Pergamon

Tetrahedron 58 (2002) 3737–3746

TETRAHEDRON

Intramolecular cyclization reactions of carbonyl derivatives of hydroxysulfones

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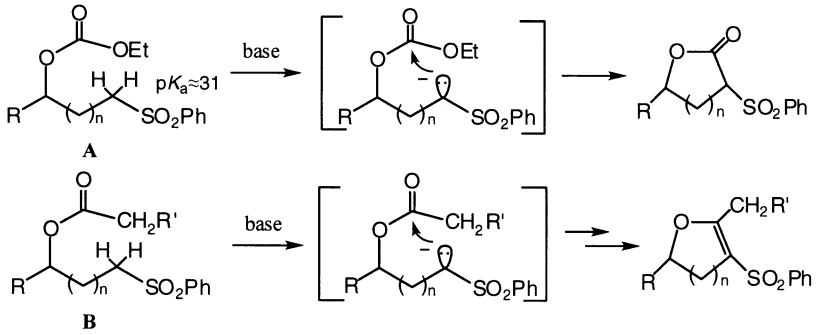
Received 4 February 2002; revised 19 March 2002; accepted 20 March 2002

Abstract—The γ and δ-hydroxysulfone *tert*-butyl ester derivatives **2a**–**e** are easily prepared from the corresponding hydroxysulfones by phase-transfer alkylation reactions. The sulfonyl carbanions of **2a**–**e** are readily generated upon treatment with LHMDS in THF at −78°C and undergo intramolecular acylation reactions to give a variety of functionalized cyclic ethers **4a**–**e** in good yields. The intramolecular aldol-type reaction of the sulfonyl carbanion of **6a** is useful for the preparation of six-membered oxacyclic ring systems with high diastereo selective control and is best carried out under equilibrating conditions (^{t}BuOK in toluene). This study clearly shows that it is possible to generate an α-sulfonyl carbanion and effect its intramolecular cyclization even in the presence of other protons of comparable acidity elsewhere in the substrate. The scope, limitations and synthetic utility of this intramolecular cyclization strategy have been examined.

1. Introduction

The intramolecular cyclization reactions of α-sulfonyl carbanions involving a variety of internal electrophiles have been a valuable approach for the preparation of carbocyclic and heterocyclic ring systems.[1–3] Our own laboratory has been focusing on the preparation of chiral hydroxysulfones and the intramolecular cyclization reactions of their derivatives. We have demonstrated in earlier work that some γ and δ-hydroxysulfone ethoxycarbonyl (Type **A**)[4] and acyl (Type **B**)[4a,5] derivatives undergo efficient cyclization upon treatment with lithium hexamethyldisilazane (LHMDS) to give a number of functionalized lactones and chiral non-racemic dihydrofurans and dihydropyrans in good yields (Scheme 1).

In substrate **A**, deprotonation of the methylene protons α to the sulfonyl moiety is a straightforward process as they are the most acidic. In acyl hydroxysulfones of the type **B**, the protons α to the ester carbonyl and the sulfone have comparable pK_a in the range of 31.[6] We did anticipate some problems in the selective deprotonation of the methylene protons α to the sulfone and achieving the subsequent cyclization. However, the fact remains that the cyclization of this class of substrates could be achieved by treatment with 1.1 equiv. of LHMDS at −78°C in high yields even in the presence of other sensitive functional groups.[5] Recently, we have also examined the synthetic potential of intramolecular alkylation and Michael addition reactions of hydroxysulfone derivatives.[7]



Scheme 1.

Keywords: hydroxysulfone; intramolecular cyclization; intramolecular aldol-type reaction; oxacyclic ring.
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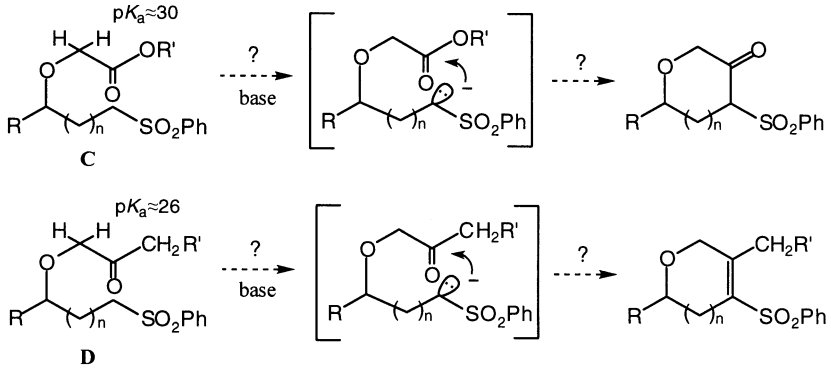
PII: S0040-4020(02)00338-1

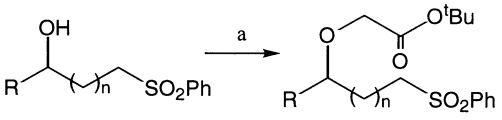


Scheme 2.

The cyclization reactions of hydroxysulfone derivatives have the potential to yield a variety of oxacyclic ring systems. There is a clear need to understand the scope and practical limitations of this class of cyclizations in order to encourage applications of this chemistry to natural products synthesis. In this paper, we show that hydroxysulfone derivatives of the types **C** and **D** can also undergo useful cyclization reactions (Scheme 2). At the outset, it was not possible to predict whether these types of substrates would undergo useful cyclization chemistry. The substrate **C** may be considered as a homologue of **A**, but protons α to the carbonyl and the sulfone have comparable acidity. The cyclization of substrates of the type **D** present an even greater challenge as they have three sets of protons of comparable acidity. In fact, the protons α to the ketone are considerably more acidic than those next to the sulfone. Hence it was not clear whether selective deprotonation next to the sulfone and the subsequent cyclization reaction could be achieved in this class of substrates.

2. Results and discussion

Our initial approach to synthesize substrates of the type **C** involved the treatment of hydroxysulfone **1a** with *tert*-butyl bromoacetate in the presence of NaH in THF. However, the desired alkylation of the sodium salt of **1a** with *tert*-butyl bromoacetate proceeded in poor yield to give **2a** along with recovered starting material and other uncharacterizable byproducts. After extensive experimentation, a phase-transfer catalyzed alkylation reaction of **1a** using 0.25 equiv. of tetrabutylammonium bisulfate (TBAB) and excess of *tert*-butyl bromoacetate (1.5 equiv.) in 50% aqueous NaOH and benzene allowed the preparation of **2a–e** in good to excellent yields (Eq. 1).[8]



1a-e

2a n=1, R=CH_3, 96%
2b n=1, R=Ph_3COCH_2, 84%
2c n=1, R=Ph, 99%
2d n=2, R=CH_3, 87%
2e n=2, R=Ph, 94%

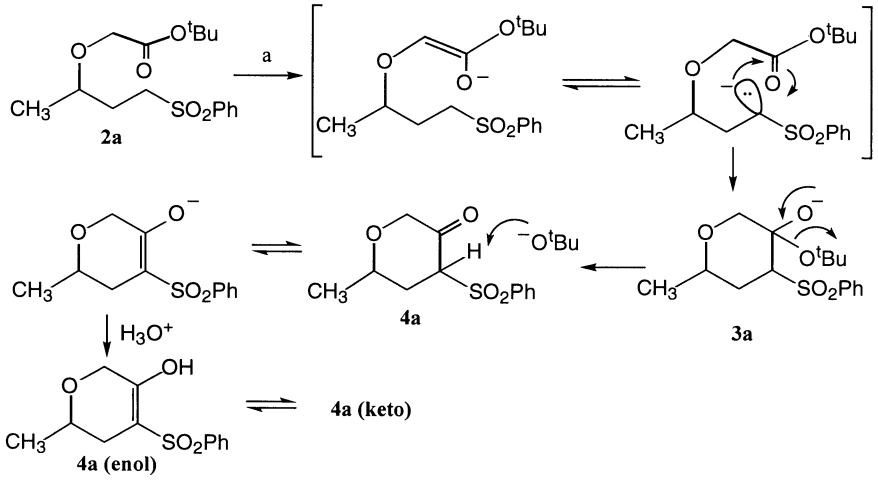
(1)

Reagents and conditions: (a) 50% NaOH, TBAB, benzene, 10°C, 30 min; then, *tert*-butyl bromoacetate, room temperature, 15 h.

To our pleasant surprise, the cyclization of **2a** could be achieved efficiently by slow addition of 2.0 equiv. of LHMDS to a solution of the substrate in THF (0.03 M) at −78°C (Scheme 3). The reaction was usually stirred for 4 h at −78°C to ensure completion. After quenching the reaction with saturated ammonium chloride followed by aqueous work-up, the cyclization product **4a** was isolated in a surprisingly high degree of purity as judged by the ^{1}H NMR analysis of the crude mixture. The desired product **4a** was isolated as an inseparable mixture of diastereomers in 87% yield after column chromatography. The ^{1}H NMR spectra of **4a** was much more complicated than expected due to the presence of significant quantities of its enol form (3452 cm^{-1} in IR for OH group, 102.1 ppm in ^{13}C NMR for sp^2 carbon of the enol). However, the percentage of the enol form could not be reliably estimated from the spectral data.

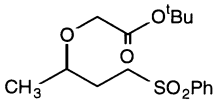
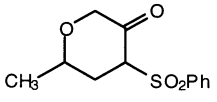
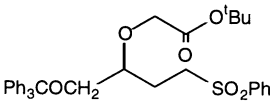
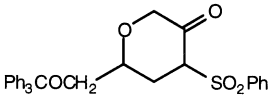
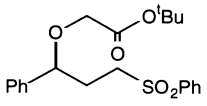
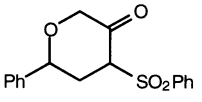
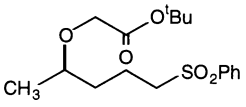
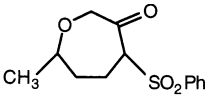
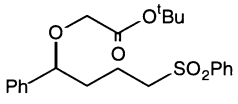
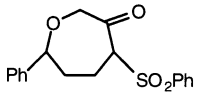
The deprotonation of **2a** was examined in some detail hoping to gain some mechanistic insight into these cyclizations. It is possible that deprotonation of this substrate preferentially occurs α to the sulfone to yield the corresponding carbanion which then undergoes the desired cyclization to give **3a**. Alternatively, deprotonation may be unselective or preferentially occurs α to the ester moiety. A subsequent fast proton transfer leads to the sulfonyl carbanion that undergoes cyclization. The intermediate **3a** then undergoes fragmentation with a release of *tert*-butoxide to give the β-ketosulfone, which is immediately deprotonated under the basic reaction conditions to give its enolate. Protonation upon work-up leads to the formation of the equilibrium mixture of the keto and enol forms of **4a**.

A simple experiment was performed hoping to shed some light on the initial site of deprotonation of sulfonyl ester **2a**. The ester **2a** was treated with LHMDS (1.0 or 2.0 equiv.) or *n*-BuLi (1.0 equiv.) at −78°C and the reaction was quenched with CD_3COOD at the same temperature after 30 min. No starting material **2a** with deuterium incorporation could be isolated at the end of the reaction. This can be ascribed to the rapid formation of the enolate of **4a** under the reaction conditions (prior to quenching with CD_3COOD) (Scheme 3). Hence, the initial site of deprotonation of **2a** cannot be unambiguously assigned based on these



Scheme 3. *Reagents and conditions*: (a) 2.0 equiv. LHMDS, THF, −78°C, 4 h, 87%.

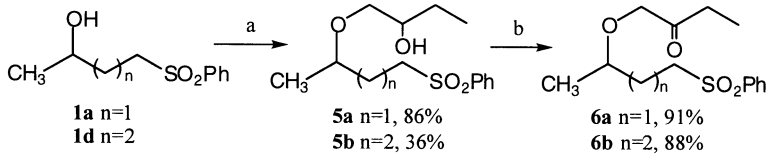
Table 1. Results for the intramolecular acylations of hydroxysulfone *tert*-butyl ester derivatives

Substrates	Cyclization products	Yield (%)
 **2a**	 **4a**	87
 **2b**	 **4b**	99
 **2c**	 **4c**	99
 **2d**	 **4d**	57
 **2e**	 **4e**	85

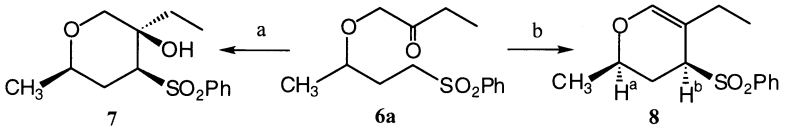
experiments. Comparison of the ^{1}H NMR spectra obtained from the deuterium quenching experiment with that of the standard, did suggest some deuterium incorporation had occurred at the α sulfonyl carbon of **4a**. However, due to the complexity of the keto–enol product mixture, the extent of deuterium incorporation could not be estimated accurately.

A variety of substrates **2a**–**e** have been found to undergo this useful cyclization reaction (Table 1). As seen from the table, the substrates **2b** and **2c** underwent intramolecular acylations upon deprotonation to give functionalized tetrahydropyrans **4b** and **4c**, respectively, in almost quantitative yield (99%). The ^{1}H and ^{13}C NMR spectra of these products were also complex due to their diastereomeric composition plus enol content. The cyclization could also be readily extended to prepare seven-membered oxacyclic ring systems such as **4d** and **4e** in satisfactory yields.

The next cyclization reaction to be examined was that of hydroxysulfones of the type **D** (Scheme 2). The keto derivatives required for this study were readily synthesized from the hydroxysulfone **1** and 1,2-epoxybutane by a two-step sequence shown in Scheme 4. Deprotonation of **1a** with potassium *tert*-butoxide generated a potassium salt which reacted with the epoxide in THF at 60°C to give the alcohol **5a** in 86% yield. The regioselectivity of the ring opening reaction was very high as only one major product was



Scheme 4. *Reagents and conditions*: (a) ^{t}BuOK, 1,2-epoxybutane, THF, 60°C, 2 d. (b) 5 mol% TPAP, NMO, CH_2Cl_2, 4 Å molecular sieves, room temperature, 30 min.



Scheme 5. *Reagents and conditions*: (a) 1.5 equiv. ^{t}BuOK, toluene, room temperature, 1 h, 64%. (b) 1.5 equiv. ^{t}BuOK, toluene, room temperature to 60°C, 2 h, 50%.

isolated. In the preparation of **5b**, the low yield (36%) is due to subsequent O-alkylation of **5b** by the excess epoxide in the reaction mixture. Conversion of the alcohols **5a**,**b** into the ketones **6a**,**b** was achieved by oxidation with a catalytic amount of tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) in CH_2Cl_2 at room temperature.[9] The sulfonyl ketones **6a**,**b** were obtained in 88–91% yields after column chromatography.

As per earlier protocol, the cyclization reaction of **6a** was first studied with LHMDS as base in THF at −78°C. However, treatment of the substrate **6a** with 1.1 or 2.0 equiv. of LHMDS in THF at −78°C did not lead to the desired cyclization. Several products were seen on TLC analysis of the reaction and these could not be easily identified. After extensive experimentation, it was found that the desired intramolecular aldol-type reaction could be achieved under equilibrating conditions with potassium *tert*-butoxide as base.[10] Treatment of **6a** with 1.5 equiv. of potassium *tert*-butoxide in toluene at room temperature for 1 h led to the formation of cyclized product **7**. The sulfonyl alcohol **7**, the thermodynamically most stable diastereomer, was obtained in 64% yield after chromatographic purification (Scheme 5). The relative stereochemistry of **7** was assigned by single crystal X-ray diffraction studies (Fig. 1). When the same reaction was carried out at 60°C, the glycal derivative **8** was isolated in 50% yield after careful chromatographic purification. The *cis* configuration of glycal **8** was determined by ^{1}H NMR analysis.[11] The formation of **8** under the more vigorous conditions can be readily explained. The cyclization of **6a** initially gives the sulfonyl alcohol **7**. However, this sulfonyl alcohol is not stable at 60°C under the basic conditions and undergoes dehydration followed by a double bond migration to give the more thermodynamically stable allylic sulfone **8**.[12]

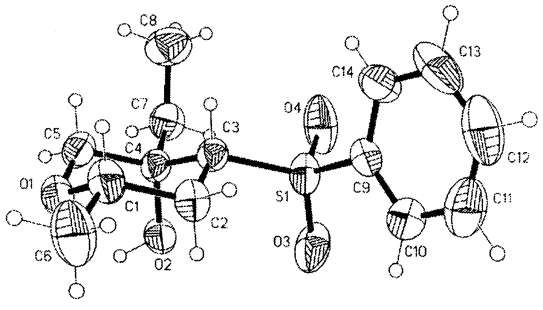
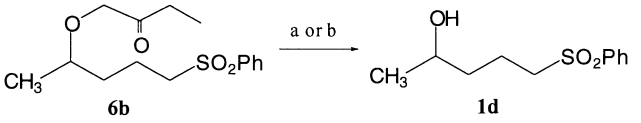


Figure 1. X-Ray structure of **7**.

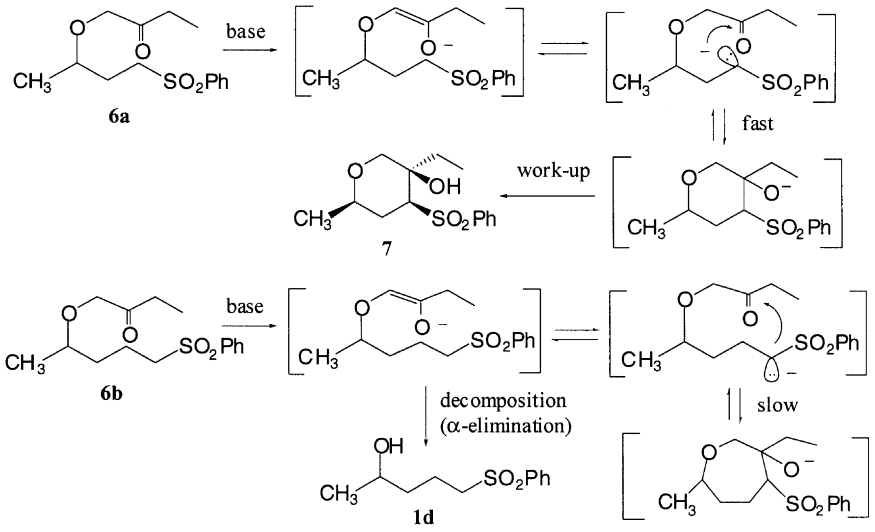
When substrate **6b** was treated with 1.5 equiv. of potassium *tert*-butoxide in toluene at room temperature or at 60°C, no cyclized product was obtained (Eq. 2). Instead, significant amounts of hydroxysulfone **1d** and some of the starting material **6b** were recovered at the end of the reaction. Based on these observations, we propose that in these substrates, the protons α to the ketone are preferentially deprotonated upon treatment with ^{t}BuOK–toluene due to their higher acidity. This enolate is in equilibrium with the α-sulfonyl carbanion (Scheme 6). Only one of the two possible enolates of **6** is shown in the scheme for simplicity. In the case of **6a**, cyclization to give the six-membered ring occurs rapidly after proton transfer. On the other hand, intramolecular cyclization of the α-sulfonyl carbanion of **6b** to give the seven-membered ring product is much slower. This allows the α-alkoxyenolate to undergo decomposition to give the hydroxysulfone **1d**.



(2)

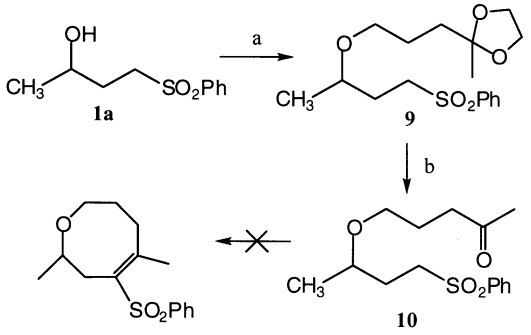
Reagents and conditions: (a) 1.5 equiv. ^{t}BuOK, toluene, room temperature, 6 h, 76%. (b) 1.5 equiv. ^{t}BuOK, toluene, room temperature to 60°C, 3 h, 85%.

The unfavorable results of the cyclization of **6b** to give a seven-membered ring could be attributed to some extent on the instability of the α-alkoxyenolate intermediate. It must be pointed out that the esters **2d** and **2e** do cyclize to give seven-membered ring systems in good yields. Hence, to clearly establish the limits of this methodology to prepare larger ring systems, it was decided to prepare the ketone **10** and examine its cyclization (Scheme 7). The enolate of **10** should not decompose upon exposure to potassium *tert*-butoxide and this substrate could possibly undergo a slow thermodynamically driven cyclization reaction. Phase-transfer alkylation reaction of **1a** with 5-chloro-2-pentanone ethylene ketal followed by deprotection of the ketal with



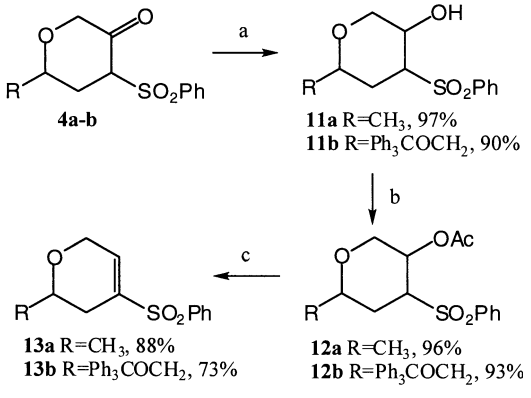
Scheme 6.

PPTS in wet acetone gave the ketone **10** in high yield. The sulfone **10** was treated with 1.5 equiv. of potassium *tert*-butoxide in toluene both at room temperature and elevated temperatures for extended periods. However, no cyclization product formed under the reaction conditions and the starting ketone **10** was largely recovered at the end of this reaction. It has been reported in the literature that the intermolecular addition of sulfonyl carbanions to ketones is enhanced by Lewis acids.[13] Hence, this cyclization was also attempted using LHMDS in the presence of boron trifluoride, but this also was not successful.



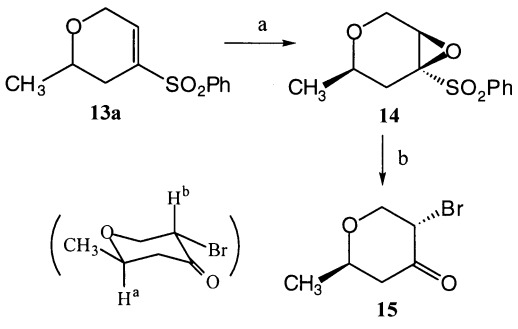
Scheme 7. *Reagents and conditions*: (a) 50% NaOH, TBAB, benzene, 10°C, 30 min; then, 5-chloro-2-pentanone ethylene ketal, 60°C, 2 d, 75%. (b) PPTS, acetone, 60°C, 5 h, 91%.

Finally, a few reactions have been explored to demonstrate the synthetic potential of cyclic ethers of the type **4a–e** prepared in this work. In one such application, the cyclization products **4a**,**b** were converted into 4-benzenesulfonyl-2-methyl-3,6-dihydro-2*H*-pyran [**13a**] in 82% yield and 4-benzenesulfonyl-2-trityloxymethyl-3,6-dihydro-2*H*-pyran [**13b**] in 61% yield, respectively, by a highly efficient reaction sequence (Scheme 8). The sequence begins with reduction of ketones **4a**,**b** by $NaBH_4$ in EtOH, followed by esterification of the resultant hydroxy group with acetic anhydride and then its elimination with DBU to give oxacyclic vinyl sulfones **13a**,**b**. Compounds of this type have been widely used as synthetic intermediates in the synthesis of oxacyclic natural products.[14]



Scheme 8. *Reagents and conditions*: (a) $NaBH_4$, EtOH, room temperature, 20 h. (d) Ac_2O, pyridine, DMAP, CH_2Cl_2, room temperature, 10 h. (c) DBU, CH_2Cl_2, room temperature, 2 h.

The vinyl sulfone **13a** can be converted to epoxysulfone **14** in 63% yield by nucleophilic epoxidation using ^{t}BuOOH–NaH in THF (Scheme 9).[15] The epoxide **14** was isolated as a single diastereomer with the methyl and phenylsulfonyl



Scheme 9. *Reagents and conditions*: (a) NaH, ^{t}BuOOH, THF, 10°C, 20 h, 63%. (b) $MgBr_2{\cdot}Et_2O$, Et_2O, room temperature, 10 h, 85%.

groups *trans* to each other as per ^{1}H NMR analysis. It is known that ring opening of such epoxides can be accomplished with a number of nucleophiles.[16] As an example treatment of **14** with $MgBr_2{\cdot}Et_2O$ gave α-bromo-substituted cyclohexanone **15**.[14b,17] This nucleophilic epoxide opening occurred with complete stereochemical control and the α-bromoketone **15** was isolated in 85% yield as a single diastereomer. Based on the analysis of coupling constants in the ^{1}H NMR spectra (H^a: ddq, J=11.8, 2.5, 6.0 Hz; H^b: ddd, J=11.3, 6.9, 1.1 Hz), the methyl and bromo groups are *trans* and occupy equatorial positions as shown in Scheme 9.

3. Conclusion

This study clearly shows that it is possible to generate an α-sulfonyl carbanion and effect its intramolecular cyclization even in the presence of other protons of comparable acidity elsewhere in the substrate. The γ and δ-hydroxysulfone *tert*-butyl ester derivatives **2a**–**e** undergo intramolecular acylation reactions to give the corresponding functionalized cyclic ethers **4a**–**e** in good yields. Both six- and seven-membered ring systems can be readily accessed by this method and the presence of β-ketosulfonyl groups allows further functionalization of these ring systems. The cyclization reactions of keto derivatives of hydroxysulfones of the type **D** are useful only for the preparation of six-membered oxacyclic ring systems with high diastereoselective control and are best carried out under equilibrating conditions (^{t}BuOK in toluene). The understanding of the scope and limitations of the intramolecular cyclization reactions of hydroxysulfone derivatives should enhance their synthetic appeal to natural products synthesis.

4. Experimental

4.1. General

Melting points were obtained on an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer FT-IR 1720X spectrometer. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 or 100 MHz) were obtained on a Varian XL 200 or a Varian Unity 400 spectrometer, respectively, with tetramethylsilane as an internal standard. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Analytical and preparative thin layer chromatography were performed on silica 60/F_{254} (EM Science, Whatman) plastic plates. Column chromatography was done on silical gel (60–200 mesh or 200–400 mesh, Merck or Fisher Scientific). Reagents were normally obtained from Aldrich Chemical Company and used as received unless otherwise noted. Lithium hexamethyldisilazane (LHMDS) was obtained from Aldrich as a 1 M solution in hexane. THF was freshly distilled from sodium-benzophenone. Other dry solvents (DMF, MeOH, methylene chloride, benzene, etc.) were obtained from Fisher Scientific in a SureSeal® container. The γ and δ-hydroxysulfones **1a**–**e** were prepared using known methods.[18]

4.2. General procedure for the preparation of *tert*-butyl esters 2a–e

4.2.1. (3-Benzenesulfonyl-1-methyl-propoxy)-acetic acid *tert*-butyl ester (2a). To a solution of **1a** (1.07 g, 5.00 mmol) in benzene (10 mL) at 10°C was added 50% aq. NaOH (4.80 mL, 60.0 mmol) followed by TBAB (0.42 g, 1.25 mmol), and the mixture was stirred at 10°C for 30 min. *tert*-Butyl bromoacetate (1.10 mL, 7.50 mmol) was then added and the mixture was stirred at room temperature for 15 h. The benzene was removed in vacuo and the residue was diluted with CH_2Cl_2 (50 mL). The organic layer was washed with brine (3×10 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (20–30% EtOAc–hexane) to give **2a** (1.57 g, 96%) as a colorless oil: IR (neat) 3067, 2977, 1747, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98–7.50 (m, 5H), 3.99–3.78 (m, 2H), 3.70–3.50 (m, 1H), 3.50–3.21 (m, 2H), 2.05–1.75 (m, 2H), 1.45 (s, 9H), 1.14 (d, J=6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7, 139.3, 133.6, 129.2, 128.0, 81.6, 74.0, 66.0, 52.7, 29.4, 28.1, 19.1. Anal. calcd for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.37. Found: C, 58.35; H, 7.14.

4.2.2. (3-Benzenesulfonyl-1-trityloxymethyl-propoxy)-acetic acid *tert*-butyl ester (2b). White solid; 84% yield; mp 43.5–45.0°C; IR (KBr) 3067, 2986, 1744, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93–7.82 (m, 2H), 7.70–7.46 (m, 3H), 7.46–7.17 (m, 15H), 4.10–3.90 (m, 2H), 3.64–3.49 (m, 1H), 3.32 (t, J=7.9 Hz, 2H), 3.24–3.04 (m, 2H), 2.10–1.85 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 143.7, 139.3, 133.5, 129.2, 128.6, 128.1, 127.9, 127.1, 87.0, 81.6, 77.3, 67.6, 65.1, 52.5, 28.1, 25.5. Anal. calcd for $C_{35}H_{38}O_6S$: C, 71.65; H, 6.53. Found: C, 71.45; H, 6.51.

4.2.3. (3-Benzenesulfonyl-1-phenyl-propoxy)-acetic acid *tert*-butyl ester (2c). Colorless oil; 99% yield; IR (neat) 3064, 2980, 1744, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98–7.20 (m, 10H), 4.48 (dd, J=8.1, 5.1 Hz, 1H), 3.88 (d, J=16.5 Hz, 1H), 3.66 (d, J=16.5 Hz, 1H), 3.56–3.28 (m, 2H), 2.30–2.00 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4, 139.8, 139.2, 133.6, 129.2, 128.7, 128.3, 128.0, 126.6, 81.6, 80.0, 65.9, 53.0, 31.2, 28.0. Anal. calcd for $C_{21}H_{26}O_5S$: C, 64.59; H, 6.71. Found: C, 64.87; H, 6.50.

4.2.4. (4-Benzenesulfonyl-1-methyl-butoxy)-acetic acid *tert*-butyl ester (2d). Colorless oil; 87% yield; IR (neat) 3064, 2974, 1747, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98–7.50 (m, 5H), 4.00–3.80 (m, 2H), 3.58–3.40 (m, 1H), 3.28–3.18 (m, 2H), 1.95–1.78 (m, 2H), 1.66–1.55 (m, 2H), 1.47 (s, 9H), 1.12 (d, J=5.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 139.4, 133.7, 129.3, 128.2, 81.4, 75.3, 66.2, 56.1, 35.0, 28.1, 19.1. Anal. calcd for $C_{17}H_{26}O_5S$: C, 59.62; H, 7.66. Found: C, 59.61; H, 7.76.

4.2.5. (4-Benzenesulfonyl-1-phenyl-butoxy)-acetic acid *tert*-butyl ester (2e). Colorless oil; 94% yield; IR (neat) 3064, 2977, 1744, 1585 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95–7.20 (m, 10H), 4.37 (dd, J=7.3, 4.4 Hz, 1H), 3.85 (d, J=16.4 Hz, 1H), 3.65 (d, J=16.4 Hz, 1H), 3.33–3.12 (m,

2H), 2.02–1.72 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4, 140.7, 139.2, 133.5, 129.2, 128.6, 128.0, 126.6, 81.3, 65.9, 55.7, 36.3, 28.0, 19.4. Anal. calcd for $C_{22}H_{28}O_5S$: C, 65.32; H, 6.98. Found: C, 65.41; H, 6.93.

4.3. General procedure for the intramolecular acylation of *tert*-butyl esters 2a–e

4.3.1. 4-Benzenesulfonyl-6-methyl-dihydropyran-3-one (4a). To a solution of **2a** (328 mg, 1.00 mmol) in THF (30 mL) at −78°C under N_2 was added LHMDS (2.00 mL, 2.00 mmol) slowly and the mixture was stirred for 4 h. The reaction was quenched with saturated NH_4Cl (2 mL). The THF was removed in vacuo and the residue was dissolved in CH_2Cl_2 (100 mL), washed with brine (50 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (15–25% EtOAc–hexane) to give a diastereomeric mixture **4a** (220 mg, 87%) as a colorless oil: IR (neat) 3452, 3067, 2977, 1747, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05–7.50 (m, 5H), 4.45–3.58 (m, 4H), 2.95–2.80 (m, 0.45H), 2.65–2.50 (m, 0.35H), 2.32–2.10 (m, 1H), 1.98–1.70 (m, 0.20H); 1.40–1.15 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.0, 161.4, 139.5, 138.2, 137.5, 134.4, 134.1, 133.7, 129.2, 128.7, 127.1, 102.1, 73.8, 71.7, 71.0, 69.3, 68.6, 68.2, 65.5, 32.9, 32.6, 20.9, 20.5. Anal. calcd for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55. Found: C, 56.61; H, 5.46.

4.3.2. 4-Benzenesulfonyl-6-trityloxymethyl-dihydropyran-3-one (4b). White solid; 99% yield (mixture of diastereomers); mp 49.0–54.0°C; IR (KBr) 3433, 3061, 2923, 1732, 1642 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03–7.20 (m, 20H), 4.50–3.65 (m, 4H), 3.40–2.97 (m, 2H), 2.89–1.90 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.1, 161.5, 143.7, 143.6, 139.7, 138.3, 134.3, 134.1, 133.6, 129.6, 129.3, 129.2, 129.0, 128.7, 127.9, 127.8, 127.3, 127.1, 102.1, 86.8, 86.7, 74.4, 74.3, 73.8, 72.3, 68.4, 68.2, 65.7, 65.5, 29.7, 28.1, 27.9, 25.0. Anal. calcd for $C_{31}H_{28}O_5S$: C, 72.63; H, 5.51. Found: C, 72.23; H, 5.67.

4.3.3. 4-Benzenesulfonyl-6-phenyl-dihydropyran-3-one (4c). White solid; 99% yield (mixture of diastereomers); mp 96.5–98.0°C; IR (KBr) 3455, 3064, 2926, 1729, 1642, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10–7.15 (m, 10H), 5.42–5.28 (m, 0.40H), 4.85–3.97 (m, 3.60H), 3.20–2.15 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.4, 161.4, 139.8, 139.5, 137.5, 134.5, 134.3, 133.7, 129.3, 128.9, 128.5, 127.3, 125.7, 102.5, 74.8, 74.3, 69.0, 66.0, 33.3, 29.6. Anal. calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10. Found: C, 64.51; H, 4.97.

4.3.4. 4-Benzenesulfonyl-7-methyl-oxepan-3-one (4d). White solid; 57% yield (mixture of diastereomers); mp 110.0–111.0°C; IR (KBr) 3064, 2920, 1717, 1585, 1450 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10–7.50 (m, 5H), 4.70–7.54 (m, 1H), 4.20 (d, J=18.1 Hz, 1H), 3.90 (d, J=18.1 Hz, 1H), 3.48–3.30 (m, 1H), 2.70–2.55 (m, 1H), 2.08–1.68 (m, 3H), 1.24 (d, J=6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.3, 138.3, 138.1, 134.0, 129.6, 128.9, 80.0, 72.4, 72.0, 35.8, 31.8, 23.9, 22.2, 21.8, 20.0. Anal. calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.02. Found: C, 58.54; H, 6.13.

4.3.5. 4-Benzenesulfonyl-7-phenyl-oxepan-3-one (4e). White solid; 85% yield (mixture of diastereomers); mp 145.0–146.5°C; IR (KBr) 3058, 2911, 1720, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.11–7.20 (m, 10H), 4.76 (dd, J=11.0, 2.5 Hz, 1H), 4.42–3.98 (m, 3H), 2.80–2.68 (m, 1H), 2.34–1.82 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.0, 141.4, 138.1, 134.0, 129.8, 128.9, 128.6, 128.0, 125.4, 85.3, 76.9, 72.7, 36.5, 28.1, 24.3. Anal. calcd for $C_{18}H_{18}O_4S$: C, 65.44; H, 5.50. Found: C, 65.15; H, 5.73.

4.3.6. 1-(3-Benzenesulfonyl-1-methyl-propoxy)-butan-2-ol (5a). To a solution of **1a** (2.14 g, 10.0 mmol) in THF (5 mL) at room temperature under N_2 was added potassium *tert*-butoxide (0.12 g, 1.00 mmol) followed by 1,2-epoxybutane (2.58 mL, 30.0 mmol), and the mixture was stirred at 60°C for 2 d. The reaction mixture was cooled to room temperature and poured into ice-water (20 mL). The crude product was extracted into EtOAc (100 mL), washed with 1N HCl (3×30 mL), $NaHCO_3$ (3×30 mL), brine (30 mL) and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (25–50% EtOAc–hexane) to give **5a** (2.45 g, 86%) as a colorless oil: IR (neat) 3511, 3061, 2977, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02–7.50 (m, 5H), 4.72–3.10 (m, 6H), 2.37 (br, 1H), 2.10–1.70 (m, 2H), 1.44 (quintet, J=7.1 Hz, 2H), 1.13 (d, J=6.2 Hz, 3H), 0.94 (t, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.3, 133.7, 129.3, 128.0, 73.4, 72.4, 71.7, 52.6, 29.4, 26.1, 19.3, 9.9. Anal. calcd for $C_{14}H_{22}O_4S$: C, 58.72; H, 7.74. Found: C, 58.97; H, 7.73.

4.3.7. 1-(4-Benzenesulfonyl-1-methyl-butoxy)-butan-2-ol (5b). To a solution of **1d** (1.11 g, 4.80 mmol) in THF (5 mL) at room temperature under N_2 was added potassium *tert*-butoxide (0.06 g, 0.48 mmol) followed by 1,2-epoxybutane (1.24 mL, 14.4 mmol), and the mixture was stirred at 60°C for 2 d. The reaction mixture was cooled to room temperature and poured into ice-water (20 mL). The crude product was extracted into EtOAc (100 mL), washed with 1N HCl (3×30 mL), $NaHCO_3$ (3×30 mL), brine (30 mL) and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (25–50% EtOAc–hexane) to give **5b** (0.53 g, 36%) as a colorless oil: IR (neat) 3508, 3061, 2969, 1585, 1447 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05–7.40 (m, 5H), 3.52–2.92 (m, 6H), 2.28 (br, 1H), 1.95–1.65 (m, 2H), 1.60–1.30 (m, 4H), 1.12 (d, J=5.9 Hz, 3H), 0.95 (t, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.3, 133.6, 129.3, 128.0, 75.2, 75.0, 72.5, 72.4, 72.1, 71.8, 56.2, 35.0, 26.3, 26.2, 19.5, 19.4, 19.0, 9.9. Anal. calcd for $C_{15}H_{24}O_4S$: C, 59.97; H, 8.05. Found: C, 60.28; H, 7.87.

4.3.8. 4-(3-Benzenesulfonyl-1-methyl-propoxy)-butan-2-one (6a). To a suspension of **5a** (350 mg, 1.21 mmol) and powdered 4 Å molecular sieves (610 mg) in CH_2Cl_2 (2.4 mL) at room temperature under N_2 was added 4-methylmorpholine *N*-oxide (210 mg, 1.82 mmol) followed by TPAP (22.0 mg, 5 mol%), and the mixture

was stirred at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel chromatography (20–30% EtOAc–hexane) to give **6a** (310 mg, 91%) as a colorless oil: IR (neat) 3067, 2974, 1729, 1585, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00–7.45 (m, 5H), 4.09 (d, J=17.1 Hz, 1H), 3.95 (d, J=17.1 Hz, 1H), 3.70–3.50 (m, 1H), 3.50–3.20 (m, 2H), 2.41 (q, J=7.2 Hz, 2H), 2.10–1.75 (m, 2H), 1.14 (d, J=5.9 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.9, 139.3, 133.7, 129.3, 130.0, 74.0, 73.1, 52.6, 32.1, 29.5, 19.1, 7.2. Anal. calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09. Found: C, 59.35; H, 7.18.

4.3.9. 1-(4-Benzenesulfonyl-1-methyl-butoxy)-butan-2-one (6b). To a suspension of **5b** (370 mg, 1.23 mmol) and powdered 4 Å molecular sieves (620 mg) in CH_2Cl_2 (2.5 mL) at room temperature under N_2 was added 4-methylmorpholine *N*-oxide (220 mg, 1.85 mmol) followed by TPAP (22.0 mg, 5 mol%), and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel chromatography (20–30% EtOAc–hexane) to give **6b** (330 mg, 88%) as a colorless oil: IR (neat) 3057, 2974, 1730, 1585, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.96–7.45 (m, 5H), 4.08 (d, J=16.9 Hz, 1H), 3.92 (d, J=16.9 Hz, 1H), 3.53–3.35 (m, 1H), 3.18 (t, J=7.8 Hz, 2H), 2.43 (t, J=7.3 Hz, 2H), 1.95–1.70 (m, 2H), 1.68–1.50 (m, 2H), 1.12 (d, J=7.1 Hz, 3H), 1.03 (t, J=7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.4, 139.4, 133.6, 129.3, 128.0, 75.5, 73.4, 56.1, 34.9, 32.2, 19.1, 19.0, 7.2. Anal. calcd for $C_{15}H_{22}O_4S$: C, 60.38; H, 7.43. Found: C, 60.46; H, 7.47.

4.3.10. (±)-(3*R*,4*S*,6*R*)-4-Benzenesulfonyl-3-ethyl-6-methyl-tetrahydropyran-3-ol (7). To a solution of **6a** (530 mg, 1.87 mmol) in toluene (37 mL) at room temperature under N_2 was added potassium *tert*-butoxide (330 mg, 2.81 mmol) and the mixture was stirred for 1 h. The reaction was quenched with water (10 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (20–50% EtOAc–hexane) to give **7** (340 mg, 64%) as a white solid: mp 106.0–108.0°C; IR (KBr) 3433, 3061, 2971, 1585, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.96–7.52 (m, 5H), 3.70 (d, J=12.1 Hz, 1H), 3.46–3.16 (m, 4H), 2.04 (q, J=7.6 Hz, 2H), 1.86 (ddd, J=13.3, 11.7, 11.9 Hz, 1H), 1.54 (ddd, J=13.3, 3.9, 2.2 Hz, 1H), 1.19 (d, J=6.2 Hz, 3H), 0.94 (t, J=7.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.8, 133.9, 129.1, 128.9, 74.7, 73.0, 71.2, 65.5, 30.8, 30.3, 21.3, 8.1. Anal. calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09. Found: C, 59.46; H, 6.91.

4.3.11. (±)-(2*R*,4*S*)-4-Benzenesulfonyl-5-ethyl-2-methyl-3,4-dihydro-2*H*-pyran (8). To a solution of **6a** (180 mg, 0.63 mmol) in toluene (13 mL) at room temperature under N_2, was added potassium *tert*-butoxide (330 mg, 2.81 mmol) and the mixture was stirred for 1 h. Then the reaction mixture was heated to 60°C and stirred for 1 h. The mixture was poured into ice-water (20 mL) and extracted with ethyl ether (3×30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (11–14% EtOAc–hexane) to give **8** (85.0 mg, 50%) as a colorless oil: IR (neat) 3064, 2971, 1651, 1585, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.92–7.50 (m, 5H), 6.52 (s, 1H), 4.09 (ddq, J=12.2, 2.2, 6.1 Hz, 1H), 3.76 (d, J=6.1 Hz, 1H), 2.32–2.00 (m, 3H), 1.58 (ddd, J=15.2, 12.2, 6.1 Hz, 1H), 1.20 (d, J=6.1 Hz, 3H), 0.98 (t, J=7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.5, 138.7, 133.8, 129.3, 128.8, 104.3, 66.8, 60.0, 29.9, 24.7, 20.9, 13.0. Anal. calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.38; H, 6.83.

4.3.12. 5-Benzenesulfonyl-pentan-2-ol (1d). The cyclization of **6b** was conducted using the same procedure that is described for **7**. The decomposition product **1b** was obtained in 76% yield. The ^1H NMR is coincident with the data reported.[18c]

4.3.13. 5-(3-Benzenesulfonyl-1-methyl-propoxy)-pentan-2-one (10). To a solution of **1a** (1.07 g, 5.00 mmol) in benzene (20 mL) at 10°C was added 50% aq. NaOH (4.80 mL, 60.0 mmol) followed by TBAB (0.42 g, 1.25 mmol), and the mixture was stirred at 10°C for 30 min. 5-Chloro-2-pentanone ethylene ketal (1.16 mL, 7.50 mmol) was then added and the mixture was stirred at 60°C for 2 d. The reaction mixture was cooled to room temperature and diluted with EtOAc (100 mL), washed with brine (3×30 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (15–30% EtOAc–hexane) to give 2-[3-(3-benzenesulfonyl-1-methyl-propoxy)-propyl]-2-methyl-[1,3]dioxolane [**9**] (1.28 g, 75%) as a colorless oil: IR (neat) 3064, 2878, 1585, 1480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.96–7.51 (m, 5H), 3.99–3.88 (m, 4H), 3.53–3.39 (m, 2H), 3.31–3.06 (m, 3H), 2.03–1.55 (m, 6H), 1.30 (s, 3H), 1.10 (d, J=6.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 133.5, 129.3, 128.0, 109.8, 72.9, 68.4, 64.6, 52.7, 35.7, 29.6, 24.7, 23.8, 19.4. To a solution of **9** (1.28 g, 3.74 mmol) in wet acetone (40 mL) was added PPTS (0.28 g, 1.12 mmol) and the mixture was refluxed at 60°C for 5 h. The reaction mixture was cooled to room temperature and the acetone was removed in vacuo. The residue was dissolved in EtOAc (100 mL), washed with $NaHCO_3$ (3×30 mL), brine (3×30 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (15–30% EtOAc–hexane) to give **10** (1.01 g, 91%) as a colorless oil: IR (neat) 3067, 2932, 1714, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98–7.53 (m, 5H), 3.55–3.38 (m, 2H), 3.32–3.04 (m, 3H), 2.47 (t, J=7.3 Hz, 2H), 2.13 (s, 3H), 2.00–1.67 (m, 4H), 1.09 (d, J=6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.1, 139.4, 133.6, 129.3, 128.0, 73.0, 67.4, 25.6, 40.3, 29.8, 29.5, 24.2, 19.3. Anal. calcd for $C_{15}H_{22}O_4S$: C, 60.38; H, 7.43. Found: C, 60.35; H, 7.59.

4.4. General procedure for the synthesis of vinyl sulfone 13

4.4.1. 4-Benzenesulfonyl-2-methyl-3,6-dihydro-2*H*-pyran (13a). To a solution of **4a** (510 mg, 2.00 mmol) in ethanol (30 mL) at 0°C was added $NaBH_4$ (482 mg, 12.7 mmol) and the mixture was stirred at room temperature for 20 h. The ethanol was removed in vacuo and the residue was dissolved

in CH_2Cl_2 (50 mL), washed with brine (50 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo gave the crude 4-benzenesulfonyl-6-methyl-tetrahydropyran-3-ol [**11a**] (mixture of two diastereomers, 495 mg, 97%) as a white solid, which was used in the next step without further purification: IR (KBr) 3485, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00–7.50 (m, 5H), 4.36–4.00 (m, 2H), 3.88–3.62 (m, 2H), 3.53–3.28 (m, 2H), 2.50–2.30 (m, 1H), 1.71–1.59 (m, 1H), 1.35–1.10 (m, 3H). To a solution of crude **11a** (348 mg, 1.50 mmol) in CH_2Cl_2 (30 mL) at room temperature under N_2 was added pyridine (140 μL, 1.80 mmol) followed by a catalytic amount of DMAP and acetic anhydride (174 μL, 1.80 mmol), and the mixture was stirred at room temperature for 10 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL), washed with brine (3×10 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (20–33% EtOAc–hexane) to give acetic acid 4-benzenesulfonyl-6-methyl-tetrahydro-pyran-3-yl ester [**12a**] (mixture of two diastereomers, 430 mg, 96%) as a colorless oil: IR (neat) 1750, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.92–7.52 (m, 5H), 5.20–5.10 (m, 1H), 4.32–4.00 (m, 2H), 3.80–3.65 (m, 2H), 2.60–2.42 (m, 1H), 1.89–1.60 (m, 4H), 1.30–1.10 (m, 3H). To a solution of **12a** (300 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added DBU (150 μL, 1.20 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with brine (3×10 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by radial chromatography using a chromatotron (20–33% EtOAc–hexane) to give **13a** (210 mg, 88%) as a white solid: mp 67.0–68.0°C; IR (KBr) 3064, 2974, 2932, 1651, 1585, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91–7.49 (m, 5H), 7.10–7.00 (br, 1H), 4.55–4.25 (m, 2H), 3.68–3.48 (m, 1H), 2.40–2.25 (m, 1H), 2.06–1.86 (m, 1H), 1.23 (d, J=6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.8, 137.9, 136.0, 133.7, 129.3, 128.2, 69.5, 65.4, 30.1, 21.0. Anal. calcd for $C_{12}H_{14}O_3S$: C, 60.49; H, 5.93. Found: C, 60.42; H, 5.90.

4.4.2. 4-Benzenesulfonyl-2-trityloxymethyl-3,6-dihydro-2*H*-pyran (13b). White solid; 61% yield; mp 65.0–67.0°C; IR (KBr) 3058, 2923, 1597, 1585, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.90–7.78 (m, 2H), 7.67–7.13 (m, 18H), 7.02 (br, 1H), 4.56–4.25 (m, 2H), 3.71–3.57 (m, 1H), 3.24 (dd, J=9.8, 5.9 Hz, 1H), 3.05 (dd, J=9.8, 4.5 Hz, 1H), 2.38–2.22 (m, 1H), 2.15–1.95 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.8, 138.8, 137.8, 135.8, 133.5, 129.2, 128.7, 128.2, 127.8, 127.1, 86.7, 72.8, 65.9, 65.4, 25.8. Anal. calcd for $C_{31}H_{28}O_4S$: C, 74.97; H, 5.68. Found: C, 75.15; H, 5.86.

4.4.3. (±)-(1*R*,4*R*,6*R*)-6-Benzenesulfonyl-4-methyl-3,7-dioxabicyclo[4.1.0] heptane (14). To a mixture of oil-free sodium hydride (60.0 mg, 2.50 mmol) in THF (10 mL) at 0°C under N_2 was added *tert*-butyl hydroperoxide (0.50 mL, 2.50 mmol, 5–6 M decane) and the mixture was stirred at room temperature for 30 min. A solution of **13a** (120 mg, 0.50 mmol) in THF (10 mL) was then added and the mixture was stirred at 10°C for 20 h. The reaction was quenched with saturated NH_4Cl (5 mL) and Na_2SO_3 (100 mg). The mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash silica gel chromatography (15–25% EtOAc–hexane) to give **14** (80.0 mg, 63%) as a colorless oil: IR (neat) 3067, 2977, 1585, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00–7.50 (m, 5H), 4.23 (d, J=13.9 Hz, 1H), 3.88 (d, J=13.9 Hz, 1H), 3.83 (s, 1H), 3.39 (ddq, J=11.1, 3.9, 6.1 Hz, 1H), 2.54 (dd, J=15.0, 3.9 Hz, 1H), 1.47 (dd, J=15.0, 11.1 Hz, 1H), 1.15 (d, J=6.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.7, 134.6, 129.4, 70.5, 69.3, 63.9, 53.2, 29.6, 21.0. Anal. calcd for $C_{12}H_{14}SO_4$: C, 58.68; H, 5.55. Found: C, 58.48; H, 5.51.

4.4.4. (±)-(2*R*,5*S*)-5-Bromo-2-methyl-tetrahydropyran-4-one (15). To a solution of **14** (80.0 mg, 0.32 mmol) in ethyl ether (5 mL) at room temperature under N_2 was added magnesium bromide diethyl ether (110 mg, 0.41 mmol) and the mixture was stirred for 10 h. The reaction mixture was diluted with ethyl ether (10 mL), filtered and the filtrate was concentrated in vacuo. The crude product was purified by Kugelrohr distillation (50°C, 0.3 mm Hg) to give **15** (51.0 mg, 85%) as a white solid: mp 61.0–62.0°C; IR (KBr) 2977, 1732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.61 (ddd, J=11.3, 6.9, 1.1 Hz, 1H), 4.44 (dd, J=11.2, 6.9 Hz, 1H), 3.84 (ddq, J=11.8, 2.5, 6.0 Hz, 1H), 3.69 (dd, J=11.3, 11.2 Hz, 1H), 2.75 (dd, J=14.2, 2.5 Hz, 1H), 2.50 (ddd, J=14.2, 11.8, 1.1 Hz, 1H), 1.34 (d, J=6.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.3, 75.4, 72.9, 52.0, 50.2, 21.6. Anal. calcd for $C_6H_9BrO_2$: C, 37.33H, 4.70. Found: C, 37.20; H, 4.62.

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 178511. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].

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