrahedron* **1983**, *39*, 3289–3291. (c) Masaki, Y.; Sakuma, K.; Kaji, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1171–1175. (d) Bäckvall, J. E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396–6403.

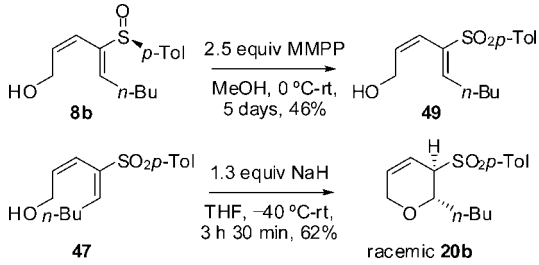
TABLE 7. S_N2' on Dihydropyranyl Allylic Sulfones with Organocuprates



entry	sulfone	R′	conditions[a]	**46/48** (yield %)	SM %
1	**20b**	*n*-Bu	*n*-Bu_2CuLi	**46a** (78)[b]	
2	**20b**	*n*-Bu	*n*-Bu_2CuLi	**46a** (46)[c]	
3	**20b**	*n*-Bu	*n*-Bu_2CuMgBr	**46a** (66)	34
4	**20b**	allyl	$allyl_2$CuMgBr	**46b** (24)[d]	47
5	**20b**	Me	Me_2CuMgBr	**46c** (52)[e]	6
6	**20b**	Ph	Ph_2CuMgBr	**46d** (93)	
7	**21a**	*n*-Bu	*n*-Bu_2CuLi	**48e** (37)	

[a] All reactions were carried out in Et_2O−THF as solvent, from 0 °C to rt. [b] 0.078 mmol scale. [c] *Z,E* Sulfonyl diene **47** was isolated as the major product. [d] 0.08 mmol scale, estimated yield; product could not be isolated. [e] 42% of **47** was isolated.

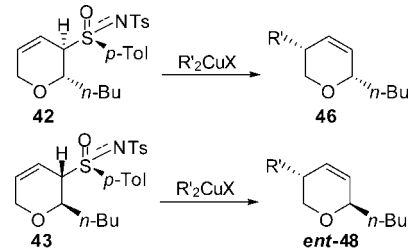
SCHEME 12. Reactivity of Hydroxymethyl Dienyl Sulfones



by comparison with the isomeric dienyl sulfone *Z,Z* **49**, generated by oxidation (MMPP) of the known *Z,Z* dienyl sulfoxide **8b** (Scheme 12). The cyclization of sulfonyl diene **47** with NaH was examined, to render racemic 2,3-*trans* **20b** as a single diastereoisomer. It should be noted that *Z,E* dienyl sulfone **47** and dienyl sulfoximine **40** afford 2,3-*trans* dihydropyrans, albeit with different selectivities; this is in sharp contrast with *Z,E* dienyl sulfoxide **9b** that yields mainly 2,3-*cis* dihydropyrans.

Seeking to avoid the formation of **47**, different sources of copper and counterions were studied (Table 7). Copper salts different from CuI did not produce any substitution product, probably because of the low reactivity of the organocuprates and the high stability of the allylic sulfone. Alternatively Grignard-derived organocuprate reagents presented a more reproducible behavior, affording similar yields of substituted product **46a** as the lithium cuprates (Table 7, entry 3). The use of an organocopper reagent and the reaction with the vinyl cuprate led only to recovery of starting material. Allyl and methyl derivatives **46b** and **46c** could be obtained with low to moderate yields (Table 7, entries 4 and 5), but when the cuprate was formed from MeMgI sulfonyl diene **47** was again the main product of the reaction. In contrast, an aromatic residue was introduced in excellent yield to produce **46d** (Table 7, entry 6), giving access to interesting cores for synthetic targets, perhaps by oxidation of the aryl group into a carboxylic acid, thus increasing the scope of the methodology.[28] Finally, the displacement of 2,3-*cis* sulfone **21a** (Table 7, entry 7) with the lithium cuprate gave a low yield of 3,6-*trans* disubstituted dihydropyran **48e**.

TABLE 8. S_N2' on Dihydropyranyl Allylic Sulfoximines with Organocuprates



entry	R′	substrate	conditions[a]	**46/*ent*-48** (yield %)	SM %
1	*n*-Bu	**42**	*n*-Bu_2CuLi	46a **46a**(46)	53
2	*n*-Bu	**42**	*n*-Bu_2CuMgBr	**46a**(70)	
3	allyl	**42**	$allyl_2$CuMgBr	**46b**(20)[b]	12
4	Me	**42**	Me_2CuMgBr	**46c**(55)	
5	*n*-Bu	**43**	*n*-Bu_2CuMgBr	***ent*-48a**(44)[c]	26

[a] All reactions were carried out in Et_2O−THF as solvent, from 0 °C to rt. [b] Small scale, product could not be isolated. Brominated byproducts were the major products. [c] 29% of brominated byproduct was isolated.

In an effort to overcome the limitations of these displacements and to compare the reactivity of both functionalities, the behavior of the related allylic sulfoximines was explored. It has been reported that allylic sulfoximines react with organocuprates with high selectivity at the α-position and with organocopper reagents in the presence of boron trifluoride and lithium iodide with an equally high selectivity at the γ-position. We thought that our cyclic allylic sulfoximines provided an opportunity to expand the scope of this study.[24a,b]

Surprisingly, the S_N2' displacement of 2,3-*trans* sulfoximine **42** gave similar results as the corresponding sulfone 2,3-*trans* **20b**, both with lithium and magnesium as counterions of the organocuprate species (Table 8, entries 1 and 2), with again the Grignard derived reagent leading to optimal results. Dihydropyran **46a** had identical spectroscopic data and optical rotation to the one derived from the reaction of sulfone **20b**. Allyl and methyl nucleophiles gave yields similar to those obtained for sulfone **20b**, (Table 8, entries 3 and 4), and we again found difficulties isolating the allylated product, obtaining brominated derivatives as major products (not shown). In the case of 2,3-*trans* diastereoisomer **43** we expected ***ent*-46** to be the major displacement product, since the starting material presented opposite configuration from **42** except for the sulfur atom. Surprisingly, we obtained 3,6-*trans* product ***ent*-48a**, (Table 8, entry 5) as the major product along with brominated derivatives (not shown).

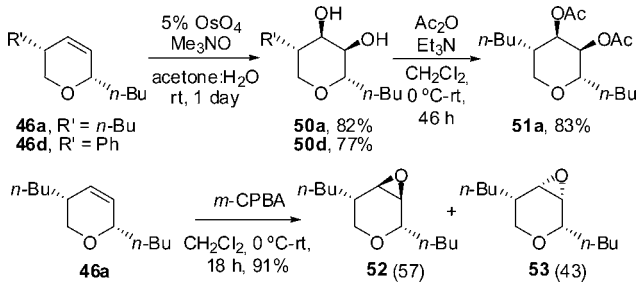
These results suggest that the sulfoximine group in the starting material is influencing the conformation of the ring thus directing the attack of the cuprate onto the allylic center. In the case of vinyl sulfoximines it has been reported that different cations and organometallic species have a profound effect on the asymmetric conjugate addition of copper reagents.[26a,30] Assuming a similar behavior for allylic derivatives, we believe that attack of the cuprate to **42** could occur *anti* as expected due

(28) Nagumo, S.; Ishii, Y.; Kakimoto, Y.-I.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 5333–5337.

(29) Brominated by-products could be formed by S_N2' substitution of sulfoximine moiety by bromide present in the reaction media resulting in a diastereomeric mixture of brominated derivatives (see Supporting Information).

(30) Pyne, S. G. *Tetrahedron Lett.* **1986**, *27*, 1691–1694.

SCHEME 13. Dihydroxylation and Epoxidation of Disubstituted Dihydropyrans



mainly to steric reasons to produce **46**. In contrast, the conformation of **43** may favor coordination of the sulfoximine to the organocuprate species and this could direct the attack to obtain the *syn* S_N2' product ***ent*-48a**.

Finally we have carried out preliminary studies on the reactivity of the S_N2' products obtained from allylic sulfones and sulfoximines, exploring the dihydroxylation and epoxidation of dihydropyrans **46a** and **46d** (Scheme 13). The dihydroxylation with OsO_4/Me_3NO occurred with complete stereoselectivity on the β face for both substrates to afford *cis* diols **50a** and **50d**, respectively, in good yields, as expected for a 3,6-*cis* disubstituted dihydropyran.[31] The stereochemical assignment was further confirmed by analysis of the coupling constants (^{1}H NMR) of diacetate **51a**, generated by acetylation of **50a**. Finally, epoxidation of **46a** with *m*-CPBA gave a mixture of diastereoisomers **52** and **53** in good yield and with negligible selectivity. These transformations outline new possibilities of synthetic applications for dihydropyranyl allylic sulfones and sulfoximines by exploiting their reactivity in S_N2' processes.

Conclusion

The base-promoted intramolecular cyclization of 2-sulfinyl dienols to obtain enantiopure sulfinyl dihydropyrans has been studied in depth. This strategy allows for creation of two asymmetric centers within a synthetically useful dihydropyran framework in an expedient manner.[32] This methodology is amenable to the preparation of seven-membered rings, albeit in low to moderate yields. The reactivity of our sulfinyl dihydropyrans toward oxidation, imination, and dihydroxylation has been explored. In this manner several routes to densely functionalized pyran derivatives have been outlined. Finally, we have examined the S_N2' displacements of allylic sulfonyl and sulfoximinoyl dihydropyrans with organocuprate reagents, to obtain 3,6-disubstituted dihydropyrans, potentially useful for the preparation of attractive synthetic targets.[33]

Experimental Section

(−)-(*S*)-2-(*Z*)-4-(*Z*)-5-Phenyl-4-(*p*-tolylsulfinyl)penta-2,4-dien-1-ol (8a). From iodide **5a** (295 mg, 0.80 mmol, 1.0 equiv), a 62:38 mixture of (*Z*)-3-(tributylstannyl)prop-2-en-1-ol, **7a**, and 2-(tributylstannyl)prop-2-en-1-ol, **7a′** (1.09 g, 3.14 mmol, 1.5 equiv of **7a**), BHT (176 mg, 0.80 mmol, 1.0 equiv), Ph_3As (50 mg, 0.16 mmol, 0.2 equiv), and $Pd_2(dba)_3\cdot CHCl_3$ (42 mg, 0.04 mmol, 0.05 equiv), according to the general procedure described in Supporting Information (12 h), diene **8a** was obtained as a single isomer. Purification by chromatography (5−80% EtOAc−hexane) afforded 229 mg of **8a** as a brown solid. A second purification (10−50% EtOAc−CH_2Cl_2) afforded **8a** (200 mg, 0.67 mmol, 83%) as a pale brown solid that was recrystallized from EtOAc−hexane. R_f 0.14 (50% EtOAc−hexane). Mp 135−137 °C. $[\alpha]^{20}_D$ −162.2 (*c* 1.00). ^{1}H NMR (300 MHz) δ 2.38 (s, 3 H), 2.67 (br s, 1 H), 3.97 (dddd, 1 H, J = 12.7, 8.3, 6.1, 0.7 Hz), 4.18 (dddd, 1 H, J = 12.7, 8.1, 4.7, 1.2 Hz), 5.76 (ddd, 1 H, J = 11.2, 2.8, 1.1 Hz), 6.12 (ddd, 1 H, J = 11.2, 8.3, 6.1 Hz), 6.98 (d, 1 H, J = 1.5 Hz), 7.26 (d, 2 H, J = 8.1 Hz), 7.36−7.46 (m, 5 H), 7.52−7.57 (m, 2 H). ^{13}C NMR (75 MHz) δ 21.4, 58.3, 121.8, 124.5 (2 C), 128.6 (2 C), 129.1, 129.8 (4 C), 133.6, 138.1, 138.2, 139.1, 141.2, 141.8. IR (KBr): 3401, 3021, 1630, 1490, 1445, 1318, 1230, 1183, 1079, 1042, 1017, 1003, 806, 759, 700 cm^{-1}. MS (ES): 619 $[2M + Na]^+$, 321 $[M + Na]^+$, 299 $[M + 1]^+$ (100%). Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08; S, 10.75. Found: C, 72.24; H, 6.12; S, 10.70.

(−)-(2*S*,3*R*,*R*$_S$)-2-Phenyl-3-(*p*-tolylsulfinyl)-3,6-dihydro-2*H*-pyran (10a). From dienyl sulfoxide **8a** (597 mg, 2 mmol) and LDA (4.4 mL, 2.2 mmol) according to the general procedure (Supporting Information, method A, 4 h), dihydropyran **10a** was obtained. Chromatography (15−50% EtOAc−hexane) afforded **12** (35 mg, 0.11 mmol, 5%) as a colorless oil and **10a** (500 mg, 1.67 mmol, 84%) as a white solid that was recrystallized from hexane.

Data for **10a**: R_f 0.34 (50% EtOAc−hexane). Mp 87−89 °C. $[\alpha]^{20}_D$ −291.7 (*c* 0.82). ^{1}H NMR (300 MHz), COSY δ 2.44 (s, 3 H, Me-*p*-Tol), 3.78 (m, 1 H, H-3), 3.91 (dq, 1 H, J = 17.6, 2.4 Hz, H-6), 4.14 (dm, 1 H, J = 17.6 Hz, H-6), 5.33 (d, 1 H, J = 2.9 Hz, H-2), 5.51 (ddtd, 1 H, J = 10.2, 4.9, 2.2, 0.5 Hz, H-4), 6.00 (dtd, 1 H, J = 10.2, 3.2, 1.0 Hz, H-5), 7.30−7.40 (m, 7 H), 7.59 (d, 2 H, J = 8.3 Hz). NOESY-1D H-2/*p*-Tol: 0.6%; H-2/Ph: 1.9%; H-2/H-3: 1.0%; H-3/H-2: 1.3%; H-3/H-4: 1.6%; H-3/*p*-Tol: 1.3%; H-3/Ph: 3.2%; H-4/H-5: 2.2%; H-4/*p*-Tol: 1.1%; H-4/H-3: 1.5%; H-5/H-4: 1.3%; H-5/H-6%: 1.1%; H-5/H-6 (4.14 ppm): 1.1%; H-5/H-6 (3.91 ppm): 1.9%; H-6/H-5: 2.1%. ^{13}C NMR (75 MHz), HSQC δ 21.5 (Me-*p*-Tol), 61.6 (C-6), 64.3 (C-3), 71.5 (C-2), 117.1 (C-4), 125.6 (2 C), 127.9 (2 C), 128.3, 128.5 (2 C), 129.7 (2 C), 133.2 (C-5), 137.3, 138.4, 142.2. IR (KBr): 2945, 2829, 1632, 1490, 1449, 1304, 1198, 1074, 1041, 1015, 960, 897, 821, 807, 752, 700 cm^{-1}. MS (ES): 619 $[2M + Na]^+$, 321 $[M + Na]^+$, 299 $[M + 1]^+$ (100%). Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08; S, 10.75. Found: C, 72.60; H, 6.26; S, 10.38.

Data for **12**: R_f 0.45 (50% EtOAc−hexane). ^{1}H NMR (300 MHz) δ 1.61 (br s, 1 H), 4.49 (t, 2 H, J = 4.6 Hz), 5.80 (dt, 1 H, J = 11.0, 1.5 Hz), 6.13 (dt, 1 H, J = 11.0, 6.3 Hz), 7.28−7.32 (m, 3 H), 7.40−7.43 (m, 2 H). MS (ES): 159 $[M + 1]^+$ (100%), 141 $[(M - 18) + 1]^+$.

(+)-(2*S*,3*S*,*R*$_S$)-2-Phenyl-3-(*p*-tolylsulfinyl)-3,6-dihydro-2*H*-pyran (11a). From dienyl sulfoxide **8a** (40 mg, 0.134 mmol) and BEMP (1.3 equiv, 51 μL, 0.174 mmol) according to the general procedure (Supporting Information, method D, 40 min) a 46:41:13 mixture of **11a**, **10a**, and **14a** was obtained. Purification by chromatography (0−20% EtOAc−CH_2Cl_2) afforded **11a** (17 mg, 0.056 mmol, 41%) as a white solid and a 75:25 mixture of **10a** and **14a** (18 mg) as a colorless oil. R_f 0.27 (30% EtOAc−CH_2Cl_2). Mp 108−110 °C. $[\alpha]^{20}_D$ +566.0 (*c* 0.70). ^{1}H NMR (400 MHz), COSY δ 2.35 (s, 3 H, CH_3 *p*-Tol), 3.33 (ap dt, 1 H, J = 5.7, 2.7 Hz, H-3), 4.40 (dq, 1 H, J = 17.4, 2.4 Hz, H-6), 4.62 (dt, 1 H, J = 17.2, 2.6 Hz, H-6), 5.07 (d, 1 H, J = 2.9 Hz, H-2), 5.50 (ddt, 1 H, J = 8.0, 5.8, 2.8 Hz, H-4), 6.34 (m, 1 H, H-5), 7.15 (d, 2 H, J = 8.2 Hz, H$_m$ *p*-Tol), 7.19 (d, 2 H, J = 8.4 Hz, H$_o$ *p*-Tol), 7.35 (d, 1 H, J = 7.1 Hz, H$_p$ Ph), 7.42 (t, 2 H, J = 7.5 Hz, H$_m$ Ph), 7.50 (d, 2 H, J = 7.5 Hz, H$_o$ Ph). NOESY-1D H-2/H-6 (4.40 ppm): 2.7%; H-2/H-3: 6.5%; H-2/Ph: 3.3%. ^{13}C NMR (100 MHz), HSQC δ 21.4 (Me *p*-Tol), 66.7 (C-3), 66.9 (C-6), 76.4 (C-2), 116.3 (C-4), 123.9 (2 C, Ar), 126.1 (2 C Ar), 128.0 (Ar-C), 128.6 (2 C Ar), 129.6 (2 C Ar), 134.7 (C-5), 138.7, 140.4, 140.6. IR (KBr): 3435, 3028,

(31) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577–6580.

(32) Enantiopure propargyl alcohols, precursors to the required substituted stannanes are readily available. See: El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017–3020. This suggests that our methodology should be broadly applicable.

(33) For a review on the synthesis of Pseudomonic acids, see: Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843–1857.

2921, 2833, 1635, 1490, 1452, 1183, 1101, 1049, 805, 752, 727, 705, 670 cm^{-1}. MS (ES): 619 $[2M + Na]^+$ (100%), 321 $[M + Na]^+$, 299 $[M + 1]^+$.

(+)-(2*R*,3*S*,R_S)-2-Phenyl-3-(*p*-tolylsulfinyl)-3,6-dihydro-2*H*-pyran (16a). From dienyl sulfoxide **9a** (30 mg, 0.100 mmol) and KH (5.2 mg, 0.130 mmol, 1.3 equiv) according to the general procedure (Supporting Information, method B, 2 h), an 85:15 mixture of **16a** and **16a′** was obtained. Purification by chromatography (20−50% EtOAc−hexane) afforded **16a** (20 mg, 0.067 mmol, 67%) and **16a′** impure with traces of **10a** (3 mg, 0.010 mmol, 10%) as colorless oils.

Data for **16a**: R_f 0.29 (50% EtOAc−hexane). $[\alpha]^{20}_D$ +248.2 (*c* 0.50). ^{1}H NMR (300 MHz), COSY δ 2.37 (s, 3 H, Me-*p*-Tol), 3.45 (ap dquint, 1 H, J = 8.3, 2.7 Hz, H-3), 4.19 (ddd, 1 H, J = 17.1, 5.6, 2.5 Hz, H-6), 4.32 (ddd, 1 H, J = 17.1, 5.5, 2.3 Hz, H-6), 4.90 (d, 1 H, J = 8.5 Hz, H-2), 5.59 (dq, 1 H, J = 10.5, 2.3 Hz, H-4), 6.20 (ddt, 1 H, J = 10.5, 3.4, 2.1 Hz, H-5), 7.26−7.45 (m, 7 H), 7.50 (dm, 2 H, J = 8.3 Hz). NOESY-1D H-2/*p*-Tol: 2.3%; H-3/H-4: 2.3%; H-3/*p*-Tol: 1.8%; H-3/Ph: 2%; H-6/H-5: 5.7%; H-6/H-5: 2%; H-6/H-2: 2.9%. ^{13}C NMR (75 MHz), HSQC δ 21.4 (Me-*p*-Tol), 65.3 (C-6), 65.7 (C-3), 75.7 (C-2), 117.3 (C-4), 124.3 (2 C), 127.6 (2 C), 128.8 (3 C), 129.8 (2 C), 134.2 (C-5), 137.6, 138.8, 141.2. IR (film): 3028, 2923, 2855, 1596, 1492, 1453, 1177, 1084, 1045, 910, 809, 757 cm^{-1}. MS (ES): 619 $[2M + Na]^+$ (100%), 321 $[M + Na]^+$, 299 $[M + 1]^+$.

Partial data for **16a′**: R_f 0.16 (10% EtOAc−CH_2Cl_2). ^{1}H NMR (300 MHz) δ 2.33 (s, 3 H), 2.45 (m, 2 H), 3.67 (ddd, 1 H, J = 11.6, 6.3, 5.1 Hz), 3.87 (dt, 1 H, J = 11.7, 5.6 Hz), 5.20 (ap dd, 1 H, J = 3.9, 2.2 Hz), 6.85 (ddd, 1 H, J = 4.6, 3.4, 1.5 Hz), 7.08−7.22 (m, 9 H).

(−)-(2*S*,3*R*)-2-*n*-Butyl-3-(*p*-tolylsulfonyl)-3,6-dihydro-2*H*-pyran (20b). From sulfoxide **10b** (569 mg, 2.04 mmol) and MMPP [1.9 g (80%), 3.06 mmol], according to the general procedure described in Supporting Information (3 h) sulfone **20b** was obtained. Purification by chromatography (10−30% EtOAc−hexane) afforded **20b** (517 mg, 1.76 mmol, 86%) as a colorless oil. R_f 0.38 (30% EtOAc−hexane). $[\alpha]^{20}_D$ −150.6 (*c* 0.59). ^{1}H NMR (300 MHz) δ 0.87 (t, 3 H, J = 7.1 Hz), 1.20−1.40 (m, 4 H), 1.62 (m, 2 H), 2.42 (s, 3 H), 3.51 (m, 1 H), 3.63 (ddd, 1 H, J = 17.6, 4.6, 2.4 Hz), 3.93 (ddd, 1 H, J = 17.6, 4.8, 2.7 Hz), 4.13 (ddd, 1 H, J = 8.7, 5.4, 3.7 Hz), 5.87 (ddt, 1 H, J = 10.2, 3.7, 2.2 Hz), 6.00 (dtd, 1 H, J = 10.2, 2.7, 1.5 Hz), 7.30 (d, 2 H, J = 8.1 Hz), 7.71 (d, 2 H, J = 8.3 Hz). ^{13}C NMR (75 MHz) δ 14.0, 21.7, 22.4, 27.6, 32.0, 60.8, 64.6, 70.8, 117.0, 129.3, 129.6, 133.0, 134.1, 144.6. IR (film): 3022, 2949, 2928, 2859, 1597, 1493, 1456, 1380, 1309, 1301, 1284, 1216, 1182, 1132, 1084, 1019, 814, 758, 708 cm^{-1}. MS (ES): 611 $[2M + Na]^+$, 317 $[M + Na]^+$, 295 $[M + 1]^+$ (100%).

(+)-(3*S*,4*S*,5*R*,6*S*)-6-Phenyl-5-(*p*-tolylsulfonyl)tetrahydro-2*H*-pyran-3,4-diol (24a). From sulfoxide **10a** (90 mg, 0.300 mmol), Me_3NO (133 mg, 1.200 mmol) and OsO_4 [0.19 mL (2.5%), 0.015 mmol], according to the general procedure described in Supporting Information (1 day), diol **24a** was obtained. Purification by chromatography (30−80% EtOAc−hexane) afforded **24a** (74 mg, 0.21 mmol, 70%) as a white solid that was recrystallized from EtOAc−hexane. R_f 0.32 (80% EtOAc−hexane). Mp 133−135 °C. $[\alpha]^{20}_D$ +35.0 (*c* 0.48). ^{1}H NMR (300 MHz), COSY δ 2.29 (s, 3 H, Me-*p*-Tol), 2.88 (s, 1 H, OH), 3.71 (dm, 1 H, J = 12.7 Hz, H-2), 3.93 (t, 1 H, J = 10.1 Hz, H-5), 4.08 (m, 1 H, H-3), 4.14 (dd, 1 H, J = 12.7, 2.2 Hz, H-2), 4.45 (d, 1 H, J = 10.0 Hz, H-6), 4.57 (ddd, 1 H, J = 10.2, 3.4, 1.6 Hz, H-4), 5.15 (dd, 1 H, J = 1.5, 0.5 Hz, OH), 6.92 (d, 2 H, J = 8.5 Hz), 6.98−7.12 (m, 7 H). ^{13}C NMR (75 MHz), HSQC δ 21.5 (Me-*p*-Tol), 67.3 (C-3), 67.6 (C-5), 67.9 (C-4), 69.5 (C-6), 78.7 (C-2), 127.4 (2 C), 128.2 (2 C), 128.8 (2 C), 129.2 (2 C), 136.1, 136.2, 144.1. IR (KBr): 3503, 3065, 2913, 2876, 1627, 1595, 1288, 1230, 1138, 1097, 882, 813, 768, 724 cm^{-1}. MS (ES): 719 $[2M + Na]^+$ (100%), 371 $[M + Na]^+$, 349 $[M + 1]^+$. Anal. Calcd for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.79; S, 9.20. Found: C, 62.36; H, 5.47; S, 9.31.

(−)-(*S*)-[(*Z*)-1-(*S*-*p*-Tolyl-*N*-tosylsulfoximinoyl)hex-1-enyl]tributylstannane (36). To a solution of **34** (144 mg, 0.37 mmol) in 2 mL of hexane−toluene (2:1) (5 mL/mmol sulfoximine) at room temperature under argon was added a solution of freshly distilled Bu_3SnH (0.11 mL, 0.407 mmol, 1.1 equiv), in 1 mL of hexane (3 mL/mmol sulfoximine). The mixture was stirred at room temperature for 21 h, and the solvent was evaporated to obtain **36**. Purification by chromatography (5−30% EtOAc−hexane) afforded stannane **36** (226 mg, 0.332 mmol, 90%) as a colorless oil. R_f 0.20 (20% EtOAc−hexane). $[\alpha]^{20}_D$ −41.2 (*c* 1.20). ^{1}H NMR (300 MHz) δ 0.82 (t, 9 H, J = 7.2 Hz), 0.87 (t, 3 H, J = 7.1 Hz), 0.98 (m, 2 H), 1.16−1.38 (m, 20 H), 2.17 (q, 2 H, J = 7.5 Hz), 2.35 (s, 3 H), 2.41 (s, 3 H), 7.01 (t, 1 H, J = 7.5 Hz), 7.17 (d, 2 H, J = 8.1 Hz), 7.28 (d, 2 H, J = 8.5 Hz), 7.70 (d, 2 H, J = 8.3 Hz), 7.76 (d, 2 H, J = 8.3 Hz). ^{13}C NMR (75 MHz) δ 12.6 (3 C), 13.6 (3 C), 21.4, 21.6, 22.5, 27.0 (4 C), 28.6 (3 C), 30.8, 33.3, 126.7 (2 C), 128.5 (2 C), 128.9 (2 C), 129.7 (2 C), 135.7, 141.5, 142.0, 144.2, 145.7, 156.4. IR (film): 2957, 2926, 2867, 1595, 1522, 1456, 1367, 1318, 1236, 1154, 1089, 1064, 1015, 813, 744, 668 cm^{-1}. MS (ES): 704 $[M + Na]^+$, 682 $[M + 1]^+$.

(+)-(*R*)-2-(*Z*)-4-(*Z*)-4-(*S*-*p*-Tolyl-*N*-tosylsulfoximinoyl)nona-2,4-dien-1-ol (41). From dienyl sulfoxide **8b** (27 mg, 0.097 mmol), *N*-tosyl phenyliminoiodinane (47 mg, 0.126 mmol, 1.3 equiv) and $Cu(OTf)_2$ (4 mg, 0.010 mmol, 0.10 equiv), according to the general procedure described in Supporting Information (5 min), sulfoximine **41** was obtained. Purification by chromatography (0−10% EtOAc−CH_2Cl_2) afforded dienyl sulfoximine **41** (26 mg, 0.058 mmol, 60%) as a colorless oil. R_f 0.14 (10% EtOAc−CH_2Cl_2). $[\alpha]^{20}_D$ +73.6 (*c* 0.92). ^{1}H NMR (300 MHz), COSY δ 0.86 (t, 3 H, J = 7.1 Hz, CH_3), 1.23−1.43 (m, 4 H, 2 CH_2), 2.36 (s, 3 H, Me-*p*-Tol), 2.41 (s, 3 H, Me-Ts), 2.65−2.74 (m, 2 H, CH_2), 3.99 (dd, 1 H, J = 13.4, 3.4 Hz, H-1), 4.26 (dd, 1 H, J = 13.4, 3.9 Hz, H-1), 5.98 (ap t, 2 H, J = 4.0 Hz, H-2, H-3), 6.08 (t, 1 H, J = 7.7 Hz, H-5), 7.23 (d, 2 H, J = 8.3 Hz, Ar-H), 7.32 (d, 2 H, J = 8.3 Hz, Ar-H), 7.82 (d, 2 H, J = 8.3 Hz, Ar-H), 7.85 (d, 2 H, J = 8.3 Hz, Ar-H). ^{13}C NMR (75 MHz), HSQC δ 13.8 (CH_3-Bu), 21.5 (Me), 21.6 (Me), 22.4 (CH_2), 28.2 (CH_2), 31.0 (CH_2), 58.4 (C-1), 124.3, 126.5 (2 C), 127.9 (2 C), 129.2 (2 C), 129.9 (2 C), 135.2, 135.6, 137.4, 141.0, 142.7, 145.4, 148.5 (C-5). IR (film): 3499, 2956, 2928, 2867, 1735, 1596, 1454, 1316, 1303, 1233, 1153, 1088, 1065, 1013, 814 cm^{-1}. MS (ES): 917 $[2M + Na]^+$, 470 $[M + Na]^+$ (100%), 448 $[M + 1]^+$.

(−)-(2*S*,3*R*,R_S)-2-*n*-Butyl-3-(*S*-*p*-tolyl-*N*-tosylsulfoximinoyl)-3,6-dihydro-2*H*-pyran (42) and (+)-(2*R*,3*S*,R_S)-2-*n*-Butyl-3-(*S*-*p*-tolyl-*N*-tosylsulfoximinoyl)-3,6-dihydro-2*H*-pyran (43). From dienyl sulfoximine **41** (24 mg, 0.054 mmol) and NaH (2 mg, 0.07 mmol, 1.3 equiv) according to the general procedure (Supporting Information, method B, 1 h 30 min), an 83:17 mixture of **43** and **42** was obtained. Purification by chromatography (10−30% EtOAc−hexane) afforded an 83:17 mixture of **43** and **42** (13 mg, 0.029 mmol, 54%) as a colorless oil. Subsequent chromatographies (30−50% Et_2O−hexane) allowed for the separation and characterization of both isomers.

Data for **42**: R_f 0.26 (50% EtOAc−hexane). Mp 89−91 °C. $[\alpha]^{20}_D$ −142.5 (*c* 0.71). ^{1}H NMR (300 MHz) δ 0.87 (t, 3 H, J = 7.1 Hz), 1.24−1.36 (m, 4 H), 1.37−1.68 (m, 2 H), 2.36 (s, 3 H), 2.40 (s, 3 H), 3.38 (d, 1 H, J = 18.1 Hz), 3.84 (ddd, 1 H, J = 18.1, 4.9, 2.0 Hz), 4.43 (m, 1 H), 4.48 (dd, 1 H, J = 9.8, 4.8 Hz), 5.94 (ddd, 1 H, J = 10.3, 2.1, 1.0 Hz), 6.02 (d, 1 H, J = 10.5 Hz), 7.23 (d, 2 H, J = 8.3 Hz), 7.28 (d, 2 H, J = 8.1 Hz), 7.76 (d, 2 H, J = 8.5 Hz), 7.86 (d, 2 H, J = 8.5 Hz). ^{1}H NMR (300 MHz, C_6D_6) δ 0.84 (t, 3 H, J = 7.2 Hz), 1.19−1.39 (m, 4 H), 1.40−1.56 (m, 2 H), 1.80 (s, 3 H), 1.82 (s, 3 H), 2.97 (dt, 1 H, J = 17.8, 2.2 Hz), 3.34 (dq, 1 H, J = 18.1, 2.4 Hz), 4.66 (hept, 1 H, J = 1.5 Hz), 4.83 (ap t, 1 H, J = 7.1 Hz), 5.27 (dq, 1 H, J = 10.2, 1.5 Hz), 5.77 (dddd, 1 H, J = 10.3, 5.4, 3.2, 1.0 Hz), 6.74 (d, 2 H, J = 9.7 Hz), 6.77 (d, 2 H, J = 7.8 Hz), 7.85 (d, 2 H, J = 8.3 Hz), 8.28 (d, 2 H, J = 8.3 Hz). ^{13}C NMR (75 MHz) δ 13.9, 21.5, 21.7, 22.3, 27.6, 30.6, 59.2, 65.8, 70.1, 115.1, 126.6 (2 C), 129.2 (4 C), 130.0 (2

C), 130.8, 134.8, 141.1, 142.6, 145.4. IR (film): 2950, 2926, 2867, 1594, 1451, 1316, 1152, 1088, 1062, 1015, 940, 812, 753 cm^{-1}. MS (ES): 917 $[2M + Na]^+$ (100%), 470 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{29}NO_4S_2$: C, 61.72; H, 6.53; N, 3.13; S, 14.33. Found: C, 61.53; H, 6.40; N, 3.20; S, 14.24.

Data for **43**: R_f 0.26 (50% EtOAc−hexane). $[\alpha]^{20}_D$ +146.0 (*c* 0.86). ^{1}H NMR (300 MHz, C_6D_6) δ 0.75 (t, 3 H, J = 7.0 Hz), 1.05−1.78 (m, 6 H), 1.80 (s, 3 H), 1.81 (s, 3 H), 2.87 (ddd, 1 H, J = 17.8, 3.2, 2.1 Hz), 3.27 (ddd, 1 H, J = 17.9, 5.1, 2.1 Hz), 4.45 (ddd, 1 H, J = 9.5, 4.2, 2.0 Hz), 4.69 (ap td, 1 H, J = 3.3, 1.5 Hz), 5.28 (d, 1 H, J = 10.3 Hz), 6.20 (dddd, 1 H, J = 10.3, 5.4, 3.2, 1.0 Hz), 6.74 (d, 2 H, J = 8.1 Hz), 6.77 (d, 2 H, J = 8.1 Hz), 7.84 (d, 2 H, J = 8.3 Hz), 8.30 (d, 2 H, J = 8.3 Hz). NOESY-1D H-2/H-3: 3%; H-2/CH_2 (Bu): 3%; H-2/Ar-H: 2%; H-3/Bu: 1.4%; H-3/H-4: 1.4%; H-6 (3.27 ppm)/H-5: 5%, H-6 (3.27 ppm)/CH_2 (Bu): 2%; H-6 (2.87 ppm)/H-5: 2.4%; H-6 (2.87 ppm)/H-3: 0.4%. ^{13}C NMR (75 MHz, $CDCl_3$), HSQC δ 13.9 (CH_3-Bu), 21.5 (Me-*p*-Tol), 21.7 (Me-Ts), 22.3 (CH_2), 27.7 (CH_2), 31.0 (CH_2), 59.3 (CH_2), 65.9 (C-3), 69.2 (C-2), 116.2 (C-4), 126.6 (2 C), 129.2 (4 C), 129.9 (2 C), 130.8, 134.4 (C-5), 140.8, 142.8, 145.3. IR (film): 3392, 2956, 2929, 2867, 1596, 1454, 1316, 1237, 1152, 1088, 1065, 1016, 814, 753, 704 cm^{-1}. MS (ES): 917 $[2M + Na]^+$ (100%), 470 $[M + Na]^+$.

(+)-(2*S*,3*S*,*R*$_S$)-2-*n*-Butyl-3-(*S*-*p*-tolyl-*N*-tosylsulfoximinoyl)-3,6-dihydro-2*H*-pyran (44). From dihydropyran **11b** (13 mg, 0.047 mmol), *N*-tosyl phenyliminoiodinane (21 mg, 0.056 mmol) and $Cu(OTf)_2$ (4 mg, 0.01 mmol), according to the general procedure described in Supporting Information (30 min), sulfoximine **44** was obtained. Purification by chromatography (10−30% EtOAc−hexane) afforded sulfoximine **44** (11 mg, 0.025 mmol, 53%) as a white solid that was recrystallized from CH_2Cl_2−hexane. R_f 0.24 (30% EtOAc−hexane). Mp 102−104 °C. $[\alpha]^{20}_D$ +131.6 (*c* 1.12). ^{1}H NMR (300 MHz, C_6D_6), COSY δ 0.87 (t, 3 H, J = 6.9 Hz, CH_3), 1.17−1.46 (m, 4 H, 2 CH_2), 1.79 (s, 3 H, Me-*p*-Tol), 1.81 (s, 3 H, Me-Ts), 1.90−2.06 (m, 2 H, CH_2), 3.06 (d, 1 H, J = 17.3 Hz, H-6), 3.24 (ddd, 1 H, J = 8.3, 5.4, 3.0 Hz, H-2), 3.36 (dd, 1 H, J = 17.6, 2.2 Hz, H-6), 4.91 (ap q, 1 H, J = 2.7 Hz, H-3), 5.29 (dd, 1 H, J = 10.2, 1.1 Hz, H-5), 6.38 (ddt, 1 H, J = 10.2, 5.7, 2.2 Hz, H-4), 6.69 (d, 2 H, J = 8.5 Hz, Ar-H), 6.77 (dd, 2 H, J = 8.0, 0.6 Hz, Ar-H), 7.81 (d, 2 H, J = 8.3 Hz, Ar-H), 8.29 (d, 2 H, J = 8.3 Hz, Ar-H). ^{13}C NMR (75 MHz, C_6D_6) δ 14.2, 21.0, 21.1, 22.8, 29.2, 32.7, 66.0, 66.1, 75.7, 120.7, 127.2 (2 C), 129.0 (2 C), 129.3 (2 C), 130.4 (2 C), 133.5, 134.0, 142.0, 142.8, 144.4. IR (KBr): 2956, 2927, 2855, 1597, 1313, 1228, 1200, 1155, 1088, 1058, 1014, 812, 751, 686, 659 cm^{-1}. MS (ES): 917 $[2M + Na]^+$ (100%), 470 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{29}NO_4S_2$: C, 61.72; H, 6.53; N, 3.13; S, 14.33. Found: C, 62.01; H, 6.39; N, 3.09; S, 14.51.

(−)-(3*R*,6*R*)-3,6-Di-*n*-butyl-3,6-dihydro-2*H*-pyran (46a). From sulfone **20b** (27 mg, 0.092 mmol), CuI (54 mg, 0.276 mmol), and butylmagnesium bromide (0.68 mL, 0.81 M, 0.552 mmol, prepared form magnesium turnings and *n*-BuBr in Et_2O), according to the general procedure described in Supporting Information (21 h), dihydropyran **46a** was obtained. Purification by chromatography (2−5%-EtOAc−hexane) afforded **46a** (12 mg, 0.061 mmol, 66%) as a colorless oil, along with recovered starting material (9 mg, 0.031 mmol, 34%). R_f 0.48 (10% EtOAc−hexane). $[\alpha]^{20}_D$ −11.1 (*c* 0.75). ^{1}H NMR (500 MHz), COSY δ 0.88 (t, 3 H, J = 7.1 Hz, CH_3), 0.88 (t, 3 H, J = 7.2 Hz, CH_3), 1.21−1.52 (m, 12 H, 6 CH_2), 1.92 (m, 1 H, H-3), 3.67 (ap d, 2 H, J = 3.9 Hz, H-2), 4.02 (hept, 1 H, J = 2.5 Hz, H-6), 5.59 (dt, 1 H, J = 10.3, 1.7 Hz, H-5), 5.78 (ddd, 1 H, J = 10.3, 4.5, 2.1 Hz, H-4). ^{13}C NMR (125 MHz), HSQC δ 14.0 (CH_3), 14.1 (CH_3), 22.8 (CH_2), 22.9 (CH_2), 27.4 (CH_2), 29.4 (CH_2), 33.1 (CH_2), 34.8 (CH_2), 34.9 (C-3), 67.2 (C-2), 74.1 (C-6), 129.3 (C-5), 129.7 (C-4). IR (film): 2962, 2920, 2850, 1650, 1459, 1376, 1261, 1091, 1020, 800 cm^{-1}. MS (ES): 219 $[M + Na]^+$, 197 $[M + 1]^+$.

(−)-(2*S*,3*R*,4*R*,5*R*)-2,5-Di-*n*-butyltetrahydro-2*H*-pyran-3,4-diol (50a). From dihydropyran **46a** (25 mg, 0.127 mmol), Me_3NO (36 mg, 0.318 mmol), and OsO_4 [75 μL (2.5%), 0.006 mmol], according to the general procedure described in Supporting Information (1 h 40 min), diol **50a** was obtained. Purification by chromatography (0−20% EtOAc−CH_2Cl_2) afforded **50a** (24 mg, 0.104 mmol, 82%) as a white solid. R_f 0.35 (20% EtOAc−CH_2Cl_2). Mp 57−59 °C. $[\alpha]^{20}_D$ −2.8 (*c* 1.23). ^{1}H NMR (300 MHz), COSY δ 0.87 (t, 3 H, J = 6.9 Hz, CH_3), 0.88 (t, 3 H, J = 7.0 Hz, CH_3), 1.23−1.51 (m, 12 H, 6 CH_2), 1.65−1.72 (m, 1 H, H-5), 2.10 (br s, 2 H, 2 OH), 3.45 (m, 2 H, H-2, H-4), 3.50 (dd, 1 H, J = 11.8, 2.5 Hz, H-6), 3.77 (dd, 1 H, J = 11.7, 3.2 Hz, H-6), 3.81 (t, 1 H, J = 2.7 Hz, H-3). ^{13}C NMR (75 MHz) δ 14.0 (2 C), 22.8 (2 C), 27.7, 28.5, 29.8, 31.2, 41.8, 64.6, 69.6, 71.3, 76.6. IR (KBr): 3339, 2958, 2926, 2857, 1465, 1291, 1262, 1082, 1020, 801, 760 cm^{-1}. MS (ES): 253 $[M + Na]^+$, 198 $[M+2-2OH]^+$ (100%). Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.72; H, 11.21.

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Supporting Information Available: Experimental details and spectral data (^{1}H NMR and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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