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# Metal-Catalyzed Oxidation and Epoxidation of α-Hydroxy Vinyl and Dienyl Sulfoxides

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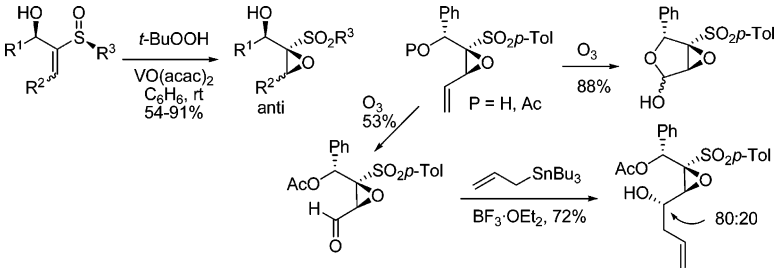
*Received October 28, 2005*

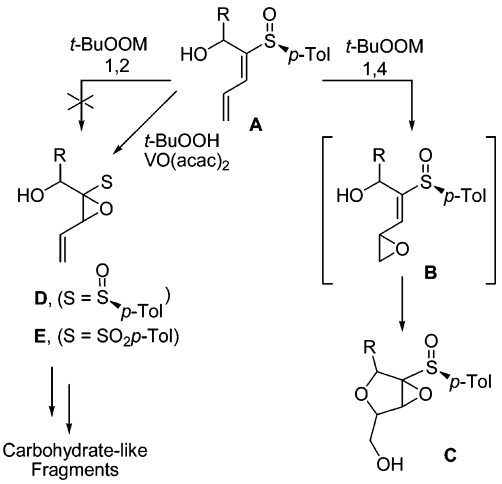



Treatment of acyclic α-hydroxyalkyl α,*β*-unsaturated sulfoxides with *t*-BuOOH/VO(acac)$_2$ results in rapid oxidation to the unsaturated sulfones followed by an unusual regio- and stereoselective epoxidation at the unsaturated sulfones; this methodology has been applied to the preparation of carbohydrate-like fragments.

## Introduction

In recent years, we have been studying in depth the nucleophilic epoxidation of alkenyl sulfoxides, a general route to enantiopure sulfinyl and sulfonyl oxiranes,[1] that are versatile synthetic intermediates.[2] In the course of these studies, we examined the nucleophilic epoxidation of hydroxy dienyl sulfoxides **A** (Scheme 1) with the expectation that monoepoxides **D** or **E**, perceived as suitable precursors to unusual carbohydrate fragments,[3] would be obtained. In contrast, tetrahydrofurans **C** were formed in moderate yields by a completely different reaction pathway.[4] At this stage, a literature survey revealed isolated examples of metal-catalyzed electrophilic epoxidations of α-hydroxyalkyl α,*β*-unsaturated esters and ketones,[5] and these conditions were identified as a straightforward option to access the desired oxiranes **D** or **E** from readily available hydroxy dienes **A**. In this paper, we describe in full our studies on the facile and highly stereo- and regioselective epoxidation of hydroxy vinyl and dienyl sulfones to produce sulfonyl oxiranes **E**.[6]

**SCHEME 1**



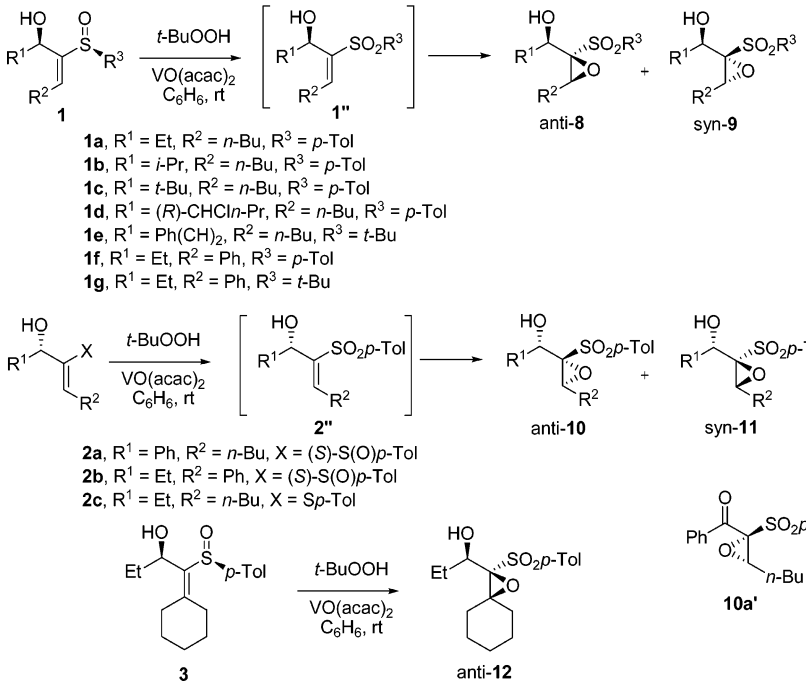

## Metal-Catalyzed Epoxidation of Alkenyl and Dienyl Sulfones

The substrates selected for this study (**1a**−**g**, **2a**−**c**, **3**, **4a**,**b**, **5**, **6a**−**d**, and **7a**−**c**) are shown below and were prepared by standard procedures (see the Supporting Information). These substrates were selected so as to provide useful information on the scope of the reaction with regard to the nature and size of the substituents, the functionality, the geometry of the substrates, etc. Table 1 summarizes the results obtained for simple *E* and

(1) (a) Fernández de la Pradilla, R.; Castro, S.; Manzano, P.; Priego, J.; Viso, A. *J. Org. Chem.* **1996**, *61*, 3586−3587. (b) Fernández de la Pradilla, R.; Castro, S.; Manzano, P.; Martín-Ortega, M.; Priego, J.; Viso, A. Rodríguez, A.; Fonseca, I. *J. Org. Chem.* **1998**, *63*, 4954−4966. (c) Fernández de la Pradilla, R.; Fernández, J.; Manzano, P.; Méndez, P.; Priego, J.; Tortosa, M.; Viso, A.; Martínez-Ripoll, M.; Rodríguez, A. *J. Org. Chem.* **2002**, *67*, 8166−8177. (d) For the highly selective preparation of spirocyclic bis-sulfinyl oxiranes by a related methodology, see: Aggarwal, V. K.; Barrell, J. K.; Worrall, J. M.; Alexander, R. *J. Org. Chem.* **1998**, *63*, 7128−7129.

10.1021/jo052244d CCC: $33.50 
Published on Web 01/21/2006

**TABLE 1. Metal-Catalyzed Oxidation/Epoxidation of Hydroxy Alkenyl Sulfoxides and Sulfides**




| entry | substrate | conditions | anti | syn | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | 10% $VO(acac)_2$, 2.5 equiv of *t*-BuOOH, 3 days | **8a** | | 76 |
| 2 | **1b** | 15% $VO(acac)_2$, 3.0 equiv of *t*-BuOOH, 28 h | **8b** | | 76 |
| 3 | **1c** | 25% $VO(acac)_2$, 4.0 equiv of *t*-BuOOH, 132 h | **8c** | | 84 |
| 4[b] | **1d** | 65% $VO(acac)_2$, 9.0 equiv of *t*-BuOOH, 56 h | **8d** | | 65 |
| 5 | **1e** | 25% $VO(acac)_2$, 8.5 equiv of *t*-BuOOH, 4 days | **8e** | | 54 |
| 6 | **1f** | 15% $VO(acac)_2$, 7.0 equiv of *t*-BuOOH, 72 h | | **9f** | 60 |
| 7 | **1g** | 30% $VO(acac)_2$, 7.0 equiv of *t*-BuOOH, 86 h | | **9g** | 44 |
| 8[c] | **2a** | 25% $VO(acac)_2$, 5.5 equiv of *t*-BuOOH, 85 h | **10a** | | 80 |
| 9 | **2b** | 15% $VO(acac)_2$, 5.0 equiv of *t*-BuOOH, 6 h | **10b** | | 87 |
| 10 | **2c** | 20% $VO(acac)_2$, 6.0 equiv of *t*-BuOOH, 20 h | **10c** | | 72 |
| 11 | **3** | 15% $VO(acac)_2$, 3.0 equiv of *t*-BuOOH, 4 h | **12** | | 91 |

[a] Combined yields of pure products after column chromatography. [b] Alkenyl sulfone **1d″** (18%) was also isolated. [c] The related keto sulfonyl oxirane **10a′** (39%) was also isolated.

*Z* alkenyl sulfoxides. All cases examined proceeded by an initial very fast oxidation to the alkenyl sulfones **1″** and **2″** with 5% $VO(acac)_2$ and 1.5 equiv of *t*-BuOOH regardless of the relative configuration of the substrates. Subsequent additions of catalyst and *t*-BuOOH were performed when necessary (TLC) to enable reaction completion, generally with rather slow kinetics, probably related with the known inactivation of the catalyst by *t*-BuOH or adventitious water.[7] The initial stage of this investigation was carried out on simple hydroxy vinyl sulfoxide **1a** (Table 1, entry 1) that gave a good overall yield of anti sulfonyl oxirane **8a** as a single isomer. Encouraged by this result, we set out to explore the scope of this process. Thus, substrates **1b** and **1c** with bulkier $R^1$ substituents cleanly afforded anti oxiranes **8b** and **8c**, respectively, in good yields (Table 1, entries 2 and 3). Sulfinyl chlorohydrin **1d** was only marginally reactive and led to a fair yield of oxirane **8d** along with a substantial amount of sulfonyl chlorohydrin **1d″** (18%) (Table 1, entry 4).

(2) For a review on the preparation and applications of α-oxy sulfones, including sulfonyl oxiranes, see: (a) Chemla, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 275−299. For other reviews on aspects of the synthesis and reactivity of sulfinyl and sulfonyl oxiranes, see: (b) Satoh, T.; Yamakawa, K. *Synlett* **1992**, 455−468. (c) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. For recent references on applications of sulfinyl and sulfonyl oxiranes, see: (d) Mori, Y.; Hayashi, H. *J. Org. Chem.* **2001**, *66*, 8666−8668. (e) Satoh, T.; Taguchi, D.; Kurabayashi, A.; Kanoto, M. *Tetrahedron* **2002**, *58*, 4217−4224. (f) Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789−1797. (g) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158−8159. (h) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557−4558. (i) For a recent application of these building blocks within synthetic studies toward yessotoxin and adriatoxin, see: Mori, Y.; Takase, T.; Noyori, R. *Tetrahedron Lett.* **2003**, *44*, 2319−2322. (j) For an application to the synthesis of a fragment of ciguatoxin, see: Inoue, M.; Yamashita, S.; Tatami, A.; Miyazaki, K.; Hirama, M. *J. Org. Chem.* **2004**, *69*, 2797−2804. (k) For an application to the synthesis of a fragment of gambierol, see: Furuta, H.; Hase, M.; Noyori, R.; Mori, Y. *Org. Lett.* **2005**, *7*, 4061−4064.

(3) For reviews on the synthesis of carbohydrate derivatives from acyclic precursors, see: (a) Ager, D. J.; East, M. B. *Tetrahedron* **1993**, *49*, 5683−5765. (b) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803−2894.

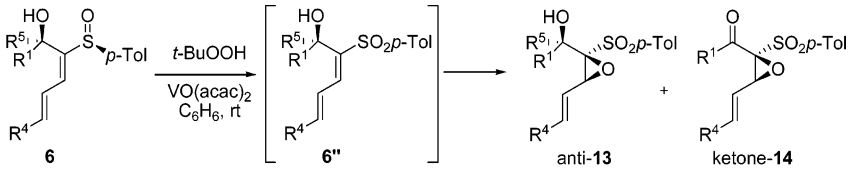
(4) (a) Fernández de la Pradilla, R.; Montero, C.; Priego, J.; Martínez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612−9613. (b) Fernández de la Pradilla, R.; Manzano, P.; Montero, C.; Priego, J.; Martínez-Ripoll, M.; Martínez-Cruz, L. A. *J. Org. Chem.* **2003**, *68*, 7755−7767.

(5) (a) Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203−212. (b) Bailey, M.; Staton, I.; Ashton, P. R.; Markó, I. E.; Ollis, W. D. *Tetrahedron: Asymmetry* **1991**, *2*, 495−509.

(6) For a preliminary communication, see: Fernández de la Pradilla, R.; Méndez, P.; Priego, J.; Viso, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1247−1249.

(7) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733−4736. (c) Mihelich, E. D. *Tetrahedron Lett.* **1979**, *20*, 4729−4732.

**TABLE 2. Metal-Catalyzed Oxidation/Epoxidation of Hydroxy Dienyl Sulfoxides**

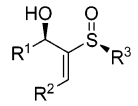



**6a**, $R^1$ = Et, $R^4$ = $R^5$ = H
**6b**, $R^1$ = Ph, $R^4$ = $R^5$ = H
**6c**, $R^1$ = $R^5$ = Me, $R^4$ = H
**6d**, $R^1$ = Et, $R^4$ = Me, $R^5$ = H

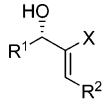
| entry | substrate | conditions | diene | anti | ketone | yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | **6a** | 20% $VO(acac)_2$, 3.0 equiv of *t*-BuOOH, 7 h | | **13a** | | 73 |
| 2 | **6b** | 15% $VO(acac)_2$, 2.5 equiv of *t*-BuOOH, 4 days | | **13b** (86) | **14b** (14) | 54 |
| 3 | **6b** | 15% $VO(acac)_2$, 2.5 equiv of *t*-BuOOH, Tol, 4 days | **6b''** (1) | **13b** (99) | | 55 |
| 4 | **6b** | 15% $VO(acac)_2$, 5.0 equiv of *t*-BuOOH, 1 day | | **13b** (72) | **14b** (28) | 87 |
| 5 | **6b** | 30% $VO(acac)_2$, 3.5 equiv of *t*-BuOOH, Tol, 2 days | | **13b** (99) | **14b** (1) | 70 |
| 6 | **6c** | 15% $VO(acac)_2$, 3.0 equiv of *t*-BuOOH, 6 h | | **13c** | | 86 |
| 7[b] | **6d** | 10% $VO(acac)_2$, 3.0 equiv of *t*-BuOOH, 90 min | **6d''** | | | 35 |

[a] Combined yields of pure products after column chromatography. [b] Sulfonyl diene **6d''** was isolated from a complex mixture of products.

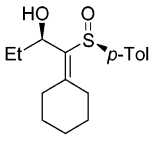
Similarly, *tert*-butylsulfinyl substrate **1e** produced a fair yield of oxirane **8e** (Table 1, entry 5).



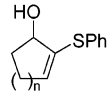
**1a**, $R^1$ = Et, $R^2$ = *n*-Bu, $R^3$ = *p*-Tol
**1b**, $R^1$ = *i*-Pr, $R^2$ = *n*-Bu, $R^3$ = *p*-Tol
**1c**, $R^1$ = *t*-Bu, $R^2$ = *n*-Bu, $R^3$ = *p*-Tol
**1d**, $R^1$ = (*R*)-CHCl*n*-Pr, $R^2$ = *n*-Bu, $R^3$ = *p*-Tol
**1e**, $R^1$ = $Ph(CH)_2$, $R^2$ = *n*-Bu, $R^3$ = *t*-Bu
**1f**, $R^1$ = Et, $R^2$ = Ph, $R^3$ = *p*-Tol
**1g**, $R^1$ = Et, $R^2$ = Ph, $R^3$ = *t*-Bu



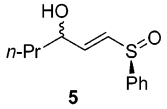
**2a**, $R^1$ = Ph, $R^2$ = *n*-Bu, X = (*S*)-S(O)*p*-Tol
**2b**, $R^1$ = Et, $R^2$ = Ph, X = (*S*)-S(O)*p*-Tol
**2c**, $R^1$ = Et, $R^2$ = *n*-Bu, X = S*p*-Tol



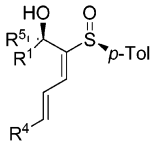
**3**



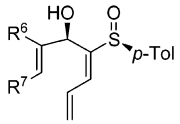
**4a**, n = 1
**4b**, n = 2



**5**



**6a**, $R^1$ = Et, $R^4$ = $R^5$ = H
**6b**, $R^1$ = Ph, $R^4$ = $R^5$ = H
**6c**, $R^1$ = $R^5$ = Me, $R^4$ = H
**6d**, $R^1$ = Et, $R^4$ = Me, $R^5$ = H



**7a**, $R^6$ = $R^7$ = H
**7b**, $R^6$ = H, $R^7$ = Me
**7c**, $R^6$ = Me, $R^7$ = H

In contrast to the above results, phenyl-substituted substrates **1f** and **1g** gave exclusively syn oxiranes **9f** and **9g** in fair yields (Table 1, entries 6 and 7), indicating that a strong 1,3-allylic strain is the prevailing element of stereocontrol in these cases (see below). At this stage, we chose to examine the influence of the geometry of the substrate on this process. Entry 8 shows that benzylic alcohol **2a** is also an adequate substrate, albeit prone to overoxidation at the benzylic position.[8] While at this stage we did not pursue the optimization of this particular case, the results found for benzylic diene **6b** discussed below suggest that by carefully monitoring the reaction and with minor experimental modifications this overoxidation should be controllable. Two additional examples of *Z* geometry were also examined with excellent results (Table 1, entries 9 and 10) with alkenyl sulfides being also adequate substrates for this process. Finally, the oxidation/epoxidation protocol was applied to tetrasubstituted alkenyl sulfoxide **3** to produce anti oxirane **12** as a single isomer and in excellent yield (Table 1, entry 11).

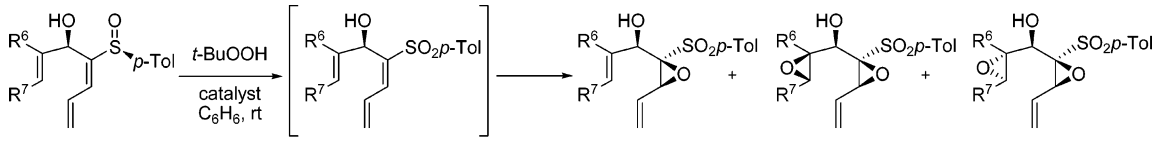
To probe if cyclic derivatives were suitable substrates, cyclopentenyl and cyclohexenyl sulfides **4a** and **4b** were subjected to the reaction conditions. In both cases, oxidation to the α-hydroxy alkenyl sulfones took place rapidly, but even under forcing conditions, we could not even detect α-hydroxy sulfonyl oxiranes. On the other hand, γ-hydroxy vinyl sulfoxide **5** was also tested under these conditions to produce a complex mixture of products derived from oxidation at sulfur and at the allylic hydroxyl without epoxidation. These results point out some limitations of the methodology.

The structure and geometry of these oxiranes were derived from their $^1H$ and $^{13}C$ NMR spectra with many of them being known compounds. The syn stereochemistry attributed to **9f** is based on a detailed comparison of its spectral data with that of very closely related compounds described in the literature.[9]

The viability and regioselectivity of this novel epoxidation for simple sulfinyl and sulfonyl dienols **6** was then examined, and the results obtained are shown in Table 2. Thus, ethyl-substituted dienol **6a** smoothly led to anti sulfonyl oxirane **13a** in good yield (Table 2, entry 1). In contrast, dienol **6b** was less reactive and gave substantial amounts of keto oxirane **14b** that was independently prepared by oxidation of **13b** with PCC (see the Supporting Information). The use of toluene diminished both the rate of epoxidation and the rate of overoxidation, and long reaction times brought about also substantial decomposition of these labile vinyl oxiranes (Table 2, entries 2 and 3). Entries 4

(8) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159−169.
(9) Jackson, R. F. W.; Standen, S. P.; Clegg, W.; McCamley, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 141−148.

**TABLE 3. Metal-Catalyzed Oxidation/Epoxidation of Hydroxy Trienyl Sulfoxides**




**7** **7a**, $R^6 = R^7 = H$; **7b**, $R^6 = H$, $R^7 = Me$; **7c**, $R^6 = Me$, $R^7 = H$ — **7"**

| entry | substrate | conditions | triene | anti | anti−anti | syn−anti | yield[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **7a** | 5% $VO(acac)_2$, 1.3 equiv of aq *t*-BuOOH, 15 min | **7a″** | | | | 70 |
| 2 | **7a** | 20% $Ti(O\text{-}i\text{-}Pr)_4$, 3.0 equiv of aq *t*-BuOOH, $CH_2Cl_2$, 5 days | **7a″** (70) | **15a** (30) | | | 39 |
| 3 | **7a** | 20% $VO(acac)_2$, 3.0 equiv of aq *t*-BuOOH, 5 days | **7a″** (50) | **15a** (50) | | | 78 |
| 4 | **7a** | 10% $VO(acac)_2$, 5.0 equiv of *t*-BuOOH, 4 h | | **15a** | | | 65 |
| 5 | **7a** | 15% $VO(acac)_2$, 9.0 equiv of *t*-BuOOH, 22 h | | **15a** (28) | **16a** (72) | | 62 |
| 6 | **7b** | 15% $VO(acac)_2$, 5.0 equiv of *t*-BuOOH, 9 h | | | **16b** (77) | **17b** (23) | 65 |
| 7 | **7b** | 25% $Ti(O\text{-}i\text{-}Pr)_4$, 4.0 equiv of *t*-BuOOH, $CH_2Cl_2$, 20 h | | | **16b** (36) | **17b** (64) | 40 |
| 8 | **7b** | 1.2 equiv $Ti(O\text{-}i\text{-}Pr)_4$, 1.6 equiv of (−)-DET, 6.0 equiv of *t*-BuOOH, $CH_2Cl_2$, 17 h | **7b″** | | | | 91 |
| 9[b] | **7c** | 15% $VO(acac)_2$, 4.5 equiv of *t*-BuOOH, 24 h | | | **16c** | | 36 |

[a] Combined yields of pure products after column chromatography. [b] Bis oxirane **16c** was isolated with difficulty from a complex mixture of products.

and 5 gather the improved conditions for the desired transformation that involve either a larger excess of *t*-BuOOH or of catalyst, if toluene is used. *gem*-Dimethyl-substituted dienol **6c** gave a good yield of oxirane **13c**. Finally, considerable experimentation was devoted to the reaction of dienol **6d**, bearing a Me substituent at the diene terminus. Despite these efforts, we could only isolate low yields of sulfonyl diene **6d″** at relatively short reaction times and from a rather complex mixture.[10]

Encouraged by the regioselectivity found for most dienes tested (**6a**−**c**), we decided to examine the behavior of the more challenging trienols **7** that have an additional allylic alcohol that may undergo epoxidation, and the results obtained are shown in Table 3. Throughout the previous studies on this method we had observed that the rate of the initial oxidation to sulfone was consistently high for different presentations of commercial *t*-BuOOH. On the other hand, the rate of the epoxidation varied widely with the aqueous reagent being slowest and commercially available anhydrous solutions in hydrocarbons being fastest. Thus, our initial experiments were conducted with 70% aqueous *t*-BuOOH, and this allowed for smooth oxidation of trienol **7a** to sulfone **7a″** (Table 3, entry 1). Catalysis by $Ti(O\text{-}i\text{-}Pr)_4$ was also tested and a small amount of anti monoepoxide **15a** was obtained in low yield (Table 3, entry 2). A substantial increase in yield and a modest increase in conversion to the desired monoepoxide **15a** was observed with $VO(acac)_2$ (Table 3, entry 3). Optimal conditions for obtaining monoepoxide **15a** entailed short reaction times and an excess of anhydrous *t*-BuOOH in benzene as solvent (Table 3, entry 4). With a larger load of catalyst and *t*-BuOOH and longer reaction times, a fair yield of the very sensitive bis oxirane **16a** was obtained as a single isomer, arising from "normal" epoxidation of the allylic alcohol moiety of **15a** (Table 3, entry 5). In contrast, trienol **7b**, with an (*E*)-1′-propenyl substituent at the hydroxylic carbon, gave exclusively bis oxiranes **16b** and **17b** by simultaneous epoxidation at both sites (Table 3, entry 6). Catalysis by $Ti(O\text{-}i\text{-}Pr)_4$ resulted in a poor yield of a 36:64 mixture of bis oxiranes **16b** and **17b** with reversal of selectivity of epoxidation at the allylic alcohol,[11] (Table 3, entry 7) and an attempt at carrying out the "asymmetric" epoxidation with *t*-BuOOH/ $Ti(O\text{-}i\text{-}Pr)_4$/(−)-DET resulted in just oxidation to the trienyl sulfone (Table 3, entry 8). Finally, trienol **7c** gave rise to complex mixtures of regioisomeric monoepoxides at short and intermediate reaction times and to a low yield of a very sensitive bis oxirane **16c**, as shown in entry 9 of Table 3.

## Synthetic Applications

Having studied in depth the scope and limitations of our metal-catalyzed epoxidation of alkenyl and dienyl sulfones, we focused our efforts on carrying out exploratory experiments to probe the application of these intermediates to the preparation of unnatural carbohydrates and tetrahydrofurans.[3] Readily available vinyl oxiranes **13a** and **13b** were selected at this stage to examine the ozonolysis of the alkene that, at short reaction times (5−7 min), gave excellent yields of the desired lactols **18a** and **18b** (Scheme 2) as ca. 90:10 mixtures of anomers.[12] The oxidation of these lactols to the related lactones was then tested, but all conditions explored failed and unreacted lactol was recovered.[13] In view of these results and seeking additional structural evidence, lactols **18** were acetylated to provide furanose derivatives **19a** and **19b** uneventfully. Finally, reduction of **18b** with $NaBH_4$ produced a good yield of epoxy diol **20**.

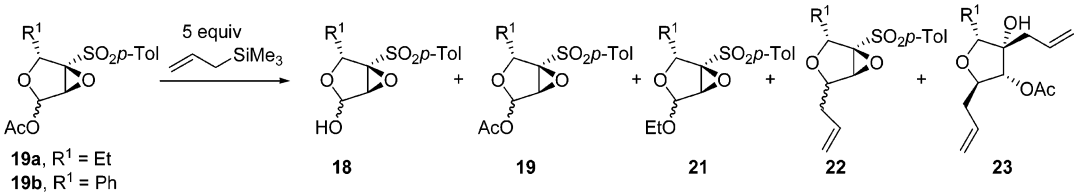
(10) For an excellent review on sulfonyl 1,3-dienes, see: Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291−2312. For reports somewhat complimentary to our own results, see: (a) Urones, J. G.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Bastida, A. J.; San Feliciano, S. G.; Díez, D.; Goodman, J. M. *Synlett* **1998**, 1361−1363. (b) Urones, J. G.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; San Feliciano, S. G.; Coca, R.; Díez, D. *Synlett* **1998**, 1364−1365.

(11) See references cited in: Adam, W.; Corma, A.; Reddy, T. I.; Renz, M. *J. Org. Chem.* **1997**, *62*, 3631−3637.

(12) At long reaction times, other products, not fully identified, presumably derived from overoxidation were obtained.

(13) These include $O_3$ followed by an excess of $H_2O_2$, PCC/NaOAc, $I_2/CaCO_3$, Dess−Martin, etc. (a) Corey, E. J.; Su, W.-G. *J. Am. Chem. Soc.* **1987**, *109*, 7534−7536. (b) Morikawa, T.; Nishiwaki, T.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 671−674. (c) Valverde, S.; García-Ochoa, S.; Martín-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1714−1715. (d) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649−651.

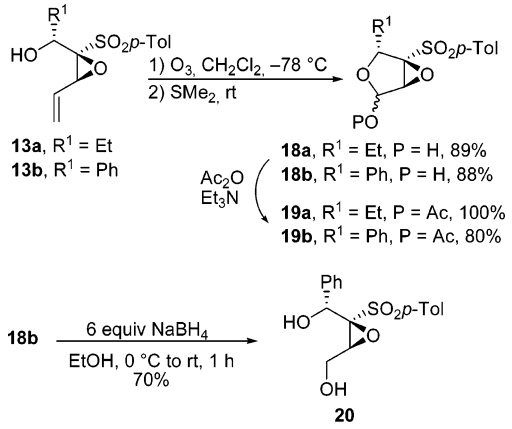
**TABLE 4. Attempts at Allylating Acetylated Lactols 19**



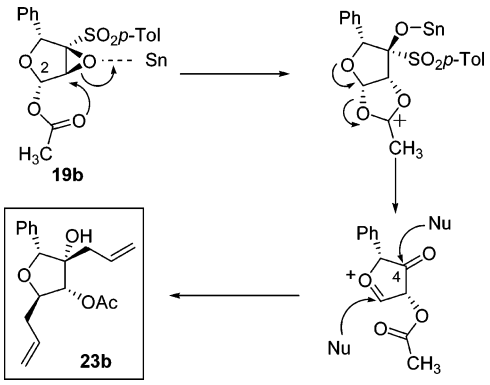

| entry | substrate | conditions | 18 | 19 | 21 | 22 | 23 | yield[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **19b** | 5.0 equiv of $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 0 °C to rt, 15 h | | 100 (14:86) | | | | 70 |
| 2 | **19b** | 5.0 equiv of $BF_3{\cdot}OEt_2$, $CH_3CN$, 0 °C to rt, 36 h | 34 (100:0) | | 64 (81:19) | 2 (60:40) | | 63 |
| 3 | **19b** | 2.0 equiv of EtOH, 3.0 equiv $BF_3{\cdot}OEt_2$, $CH_3CN$, 0 °C to rt, 19 h | | 100 (94:6) | | | | 75 |
| 4 | **19b** | 2.0 equiv of $SnCl_4$, $CH_2Cl_2$, −70 °C to rt, 14 h | | | | | **23b** | 48 |

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

**SCHEME 2**




**SCHEME 3**




The Lewis acid catalyzed allylation of lactols related to **18** but lacking the sulfonyl oxirane moiety with allyl silanes is a well-studied protocol to access substituted tetrahydrofurans.[14] As observed before for the oxidation, these lactols turned out to be notoriously unreactive under these conditions. Since these transformations are also documented for anomeric acetates,[15] the allylation of acetates **19a** and **19b** was attempted and the results obtained are shown in Table 4. With $BF_3{\cdot}OEt_2$, all conditions tested resulted in either recovery of starting material (Table 4, entry 1) or production of a complex mixture of deacetylated lactol **18**, *O*-ethyl glycoside **21b** (as an 81:19 mixture of diastereomers at the anomeric center), and just trace amounts of the desired product **22** (Table 4, entry 2). Interestingly, these acetates are unreactive even to glycosylation with EtOH (Table 4, entry 3); therefore, ethyl glycoside **21b** is likely to be derived from acetate **19b** by carboxylate reduction under the reaction conditions. Substrate **19a**, with a less bulky Et substituent, gave equally disappointing results that largely paralleled those of **19b**. This unexpected lack of reactivity,[16] prompted us to test $SnCl_4$ as a Lewis acid promoter and this gave rise to a fair yield of a very interesting diallylated tetrahydrofuran **23b** albeit in low yield. A tentative reaction pathway to account for the production of **23b** is shown in Scheme 3.

In view of these results, we decided to examine the allylation of open-chain epoxy aldehydes[17] instead of the cyclic lactols, and the results obtained are shown in Scheme 4. Thus, hydroxy vinyl oxirane **13b** was acetylated uneventfully to provide **24b** that underwent ozonolysis to produce aldehyde **25b** in modest yield, along with a relatively large amount of acid **26b**. At this stage we did not attempt to improve this transformation but instead the $BF_3{\cdot}OEt_2$-catalyzed allylation of aldehyde **25b** with allyltributylstannane was explored leading to a separable 80:20 mixture of homoallylic alcohols **27b** and **28b**[18] that should be inmediate precursors to unusual hexoses upon, for instance, ozonolysis. To rule out that these alcohols were isomeric due to acetyl group migration, an 80:20 mixture of monoacetates

(14) (a) Schmitt, A.; Reissig, H.-U. *Synlett* **1990**, 40−42. (b) Brückner, C.; Holzinger, H.; Reissig, H.-U. *J. Org. Chem.* **1988**, *52*, 2450−2456. (c) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893−3901. (d) Pilli, R. A.; Riatto, V. B. *Tetrahedron: Asymmetry* **2000**, *11*, 3675−3686.

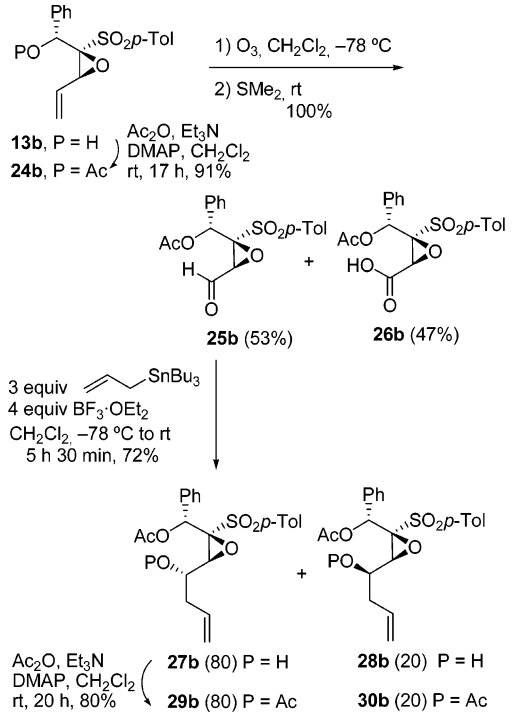
(15) (a) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C. Xu, Z. *Tetrahedron Lett.* **1983**, *24*, 1563−1566. (b) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815−6818. For recent developments in this field, see: (c) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209. (d) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063−2066.

(16) Interestingly, hindered isopropylidenedioxy ribose acetates are allylated under similar conditions, see: Wilcox, C. S.; Otoski, R. M. *Tetrahedron Lett.* **1986**, *27*, 1011−1014.

(17) (a) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4728−4731. (b) Howe, G. P.; Wang, S.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2629−2632. (c) Wang, S.; Howe, G. P.; Mahal, R. S.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3351−3354. (d) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30. (e) For a leading reference on reagent controlled allylation of α,β-epoxy aldehydes, see: Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636−1648. (f) See also: Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P. *Tetrahedron Lett.* **1998**, *39*, 7251−7254.

(18) The stereochemistry of the new chiral center is assigned tentatively in analogy with the results of Procter for nucleophilic additions to α,β-epoxy aldehydes. See ref 17b.

**SCHEME 4**




**27b** and **28b** was acetylated to produce an inseparable mixture of diacetates **29b** and **30b**.

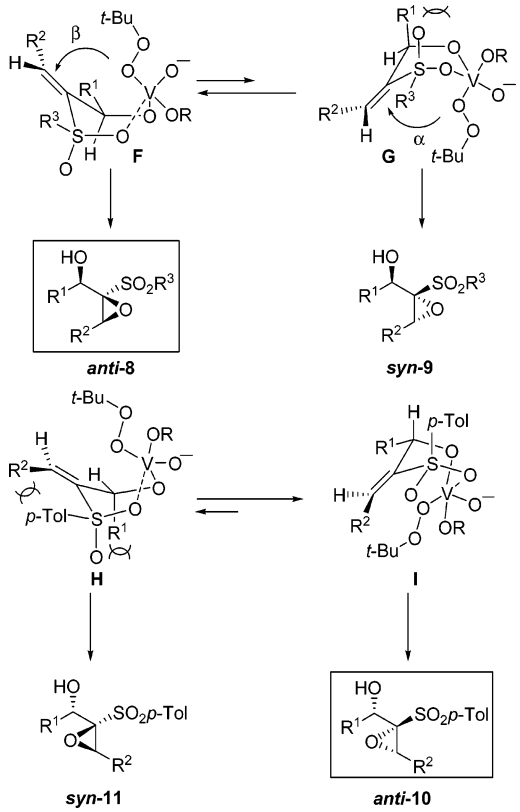
## Results and Discussion

The key findings of this study are the viability and stereoselectivity of the process for simple substrates and the regioselectivity found for some dienols and even trienols. These findings can be tentatively rationalized by considering, after the initial rapid oxidation at sulfur, a certain degree of coordination between the sulfonyl oxygens and the metal to produce a cyclic boatlike arrangement for the reactive conformers such as **F** and **G** (Scheme 5).[19] The precise balance of allylic 1,3-strain between $R^1$ and $R^2$ or diaxial interactions ($R^1-O$ or $R^1-R^3$, since both sulfonyl oxygens could in principle interact with the metal) would dictate the favored reactive conformer. This proposal accounts for the viability of the process and the lack of reactivity of $\gamma$-hydroxy vinyl substrate **5** as well as for the reversal of stereoselectivity found when $R^2$ = Ph (see Table 1) due to an overwhelming allylic 1,3-strain between the conjugated phenyl moiety ($R^2$) and the ethyl substituent ($R^1$) in conformer **F**. The anti selectivity found for the *Z* isomers can be understood similarly in terms of reactive conformers **H** and **I** (Scheme 5) by considering the balance of allylic strain between $R^2$ and *p*-Tol (or O) and 1,3-diaxial interactions between $R^1$ and oxygen (or *p*-Tol).

## Conclusions

To summarize, readily available acyclic hydroxy vinyl and dienyl sulfoxides undergo a facile one-pot metal-catalyzed oxidation and epoxidation with high diastereoselectivity that complements in most cases the results obtained for the nucleophilic epoxidation of these substrates. The application of this methodology to the straightforward preparation of unusual carbohydrate-like fragments through hydroxy sulfonyl diene monoepoxides has been outlined. Additional applications of this protocol are being examined in our laboratories.

**SCHEME 5**




## Experimental Section

**General Procedure for Oxidation/Epoxidation of Unsaturated Sulfoxides with VO(acac)$_2$/*t*-BuOOH.** To a solution of the vinyl or dienyl sulfoxide in anhydrous benzene (4 mL/mmol) was added the catalyst, generally VO(acac)$_2$ (0.01 M in benzene, 0.05 equiv). After the solution was stirred for 5 min at rt, *t*-BuOOH was added (0.5 M in benzene, typically 80% in *t*-BuOO*t*-Bu), and the mixture changed from blue to red. A rapid oxidation to the alkenyl or dienyl sulfone followed, and if necessary, additional amounts of VO(acac)$_2$ and *t*-BuOOH were added at 1−3 h intervals or upon discoloration of the mixture, until disappearance of the alkenyl sulfone. Upon completion (TLC), the reaction was quenched with 1 M $Na_2S_2O_4$ and diluted with EtOAc (8 mL/mmol), and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with a saturated solution of NaCl (4 mL/mmol), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product that was purified by chromatography on silica gel using the appropriate mixture of eluents. In most cases, especially those involving the obtention of vinyl oxiranes, higher yields were obtained with 5 equiv of *t*-BuOOH and purifying the crude products as soon as possible. The precise rate of the epoxidation is highly dependent on the type of commercial *t*-BuOOH used with the aqueous reagent being slowest and the commercially available anhydrous reagents being fastest.

**Synthesis of (−)-(1′*R*,2*S*,3*S*)-3-*n*-Butyl-2-(1′-hydroxy-2′,2′-dimethylpropyl)-2-(*p*-tolylsulfonyl)oxirane, 8c.** From a solution of vinyl sulfoxide **1c**[1c] (34 mg, 0.11 mmol) in $C_6H_6$ (1.7 mL) with VO(acac)$_2$ (0.25 equiv) and *t*-BuOOH (4.0 equiv) according to the

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

general procedure (132 h) was obtained epoxy sulfone **8c** (31 mg, 84%) as a white solid after chromatography (50−100% $CH_2Cl_2$−hexane). The data was identical to that found before.[1c]

**Synthesis of (±)-(1′*S*,2*R*,3*S*)-2-(1′-Hydroxypropyl)-3-phenyl-2-(*p*-tolylsulfonyl)oxirane, 10b.** From a solution of vinyl sulfoxide **2b**[1c] (32 mg, 0.113 mmol) in $C_6H_6$ (2.0 mL) with $VO(acac)_2$ (0.15 equiv) and *t*-BuOOH (5.0 equiv) according to the general procedure (6 h) was obtained epoxy sulfone **10b** (33 mg, 87%) after chromatography (0−10% EtOAc−$CH_2Cl_2$). The data was identical to that found before.[1c]

**Epoxidation of (±)−(2*R*,*S*$_S$)-1-Cyclohexylidenyl-1-(*p*-tolylsulfinyl)butan-2-ol, 3.** From a solution of vinyl sulfoxide **3** (66 mg, 0.24 mmol) in $C_6H_6$ (0.4 mL) with $VO(acac)_2$ (0.15 equiv) and *t*-BuOOH (3.0 equiv) according to the general procedure (4 h) was obtained epoxy sulfone **12** (66 mg, 91%) after chromatography (0−50% EtOAc−hexane) as a white solid that was recrystallized from $CH_2Cl_2$−hexane. Data for **12**: mp 110−112 °C; $R_f$ = 0.30 (20% EtOAc−hexane); $^1$H NMR (200 MHz) $\delta$ 0.98 (t, 3 H, $J$ = 7.4 Hz), 1.44−1.92 (m, 10 H), 1.92−2.02 (m, 2 H), 2.14 (m, 1 H), 2.43 (s, 3 H), 3.81−3.85 (m, 1 H), 7.34 (d, 2 H, $J$ = 7.9 Hz), 7.78 (d, 2 H, $J$ = 8.4 Hz); $^{13}$C NMR (50 MHz) $\delta$ 11.3, 21.7, 24.9 (2 C), 25.3, 26.2, 30.7, 31.1, 71.3, 72.3, 83.9, 128.5 (2 C), 129.8 (2 C), 136.2, 145.0. IR (KBr): 3511, 3434, 2939, 1289, 1145, 659 cm$^{-1}$; MS (ES) 671 $[2M + Na]^+$, 347 $[M + Na]^+$ (100). Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46; S, 9.88. Found: C, 62.75; H, 7.35; S, 10.12.

**Synthesis of (+)-(1′*R*,2*S*,3*S*)-2-(1′-Hydroxybenzyl)-2-(*p*-tolylsulfonyl)-3-vinyloxirane, 13b.** From a solution of dienyl sulfoxide **6b**[9] (300 mg, 1.01 mmol) in $C_6H_6$ (5.0 mL) with $VO(acac)_2$ (0.15 equiv) and *t*-BuOOH (5.0 equiv, 5.0−6.0 M in decane) according to the general procedure (1 day) was obtained a 72:28 mixture of **13b** and **14b**. Chromatography (5−30% EtOAc−hexane, then 0−5% EtOAc−$CH_2Cl_2$) gave sulfonyl oxirane **13b** (221 mg, 67%) as a white solid recrystallized from $Et_2O$−hexane. Long reaction times (2−6 days) and the use of more than 3.5 equiv of *t*-BuOOH led to increased amounts of ketone **14b**; alternatively, short reaction times (6−7 h) and lesser amounts of *t*-BuOOH substantially diminish the rate of the reaction and significant amounts of dienyl sulfone are produced. Under optimized conditions (30% $VO(acac)_2$, 3.5 equiv of *t*-BuOOH, in toluene, 2 days), hydroxy oxirane **13b** was obtained along with small amounts of dienyl sulfone. Data for **13b**: mp 132−134 °C; $R_f$ = 0.35 (30% EtOAc−hexane), 0.24 (1% EtOAc−$CH_2Cl_2$); $[\alpha]^{20}_D$ = +10.8 ($c$ = 0.60); $^1$H NMR (300 MHz) $\delta$ 2.32 (s, 3 H), 3.80 (d, 1 H, $J$ = 10.6 Hz), 4.56 (d, 1 H, $J$ = 6.2 Hz), 4.94 (d, 1 H, $J$ = 10.6 Hz), 5.58 (d, 1 H, $J$ = 10.6 Hz), 5.71 (d, 1 H, $J$ = 17.1 Hz), 5.97 (ddd, 1 H, $J$ = 17.1, 10.7, 6.2 Hz), 6.97 (d, 2 H, $J$ = 8.1 Hz), 7.03−7.15 (m, 5 H), 7.22 (d, 2 H, $J$ = 7.5 Hz); $^{13}$C NMR (50 MHz) $\delta$ 21.6, 62.1, 70.6, 78.0, 124.1, 125.8 (2 C), 127.7, 128.0 (2 C), 128.8, 128.9 (2 C), 129.1 (2 C), 133.9, 137.9, 144.6; IR (KBr) 3530, 3480, 2930, 1600, 1500, 1490, 1460, 1315, 1300, 1180, 1160, 1150, 1090, 1060, 1000, 940, 810, 780, 750, 710, 670 cm$^{-1}$; MS (EI) 174, 157, 146, 139, 129, 118, 107, 91 (100), 77, 65, 57, 39; MS (APCI) 329 $[M - 1]^-$, 155 (100). Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49; S; 9.70. Found: C, 65.48; H, 5.45; S, 9.65.

**Acknowledgment.** This research was supported by DGICYT (BQU2003-02921) and CAM (GR/SAL/0823/2004). We thank JANSSEN-CILAG for generous additional support. We thank CSIC for a doctoral fellowship to A.C.

**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.

JO052244D