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Synthesis of β-hydroxy sulfones via opening of hydrophilic epoxides with zinc sulfinates in aqueous media

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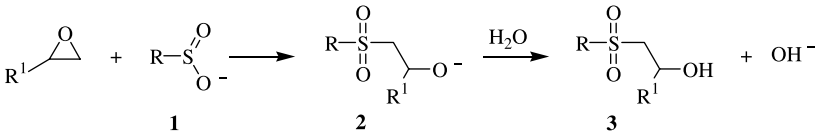
Abstract—Reaction of hydrophilic epoxides (ethylene oxide and propylene oxide) with readily accessible zinc sulfinates in aqueous solution under essentially neutral conditions afforded β-hydroxy sulfones in good yields. This method avoids the need for organic solvents and produces ZnO as the only major reaction byproduct. 2-(Methylsulfonyl)ethanol, a common reagent for the protection of various functional groups, was obtained by this methodology from ethylene oxide in 78% yield. Reaction of various simple zinc alkane- and benzenesulfinates with propylene oxide proceeded regioselectively in 63–67% yield. The corresponding opening of these epoxides with zinc 1,3-butadiene-1-sulfinate afforded 1-butadienyl β-hydroxyalkyl sulfones in 30% yield. Mechanistic studies revealed that the yields of these products were limited by their consumption in competing intra- and intermolecular Michael addition processes.

1. Introduction

S-Alkylation of sulfinate anions with alkyl halides is an established method for the synthesis of aliphatic sulfones.[1–7] However, the preparation of β-hydroxy sulfones by opening epoxides with sulfinate ions has been much less thoroughly investigated. There are two specific problems inherent to this transformation: (i) the low solubility of sulfinate salts in organic solvents necessitates the use of water as a cosolvent; (ii) the generation of a basic alkoxide adduct (**2**) leads to a progressive increase in the basicity of the reaction medium (Scheme 1). This, in turn, promotes side reactions involving the starting epoxide. In addition, the newly formed β-hydroxy sulfone product **3**, if hydrophilic, is prone to decomposition in strongly basic aqueous medium.

In an early report, direct opening of two simple symmetrical epoxides by sodium *p*-toluenesulfinate in aqueous alcohol was reported to proceed in 50–55% yield,[8] however, we were unable to reproduce these results. The necessity of adjusting pH during the reaction was recognized, yet, even with careful portionwise addition of acid to the reaction mixture while opening simple monosubstituted epoxides, the isolated yields of β-hydroxy sulfone products were low (25–40%).[9] Lewis acid catalysis with magnesium nitrate was used[10] to open propylene oxide with simple sodium arenesulfinates. However, good yields (64–83%) of products were observed only if propylene oxide was used as the solvent. Lower yields (23–42%) were noted when stoichiometric amounts of longer chain 1,2-epoxyalkanes were employed, and these reactions failed completely when using other epoxides or when employing sulfinates bearing an electron-withdrawing arene substituent.

More recently, the use of two-phase reaction systems in the presence of tetra-*n*-butylammonium chloride or bromide,[7] montmorillonite clay,[11] or polyethylene glycol 4000[12] have been exploited. Under all these protocols the aqueous phase



1 **2** **3**

Scheme 1.

Keywords: Zinc sulfinate; β-Hydroxy sulfone; Epoxide; Butadiene sulfone; Butadienyl sulfones.
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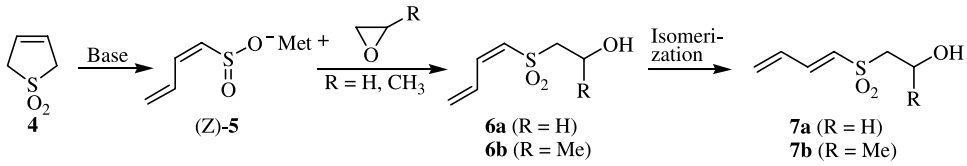


Scheme 2.

still became strongly basic during the reaction; however, the decomposition of unreacted epoxide and β-hydroxy sulfone product was prevented by their partitioning into the organic phase. These protocols frequently provided good yields of β-hydroxy sulfone products but only when hydrophobic epoxides (such as cyclohexene oxide) were used. To the best of our knowledge, besides sodium arenesulfinates, only polyfluoroalkanesulfinate anions have been employed to date in epoxide ring opening reactions.[13,14]

As part of a study aimed at the development of new sulfonyl tethers for intramolecular Diels–Alder cycloaddition reactions,[15] we needed to synthesize several 1-(*E*)-butadienyl β-hydroxyalkyl sulfones (**7**). An epoxide opening reaction with butadiene-1-sulfinate anion (*Z*)-**5**, readily accessible via treatment of commercially available and inexpensive 2,5-dihydrothiophene-1,1-dioxide (butadiene sulfone, **4**) with base[1–3,16–18] seemed an attractive entry to this type of compounds (Scheme 2). S-Alkylation of both (*Z*)-1,3-butadiene-1-sulfinate ((*Z*)-**5**) and (*Z*)-2-methyl-1,3-butadiene-1-sulfinate anions has been reported,[1–5,19] however, to best of our knowledge, epoxide opening reactions with alkene-1-sulfinate salts have not been explored. Our need to use hydrophilic epoxides and the anticipation that both **6** and **7** would be quite water-soluble and would prove unstable under strongly basic conditions, made problematic the use of the previously developed two-phase systems described above. Thus, designing a reliable method for opening epoxides (including hydrophilic epoxides) with various sulfinate salts under essentially neutral reaction conditions became necessary.

In the present paper, we report that zinc sulfinates are, indeed, effective nucleophiles for the ring opening of ethylene oxide and propylene oxide under essentially neutral conditions in a simple one-phase aqueous reaction, providing an attractive new entry to the synthesis of base-sensitive β-hydroxy sulfones and β-hydroxy sulfones derived from water-soluble epoxides and sulfinate anions.

2. Results and discussion

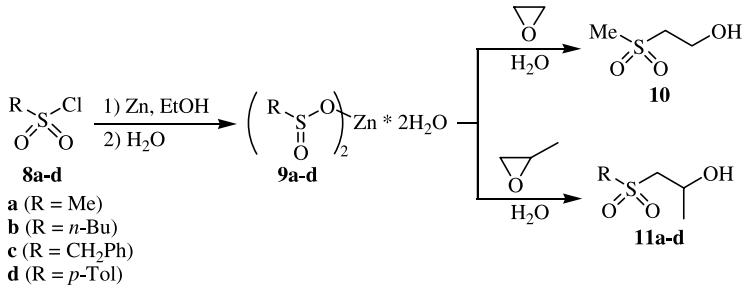
2.1. Synthesis of simple Zn sulfinates and their reactions with epoxides

As a first step, we decided to evaluate the applicability of some of the previously reported two-phase reaction systems for opening hydrophilic epoxides. We treated sodium methanesulfinate with propylene oxide[20] in the presence of Bu_4NBr under the conditions described by Crandall and Pradat.[7] The resulting reaction mixture was strongly basic (pH 14 for the aqueous phase). The ^1H NMR spectrum of the crude reaction product showed that only 20% of the desired β-hydroxy sulfone was formed along with 35% of propylene glycol. When the reaction was performed in the presence of montmorillonite clay,[11] formation of a strongly basic aqueous phase (pH 14) was again observed. Workup gave 31% of crude β-hydroxy sulfone, which was approximately 80% pure by ^1H NMR analysis. The slightly better yield of the desired product under these conditions could originate from partial neutralization of base formed during the reaction by acidic sites in the montmorillonite clay. We presumed that high yields for these two-phase methods might be expected only if (i) the starting epoxide resides primarily in the organic layer (i.e., is hydrophobic), and (ii) the β-hydroxy sulfone product is relatively stable under strongly basic conditions and/or also preferentially partitions into the organic layer.

We considered that epoxide opening with sulfinate anion **1** might be achieved in aqueous medium if we used metal sulfinates $(RSO_2)_nMet$ for which the corresponding metal hydroxides $Met(OH)_n$ are insoluble in water and would thus precipitate from the reaction medium, effectively maintaining neutral reaction conditions in solution. Ideally, the metal sulfinates should be readily available and inexpensive. To make large-scale synthesis possible, the corresponding metal hydroxides should precipitate in a form that can be removed by simple filtration. After considerable experimental work, we have found that zinc sulfinates fulfill all the above requirements. Zinc sulfinates can be conveniently prepared by direct reduction of sulfonyl chlorides with zinc powder.[21–23] In most reported cases, however, after the reduction is finished, the reaction mixture has been either acidified to obtain the corresponding sulfinic acids[21] or treated with excess aq $NaOH/Na_2CO_3$ solution to produce the corresponding sodium sulfinates.[22] Only in two cases have zinc arenesulfinates $Zn(O_2SAr)\cdot nH_2O$[23] and $Zn(O_2SCH_2NHC_6H_5)\cdot nH_2O$[24] been isolated, albeit in low to moderate yields.

In our hands, Zn reduction of commercially available sulfonyl chlorides **8a–d** afforded the respective Zn sulfinates **9a–d** as crystalline dihydrates[25] (Scheme 3, Table 1) in excellent to good yields. The reaction of Zn sulfinates **9a–c** with ethylene oxide or propylene oxide provided good yields of the desired β-hydroxy sulfones **11a–c** and **10** (Table 1) after a straightforward workup, which did not require column chromatography.

2-(Methylsulfonyl)ethanol (**10**) (Table 1, entry 1) is widely used in protecting various functional groups;[26] given the straightforward nature of the chemistry involved, we believe that that our method could be adapted to produce **10** on a very large scale. Given the low cost of the reagents used (methylsulphonyl chloride, zinc powder, ethanol, ethylene oxide and water) and the minimal amount of waste generated (ethanolic $ZnCl_2$ solution and clean ZnO), this



Scheme 3.

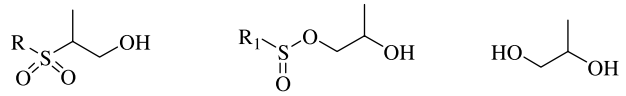
Table 1. Regioselective opening of epoxides using zinc sulfinates **9a–d**

Entry	RSO_2Cl	Yield of Zn salt (%)	Epoxide used (equiv)	Reaction conditions	Molar ratio of **11/12/13/14**[a,b]	β-Hydroxy sulfone product	Isolated yield (%)
1	**8a**	**9a** (90)	Ethylene oxide (1.3)	2 h, 70 °C	—	**10**	82[c]
2	**8a**	**9a** (92)	Propylene oxide (1.4)	2 h, 75 °C	86/8/6/21	**11a**	65[d]
3	**8b**	**9b** (92)	Propylene oxide (1.6)	12 h, 70 °C	85/8/7/34	**11b**	67[d]
4	**8b**	**9b** (92)	Propylene oxide (1.6)	4 h, 80 °C, ultrasound	85/8/7/42	**11b**	64[d]
5	**8c**	**9c** (91)	Propylene oxide (2.0)	7 h, 70 °C	85/8/7/85	**11c**	63[e]
6	**8d**	**9d** (78)	Propylene oxide (1.7)	16 h, 70 °C	93/7/0/93	**11d**	41[e]
7	n/a	**9d** (n/a)[f]	Propylene oxide (1.7)	4 h, 75 °C	93/7/0/20	**11d**	64[e]

[a] Determined through NMR analysis of the crude reaction product.
[b] **14** is generated via hydrolysis of excess propylene oxide in situ.
[c] Isolated yield after distillation.
[d] Isolated yield after purification by distillation followed by crystallization.
[e] Isolated yield after purification by crystallization.
[f] Obtained in situ from commercially available sodium *p*-toluenesulfinate and zinc chloride (0.5 equiv).

approach for the synthesis of **10** is quite environmentally friendly.

In most cases, the synthesis of **11a–c** was accompanied by the formation of less than 15% of two byproducts (Fig. 1): the corresponding regioisomeric sulfones **12a–c**, formed as a result of propylene oxide opening at the more substituted epoxy carbon, and sulfinate esters **13a–c** (as 1:1 diastereomeric mixtures), resulting from O-attack of the sulfinate anion on the epoxide. The structures of **12a–c** and **13a–c** were tentatively assigned from their mixtures with **11a–c** using NMR analysis.[27] Interestingly, in the case of *p*-tolyl sulfone **11d** we did not observe the formation of the corresponding sulfinate ester **13d**.[28]



12a-d **13a-d** **14**

Figure 1.

The isolation of the desired β-hydroxy sulfone products was rather simple: after removal of ZnO by filtration, the resulting aqueous solution was concentrated under reduced pressure and the residue was distilled (for **10**, **11a** and **11b**) or recrystallized from water (**11c** and **11d**.) While distilled 2-(methylsulfonyl)ethanol (**10**) was essentially pure, distilled **11a** and **11b** were sometimes contaminated with 5–9% of the regioisomer **12**. Optional recrystallization from toluene afforded **11a** and **11b** with up to 99% purity.

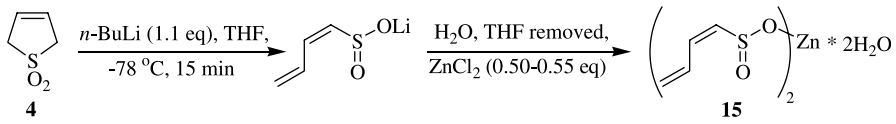
However, only 41% yield was obtained in the case of Zn *p*-toluenesulfinate **9d** (Table 1, entry 6), presumably due to the very limited solubility of **9d** in water. For less water-soluble sulfinate salts **9b–d**, we considered that it might be possible to facilitate reaction in the heterogeneous mixture using ultrasonication. Unfortunately, this approach had little impact on the reaction of **9b** (Table 1, compare entries 3 and 4), and so it was not investigated further.

We observed that the reactivity of zinc sulfinate salts was significantly enhanced if these salts were freshly prepared by an ion-exchange reaction from sodium sulfinates and $ZnCl_2$. Thus, we treated commercially available Na *p*-toluenesulfinate with $ZnCl_2$ (0.5 equiv) and immediately added propylene oxide to the resulting white slurry. To our delight, the reaction was completed in 4 h to give 64% isolated yield of the desired sulfone **11d** (Table 1, entry 7).

It is important to note that, during all these reactions, the pH of the solution was well controlled by the formation of insoluble ZnO (a solution pH of around 6.5 was observed at the end of the reaction).

2.2. Epoxide opening with zinc (*Z*)-buta-1,3-diene-1-sulfinate

Given that we had successfully developed a practical approach for the synthesis of β-hydroxy sulfones **10** and **11a–d** using simple Zn sulfinate salts **9a–d**, we were now in a position to explore the preparation of the more challenging 1-butadienyl β-hydroxyalkyl sulfones **6** and **7** required for our Diels–Alder studies (see Scheme 2). The presence of an unsaturated sulfone moiety, which provides a potent Michael acceptor motif, was recognized as a significant challenge to the successful execution of these studies. This work required the use of Zn (*Z*)-buta-1,3-diene-1-sulfinate



Scheme 4.

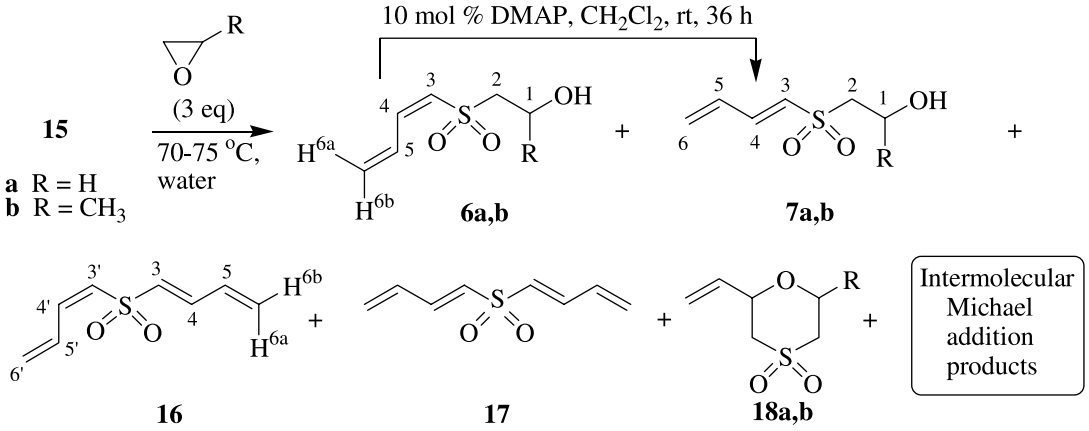
(**15**), which we anticipated would be accessible from commercially available 2,5-dihydrothiophene-1,1-dioxide (butadiene sulfone, **4**). Treatment of butadiene sulfone (**4**) with *n*-BuLi followed by addition of water and removal of the THF in vacuo afforded a clear solution of Li (*Z*)-buta-1,3-diene-1-sulfinate. This solution was treated with $ZnCl_2$ to afford Zn (*Z*)-buta-1,3-diene-1-sulfinate (**15**) as a white precipitate (Scheme 4).

Zinc sulfinate **15** could be isolated as a stable white solid dihydrate in 70–75% yield and was characterized by ^1H and ^{13}C NMR spectroscopy, and elemental analysis. However, we observed that excessive washing of **15** with water significantly decreased its reactivity toward epoxide opening chemistry (see later).

In practice, the Zn sulfinate **15** was prepared in situ and then allowed to react directly with added epoxide (3 equiv, 70–75 °C). ^1H NMR analysis of the crude product obtained from the reaction of **15** with propylene oxide showed the presence of a mixture of (*Z*)-butadienyl sulfone **6b**, (*E*)-butadienyl sulfone **7b**, (*E*,*Z*)-bis-butadienyl sulfone (**16**) and (*E*,*E*)-bis-butadienyl sulfone (**17**) (see Scheme 5 and Table 2, entry 1). Unfortunately, the desired products **6b** and **7b** were not separable by column chromatography. Similar results were obtained on reaction with ethylene oxide (Table 2, entry 7), however, a small amount of cyclization product **18a** was also observed.

To our delight, when mixtures of products **6** and **7** were treated with DMAP in dichloromethane, quantitative (*Z*)- to (*E*)-isomerization occurred to cleanly afford the desired (*E*)-1-butadienyl β-hydroxyalkyl sulfones **7a** and **7b** in ca. 30% overall yields from butadiene sulfone (**4**).

A series of experiments were run with varying amounts of $ZnCl_2$ and for various reaction times (see Table 2). The pH values shown in Table 2 were measured at the end of



Scheme 5.

Table 2. Preparation of butadienyl sulfones **6** and **7** (75 °C, water)

Entry	R	Equiv $ZnCl_2$	Time (h)	pH[a]	Approximate product ratio[b]				Yield **6**+**7** (%)[c]
					6	**7**	*cis*-**18**	*trans*-**18**	
1	CH_3	0.50–0.52	1.7	8.3–8.6	1	1	0	0	25[d]
2	CH_3	0.50–0.52	3	8.3–8.6	1	3.5	Traces	0	30
3	CH_3	0.50–0.52	5	8.3–8.6	1	7	0.2	0.1	23[e]
4	CH_3	0.49–0.50	3	10.2	1	3.5	0.6	0.3	30
5	CH_3	0.49–0.50	5	10.2	1	7	4.4	1.2	—
6	CH_3	0.35	3	14	0	0.2	4.8	1	—
7	H	0.50–0.52	3	8.3–8.6	1	3.3	0.4	n/a	30
8	CH_3	0.50[f]	2	6.5	1	0	0	0	20[d,g]
9	CH_3	0.50[f]	8	6.5	1	0	0	0	13[d,g]
10	CH_3	0.50[f,h]	9	6.5	1	0	0	0	13[d,g]

[a] Measured at the end of the reaction prior to workup.
[b] Measured by ^1H NMR analysis of the crude product. Bis-butadienyl sulfones **16** and **17** are not included; the ratio of **16**/**17** closely paralleled the ratio of **6**/**7**.
[c] Isolated yield after purification by column chromatography.
[d] Large amounts of intermolecular Michael addition products were seen in the crude ^1H NMR spectrum.
[e] Trace amounts of intermolecular Michael addition products were seen in the crude ^1H NMR spectrum.
[f] Compound **15** was thoroughly washed with water and dried before use.
[g] Isolated as a 3:1 inseparable mixture of **6** and buta-1,3-diene-1-sulfinate ester.
[h] LiOH (0.1 equiv) was added.

the indicated reaction time. If the reactions corresponding to entries 1–5 were interrupted after 1–1.5 h, the pH of the reaction medium was around 6.5. Importantly, the amount of ZnO precipitate formed in runs 1–3 was the same and corresponded to a quantitative recovery of Zn based on initially added $ZnCl_2$. This means that Zn sulfinate **15** was consumed and the formation of ZnO completed after 1.7 h. As long as Zn sulfinate **15** was present in the reaction medium, the pH of the solution was well controlled by the formation of insoluble ZnO and remained essentially neutral (pH 6.5). After all Zn sulfinate **15** had been consumed, the pH increased, with smaller amounts of added $ZnCl_2$ resulting in higher final solution pH levels (compare entries 2, 4 and 6 in Table 2).

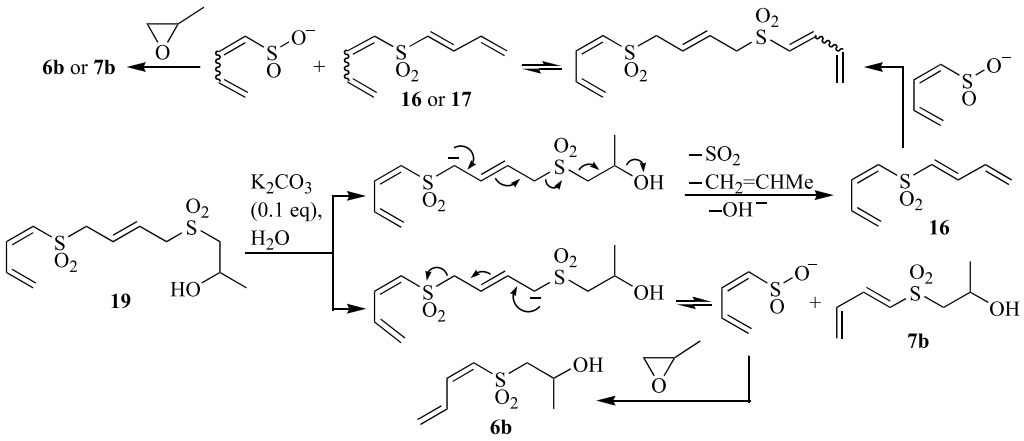
Attempts to purify zinc salt **15** before use through thorough washing with water and drying resulted in incomplete conversion—a significant amount of **15** remained unreacted (see entries 8 and 9). In these runs, low yields of (*Z*)-butadienyl sulfone **6b** contaminated with *O*-alkylated (buta-1,3-diene-1-sulfinate ester) byproducts were observed (entries 8 and 9). The higher reactivity of **15** formed in situ does not appear to correlate with the possible presence of Li^+ ions in the crude Zn sulfinate salt—the addition of 10 mol% LiOH had no impact on the reaction (entry 10).

The accumulated data allowed us to draw the following important conclusions about the reaction mechanism:

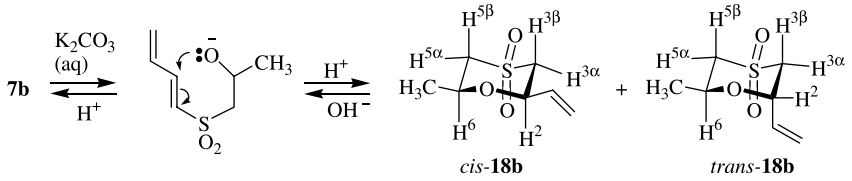
1. The formation of oligomeric intermolecular Michael addition byproducts is reversible under basic conditions (pH 8.3 and higher). At very short reaction times (1–1.5 h or less), the pH of the reaction solution (6.5) allows for accumulation of intermolecular Michael addition products. Beyond this point, the reaction becomes slightly basic (pH 8.3–8.6), which allows for the gradual conversion of these intermolecular Michael addition products (via a retro-Michael process) to afford bis-butadienyl sulfones **16** and **17**, and (*E*)-β-hydroxy sulfone **7b**. As a result, longer reaction times lead to the recovery of smaller amounts of intermolecular Michael addition products (compare entries 1 and 3). Since the only source of (*E*)-β-hydroxy sulfone **7b** is from this base-mediated retro-Michael process, the ratio of **7b** to **6b** increases with longer reaction times (compare entries 1–3). This is also supported by the complete absence of **7b** when the reaction medium remains completely non-basic (see entries 8–10), precluding retro-Michael reactions. To further support this conclusion, we subjected the (*E*,*Z*)-dimer **19** (one of the intermolecular Michael addition byproducts isolated from the reaction mixture in the run presented in Table 2, entry 1) to an aqueous solution of propylene oxide in the presence of a base (Scheme 6). The resulting crude reaction mixture contained 31% of dimers **19** (now as a mixture of (*E*,*Z*)- and (*E*,*E*)-stereoisomers), 7% of the product **6b**, 40% of the product **7b**, along with 32% of the bis-butadienyl sulfones **16** and **17**. Compounds **16** and **17** were commonly present as byproducts in reaction runs 1–7 represented in Table 2. It seemed logical that the formation of **16** and **17** (being essentially irreversible due to loss of SO_2 and propylene) was the major cause of the moderate yields obtained for the desired products **6** and **7** during reaction runs 1–7. Compounds **16** and **17**, as well as (*E*)-β-hydroxy sulfone **7b**, were completely absent during the reaction runs 8–10 (Table 2), where the pH of the reaction mixture never became basic and the decomposition of the intermolecular Michael addition byproducts did not occur.

2. Cyclized byproducts **18** were formed via base-mediated intramolecular Michael-type cyclization from initially produced butadienyl β-hydroxyalkyl sulfones **6** and **7**. This conclusion is supported by the fact that the combined yield of **6** and **7** reached a maximum after about 3 h, and then the formation of the cyclized byproducts **18** became noticeable (Table 2, entries 1, 2, 3 and 7). Using less than 0.50 equiv $ZnCl_2$ resulted in a higher solution pH at the end of the reaction, which correlated with the increasing formation of the cyclized byproducts **18**. Several additional experiments showed, that under basic conditions, **6b**, **7b**, *cis*-**18b** and *trans*-**18b** could equilibrate (Scheme 7, Table 3).

3. *O*-Alkylated (buta-1,3-diene-1-sulfinate ester) byproducts, observed when Zn sulfinate **15** had not been completely consumed before the workup (entries 8–10), are absent in the runs corresponding to entries 1–7 because of hydrolysis of these byproducts under the slightly basic conditions at the end of the reaction. When the mixtures of *S*-alkylated and *O*-alkylated products obtained in the runs



Scheme 6.



Scheme 7.

Table 3. Equilibration of **7b** in the presence of 0.2 equiv of aq K_2CO_3

Entry	Reactants	Conditions		Product ratio[a]		
		Time (h)	Temperature (°C)	**7b**	*cis*-**18b**	*trans*-**18b**
1	**7b**	5	75	11	71	18
2	**7b**	9	75	4	82	14
3	*cis*-**18b**:*trans*-**18b** 1:1	10	80	6	92	2

[a] Measured by ^{1}H NMR analysis of the crude product. The stereochemistry of the *cis*- and *trans*-diastereomers of **18** was assigned based on a careful analysis of their ^{1}H NMR spectra.[29,30]

corresponding to entries 8 and 9 were treated with saturated aqueous $NaHCO_3$ at rt, complete hydrolysis of the *O*-alkylated products was observed after 4 h, and clean sulfone **6b** was separated.

Unfortunately we were unable to efficiently suppress byproduct formation by changing the reaction conditions and isolated yields of the desired 1-butadienyl β-hydroxyalkyl sulfone products **6** and **7** remained at 30%. Nevertheless, the low cost of the reagents involved and our ability to quantitatively isomerize **6** to **7** before the separation of **7**, make this method an attractive entry for the preparation of (*E*)-1-butadienyl β-hydroxyalkyl sulfones **7** on a multigram scale.

3. Conclusion

A series of β-hydroxy sulfones **10** and **11a–d** were synthesized in good yields under neutral aqueous conditions by the nucleophilic opening of ethylene oxide or propylene oxide with simple zinc sulfinates **9a–d**. These Zn sulfinate salts were readily accessible by reduction of the corresponding sulfonyl chlorides **8a–d** or from the corresponding sodium or lithium sulfinate salts. These reactions favored S-attack of the sulfinate anion over O-attack and, in the case of propylene oxide, proceeded with high regioselectivity. This method allows easy and environmentally friendly access to β-hydroxy sulfones and represents a significant improvement over previously available epoxide ring opening reactions with sulfinate nucleophiles.

The corresponding opening of these epoxides with zinc (*Z*)-buta-1,3-diene-1-sulfinate **15**, followed by DMAP-mediated isomerization, afforded (*E*)-1-butadienyl β-hydroxyalkyl sulfones **7a**,**b** in 30% isolated yield. Detailed mechanistic studies revealed that the yields of these products were limited by their consumption in competing intra- and intermolecular Michael addition processes. Nevertheless, in spite of these competing side reactions, this method provides a convenient and inexpensive one-pot approach for the preparation of sensitive (*E*)-butadienyl β-hydroxyalkyl sulfones **7a**,**b** from commercially available butadiene sulfone (**4**). Currently, we are exploring the utility of compounds such as **7a**,**b** as building blocks for intramolecular Diels–Alder cycloaddition chemistry using sulfone tethers. Preliminary studies along these lines have already been reported[15b] and full details of this chemistry will be forthcoming in due course.

4. Experimental

4.1. General

Unless otherwise indicated, ^{1}H NMR spectra were recorded on a Bruker AMX 300 NMR spectrometer at 300 MHz, using TMS as an internal reference. ^{13}C NMR spectra were recorded on the same spectrometer at 75 MHz, with $CDCl_3$ or DMSO-d_6 as an internal reference. Indicated NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. TLC analysis was performed using silica coated plates (Sorbent Technologies). Flash column chromatography was conducted on silica gel Premium Rf Grade (40–75 μm (200×400 mesh), Sorbent Technologies). The glass pressure vessel (150 mL) was purchased from Chemglass and used with magnetic stirring. Commercial reagents and solvents (Acros) (including anhydrous EtOH and CH_2Cl_2) were used as received. THF was freshly distilled from Na/benzophenone. Deionized water was used for aqueous reactions. Unless otherwise stated, no effort was made to exclude air. Commercially available 2.5 M *n*-BuLi solution in hexanes (Aldrich) was used. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Combustion analyses were conducted by Chemisar Laboratories Inc., Ontario, Canada.

In the absence of solvent, compounds **6a**,**b**, **7a**,**b**, **16**, **17** and **19** are prone to very fast polymerization. 2,6-Di-*tert*-butyl-4-methylphenol (ca. 0.1 g per 100 mL) was added to the fractions containing these compounds before their concentration. The removal of solvents was performed in vacuo at 0–5 °C; the oily residue was immediately diluted with dichloromethane and stored at −5 °C. As a result,

combustion analysis data could not be obtained for these compounds.

The yields of compounds **6a**,**b**, **7a**,**b**, **16**, **17** and **19** were calculated by ^{1}H NMR analysis using 2,6-di-*tert*-butyl-4-methylphenol as an internal standard. To evaluate the reliability of these calculations, in several cases the solvent was removed in high vacuo and the isolated yield was compared with that established by use of an internal standard. These yields were always in good agreement (no more than 1% deviation).

4.2. General procedure for preparation of zinc sulfinate salts—zinc methanesulfinate dihydrate (9a)

Anhydrous ethanol (80 mL) containing zinc powder (9.35 g, 143 mmol, 1.11 equiv) was heated to reflux with stirring. Mesyl chloride (**8a**) (10.0 mL, 129 mmol, 1.00 equiv) was added dropwise over 10 min through the condenser, so as to maintain even boiling. The first portion of mesyl chloride should be added very carefully, making sure that the reaction initiates, otherwise the reaction mixture effervesces vigorously. Additional anhydrous ethanol (10 mL) was used to wash the condenser. No precipitate was formed while the zinc almost totally dissolved. The reaction mixture was refluxed for 15 min. It was then allowed to cool over 30 min with stirring and was filtered. The residual zinc powder (0.44 g, 6.7 mmol, 0.05 equiv) recovered on the filter was washed with ethanol (10 mL). Upon the addition of water (10 mL) with stirring to the combined filtrates (ca. 100 mL), a white precipitate slowly formed. Crystallization was continued for 30 min at rt, then for 1 h at 0 °C. The resulting white crystalline solid was filtered, washed with ice-cold ethanol (2×10 mL) and was allowed to air-dry at rt overnight. The title compound **9a** was obtained as a white solid (15.5 g, 59.5 mmol, 92%, mp 117–118 °C (dec); after drying (0.1 mmHg, at 60 °C) mp 133 °C). ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 6H, CH_3), 3.42 (s, 4H, H_2O); ^{13}C NMR (DMSO-d_6) δ 48.8. Anal. Calcd for $C_2H_{10}O_6S_2Zn$: C, 9.25; H, 3.88; S, 24.70; Zn, 25.19. Found: C, 9.01; H, 3.85; S, 24.97; Zn, 25.03.

4.3. Synthesis of β-hydroxy sulfones 10 and 11

4.3.1. General procedure for preparation of β-hydroxy sulfones—(methylsulfonyl)ethanol (10).[31] A suspension of zinc methanesulfinate **9a** (15.2 g, 58.7 mmol, 1.00 equiv) and ethylene oxide (7.80 mL, 156 mmol, 2.66 equiv) in water (150 mL) was heated in a glass pressure vessel at 70 °C with magnetic stirring for 2 h. The reaction mixture was filtered while still hot. The filtered ZnO precipitate was washed with water (2×10 mL). The combined filtrates were concentrated in vacuo to remove most of the water. The crude product was distilled (bp 140–145 °C at 0.1 mmHg) to give the title compound **10** as a colorless oil (11.4 g, 92.1 mmol, 78%). ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H, CH_3), 3.28 (t, J=5.4 Hz, 2H, SO_2CH_2), 4.07 (t, J=5.4 Hz, 2H, O–CH_2); ^{13}C NMR ($CDCl_3$) δ 42.8, 56.4, 56.9.

4.3.2. 1-(Methylsulfonyl)propan-2-ol (11a).[32] The reaction was performed according to general procedure Section 4.3.2 using zinc methanesulfinate (**9a**) (8.31 g, 32.0 mmol, 1.00 equiv) and propylene oxide (6.10 mL, 87.2 mmol, 2.73 equiv) in water (80 mL) at 75 °C for 2 h 30 min. The crude product was distilled (bp 117–121 °C at 0.1 mmHg) to give 7.30 g (52.9 mmol, 83%) of **11a** contaminated with approx 6–7% of propylene glycol (**14**). Crystallization of the distillate from toluene (270 mL) gave clean **11a** (5.20 g, 37.6 mmol, 59%), mp 67–69 °C. Concentration of the mother liquor in vacuo to ca. 100 mL gave an additional crop of clean **11a** (0.53 g, 3.84 mmol, 6%). The combined yield of **11a** was 65%. ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J=6.4 Hz, 3H, O–CHCH_3), 3.00–3.12 (m, 1H, $SO_2CH_AH_BCH$), 3.05 (s, 3H, CH_3SO_2), 3.21 (dd, J=14.5, 9.9 Hz, 1H, $SO_2CH_AH_BCH$), 4.36–4.47 (m, 1H, O–CHCH$_3$); ^{13}C NMR ($CDCl_3$) δ 23.4, 42.7, 62.1, 63.0.

^{1}H NMR analysis of the crude reaction mixture before distillation showed the presence of **11a**, **12a**, **13a** and propylene glycol in an 86/8/6/21 ratio.

2-(Methylsulfonyl)propan-1-ol (**12a**)[27] (assigned from the mixture with **11a** and **13a**): ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J=7.2 Hz, 3H, SO_2–CHCH_3), 2.99 (d, J=0.4 Hz, 3H, CH_3SO_2), 3.14–3.24 (masked) (m, 1H, SO_2–CHCH$_3$), 3.94–3.96 (m, 2H, CHCH_AH_BOH); ^{13}C NMR ($CDCl_3$) δ 10.4, 40.4, 60.8, 61.7.

2-Hydroxypropyl methanesulfinate (**13a**) (obtained as a 1:1 mixture of diastereomers; assigned from the mixture with **11a** and **12a**): ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J=6.4 Hz)/1.21 (d, J=6.4 Hz) (3H total, O–CHCH_3), 2.71 (s)/2.71(s), separated by 1 Hz (3H total, CH_3SO), 3.90–4.12 (m, 3H, SO–O–CH_AH_BCH); ^{13}C NMR ($CDCl_3$) δ 18.7/19.0, 44.2, 66.3/66.4, 74.2/74.5.

4.3.3. Preparation of 1-(4-methylphenylsulfonyl)propan-2-ol (11d)[9,33] **from sodium *p*-toluenesulfinate** A solution of commercially available sodium *p*-toluenesulfinate hydrate (0.9% water) (2.92 g, 16.2 mmol, 1.00 equiv) in water (40 mL) was placed in a 150 mL glass pressure vessel and was treated with aq $ZnCl_2$ (20 mL of an aq solution containing 1.10 g (8.1 mmol, 0.50 equiv) of $ZnCl_2$) with magnetic stirring. A white precipitate formed. Propylene oxide (1.90 mL, 27.2 mmol, 1.68 equiv) was added and the reaction mixture was heated at 75 °C with magnetic stirring for 4 h, and was then filtered while still hot. The filtered ZnO precipitate was washed with water (2×20 mL) and the combined filtrates (ca. 100 mL) were allowed to crystallize for 3 h to afford the title compound **11d** as a white crystalline solid (1.66 g, 7.75 mmol, 48%). The mother liquor was concentrated in vacuo and coevaporated with toluene (2×20 mL). This afforded a colorless oil, which was treated with dichloromethane (40 mL) and the insoluble solid residue (0.84 g) was filtered out. The filtrate was concentrated in vacuo to afford a colorless oil (1.65 g). ^{1}H NMR analysis of this oil showed the presence of **11d**, **12d**, and propylene glycol in an 81/19/95 ratio. Crystallization from water (40 mL) gave an additional crop of clean title compound **11d** (0.560 g, 2.61 mmol, 16%). The combined yield of **11d** was 64%. ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J=6.4 Hz, 3H, O–CHCH_3), 2.45 (s, 3H, CH_3-Ar), 3.14 (dd, J=14.3, 2.8 Hz, 1H, $SO_2CH_AH_BCH$), 3.27 (dd, J=14.3, 8.6 Hz, 1H, $SO_2CH_AH_BCH$), 4.30 (dqd, J=9.0, 6.4, 2.8 Hz, 1H, O–CHCH$_3$), 7.39 (d, J=8.5 Hz, 2H, Ar), 7.80 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.7, 62.5, 63.5, 128.1, 130.3, 136.3, 145.4.

2-(4-Methylphenylsulfonyl)propan-1-ol (**12d**) (assigned from the mixture with **11d**): ^{1}H NMR ($CDCl_3$) δ 1.24 (d, $J=6.4$ Hz, 3H, O–CHCH_3, coincides with **11d**), 2.45 (s, 3H, CH_3-Ar, coincides with **11d**), 3.21–3.37 (masked by **11d**) (m, 1H, SO_2–CHCH$_3$), 3.73 (dd, $J=12.1$, 5.0 Hz, 1H, CHCH_AH$_B$OH), 3.98 (dd, $J=12.1$, 6.2 Hz, 1H, CHCH$_A$-H_BOH), 7.39 (app. d, $J=8.5$ Hz, 2H, Ar, coincides with **11d**), 7.76 (app. d, $J=8.3$ Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.4, 18.9, 61.3, 61.8, 128.9, 130.0, 134.1, 139.7.

4.4. Synthesis of 1,3-butadienyl sulfone derivatives

4.4.1. Zinc (*Z*)-buta-1,3-diene-1-sulfinate dihydrate (15). 2,5-Dihydrothiophene-1,1-dioxide (butadiene sulfone, **4**) (4.73 g, 40.0 mmol, 1.00 equiv) was dissolved in anhydrous THF (120 mL) under argon, and cooled in a dry ice/acetone bath. *n*-BuLi (2.5 M in hexanes, 16.00 mL, 40.0 mmol, 1.00 equiv) was added dropwise over 25 min, maintaining the reaction temperature below −68 °C. Initially a yellow solution was observed and then a cream precipitate formed. The addition of *n*-BuLi was stopped after a bright red coloration had developed in the reaction mixture. The reaction mixture was allowed to warm up to −50 °C, and then water (30 mL) and hydroquinone (ca. 0.05 g) were added. The precipitate immediately dissolved, and the red coloration disappeared. The organic solvents were removed in vacuo, resulting in a light yellow aqueous solution (ca. 30 mL) of lithium (*Z*)-buta-1,3-diene-1-sulfinate. The solution was cooled in ice, and a solution of $ZnCl_2$ (2.705 g, 19.85 mmol) in water (5 mL) was added dropwise with stirring. The reaction mixture was left in an ice bath for 20 min, and then the resulting white precipitate was filtered, washed with ice-cold water (20 mL) followed by dichloromethane (20 mL) and dried in vacuo. The title compound **15** was obtained as a cream solid (4.80 g, 14.3 mmol, 72%), mp 128–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.43 (s, 4H, H_2O), 5.26 (br d, $J=10.0$ Hz, 2H, H$_{cis}$H$_{trans}$C=CH), 5.34 (br d, $J=16.8$ Hz, 2H, H_{cis}H$_{trans}$C=CH), 6.02 (br d, $J=$ 10.0 Hz, 2H, =CH–SO_2), 6.26 (dd, $J=11.2$, 10.4 Hz, 2H, CH=CH–SO_2), 6.94 (dddd, $J=16.8$, 11.2, 10.1, 1.0 Hz, 2H, CH_2=CH); ^{13}C NMR (DMSO-d_6) δ 121.8, 131.2, 131.6, 146.6. Anal. Calcd for $C_8H_{14}O_6S_2Zn$: C, 28.62; H, 4.20; S, 19.10; Zn, 19.48. Found: C, 28.04; H, 4.33; S, 18.61; Zn, 19.01.

4.4.2. 1-((*E*)-Buta-1,3-diene-1-sulfonyl)ethanol (7a). The light yellow aqueous solution (ca. 30 mL) of Li (*Z*)-buta-1,3-diene-1-sulfinate (40.0 mmol) obtained in experiment Section 4.4.1 was added dropwise with stirring and cooling in ice to the glass pressure vessel containing $ZnCl_2$ (2.67–2.84 g, 19.6–20.8 mmol, 0.49–0.52 equiv) in water (60 mL). A white precipitate of zinc (*Z*)-buta-1,3-diene-1-sulfinate was formed. Ethylene oxide (6 mL, 120 mmol, 3 equiv) was added, and the solution was heated with stirring for 3 h at 70–75 °C. The resulting reaction mixture was cooled to rt and filtered. The precipitate was washed with water (3×20 mL) and the combined aqueous filtrate was extracted with dichloromethane (4×100 mL). The combined dichloromethane extracts (ca. 400 mL) were treated with 2,6-di-*tert*-butyl-4-methylphenol (0.200 g, 0.908 mmol), dried ($MgSO_4$), filtered, concentrated to a volume of ca. 150 mL and treated with DMAP (0.500 g, 4.09 mmol). The resulting solution was kept at rt for 36 h, and was then subjected to column chromatography (silica, EtOAc/hexanes 1.5:1) to afford the title compound **7a** as a colorless oil (1.95 g, 12.0 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 3.22 (t, $J=6.0$ Hz, 1H, OH), 3.26–3.31 (m, 2H, H^2), 4.02–4.10 (m, 2H, H^1), 5.68 (br d, $J=10.0$ Hz, 1H, H^{6b}), 5.77 (br d, $J=16.9$ Hz, 1H, H^{6a}), 6.47 (dd, $J=14.9$, 0.6 Hz, 1H, H^3), 6.48 (dddd, $J=16.9$, 10.9, 10.0, 0.6 Hz, 1H, H^5), 7.21 (br dd, $J=15.0$, 10.8 Hz, 1H, H^4); ^{13}C NMR ($CDCl_3$) δ 56.4, 57.4, 129.0 (two signals coincide), 132.5, 144.3.

4.4.3. 1-((*E*)-Buta-1,3-diene-1-sulfonyl)propan-2-ol (7b). The title compound **7b** was prepared from propylene oxide (8.4 mL, 120 mmol, 3 equiv) according to the procedure described above for **7a**, as a colorless oil (2.14 g, 12.1 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 1.31 (d, $J=6.4$ Hz, 3H, CH_3), 3.09 (dd, $J=14.4$, 2.8 Hz, 1H, H^2), 3.17 (dd, $J=$ 14.5, 8.7 Hz, 1H, H^2), 3.21 (d, $J=2.8$ Hz, 1H, OH), 4.39 (app. dqt $J=9.0$, 6.3, 2.8 Hz, 1H, H^1), 5.69 (br d, $J=$ 10.0 Hz, 1H, H^{6b}), 5.77 (br d, $J=16.7$ Hz, 1H, H^{6a}), 6.43 (br d, $J=15.0$ Hz, 1H, H^3), 6.47 (dddd, $J=16.9$, 10.8, 10.0, 0.5 Hz, 1H, H^5), 7.22 (br dd, $J=15.0$, 10.9 Hz, 1H, H^4); ^{13}C NMR ($CDCl_3$) δ 22.9, 62.4, 62.7, 128.7, 129.4, 132.4, 144.8.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.043. Synthetic procedures, ^{1}H and ^{13}C NMR data for compounds **9b–d**, **11b**,**c**, **11d** (synthesis from **8d**), **6a**,**b**, **16**, **17**, **18a**, *cis*-**18b**, *trans*-**18b** and **19**; partial ^{1}H and ^{13}C NMR data for compounds **12b**,**c**, **13b**,**c**; copies of ^{1}H and ^{13}C NMR spectra of compounds **9b**, **15**, **6a**,**b**, **7a**,**b**, **17**, a mixture of **16/17** (1/1.35), **18a**, *cis*-**18b**, *trans*-**18b** and **19**.

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20. Both Crandall[7] and Bhattacharyya[11] used a 1.5/1 ratio of *p*-toluenesulfinate/epoxide in their studies, presumably to avoid problems associated with the rapid hydrolysis of the epoxide during the latter stages of their reactions (pH 14). Since we needed to employ valuable sulfinate salts and inexpensive epoxides in future studies, we employed a 1/1.37 ratio of sulfinate/epoxide. This also allowed direct comparison with our studies using Zn sulfinates (see Section 2).
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28. However, if the reaction of Zn sulfinate **9d** was interrupted after 1 h 30 min, small pairs of resonances were observed in the ^{13}C NMR spectrum of the reaction mixture at 66.0/66.2 and 70.40/70.46 ppm. By comparison with the sulfinate esters **13a–c** obtained earlier, we tentatively attribute these signals to the C1 and C2 carbons of the 2-hydroxypropyl fragments in the two diastereomers of **13d**.
29. The ^1H NMR spectrum of *cis*-**18b** shows strong support for a predominant conformation having both the vinyl and methyl substituents equatorial. The assignment of the axial protons $H^{3\beta}$ and H^6 was based on the large coupling constants observed for the pairs $H^2/H^{3\beta}$ and $H^{5\beta}/H^6$ (11.2–11.0 Hz); consequently, small coupling constants were observed for the pairs $H^2/H^{3\alpha}$ and $H^{5\alpha}/H^6$ (1.9–2.0 Hz). Equatorial protons $H^{3\alpha}$ and $H^{5\alpha}$ demonstrate strong W coupling (3.5 Hz). Similar patterns were observed for the ^1H NMR spectrum of **18a**.
30. The ^1H NMR spectrum of *trans*-**18b** shows that, as might be expected, two major conformations are present in $CDCl_3$ solution. The coupling constants of H^6 with the two protons H^5 became closer (7.1, 2.9 Hz), while the coupling between H^2 and the two H^3 protons are now very similar (5.7, 4.4 Hz). W-Coupling is now observed for both pairs of *syn*-protons H^3 and H^5 (2.3, 1.7 Hz).
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