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TETRAHEDRON:
ASYMMETRY

On the diastereoselective Meth-Cohn epoxidation of camphor-derived vinyl sulfones

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Abstract—Some camphor-derived vinyl sulfones bearing oxygen functionality at the allylic position have been synthesized and their nucleophilic epoxidation reactions under Meth-Cohn conditions have been explored. The γ-oxygenated camphor-derived vinyl sulfones underwent mildly diastereoselective nucleophilic epoxidation reactions, affording the derived sulfonyloxiranes in up to 5.8:1 dr. The observed diastereoselectivities were sensitive to the reaction conditions employed. In contrast, no stereoselectivity was observed in the nucleophilic epoxidation of the corresponding γ-oxygenated isobornyl vinyl sulfone. A tentative mechanism has been proposed to explain the origins of the diastereoselectivity.

1. Introduction

Unsaturated sulfones are versatile intermediates in organic synthesis, acting as both electron deficient olefins in a wide range of cycloaddition processes, and as Michael acceptors with a number of carbon and heteroatom nucleophiles.[1] In recent years, unsaturated sulfones have also been extensively used as substrates in catalytic asymmetric synthesis.[2,3] However, although applications of chiral sulfones in asymmetric synthesis have been reported,[4] there appears to have been no reports of the applications of vinyl sulfones **1** which possess homochiral alkyl groups R* directly attached to the sulfur atom (Figure 1). Given the widespread use of camphor derivatives as chiral auxiliaries,[5] we reasoned that vinyl sulfones bearing the camphorsulfonyl moiety **2** would be promising candidates for the preparation of enantiomerically enriched compounds.[6]

Vinyl sulfones also act as synthetic precursors to α-functionalised carbonyl compounds. Nucleophilic epoxidation of vinyl sulfones with a metal alkyl peroxide under anhydrous conditions (Meth-Cohn epoxidation),[7] or under classical Weitz-Scheffer conditions[8] generates sulfonyloxiranes that react regiospecifically at the β-position with a range of heteroatom nucleophiles to generate α-functionalised carbonyl compounds.[9,10] In addition, Sharpless asymmetric dihydroxylation of vinyl sulfones generates enantioenriched α-hydroxy aldehydes directly in a single step.[11] Jackson previously reported the synthesis and nucleophilic epoxidation of achiral (*E*)-3-benzyloxyprop-1-enyl phenyl sulfone **3** (Figure 1),[12] and showed that subsequent cleavage of related sulfonyloxiranes with magnesium bromide affords α-bromo ketones.[13] In addition, Mori reported the nucleophilic epoxidation of the (*Z*)-isomer of **3** which afforded the corresponding *cis*-sulfonyloxiranes.[14] Furthermore, an asymmetric variant of this methodology has been developed, involving diastereoselective nucleophilic epoxidation of vinyl sulfoximines derived from isopropylideneglyceraldehyde.[15] Sulfone **3** could thus be an attractive precursor to 3-*O*-benzylglyceraldehyde **4** (Figure 1) using the above methodologies, and we envisaged that camphor-derived vinyl sulfones would be potential precursors for the asymmetric synthesis of α-hydroxy aldehydes such as **4** using these methodologies.[16] In this paper, we extend our recent investigations[17] on the utility of camphor-derived sulfones in asymmetric synthesis and report our findings on the use of camphor-derived vinyl sulfones as potential precursors to enantioenriched α-hydroxy aldehydes such as **4**.

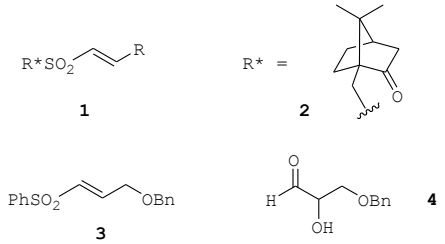
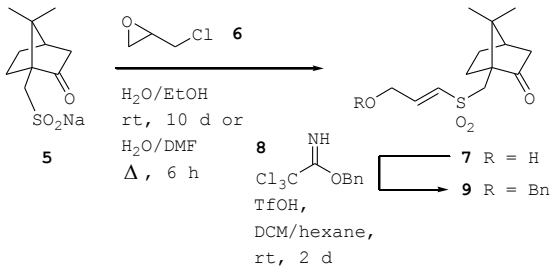


Figure 1. Homochiral camphor-derived vinyl sulfones and the structures of (*E*)-3-benzyloxyprop-1-enyl phenyl sulfone and 3-*O*-benzylglyceraldehyde.

2. Results and Discussion

We began by synthesizing camphor-derived vinyl sulfone **7** from sodium (−)-camphor-10-sulfinate **5**,[18] which was itself prepared from (+)-camphor-10-sulfonic acid as previously

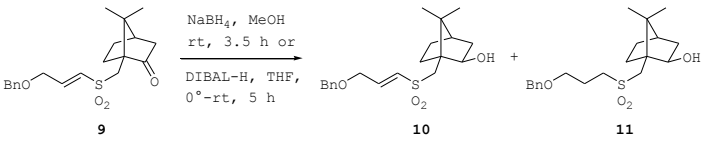
described.[19] The novel γ-hydroxy vinyl sulfone **7** was prepared in 73 % yield by treatment of sodium (−)-camphor-10-sulfinate **5** with epichlorohydrin **6** using conditions employed for the synthesis of the corresponding achiral phenylsulfonyl compound.[20] Comparable yields of **7** were also obtained using conditions previously reported by Jackson.[13] The free alcohol **7** was subsequently converted into its benzyl ether **9**[12] by treatment with benzyl-2,2,2-trichloroacetimidate **8** in DCM/hexane in the presence of an acid catalyst (Scheme 1).[21] As noted earlier,[19] attempts to synthesize **9** (and related vinyl sulfones) by iodosulfonylation of allyl benzyl ether with (+)-camphorsulfonyl iodide (generated *in situ* from sodium (−)-camphor-10-sulfinate **5** and iodine) met with no success, and led instead to the formation of (−)-10-iodocamphor.



Scheme 1.

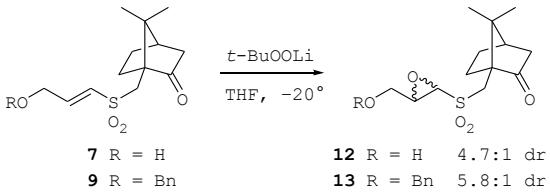
The presence of a hydroxyl group in the chiral auxiliary provides the possibility of coordination-controlled stereoselectivity in the nucleophilic epoxidation reactions of chiral vinyl sulfones using metal alkyl peroxides. Accordingly, camphor-derived vinyl sulfone **9** was reduced to the corresponding *exo*-configured isobornyl vinyl sulfone **10** using either sodium borohydride in methanol, or DIBAL-H in THF (Scheme 2). In each case, substantial amounts of the saturated sulfone **11** were also formed via further reduction of the C–C double bond of **10**. No traces of the corresponding *endo*-configured bornyl vinyl sulfone were detected in the crude products of these reactions.

We began by studying the nucleophilic epoxidation of vinyl sulfone **9** under conditions reported by Meth-Cohn using lithium *tert*-butyl peroxide in anhydrous THF.[7] Initial experiments conducted on a small scale using excess (4 equivalents) lithium *tert*-butyl peroxide in THF gave the product sulfonyloxiranes **13** as 1:1 mixtures of diastereomers, as determined by ^{1}H NMR spectroscopy. However, when the reaction was conducted on a larger scale using a smaller excess (3 equivalents) of lithium *tert*-butyl peroxide, a 5.8:1 ratio of diastereomers of **13** was obtained (Scheme 3). In another experiment using two equivalents of reagent, a 2.1:1 diastereomer ratio of **13** was obtained. The inseparable diastereomers of **13** were recovered as oils in rather poor yields (45 %) following chromatography.[22] It was thus not possible to determine the relative configuration of the oxirane ring in the major diastereomer. Our studies on the nucleophilic epoxidation of vinyl sulfones **7**, **9** and **10** are summarised in Table 1.



Scheme 2.

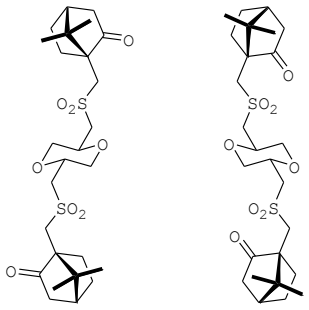
Under similar conditions, nucleophilic epoxidation of the free alcohol **7** with lithium *tert*-butyl peroxide afforded in very low yield (15 %) the sulfonyloxiranes **12** as a 4.7:1 inseparable mixture of diastereomers as judged by ^{1}H NMR spectroscopy (Scheme 3). The possibility that the unprotected hydroxyl group of **12** underwent Payne rearrangement with subsequent elimination of lithium camphor-10-sulfinate under the basic reaction conditions may account for the low yield of the sulfonyloxiranes **12**. Indeed, evaporation of the aqueous phase afforded a white solid which was shown by ^{1}H NMR spectroscopy in D_2O to contain lithium camphor-10-sulfinate. In addition to **12**, a significant quantity of the bis-camphorsulfonylmethyl-1,4-dioxane **14** was also obtained as a pair of diastereomers (ca. 1:1 d.r.) from the crude reaction product (Figure 2). These are clearly formed by bimolecular Michael addition to the double bond of **7** of the oxyanion derived from **7** which is formed under the basic conditions of the epoxidation reaction.[23]



Scheme 3.

The origins of the variable diastereoselectivity in the Meth-Cohn epoxidation of sulfones **7** and **9** are unclear. Most examples of diastereoselective nucleophilic epoxidation of chiral electron deficient olefins involve substrates bearing asymmetric centres at the allylic position.[24] The observed diastereoselectivity is then influenced by a number of factors, including the conformational preferences of the substrate, coordination and solvent effects and the steric bulk and metal counter ion used in the epoxidising reagent. Jackson observed high levels of *syn*-diastereoselectivity in the nucleophilic epoxidation of chiral γ-hydroxy vinyl sulfones using lithium *tert*-butyl peroxide in THF; a result attributed to coordination of the lithium ion of the reagent to the allylic oxygen prior to oxygen atom delivery to the olefin.[25] Exclusive *syn*-diastereoselectivity was also observed in the nucleophilic epoxidation of enantiomerically pure γ-hydroxy-1-arylthio-1-nitroalkenes.[26]

In addition, variations in the extent of *syn*-diastereoselectivity were observed by Jackson in the nucleophilic epoxidation of γ-oxygenated vinyl sulfoximines depending on the steric bulk of the reagent (*t*-BuOOH v Ph_3COOH) and the metal counter ion used (Li^+ v Na^+ v K^+), with the highest stereoselectivities being observed with lithium triphenylmethyl peroxide.[27] It has also been reported that protection of the hydroxyl group of α-(1-hydroxyalkyl) vinyl sulfones as silyl ethers can switch the mode of diastereoselection from *syn* (coordination controlled) to *anti* (sterically controlled).[28]



14 1:1 dr

Figure 2. Structures of both diastereomers of 1,4-dioxane **14**.

In order to verify if coordination and/or hydrogen bonding effects were responsible for the diastereoselectivity observed in the epoxidation of sulfones **7** and **9**, the reaction was repeated in toluene, a solvent in which the effects of coordination would be expected to be enhanced. Higher levels of *syn*-diastereoselectivity were observed by Jackson in the nucleophilic epoxidation of γ-oxygenated-1-arylthio-1-nitroalkenes with lithium *tert*-butyl peroxide when toluene was used as the solvent rather than THF.[29] In the event, epoxidation of **9** with lithium *tert*-butyl peroxide in toluene gave a 1:1 mixture of diastereomers, suggesting that coordination and/or hydrogen bonding effects were not responsible for the diastereoselectivity previously observed in THF.

The nucleophilic epoxidation of **9** in THF was then carried out using the more sterically bulky reagent lithium triphenylmethyl peroxide.[30] Although we anticipated that higher levels of diastereoselectivity might be observed with this reagent, a 1:1 mixture of diastereomers of **13** was still obtained. The nucleophilic epoxidations of **9** were also carried out in the presence of Lewis acids in an attempt to enforce chelation control by coordination of the carbonyl and sulfone oxygens to the Lewis acid. However, no diastereoselectivity was observed when either magnesium chloride or titanium(IV) isopropoxide were employed in the epoxidation reactions.

We next examined the nucleophilic epoxidation reaction of **9** under classical Weitz-Scheffer conditions.[8] Once again however, a 1:1 ratio of diastereomeric sulfonyloxiranes **13** was obtained on treatment of **9** with sodium hydroperoxide in acetone. Attempts to effect an intramolecular epoxidation of **9** by *in situ* conversion of the carbonyl group of the auxiliary into a dioxirane moiety using either oxone/acetonitrile[31] or hydrogen peroxide/acetonitrile[32] were unsuccessful, and starting material was recovered in each case. This result is not totally surprising, given that vinyl sulfones are unreactive towards electrophilic epoxidising reagents.[33]

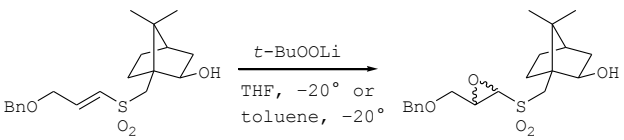
Table 1. Studies on the diastereoselective nucleophilic epoxidation reactions of camphor-derived vinyl sulfones **7**, **9** and **10**.

Entry	Vinyl sulfone	Reagent (equiv)	Solvent	Conditions	Yield (%)[a] (dr)[b]
1	**9**	*t*-BuOOLi (4)	THF	−20 °C, 3 h	**13** 66 (1:1)
2	**9**	*t*-BuOOLi (3)	THF	−20 °C, 3 h	**13** 70/45 (5.8:1)
3	**9**	*t*-BuOOLi (2)	THF	−20 °C, 2.5 h	**13** 72 (2.1:1)
4	**7**	*t*-BuOOLi (3)	THF	−20 °C, 2 h	**12** 47/15 (4.7:1)
5	**9**	Ph_3COOLi (2)	THF	−20 °C, 6 h	**13** 69 (1:1)
6	**9**	*t*-BuOOLi (3)	toluene	−20 °C, 4 h	**13** 78/58 (1:1)
7	**9**	*t*-BuOOLi (4)	THF	$Ti(O\textit{i}\text{-}Pr)_4$, −20 °C, 2 h	**13** 70 (1:1)
8	**9**	*t*-BuOOLi (4)	THF	$MgCl_2$, −20 °C, 2.5 h	**13** 63 (1:1)
9	**9**	HOONa (3)	acetone	40 °C, 3 h	**13** 68 (1:1)
10	**10**	*t*-BuOOLi (2)	toluene	−20 °C–rt, 52 h	**15** 100/95 (1:1)
11	**10**	*t*-BuOOLi (2)	THF	−20 °C–rt, 50 h	**15** 94/91 (1:1)

[a] Yield of crude product given first, followed by yield of purified product where appropriate.

[b] Determined from ^{1}H NMR spectroscopy of crude product.

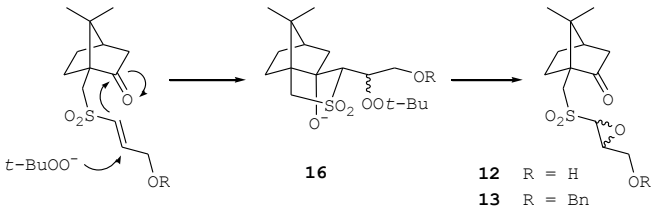
In order to shed more light on the role of the camphor auxiliary in the nucleophilic epoxidations of sulfones **7** and **9**, the epoxidation of isobornyl vinyl sulfone **10** was next examined. The reactions of **10** with lithium *tert*-butyl peroxide in either toluene or THF were quite slow, and took over 48 hours to reach completion. The rates of these reactions were significantly slower than those of **7** and **9**, and analogous achiral sulfones.[7,12] The sulfonyloxiranes **15** were isolated in excellent yields as 1:1 inseparable mixtures of diastereomers in each case following chromatography (Scheme 4). This result suggests that the carbonyl groups of **7** and **9** played a key role in the diastereoselection observed in the epoxidations of the ketones **7** and **9** in THF, although the reaction is clearly sensitive to the conditions employed. It should be mentioned that the lack of diastereoselection observed in the epoxidation of the alcohol **10** does not rule out lithium ion coordination by the hydroxyl group of **10**. Coordination could have occurred, but a lack of rotamer control in the sulfonyl side-chain may have led to the observed lack of diastereoselection.



10 **15** 1:1 dr

Scheme 4.

The above results suggest that lithium ion coordination and/or hydrogen bonding effects are not responsible for the diastereoselectivities observed in the nucleophilic epoxidation reactions of sulfones **7** and **9** with lithium *tert*-butyl peroxide. A tentative mechanism can be proposed involving participation of the carbonyl group of the auxiliary (Scheme 5). The sulfonyl carbanion formed by Michael addition of the reagent to the double bond of either **7** or its benzyl ether **9** could cyclise with the auxiliary, forming the *endo*-configured tricyclic oxyanion intermediate **16** as one of two possible diastereomers epimeric at the β-position.[34] Collapse of this intermediate and subsequent elimination of lithium *tert*-butoxide affords the product sulfonyloxiranes **12** and **13**.



Scheme 5.

Finally, with the sulfonyloxiranes **13** in hand, we briefly explored the hydrolytic ring-opening of **13** with sodium hydroxide. Unfortunately, when **13** was hydrolysed using sodium hydroxide in isopropanol at reflux, benzyl alcohol was obtained as the sole product, presumably arising via β-elimination from the target aldehyde **4** (Figure 1) formed *in situ*. We also briefly explored the non-asymmetric Upjohn dihydroxylation[35] of vinyl sulfone **9**. In this case, benzyl alcohol was also obtained when vinyl sulfone **9** was treated with osmium tetroxide/*N*-methylmorpholine-*N*-oxide in acetone/water at ambient temperature for 6 days. Efforts to find milder conditions for the preparation of **4** by hydrolysis of **13** and related achiral arylsulfonyloxiranes (eg: by using anhydrous hydroxide ion under Gassman conditions),[36] or by asymmetric dihydroxylation of the corresponding achiral vinyl sulfone **3** have so far met with no success.[37]

3. Conclusion

It has been found that γ-oxygenated camphor-derived vinyl sulfones undergo mildly diastereoselective nucleophilic epoxidation reactions under Meth-Cohn conditions. The observed diastereoselectivity is sensitive to the reaction conditions employed, with the highest stereoselectivities being observed using lithium *tert*-butyl peroxide (2 equivalents) in anhydrous THF. In contrast, no stereoselectivity was observed in the nucleophilic epoxidations of a γ-oxygenated isobornyl-derived vinyl sulfone. A tentative mechanism has been proposed to account for the stereoselectivity, involving participation of the carbonyl group of the chiral auxiliary. The application of these compounds to the asymmetric synthesis of 3-*O*-benzylglyceraldehyde was unsuccessful.

4. Experimental

4.1. General

NMR spectra were recorded using a Bruker AVANCE DPX 400 MHz spectrometer (400.1 MHz for ^{1}H and 100.6 MHz for ^{13}C). Chemical shifts are reported in parts per million. Coupling constants (*J*) are quoted in Hertz. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. IR spectra were recorded for Nujol mulls (N) or liquid films (L) on a Mattson Genesis II FTIR spectrometer. Mass spectra were obtained under electrospray conditions using a Micromass LCT instrument. Uncorrected melting points (Mp) were measured in unsealed capillary tubes using a Griffin melting point apparatus. Anhydrous solutions of *tert*-butyl hydroperoxide in benzene were prepared by azeotropic distillation of commercially available 70 % solutions of *tert*-butyl hydroperoxide in water according to the procedure of Sharpless.[38] Concentrations were estimated by ^{1}H NMR. Triphenylmethyl hydroperoxide was prepared according to the procedure of Eberhard.[30] Tetrahydrofuran (THF) was dried and distilled over sodium-benzophenone ketyl prior to use. Toluene was dried over anhydrous calcium chloride prior to use. All other solvents and reagents were purified by standard techniques. Organic extracts of reaction products were dried over anhydrous magnesium sulfate.

4.2 (1*S*,4*R*)-1-({[(1'*E*)-3'-Hydroxyprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 7.

4.2.1 Method A:

Sodium sulfinate **5** (9.5 g, 39 mmol) was dissolved in water (42 mL) and ethanol (10.5 mL) and epichlorohydrin **6** (6.2 mL, 79 mmol) was added. The solution was stirred at room temperature for 10 days. The solution was then diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried and evaporated to yield an oil. Removal of excess epichlorohydrin on an oil pump (ca. 0.1 mm Hg) afforded the title compound **7** as an oil (9.65 g, 88 %) which slowly crystallised after several days. A small portion of the product was triturated with a small volume of ether to afford an analytical sample of the title compound **7** as a white solid.

4.2.2 Method B:

Sodium sulfinate **5** (0.95 g, 3.9 mmol) was dissolved in water (10 mL) and DMF (0.5 mL) and epichlorohydrin **6** (0.62 mL, 7.9 mmol) was added. The solution was heated

under reflux for 6 hrs. The solution was then allowed to cool to room temperature, diluted with water (50 ml) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried and evaporated to yield an oil. Removal of excess epichlorohydrin on an oil pump (ca. 0.1 mm Hg) afforded the title compound **7** as an oil (0.92 g, 85 %) which slowly crystallised after several days. Mp 71 °C (ether). $[\alpha]_D$ = +26.8 (*c* 0.5, MeOH, 26 °C). IR ν_{max} (N) 3523 (O–H), 3061, 2923, 1740 (C=O), 1635 (C=C), 1454, 1414, 1375, 1310 (SO_2), 1199, 1130 (SO_2), 1104, 1052, 1018, 943, 837, 788, 674 cm^{-1}. ^1H NMR ($CDCl_3$): 0.86 (s, 3H, 7-CH_3), 1.07 (s, 3H, 7-CH_3), 1.42–1.48 (m, 1H), 1.70–1.77 (m, 1H), 1.93 (d, ^2J = 18.4, 1H, 3-CH_2 *endo*), 2.02–2.08 (m, 1H), 2.12 (t, ^3J = 4.5, 1H, 4-C*H*), 2.37 (dt, ^2J = 18.4, ^3J = 4.5, 1H, 3-CH_2 *exo*), 2.46 (m, 1H), 2.87 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.44 (d, ^2J = 15.0, 1H, CH_2SO_2), 4.40 (dd, ^3J = 3.4, ^4J = 2.7, 2H, 3'-CH_2), 6.83 (dt, ^3J = 15.0, ^4J = 2.7, 1H, 1'-C*H*), 6.96 (dt, ^3J = 15.0, 3.4, 1H, 2'-C*H*). ^{13}C NMR ($CDCl_3$): 19.2 (7-*C*H_3), 19.2 (7-*C*H_3), 24.3 (C-5), 26.5 (C-6), 41.9 (C-4), 42.1 (C-3), 48.1 (C-7), 51.4 (*C*H_2SO_2), 58.2 (C-1), 60.3 (C-3'), 128.8 (C-1'), 146.0 (C-2'), 214.9 (C-2). HRMS (EI, MeOH) *m*/*z* calcd for $C_{13}H_{20}O_4S$ $[M + Na]^+$: 295.0979; found: 295.0930.

4.3 (1*S*,4*R*)-1-({[(1'*E*)-3'-Benzyloxyprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 9.

Sulfone **7** (2.5 g, 9.1 mmol) was dissolved in dry DCM (40 mL) and dry hexane (80 mL) and benzyl-2,2,2-trichloroacetimidate **8** (2.5 mL, 13.6 mmol) was added. Trifluoromethanesulfonic acid (1 mL) was added dropwise and the solution was stirred at room temperature for 48 hrs. Hexane (100 mL) was added and the precipitated trichloroacetamide was filtered. The filtrate was diluted with ether (100 mL) and then washed with satd. aq. sodium hydrogen carbonate (50 mL) and brine (50 mL), dried and evaporated to yield an oil. Column chromatography on silica gel, eluting with ethyl acetate/hexane (1:2) afforded the title compound **9** as a colourless oil (2.2 g, 66 %). $[\alpha]_D$ = +27.3 (*c* 0.57, MeOH, 26 °C). IR ν_{max} (L) 3062, 3029, 2959, 1740 (C=O), 1639 (C=C), 1601 (Ar C–C), 1495, 1454, 1392, 1360, 1314 (SO_2), 1279, 1201, 1121 (SO_2), 1051, 1026, 945, 908, 831, 784, 739, 699 cm^{-1}. ^1H NMR ($CDCl_3$): 0.87 (s, 3H, 7-CH_3), 1.09 (s, 3H, 7-CH_3), 1.41–1.47 (m, 1H), 1.69–1.74 (m, 1H), 1.93 (d, ^2J = 18.5, 1H, 3-CH_2 *endo*), 2.01–2.08 (m, 1H), 2.12 (t, ^3J = 4.5, 1H, 4-C*H*), 2.38 (dt, ^2J = 18.5, ^3J = 4.5, 1H, 3-CH_2 *exo*), 2.50 (m, 1H), 2.86 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.45 (d, ^2J = 15.0, 1H, CH_2SO_2), 4.24 (dd, ^3J = 3.0, ^4J = 1.5, 2H, 3'-CH_2), 4.60 (s, 2H, benzyl CH_2), 6.85 (dt, ^3J = 15.0, ^4J = 1.5, 1H, 1'-C*H*), 6.92 (dt, ^3J = 15.0, 3.0, 1H, 2'-C*H*), 7.31–7.38 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$): 19.2 (7-*C*H_3), 19.3 (7-*C*H_3), 24.3 (C-5), 26.6 (C-6), 42.0 (C-4), 42.1 (C-3), 47.9 (C-7), 51.3 (*C*H_2SO_2), 58.2 (C-1), 67.1 (C-3'), 72.5 (benzyl *C*H_2), 127.2 (Ar C-3), 127.5 (Ar C-4), 128.0 (Ar C-2), 129.9 (C-1'), 136.9 (Ar C-1), 142.7 (C-2'), 214.3 (C-2). HRMS (EI, MeOH) *m*/*z* calcd for $C_{20}H_{26}O_4S$ $[M + Na]^+$: 385.1449; found: 385.1455.

4.4 Reduction of Vinyl Sulfone 9.

4.4.1 Method A: With Sodium Borohydride.

Sulfone **9** (0.4 g, 1.1 mmol) was dissolved in methanol (20 mL) and sodium borohydride (0.16 g, 4.4 mmol) was added. The solution was stirred at room temperature for 3.5 hrs. The solution was then diluted with satd. aq. ammonium chloride (50 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried and evaporated to yield an oil (0.36 g). The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (1:3) to yield two products. The first product to elute was sulfone **10** (0.18 g, 45 %) as a colourless oil. The second product to elute was sulfone **11** (0.13 g, 32 %) as a colourless oil.

4.4.2 Method B: With Diisobutylaluminium Hydride.

Sulfone **9** (1.04 g, 2.8 mmol) was dissolved in dry THF (8 mL) under an atmosphere of nitrogen and cooled to 0 °C. Diisobutylaluminium hydride (3.43 mL, 1.5 M in toluene, 5.1 mmol) was added via syringe and the solution was stirred at 0 °C for 1 hr. The solution was then allowed to warm to room temperature and stirring was continued for an additional 4 hrs. The solution was then diluted with ammonium hydroxide (50 mL) and DCM (100 mL) and the phases were stirred vigorously for 1.5 hrs. The combined phases were filtered through Celite© and the filtrate was transferred to a separating funnel. The phases were mixed and separated and the aqueous phase was extracted with DCM (50 mL). The combined organic extracts were washed with brine (50 mL), dried and evaporated to yield an oil (1.0 g). The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (1:3) to yield two products. The first product to elute was sulfone **10** (0.34 g, 32 %) as a colourless oil. The second product to elute was sulfone **11** (0.50 g, 48 %) as a colourless oil.

4.5 (1*S*,2*R*,4*R*)-1-({[(1'*E*)-3'-Benzyloxyprop-1'-enyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 10.

$[\alpha]_D$ = −23.7 (*c* 0.7, MeOH, 25 °C). IR ν_{max} (L) 3517 (O–H), 2954, 2879, 1640 (C=C), 1601 (Ar C–C), 1495, 1454, 1389, 1307 (SO_2), 1123 (SO_2), 1075, 1027, 949, 880, 825, 737, 698 cm^{-1}. ^1H NMR ($CDCl_3$): 0.82 (s, 3H, 7-CH_3), 1.08 (s, 3H, 7-CH_3), 1.13–1.18 (m, 1H), 1.55–1.63 (m, 1H), 1.68–1.84 (m, 5H), 2.86 (d, ^2J = 13.5, 1H, CH_2SO_2), 3.41 (d, ^2J = 13.5, 1H, CH_2SO_2), 4.18 (dd, ^3J = 8.0, 4.0, 1H, 2-C*H*), 4.27 (dd, ^3J = 3.0, ^4J = 2.0, 2H, 3'-CH_2), 4.62 (s, 2H, benzyl CH_2), 6.75 (dt, ^3J = 15.0, ^4J = 2.0, 1H, 1'-C*H*), 6.98 (dt, ^3J = 15.0, 3.0, 1H, 2'-C*H*), 7.28–7.43 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$): 19.3 (7-*C*H_3), 20.0 (7-*C*H_3), 27.0 (C-5), 30.2 (C-6), 38.5 (C-3), 43.6 (C-4), 48.6 (C-7), 50.3 (C-1), 53.7 (*C*H_2SO_2), 67.0 (C-3'), 72.8 (benzyl *C*H_2), 75.8 (C-2), 127.2 (Ar C-3), 127.6 (Ar C-4), 128.1 (Ar C-2), 128.9 (C-1'), 136.6 (Ar C-1), 143.8 (C-2'). HRMS (EI, MeOH) *m*/*z* calcd for $C_{20}H_{28}O_4S$ $[M + Na]^+$: 387.1605; found: 387.1606.

4.6 (1*S*,2*R*,4*R*)-1-({[3'-Benzyloxypropyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 11.

$[\alpha]_D$ = −20.0 (*c* 0.13, MeOH, 25 °C). IR ν_{max} (L) 3512 (O–H), 2954, 2878, 1602 (Ar C–C), 1454, 1370, 1307 (SO_2), 1124 (SO_2), 1075, 1027, 879, 830, 738, 698 cm^{-1}. ^1H NMR ($CDCl_3$): 0.83 (s, 3H, 7-CH_3), 1.08 (s, 3H, 7-CH_3), 1.13–1.18 (m, 1H), 1.57–1.62 (m, 1H), 1.70–1.87 (m, 1H), 2.14–2.21 (m, 2H, 2'-CH_2), 2.85 (d, ^2J = 13.5, 1H, CH_2SO_2), 3.19 (app dd, ^3J = 7.5, 6.0, 2H, 1'-CH_2), 3.40 (d, ^2J = 13.5, 1H, CH_2SO_2), 3.62 (t, ^3J = 6.0, 2H, 3'-CH_2), 4.16 (dd, ^3J = 8.5, 4.0, 1H, 2-C*H*), 4.53 (s, 2H, benzyl CH_2), 7.31–7.39 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$): 19.4 (7-*C*H_3), 20.1 (7-*C*H_3), 22.3 (C-2'), 27.0 (C-5), 30.0 (C-6), 38.5 (C-3), 43.6 (C-4), 48.6 (C-7), 50.0 (C-1), 51.2 (C-1'), 52.0 (*C*H_2SO_2), 67.3 (C-3'), 72.6 (benzyl *C*H_2), 75.7 (C-2), 127.2 (Ar C-3), 127.4 (Ar C-4), 128.0 (Ar C-2), 137.3 (Ar C-1). HRMS (EI, MeOH) *m*/*z* calcd for $C_{20}H_{30}O_4S$ $[M + Na]^+$: 389.1762; found: 389.1743.

4.7 Meth-Cohn Epoxidation of Vinyl Sulfones 7, 9 and 10: General Procedure.

n-Butyllithium (2.4 mL, 2.5 M, 6.0 mmol for sulfone **7**, 3.8 mL, 2.5 M, 9.5 mmol for sulfone **9**, 0.46 mL, 2.5 M, 1.1 mmol for sulfone **10**) was added dropwise via syringe to a solution of *tert*-butyl hydroperoxide (5.0 mL, 1.17 M in benzene, 6.0 mmol for sulfone **7**, 8.0 mL, 1.17 M in benzene, 9.5 mmol for sulfone **9**, 0.98 mL, 1.17 M in benzene, 1.1 mmol for sulfone **10**) in dry THF (6 mL for sulfone **7**, 7 mL for sulfone **9**, 4 mL for sulfone **10**) at −78 °C under an atmosphere of nitrogen. The solution was allowed to warm to −20 °C and a solution of sulfone **7**, **9** or **10** (0.55 g, 2.0 mmol for sulfone **7**, 1.15 g, 3.1 mmol for sulfone **9**, 0.21 g, 0.55 mmol for sulfone **10**) in dry THF (8 mL for sulfone **7**, 14 mL for sulfone **9**, 4 mL for sulfone **10**) was added dropwise via syringe. The solution was stirred at −20 °C for 2 hrs (for sulfone **7**), −20 °C for 2.5 hrs (for sulfone **9**) or −20 °C for 4 h and then the solution was allowed to warm to room temperature and stirring was continued for an additional 46 hrs (for sulfone **10**). The solution was then allowed to warm to room temperature, quenched with satd. aq. sodium sulfite (50 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate and evaporated to yield the crude sulfonyloxiranes **12**, **13** or **15** as colourless oils whose diastereomer ratios were determined by ^1H NMR spectroscopy. In some cases the crude products were purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (1:2) to afford the pure sulfonyloxiranes **12**, **13** or **15** as colourless oils.

4.8 (1*S*,4*R*)-1-({[3'-(Hydroxymethyl)oxiran-2'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 12.

Obtained during the nucleophilic epoxidation of vinyl sulfone **7** as a colourless oil (0.09 g, 15 %, 4.7:1 dr). IR ν_{max} (L) 3504 (O–H), 2960, 1739 (C=O), 1454, 1394, 1320 (SO_2), 1274, 1216, 1137 (SO_2), 1054, 916, 881, 826, 734, 678 cm^{-1}. Major diastereomer: ^1H NMR ($CDCl_3$): 0.90 (s, 3H, 7-CH_3), 1.04 (s, 3H, 7-CH_3), 1.46–1.52 (m, 1H), 1.90–2.01 (m, 1H), 1.96 (d, ^2J = 18.5, 1H, 3-CH_2 *endo*), 2.02–2.10 (m, 1H), 2.16 (t, ^3J = 4.0, 1H, 4-C*H*), 2.24–2.31 (m, 1H), 2.41 (dt, ^2J = 18.5, ^3J = 4.0, 1H, 3-CH_2 *exo*), 2.88 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.53 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.78–3.80 (m, 1H, 3'-C*H*), 3.87 (dd, ^2J = 13.5, ^3J = 3.0, 1H, CH_2OH), 4.05 (dd, ^2J = 13.5, ^3J = 2.0, 1H, CH_2OH), 4.68 (d, ^3J = 1.5, 1H, 2'-C*H*). ^{13}C NMR ($CDCl_3$): 19.0 (7-*C*H_3), 19.3 (7-*C*H_3), 25.3 (C-5), 26.6 (C-6), 42.1 (C-4), 42.1 (C-3), 48.4 (C-7), 49.4 (*C*H_2SO_2), 56.9 (C-3'), 58.5 (*C*H_2OH), 58.6 (C-1), 65.2 (C-2'), 215.0 (C-2). Minor diastereomer: ^1H NMR ($CDCl_3$): 0.89 (s, 3H, 7-CH_3), 1.07 (s, 3H, 7-CH_3), 1.46–1.52 (m, 1H), 1.75–1.82 (m, 1H), 1.90–2.01 (m, 1H), 1.96 (d, ^2J = 18.5, 1H, 3-CH_2 *endo*), 2.02–2.10 (m, 1H), 2.16 (t, ^3J = 4.0, 1H, 4-C*H*), 2.41 (dt, ^2J = 18.5, ^3J = 4.0, 1H, 3-CH_2 *exo*), 2.92 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.53 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.73–3.75 (m, 1H, 3'-C*H*), 3.87 (dd, ^2J = 13.5, ^3J = 3.0, 1H, CH_2OH), 4.05 (dd, ^2J = 13.5, ^3J = 2.0, 1H, CH_2OH), 4.53 (d, ^3J = 1.5, 1H, 2'-C*H*). ^{13}C NMR ($CDCl_3$): not observed. HRMS (EI, MeOH) *m*/*z* calcd for $C_{13}H_{20}O_5S$ $[M + Na]^+$: 311.0917; found: 311.0928.

4.9 (1*S*,4*R*)-1,1'-[1',4'-Dioxane-2',5'-diylbis(methylenesulfonylmethylene)]bis(7,7-dimethylbicyclo[2.2.1]heptan-2-one) 14.

Obtained as a side-product during the nucleophilic epoxidation of vinyl sulfone **7** as a white solid (0.15 g, 27 %, 1:1 dr). Compound **14** precipitated from the crude product on addition of the chromatography solvent system and was collected by filtration. Mp 211 °C (ether). IR ν_{max} (N) 2919, 1728 (C=O), 1458, 1376, 1306 (SO_2), 1120 (SO_2), 1053, 1020, 921, 790, 723, 663 cm^{-1}. Both diastereomers: ^1H NMR ($CDCl_3$): 0.90 (s, 12H, 7-CH_3), 1.06 (s, 6H, 7-CH_3), 1.09 (s, 6H, 7-CH_3), 1.45–1.51 (m, 4H), 1.77–1.84 (m, 2H), 1.90–1.97 (m, 2H), 1.95 (d, ^2J = 18.0, 2H, 3-CH_2 *endo*), 1.96 (d, ^2J = 18.5, 2H, 3-CH_2 *endo*), 2.03–2.11 (m, 4H), 2.13–2.16 (m, 4H, 4-C*H*), 2.29–2.48 (m, 8H), 2.89 (d, ^2J = 15.0, 2H, 1-CH_2SO_2), 2.96 (dd, ^2J = 14.5, ^3J = 4.0, 2H, 2' and 5'-CH_2SO_2), 2.97 (d, ^2J = 15.0, 2H, 1-CH_2SO_2), 3.11 (dd, ^2J = 14.5, ^3J = 4.0, 2H, 2' and 5'-CH_2SO_2), 3.29 (dd, ^2J = 14.5, ^3J = 7.5, 2H, 2' and 5'-CH_2SO_2), 3.58 (app t, ^2J = 11.5, ^3J = 11.5, 4H, 3' and 6'-CH_2 *axial*), 3.64 (d, ^2J = 15.0, 4H, 1-CH_2SO_2), 3.76 (dd, ^2J = 14.5, ^3J = 9.0, 2H, 2' and 5'-CH_2SO_2), 3.91 (dd, ^2J = 11.5, ^3J = 2.5, 2H, 3' and 6'-CH_2 *equatorial*), 3.96 (dd, ^2J = 11.5, ^3J = 2.5, 2H, 3' and 6'-CH_2 *equatorial*), 4.18–4.23 (m, 2H, 2' and 5'-C*H axial*), 4.23–4.29 (m, 2H, 2' and 5'-C*H axial*). ^{13}C NMR ($CDCl_3$): 19.2 (7-*C*H_3), 19.3 (7-*C*H_3), 19.3 (7-*C*H_3), 19.3 (7-*C*H_3), 24.5 (C-5), 25.2 (C-5), 26.6 (C-6), 26.7 (C-6), 42.0 (C-4), 42.1 (C-4), 42.1 (C-3), 42.2 (C-3), 48.0 (C-7), 48.2 (C-7), 51.6 (1-*C*H_2SO_2), 52.8 (1-*C*H_2SO_2), 56.4 (2' and 5'-*C*H_2SO_2), 56.4 (2' and 5'-*C*H_2SO_2), 58.3 (C-1), 58.8 (C-1), 69.1 (C-3' and C-6'), 69.1 (C-3' and C-6'), 69.2 (C-2' and C-5'), 69.7 (C-2' and C-5'), 214.6 (C-2), 214.6 (C-2). HRMS (EI, MeOH) *m*/*z* calcd for $C_{26}H_{40}O_8S_2$ $[M + Na]^+$: 567.2061; found: 567.2039.

4.10 (1*S*,4*R*)-1-({[3'-(Benzyloxymethyl)oxiran-2'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one 13.

Obtained during the nucleophilic epoxidation of vinyl sulfone **9** as a colourless oil (0.55 g, 45 %, 5.8:1 dr). IR ν_{max} (L) 3029, 2959, 1744 (C=O), 1601 (Ar C–C), 1454, 1393, 1323 (SO_2), 1273, 1216, 1139 (SO_2), 1051, 965, 917, 825, 741, 699 cm^{-1}. Major diastereomer: ^{1}H NMR ($CDCl_3$): 0.91 (s, 3H, 7-CH_3), 1.09 (s, 3H, 7-CH_3), 1.46–1.52 (m, 1H), 1.78–1.85 (m, 1H), 2.00 (d, ^2J = 18.5, 1H, 3-CH_2 *endo*), 2.04–2.11 (m, 1H), 2.16 (t, ^3J = 4.5, 1H, 4-C*H*), 2.33–2.44 (m, 2H), 2.92 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.55 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.67 (dd, ^2J = 12.0, ^3J = 4.5, 1H, CH_2OCH$_2$Ph), 3.80 (app qu, ^3J = 2.0, 1H, 3'-C*H*), 3.93 (dd, ^2J = 12.0, ^3J = 2.0, 1H, CH_2OCH$_2$Ph), 4.49 (d, ^3J = 1.5, 1H, 2'-C*H*), 4.58 (s, 2H, CH$_2$OCH_2Ph), 7.28–7.40 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$): 19.1 (7-*C*H$_3$), 19.2 (7-*C*H$_3$), 24.6 (C-5), 26.5 (C-6), 42.0 (C-3), 42.1 (C-4), 48.0 (C-7), 49.8 (*C*H$_2$SO$_2$), 54.6 (C-3'), 57.9 (C-1), 64.6 (C-2'), 66.2 (*C*H$_2$OCH$_2$Ph), 73.0 (CH$_2$O*C*H$_2$Ph), 127.3 (Ar C-3), 127.5 (Ar C-4), 128.0 (Ar C-2), 136.7 (Ar C-1), 214.4 (C-2). Minor diastereomer: ^{1}H NMR ($CDCl_3$): 0.91 (s, 3H, 7-CH_3), 1.05 (s, 3H, 7-CH_3), 1.34–1.52 (m, 2H), 1.96 (d, ^2J = 18.5, 1H, 3-CH_2 *endo*), 2.00–2.11 (m, 1H), 2.15 (t, ^3J = 4.5, 1H, 4-C*H*), 2.24–2.31 (m, 1H), 2.36–2.45 (m, 1H), 2.89 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.53 (d, ^2J = 15.0, 1H, CH_2SO_2), 3.65 (dd, ^2J = 12.0, ^3J = 4.5, 1H, CH_2OCH$_2$Ph), 3.85 (app qu, ^3J = 2.0, 1H, 3'-C*H*), 3.92 (dd, ^2J = 12.0, ^3J = 2.0, 1H, CH_2OCH$_2$Ph), 4.59 (s, 2H, CH$_2$OCH_2Ph), 4.66 (d, ^3J = 2.0, 1H, 2'-C*H*), 7.29–7.39 (m, 5H, Ar*H*). ^{13}C NMR ($CDCl_3$): 19.1 (7-*C*H$_3$), 19.3 (7-*C*H$_3$), 25.4 (C-5), 26.6 (C-6), 42.1 (C-3), 42.1 (C-4), 48.3 (C-7), 49.4 (*C*H$_2$SO$_2$), 55.7 (C-3'), 58.6 (C-1), 65.3 (C-2'), 66.2 (*C*H$_2$OCH$_2$Ph), 73.0 (CH$_2$O*C*H$_2$Ph), 127.3 (Ar C-3), 127.5 (Ar C-4), 128.0 (Ar C-2), 136.7 (Ar C-1), 214.4 (C-2). HRMS (EI, MeOH) *m*/*z* calcd for $C_{20}H_{26}O_5S$ [M + Na]$^+$: 401.1398; found: 401.1401.

4.11 (1*S*,2*R*,4*R*)-1-({[3'-(Benzyloxymethyl)oxiran-2'-yl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol 15.

Obtained during the nucleophilic epoxidation of vinyl sulfone **10** as a colourless oil (0.21 g, 95 %, 1:1 dr). IR ν_{max} (L) 3537 (O–H), 2955, 2880, 1601 (Ar C–C), 1455, 1390, 1372, 1318 (SO_2), 1251, 1134 (SO_2), 1075, 1026, 916, 878, 739, 699 cm^{-1}. Both diastereomers: ^{1}H NMR ($CDCl_3$): 0.86 (s, 3H, 7-CH_3), 0.87 (s, 3H, 7-CH_3), 1.09 (s, 3H, 7-CH_3), 1.10 (s, 3H, 7-CH_3), 1.14–1.19 (m, 2H), 1.54–1.61 (m, 2H), 1.75–1.88 (m, 10H), 2.98 (d, ^2J = 13.5, 1H, CH_2SO_2), 3.04 (d, ^2J = 13.5, 1H, CH_2SO_2), 3.50 (d, ^2J = 13.5, 1H, CH_2SO_2), 3.56 (d, ^2J = 13.5, 1H, CH_2SO_2), 3.74 (app dt, ^2J = 12.0, ^3J = 3.5, 2H, CH_2OCH$_2$Ph), 3.84–3.87 (m, 2H, 3'-C*H*), 3.93 (d, ^2J = 12.0, 2H, CH_2OCH$_2$Ph), 4.15 (dd, ^3J = 8.5, 4.0, 2H, 2-C*H*), 4.27 (s, 2H, 2'-C*H*), 4.58 (s, 4H, CH$_2$OCH_2Ph), 7.32–7.40 (m, 10H, Ar*H*). ^{13}C NMR ($CDCl_3$): 19.4 (7-*C*H$_3$), 19.4 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 20.0 (7-*C*H$_3$), 27.0 (C-5), 27.0 (C-5), 30.0 (C-6), 30.0 (C-6), 38.7 (C-3), 38.7 (C-3), 43.6 (C-4), 43.6 (C-4), 48.7 (C-7), 48.7 (C-7), 49.8 (C-1), 50.0 (C-1), 50.2 (*C*H$_2$SO$_2$), 50.4 (*C*H$_2$SO$_2$), 54.8 (C-3'), 55.3 (C-3'), 64.0 (C-2'), 64.1 (C-2'), 65.4 (*C*H$_2$OCH$_2$Ph), 65.4 (*C*H$_2$OCH$_2$Ph), 73.1 (CH$_2$O*C*H$_2$Ph), 73.1 (CH$_2$O*C*H$_2$Ph), 75.7 (C-2), 75.8 (C-2), 127.3 (Ar C-3), 127.3 (Ar C-3), 127.6 (Ar C-4), 127.6 (Ar C-4), 128.1 (Ar C-2), 128.1 (Ar C-2), 136.5 (Ar C-1), 136.6 (Ar C-1). HRMS (EI, MeOH) *m*/*z* calcd for $C_{20}H_{28}O_5S$ [M + Na]$^+$: 403.1554; found: 403.1550.

Acknowledgments

The authors gratefully acknowledge Dr. John E. O'Brien and Dr. Manuel Reuther for obtaining NMR spectra and Dr. Martin Feeney for obtaining mass spectra. One of us (F. W. L.) received financial support from Trinity College Dublin.

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