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Sulfur-Directed Synthesis of Enantiopure Hydroxy 2-Sulfinyl Butadienes.[1]

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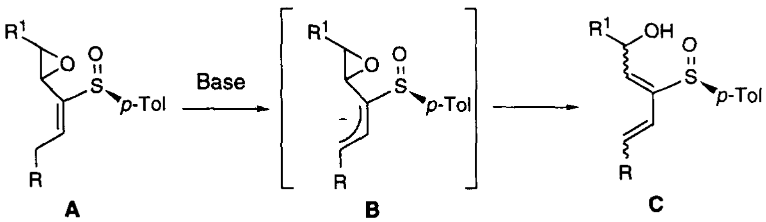
***Abstract*:** Epoxy vinyl sulfoxides, generated *in situ* from sulfinyl chlorohydrins, undergo an efficient base-induced rearrangement to generate enantiopure hydroxy 2-sulfinyl dienes. The chiral sulfur auxiliary controls the *E*-*Z* stereoselectivity of the trisubstituted alkene.

The development of efficient syntheses of new enantiopure butadienes remains a current challenge in contemporary organic synthesis.[3] Within this field, 2-sulfinyl dienes stand as especially promising substrates since simple examples of these molecules are readily available,[4] display high π-facial selectivity upon Diels-Alder cycloaddition,[5] and the resulting vinyl sulfoxides may undergo subsequent asymmetric transformations.[6] In this communication we report the first examples of a short and highly stereoselective protocol to produce acyclic 2-sulfinyl dienes bearing an additional allylic hydroxyl chiral center. The geometry of the trisubstituted alkene of these dienes is controlled by the chiral sulfur atom.

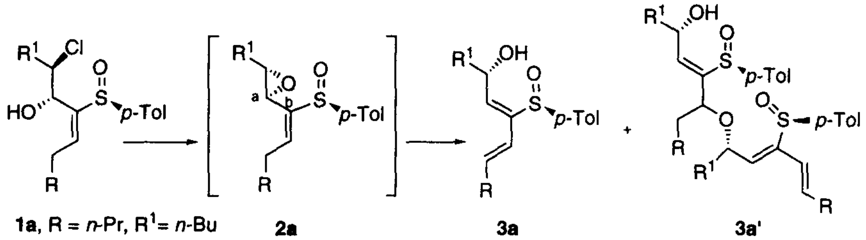
At the inception of this research we envisioned that the treatment of readily available oxiranes **A** (Scheme 1)[7] with base would produce a transient allyl sulfinyl metal species, **B**, which would undergo epoxide cleavage to provide dienes **C**.[8] We considered that the geometry of the trisubstituted double bond could be controlled by the combination of a well defined stereochemical pathway for epoxide cleavage with the stereocontrolling capabilities of the chiral sulfur atom,[9] while the thermodynamically more stable *E* isomer was expected for the disubstituted double bond.



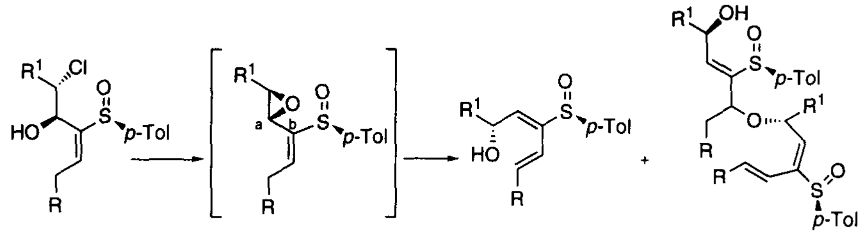
Scheme 1

With these considerations in mind, epoxides **2a** and **5a** (Table 1) were submitted to a number of basic conditions (*n*-BuLi, LDA, NaH, KOH, etc.) in different solvents (THF, Et_2O, *i*-PrOH, *t*-BuOH, etc) with limited success. After considerable experimentation, we found that the best results were obtained by adding a suspension of KO-*t*-Bu in THF to a cold (0 °C) THF solution of the vinyl oxirane, under strictly anhydrous conditions. Following this procedure, oxirane **2a** yielded exclusively the *Z,E* diene **3a** and diastereomeric oxirane **5a** produced the *E,E* diene **6a** as a single isomer. The subsequent development of a one-pot procedure from the chlorohydrin precursors was straightforward; indeed, the sequential treatment of chlorohydrin **1a** (Table 1, entry 1) with two portions of KO-*t*-Bu led to a good yield of highly substituted *Z,E* diene **3a**.[10] In a similar fashion, substrates **1b** and **1c**, which possess acidic benzylic hydrogens,[11] led to sulfinyl dienes **3b** and **3c** respectively by selective allylic deprotonation and with good overall yields (Table 1, entries 2 and 3).

Table 1. Stereocontrolled Synthesis of Hydroxy Sulfinyl Dienes.



1a, R = *n*-Pr, R^1 = *n*-Bu	**2a**	**3a**	**3a'**
1b, R = Me, R^1 = CH_2Ph	**2b**	**3b**	**3b'**
1c, R = *i*-Pr, R^1 = CH_2Ph	**2c**	**3c**	**3c'**



4a, R = *n*-Pr, R^1 = *n*-Bu	**5a**	**6a**	**6a'**
4b, R = Me, R^1 = CH_2Ph	**5b**	**6b**	**6b'**
4c, R = *i*-Pr, R^1 = CH_2Ph	**5c**	**6c**	**6c'**
7, Sulfone analog, R = *n*-Pr, R^1 = *n*-Bu	**8**	**9**	

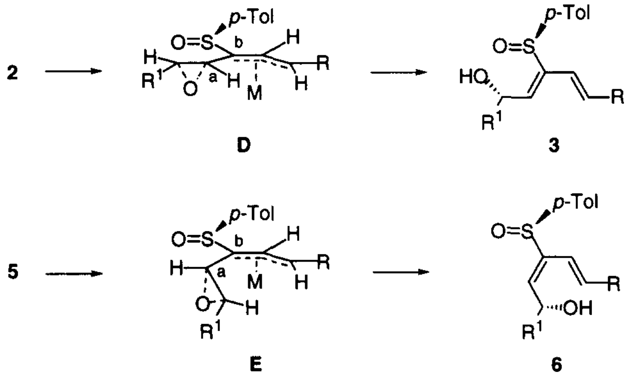
Entry	Substrate	Time (min)	Product	Yield (%)[a]
1[b]	**1a**	90	**3a**	68
2[b]	**1b**	75	**3b**	65
3[b]	**1c**	75	**3c**	55
4[b]	**4a**	75	**6a**	50
5[b]	**4b**	75	**6b**	47
6[b]	**4c**	240	**6c**	48
7[c]	**7**	300	**9**	53

[a] Unoptimized yields of pure products after chromatography on silica gel. [b] Reaction performed by sequential addition of two portions of a suspension of 1.1 equiv of KO-*t*-Bu in THF from 0 °C to rt. Examination of the crude reaction mixtures by ^1H NMR showed the presence of small amounts (*ca.* 15%) of "dimers" **3'** and **6'**. [c] Reaction performed by addition of a suspension of 2.2 equiv of KO-*t*-Bu in THF to a cold (-78 °C) solution of **7** and slow warming to rt over 5 h.

In sharp contrast, diastereomeric chlorohydrins **4** led exclusively to the *E,E* dienes **6** as single isomers and in fair overall yields (Table 1, entries 4, 5 and 6). Interestingly, small amounts (*ca.* 15%) of by-products whose structure was tentatively assigned as the "dimers" **3'** and **6'**, derived from S_N2' cleavage of the vinyl oxiranes by the dienols, were obtained as single isomers along with the desired dienes. It should be pointed out that the use of non strictly anhydrous conditions and/or prolonged (2-3 days) reaction times resulted in formation of significant amounts of diastereomeric dienes, easily detected by ^1H NMR. Finally, the sulfone analog **7**, obtained by MMPP oxidation of **4a**, led exclusively to the *E,E* sulfonyl diene **9**.

The general structure and geometry of these dienes could be established readily from their ^1H and ^{13}C NMR spectral features including differential NOE experiments. The *E* geometry of the C-8 C-9 double bond for **3a** and **6a** derives from a vicinal coupling constant of 15.6 Hz. On the other hand, the stereochemistry of the trisubstituted alkene, C-6 C-7, derives from the chemical shift found for H-6, which is deshielded for the *E* isomer, **6a** (6.35 ppm) due to the effect of the sulfinyl moiety, relative to the *Z* isomer **3a** (6.03 ppm). A similar trend was observed for H-5, (**3a**, 4.90 ppm; **6a**, 4.52 ppm). Furthermore these assignments were secured by NOE measurements: for **3a**, a 3.0% enhancement was found for H-5 upon irradiation of the ortho ArH; alternatively, for **6a**, a 1.3% enhancement was found for the ortho ArH upon irradiation at H-6. Finally, our ability to detect the formation of diastereomeric dienes by ^1H NMR (see above) conclusively establishes that our sulfinyl dienes, obtained under standard conditions, are enantio- and diastereomerically pure. Indeed, since allylic alcohols are configurationally stable under basic conditions,[12] epimerization must be taking place at sulfur by protonation of the allyl metal species to produce a configurationally unstable allylic sulfoxide.[13]

The remarkable degree of stereocontrol exerted by the chiral sulfur atom on the geometry of the trisubstituted double bond is unprecedented and may be tentatively rationalized in terms of a stereochemically well defined allyl metal species, **B** (Scheme 1) combined with a highly stereoselective β elimination step.[14] Thus for epoxides **2** (Scheme 2), allyllic deprotonation may result in an allyl metal species which places the metal essentially at the α face of the molecule, **D**,[15] and *syn* elimination would lead to *Z* dienes **3** while for diastereomeric epoxides **5**, metalation, followed by rotation about C_a-C_b bond to yield **E**, and *syn* elimination would produce *E* dienes **6**.



Scheme 2

In conclusion, we have shown that enantiomerically pure epoxy vinyl sulfoxides, readily available by two short and convergent routes,[7] undergo a base-induced rearrangement giving rise to hydroxy 2-sulfinyl dienes with remarkable geometric selectivity, completely controlled by the absolute configuration of the chiral sulfur atom. Further studies to define the scope of this novel finding and apply the resulting hydroxy dienyl sulfoxides in synthesis are underway in our laboratories.

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