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Efficient Synthesis of Bicyclo[2.2.1]heptane Derivatives *Via* Stereoselective Intramolecular Michael Reactions of Vinyl Sulfones

Mark A. Collins*[1] and D. Neville Jones

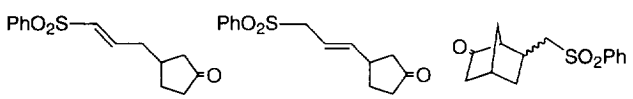
Department of Chemistry, The University, Sheffield, S3 7HF, UK.

Abstract: Efficient synthesis of 6-*endo*-methyl substituted bicyclo[2.2.1]heptane derivatives formed *via* completely diastereoselective intramolecular Michael addition reactions of vinyl sulfones, derived from allyl sulfones and cyclopentenones, are described.

Background

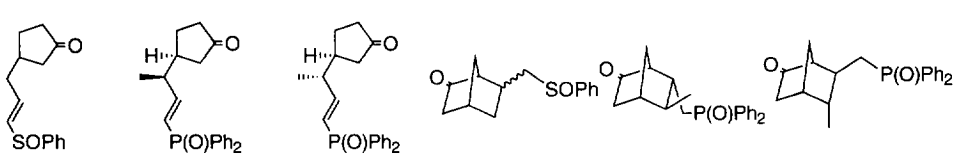
Allyl[2] and vinyl[3] sulfones are versatile synthetic intermediates. Highly stereoselective formation of chiral centres located α- and γ- to the sulfone group[4] is a feature of Michael additions of allyl sulfones to cyclic enones, and has been exploited in this laboratory as a key feature in a stereoselective synthesis of estradiol,[5] and in formal syntheses of pseudoguaianolides.[6] We now report on the completely diastereoselective formation of chiral centres located β- to the sulfone group during intramolecular Michael reactions of vinyl sulfones arising from γ-1,4-addition of allyl sulfones to cyclopentenones.[4,7,8]

Pivnittski[9] reported that treatment of the vinyl sulfone **1** with potassium t-butoxide produced a mixture of the β,γ-unsaturated sulfone **2** and the bicyclo[2.2.1]heptan-2-ones **3**. The action of a weaker base, 1,5-diazabicyclo[4.3.0]non-5-ene (DBU), led exclusively to the β,γ-unsaturated sulfone **2**. Allyl and vinyl sulfones exist in equilibrium under basic conditions, and the allyl sulfones usually predominate.[10]



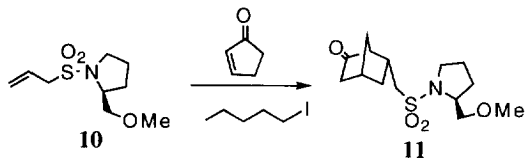
1 **2** **3**

Haynes[11] reported that treatment of the vinyl sulfoxide **4** and vinyl phosphine oxides **5** and **6** with potassium t-butoxide resulted in the diastereoselective formation of intramolecular Michael addition products **7**, **8** and **9** respectively. The sulfoxides **7** were obtained as an inseparable mixture (80:20) of diastereoisomers, while **5** gave only **8** and **6** gave only **9**.



4 **5** **6** **7** **8** **9**

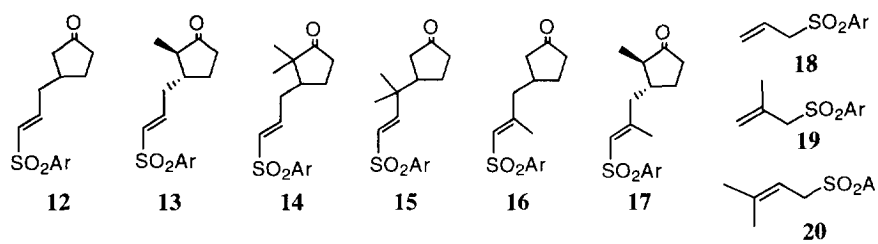
Our interest in these intramolecular conjugate addition reactions began when the attempted three component coupling[6] of the lithio anion of sulfonamide **10** (generated with butyllithium in THF at -78 °C), cyclopentenone and iodopentane produced only the 6-*endo*-substituted bicyclo[2.2.1]heptan-2-one **11**, in 61% yield as a single diastereoisomer (Scheme 1). We decided to investigate the scope and limitations of intramolecular Michael addition reactions of vinyl sulfones derived from allyl sulfones, rather than synthetically more limited sulfonamides, as a means for efficient and stereoselective construction of bicyclo[2.2.1]heptane derivatives.



Scheme 1. Attempted Three Component Coupling Reaction With Allyl Sulfonamide.

Results and Discussion

The γ-1,4 addition products **12** - **17** (Ar= 4-methylphenyl) were prepared from the allyl sulfones **18** - **20** and either cyclopentenone or 2-methylcyclopentenone according to literature procedures for γ-1,4 addition of allyl sulfones to cyclic enones.[4,7,12] Formation of **14** required trapping the intermediate enolate anion with iodomethane, and vinyl sulfones **13** and **17** were isolated as single diastereoisomers.[13]



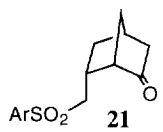
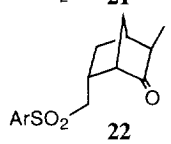
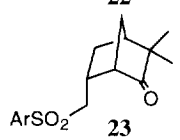
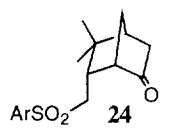
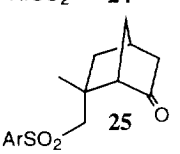
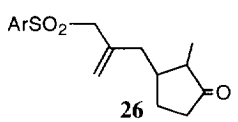
Ar= 4-Methylphenyl

During three component coupling procedures, one-step formation of bicyclic compounds from the sulfone **18** occasionally occurred. This happened in high yield, both with (i.e. **23** from **18**, 83%),[14] and without trapping (Scheme 1) of the electrophile. We were unable to translate this capricious reaction into a useful procedure. The cyclization may be promoted by the presence of lithium halide in the reaction mixture as these are known to change the nature of enolate aggregates in solution. Seebach has noted that LiX additives not part of the stoichiometric equation may decisively change the properties of an enolate.[15] This mode of cyclization may be avoided by changing from a lithio to a tin enolate before addition of the electrophile.[6]

Treatment of the isolated γ-1,4 addition products **12** - **15** with lithium hydroxide in boiling THF for between 16 and 24 hours proceeded cleanly to provide the bicyclic compounds **21** - **24** in excellent yields (Table 1). In contrast, cyclization of the 2'-methyl substituted γ-1,4 addition products **16** and **17** did not proceed smoothly. Treatment of **17** with lithium hydroxide in boiling THF for two days led to formation of the isomeric allylic sulfone **26** in quantitative yield.[10] NMR analysis of the reaction mixture when **16** was treated with lithium hydroxide in boiling THF for 36 hours revealed that the singlet at δ6.20 due to the vinylic proton was diminished, and that singlets (corresponding to the methylene protons of the allyl sulfone isomer of **16**)

were appearing at δ5.05 and δ4.80, while doublets were also appearing at δ2.85 and δ3.15 (α-sulfonyl protons of the bicyclic compound **25**). After 5 days the singlet at δ6.20 had further diminished while the vinylic resonances at δ5.05 and δ4.80 had intensified, as had the doublets at δ2.85 and δ3.15. The bicyclic compound **25** (18%) was crystallized from the crude reaction mixture. The bicyclic compounds **11** and **21** - **25** all formed as single diastereoisomers. The configuration at C-6 was deduced by NMR spectroscopy[16] and unambiguously confirmed by X-ray crystallographic analysis of **24** (Figure 1).

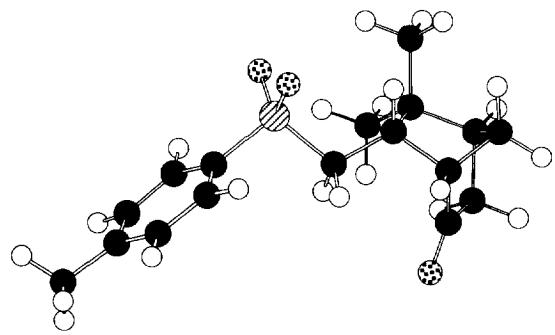
Table 1. Results of Subjecting The γ-1,4 Addition Products to LiOH in Boiling THF.

Sulfone	Product	Yield
12	 **21**	97%
13	 **22**	97%
14	 **23**	95%
15	 **24**	96%
16	 **25**	18%
17	 **26**	100%

Treatment of γ-1,4 addition product **12** with potassium t-butoxide in THF for 2 days gave rise to a mixture of two diastereoisomeric bicyclic products (in the ratio *c.a.* 1:1), thus confirming that stereoselective formation of only the 6-*endo*-methylsulfonyl diastereoisomer is due to the presence of lithium ion. Coordination between the lithium cation, the enolate oxygen and the sulfonyl oxygens holds the enolate in a conformation in which the

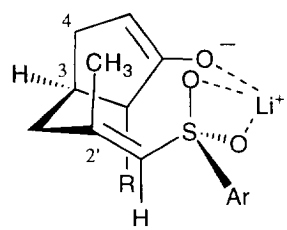
sulfonyl group is located on the opposite face of the newly formed ring to C-4 of the cyclopentanone ring. With potassium ion no chelation occurs and a mixture of diastereoisomers is the result. The failure of vinyl sulfones **16** and **17** to cyclize smoothly is the result of unfavourable 1,3-diaxial interactions between the C(3)-C(4) bond and the methyl group at C-2' which prevents attainment of the conformation required for cyclization (Figure 2).[17]

Figure 1. X-Ray Crystal Structure of **24**.



After reduction[18] of the bicyclic ketones **21** - **24** with sodium borohydride, or in the case of the 3,3-dimethyl compound **23** with lithium aluminium hydride, to give the *endo*-alcohols **27** - **29**,[19] desulfonylation was accomplished with 6% sodium amalgam[20] to produce the bicyclic compounds **31** - **34**, all of which possessed the characteristic odour of camphor (Table 2).

Figure 2. Conformation of The Intermediate Enolate Anion.

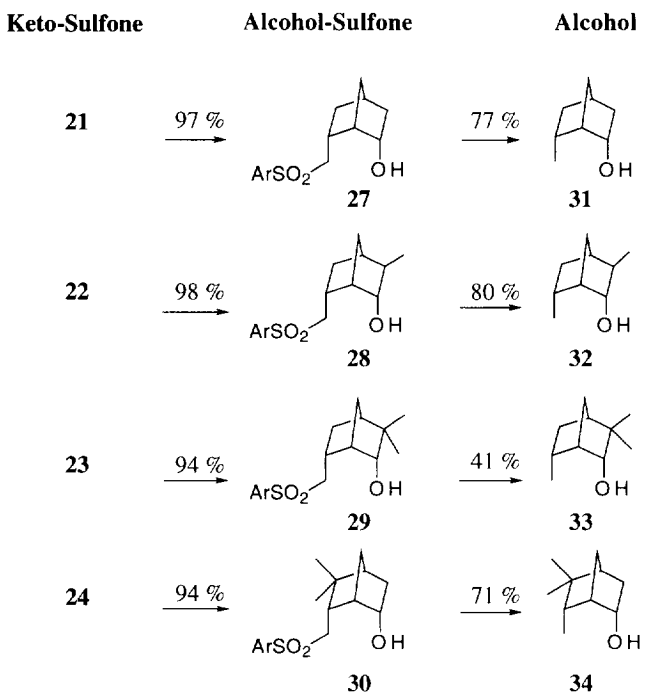


16: R= H
17: R= Me

Conclusion

We have established methodology for the stereoselective construction of 6-*endo*-methylsulfonyl substituted bicyclo[2.21]heptan-2-ones in high yield, and have demonstrated that these compounds may be smoothly desulfonylated if first reduced to alcohols.

Table 2. Reduction and Desulfonylation of the Bicyclo[2.2.1]heptan-2-ones.



Experimental

All melting points were determined with a Kofler hot-stage apparatus and are uncorrected, recrystallization solvent (if any) in parentheses. Chemical shifts for NMR spectra are quoted in ppm downfield from internal tetramethylsilane, and the line separations are expressed in Hertz. The following abbreviations are used to describe NMR signals: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. ^{1}H NMR spectra were recorded on either a Bruker AM-250 or a Bruker WH-400 spectrometer operating at 250 and 400 MHz respectively. Mass spectra were obtained on a Kratos MS-25 instrument, operating in either chemical ionization (CI) or electron impact (EI) mode. Microanalytical data were obtained on a Perkin-Elmer 2400 CHN elemental analyzer. Infra-red spectra were obtained on Perkin-Elmer 684 or 157G instruments, state as specified. Yields are for material assessed as homogenous by TLC and ^{1}H NMR. Thin layer chromatography (TLC) was performed on Merck 0.2 mm aluminium-backed silica plates and visualized using UV light or developed using cerium (IV) sulfate spray. Flash column chromatography[21] was performed using Merck silica gel 60 (230-400 mesh). Petroleum ether (40-60) and ethyl acetate were distilled prior to use. Evaporation refers to the removal of solvent under reduced pressure. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride prior to use.

6-*endo*-Methyl-((*S*)-(2-methoxymethylpyrrolidinyl)sulfonylbicyclo[2.2.1]heptan-2-one (11)

The allyl sulfonamide **10** (0.95 g, 4.32 mmol) was dissolved in dry THF (20 ml) and cooled to -78 ℃ under argon. Following addition of n-butyllithium (2.5 M, 1.0 eq, 1.73 ml) the solution was allowed to stand

for 15 min and then treated with cyclopentenone (1.05 eq, 0.38 ml, 4.54 mmol). After 1h 1-iodopentane (5 eq, 2.82 ml, 0.02 mol) was added. The solution was left for 1 h at -78 °C and then allowed to reach room temperature and stir for 16 h. Saturated aqueous ammonium chloride solution (10 ml) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 15 ml) and the combined organic layers were washed with brine (60 ml) and dried over magnesium sulfate. Evaporation left a residue which was purified by flash column chromatography on silica eluting with 30% ethyl acetate / light petroleum to give the product **11** (0.58 g, 61%) as a yellow oil. (Found C, 55.5; H, 7.65; N, 4.3; $(M+NH_4)^+$ 319. $C_{14}H_{23}O_4NS$ requires C, 55.8; H, 7.7; N, 4.65; $(M+NH_4)^+$ 319). ν_{max} ($CHCl_3$ solution) 1745 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.95(1H, m), 3.55-3.30(3H, m), 3.35(3H, m), 3.20(1H, m), rest of spectrum complex.

3-(3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (12)

The sulfone **18** (2.83 g, 14.5 mmol) in dry THF (50 ml) at -78 °C under argon was treated with n-butyllithium (1.01 eq, 2.5 M, 5.79 ml). After 15 min, cyclopentenone (1.2 eq, 1.46 ml, 17.3 mmol) was added, followed 5 min later by chlorotrimethylsilane (3 eq, 5.5 ml, 43.4 mmol). The solution was removed from the cooling bath, allowed to reach room temperature over 1 h, and saturated aqueous ammonium chloride solution (50 ml) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 50 ml). The combined organic layers were washed with brine (150 ml) and dried over magnesium sulfate. Evaporation left a residue which was purified by flash column chromatography on silica eluting with 45% ethyl acetate / light petroleum to give the product **12** (2.06 g, 62%) as a clear oil. (Found C, 64.75; H, 6.8; S, 11.5; M^+ 278. $C_{15}H_{18}O_3S$ requires C, 64.7; H, 6.5; S, 11.5; M^+ 278). ν_{max} (CH_2Cl_2 solution) 1740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75(2H, d, J=8Hz), 7.35(2H, d, J=8Hz), 6.93(1H, dt, J=15, 8Hz), 6.37(1H, dd, J=15, 1.5Hz), 2.45(3H, s), 2.44-2.10(7H, m), 1.83(1H, m), 1.56(1H, m).

2-Methyl-3-(3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (13)

Following the typical procedure (above), from the sulfone **18** (1.99 g, 10.1 mmol), cyclopentenone (1.2 eq, 1.02 ml, 12.2 mmol) and chlorotrimethylsilane (3 eq, 3.86 ml, 30.4 mmol), the product **13** was isolated (2.14 g, 72%) as a clear oil. (Found C, 65.55; H, 6.9; S, 11.2; M^+ 292. $C_{16}H_{20}O_3S$ requires C, 65.7; H, 6.9; S, 11.0; M^+ 292). ν_{max} (CH_2Cl_2 solution) 1740 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.86(2H, d, J=8Hz), 6.83(2H, d, J=8Hz), 6.79(1H, d, J=15Hz), 6.07(1H, dt, J=15, 1.5Hz), 1.88(3H, s), 1.92-1.76(2H, m), 1.58(1H, ddd, J=18.5, 11, 9Hz), 1.39-0.97(3H, m), 1.09(1H, ddd, J=11, 7 , 1Hz), 0.83(3H, d, J=7Hz), 0.63(1H, m).

2,2-Dimethyl-3-(3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (14)

Following the typical procedure (above), from the sulfone **18** (0.86 g, 4.36 mmol), 2-methylcyclopentenone (1.05 eq, 0.45 ml, 4.58 mmol) and iodomethane (10 eq, 2.72 ml, 43.6 mmol), the product **14** was isolated (0.49 g, 46%), mp 73-74 °C (ethanol). (Found C, 66.5; H, 7.3; S, 10.8; $(M+NH_4)^+$ 324. $C_{17}H_{22}O_3S$ requires C, 66.6; H, 7.2; S, 10.5; $(M+NH_4)^+$ 324). ν_{max} (CH_2Cl_2 solution) 1737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37(2H, d, J=8Hz), 7.79(2H, d, J=8Hz), 6.99(1H, dt, J=15, 8.5Hz), 6.42(1H, dd, J=15, 1.5Hz), 2.47(3H, s), 2.48-1.50(7H, m), 1.05(3H, s), 0.75(3H, s).

3-(1',1'-Dimethyl-3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (15)

Following the typical procedure (above), from the sulfone **20** (3.95 g, 17.6 mmol) and cyclopentenone (1.0 eq, 1.48 ml, 17.6 mmol), the product **15** was isolated (2.03 g, 32%, 52% conversion of reacted starting sulfone) as a white solid, mp 104-8 °C (ethyl acetate / light petroleum). (Found C, 66.65; H, 7.2; S, 10.3; M^+ 306. $C_{17}H_{22}O_3S$ requires C, 66.6; H, 7.2; S, 10.4; M^+ 306). ν_{max} (CH_2Cl_2 solution) 1741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.75(2H, d, J=8Hz), 7.34(2H, d, J=8Hz), 6.95(1H, d, J=15Hz), 6.35(1H, d, J=15Hz), 2.43(3H, s), 2.40-1.50(7H, m), 1.10(6H, bs).

3-(2'-Methyl-3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (16)

Following the typical procedure (above), from the sulfone **19** (0.66 g, 3.15 mmol), cyclopentenone (1.2 eq, 0.32 ml, 3.78 mmol) and chlorotrimethylsilane (3 eq, 1.58 ml, 9.46 mmol), the product **16** was isolated (0.29 g, 32%, 49% conversion of reacted starting sulfone), as a colourless oil. (Found C, 65.5; H, 6.9; S, 11.1; M^+ 292. $C_{16}H_{20}O_3S$ requires C, 65.7; H, 6.9; S, 11.0; M^+ 292). ν_{max} (CH_2Cl_2 solution) 1740 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.78(2H, d, J=8Hz), 7.34(2H, d, J=8Hz), 6.20(1H, q, J=1.5Hz), 2.44(3H, s), 2.15(3H, s), 2.50-1.4(9H, m).

2-Methyl-3-(2'-methyl-3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (17)

Following the typical procedure (above), from the sulfone **19** (1.01 g, 4.81 mmol), 2-methylcyclopentenone (1.1 eq, 0.52 ml, 5.3 mmol) and chlorotrimethylsilane (3 eq, 2.41 ml, 14.4 mmol), the product **17** was isolated (43%, 57% conversion of reacted starting sulfone), as a white solid, mp 87-89 °C (ethyl acetate / light petroleum). (Found C, 66.6; H, 7.2; S, 10.4; $(M+NH_4)^+$ 324. $C_{17}H_{22}O_3S$ requires C, 66.6; H, 7.2; S, 10.4; $(M+NH_4)^+$ 324). ν_{max} (CH_2Cl_2 solution) 1740 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.80(2H, d, J=8Hz), 7.34(2H, d, J=8Hz), 6.25(1H, q, J=1Hz), 2.46(3H, s), 2.50-2.20(2H, m), 2.16(3H, d, J=1Hz), 2.15-1.65(5H, m), 1.33(1H, m), 1.01(3H, d, J=7Hz).

6-*endo*-Methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (21)

3-(3'-(4-Methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (**12**) (0.19 g, 0.72 mmol) was dissolved in THF (2 ml) and lithium hydroxide.mono hydrate (1.0 eq, 30 mg, 0.72 mmol) was added. The reaction mixture was boiled for 16 h, allowed to cool, and saturated aqueous ammonium chloride solution (5 ml) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 5 ml). The combined organic layers were washed with brine (15 ml) and dried over magnesium sulfate. Evaporation left a residue which was purified by flash column chromatography on silica eluting with 30% ethyl acetate / light petroleum to give the product **21** (0.19 g, 97%) as an oil which crystallized on addition of ethyl acetate, mp 109-11 °C (ethanol). (Found C, 65.0; H, 6.6; S, 11.6; $(M+NH_4)^+$ 296. $C_{15}H_{18}O_3S$ requires C, 64.7; H, 6.5; S, 11.5; $(M+NH_4)^+$ 296). ν_{max} (CH_2Cl_2 solution) 1742 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.54(2H, d, J=8Hz), 6.58(2H, d, J=8Hz), 3.08(1H, dd, J=14, 4.5Hz), 2.70(1H, dd, J=14, 9Hz), 2.55(1H, m), 2.15(1H, m), 1.86(3H, s), 1.87-1.74(2H, m), 1.82(1H, dt, J=17, 4Hz), 1.27(1H, dd, J=17, 4.5Hz), 0.99(1H, dq, J=11, 2.5Hz), 0.90(2H, m).

3-*exo*-Methyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (22)

Following the typical procedure (above), from 2-methyl-3-(3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (**13**) (0.32 g, 1.09 mmol), THF (20 ml), and lithium hydroxide (1.0 eq, 46 mg, 1.09 mmol), was obtained an oil, which after flashing through a short silica column crystallized on addition of ether to give the product **22** (0.31 g, 97%), mp 109-11 °C (ethanol). (Found C, 65.8; H, 7.0; S, 11.2; M^+ 292. $C_{16}H_{20}O_3S$ requires C, 65.7; H, 6.9; S, 11.0; M^+ 292). ν_{max} (CH_2Cl_2 solution) 1740 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.54(2H, d, J=8Hz), 6.58(2H, d, J=8Hz), 3.04(1H, dd, J=14, 4.5Hz), 2.68(1H, dd, J=14, 9.5Hz), 2.53(1H, m), 2.13(1H, m), 1.89(3H, s), 1.85(1H, ddd, J=13, 11, 4.5Hz), 1.60(1H, m), 1.27(1H, bd, J=11Hz), 1.25(1H, ddd, J=10, 7, 3Hz), 0.96(1H, ddd, J=13, 5, 2.5Hz), 0.87(1H, bd, J=11Hz), 0.72(3H, d, J=7Hz).

3,3-Dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (23)

Following the typical procedure (above), from 2,2-dimethyl-3-(3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (**14**) (50 mg, 0.16 mmol), THF (1 ml) and lithium hydroxide (1.0 eq, 7 mg, 0.16 mmol), was obtained an oil which was purified by flashing through a short silica column to give the product **47** (48 mg, 98%) as a clear oil. (Found C, 66.8; H, 7.4; S, 10.2; $(M+NH_4)^+$ 324. $C_{17}H_{22}O_3S$ requires C, 66.6; H, 7.2; S, 10.5; $(M+NH_4)^+$ 324). ν_{max} (CH_2Cl_2 solution) 1737 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.72(2H, d, J=8Hz), 6.75(2H, d, J=8Hz), 3.13(1H, dd, J=14, 5Hz), 2.82(1H, dd, J=14, 10Hz), 2.63(1H, m), 2.17(1H, m), 1.87(3H, s), 1.66(1H, ddd, J=13, 11, 4.5Hz), 1.59(1H, m), 1.51(1H, ddd, J=13, 5, 3Hz), 1.46(1H, ddt, J=11, 4.5, 11Hz), 0.91(1H, dt, J=11, 1.5Hz), 0.77(3H, s), 0.74(3H, s).

5,5-Dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (24)

Following the typical procedure (above), from 3-(1',1'-dimethyl-3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (**15**) (0.14 g, 0.47 mmol), THF (5 ml) and lithium hydroxide (1.0 eq, 22 mg, 0.47 mmol) was obtained an oil which was purified by flash column chromatography on silica eluting with 40% ethyl acetate / light petroleum to give the product **24** (0.14 g, 96%) as an oil which crystallized on addition of ethyl acetate, mp 146 °C (ethyl acetate). (Found C, 66.5; H, 7.15; S, 10.3; $(M+H)^+$ 307. $C_{17}H_{22}O_3S$ requires C, 66.6; H, 7.2; S, 10.5; $(M+H)^+$ 307). ν_{max} (CH_2Cl_2 solution) 1740 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.80(2H, d, J=8Hz), 7.36(2H, d, J=8Hz), 2.97(2H, m), 2.60(1H, m), 2.45(3H, s), 2.41-2.39(1H, m), 2.28-1.88(4H, m), 1.70(1H, dt, J=11, 1.5Hz), 1.23(3H, s), 0.90(3H, s).

6-*exo*-Methyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (25)

Following the typical procedure (above), 3-(2'-methyl-3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (**16**) (0.14 g, 0.5 mmol) was dissolved in THF (10 ml) and lithium hydroxide.mono hydrate (1.0 eq, 22 mg, 0.51 mmol) was added. The reaction mixture was boiled for 5 days, allowed to cool, and saturated aqueous ammonium chloride solution (5 ml) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (30 ml) and dried over magnesium sulfate. Evaporation left a residue from which the product **25** (27 mg, 18%) was obtained as white needles after addition of ethyl acetate, mp 115-8 °C (ethyl acetate). (Found C, 65.7; H, 6.7; S, 10.8; $(M+H)^+$ 293. $C_{16}H_{20}O_3S$ requires C, 65.7; H, 6.9; S, 11.0; $(M+H)^+$ 293). ν_{max} (CH_2Cl_2 solution) 1742 cm^{-1}. ^1H NMR

(250 MHz, $CDCl_3$) δ 7.34(2H, d, J=8Hz), 7.27(2H, d, J=8Hz), 3.15(1H, d, J=14Hz), 2.85(1H, d, J=14Hz), 2.70(1H, m), 2.49(1H, m), 2.44(3H, s), 2.05(2H, m), 1.90-1.65(4H, m), 1.51(3H, s).

2-Methyl-3-(2'-*exo*-methylene-3'-(4-methylphenyl)sulfonylpropyl)cyclopentane (26)

2-Methyl-3-(2'-methyl-3'-(4-methylphenyl)sulfonylprop-2'-enyl)cyclopentanone (**17**) (66 mg, 0.22 mmol) was dissolved in THF (3 ml) and lithium hydroxide.mono hydrate (1.0 eq, 10 mg, 0.22 mmol) was added. The reaction mixture was boiled for 36 h, allowed to cool, and saturated aqueous ammonium chloride solution (5 ml) was added. The layers were separated and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (20 ml) and dried over magnesium sulfate. Evaporation left a residue which was purified by flash column chromatography on silica eluting with 30% ethyl acetate / light petroleum to give the product **26** (66 mg, 100%) as a colourless oil. (Found C, 66.3; H, 7.0; M^+ 306.1290. $C_{17}H_{22}O_3S$ requires C, 66.6; H, 7.2; M^+ 306.1285). ν_{max} (CH_2Cl_2 solution) 1737 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.76(2H, d, J=8Hz), 7.35(2H, d, J=8Hz), 5.12(1H, bs), 4.86(1H, bs), 3.79(2H, m), 2.46(3H, s), 2.62-1.7(8H, m), 1.05(3H, d, J=6.5Hz).

6-*endo*-Methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-ol (27)

6-*endo*-Methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (**21**) (1.42 g, 5.1 mmol) was dissolved in methanol (100 ml) and treated with sodium borohydride (5 eq, 0.96 g, 25.3 mmol). The reaction mixture was stirred 2 h at room temperature and then quenched by the dropwise addition of 2N HCl until no more gas was seen to be evolved. Evaporation left a residue was partitioned between ethyl acetate (30 ml) and water (30 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with brine (60 ml) and dried over magnesium sulfate. Evaporation left a residue which was purified by flash column chromatography on silica eluting with 30% ethyl acetate / light petroleum to give the product **27** (1.37 g, 97%) as an oil. (Found C, 64.0; H, 7.15; S, 11.3; $(M+NH_4)^+$ 298. $C_{15}H_{20}O_3S$ requires C, 64.25; H, 7.2; S, 11.4; $(M+NH_4)^+$ 298). ν_{max} (CH_2Cl_2 solution) 3605 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.75(2H, d, J=8Hz), 6.80(2H, d, J=8Hz), 4.20(1H, m), 4.03(1H, dd, J=14, 8.5Hz), 3.36(1H, dd, J=14, 7Hz), 3.88(1H, bs), 2.53(1H, m), 2.49(1H, m), 1.88(3H, s), 1.90-1.67(3H, m), 1.05-0.95(3H, m), 0.85(1H, ddd, J=12, 6, 2.5Hz).

3-*exo*-Methyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-ol (28)

Following the general procedure (above), from 3-*exo*-methyl-6-*endo*-methyl(4-methylphenyl)-sulfonylbicyclo[2.2.1]heptan-2-one (**22**) (0.88 g, 3.14 mmol), methanol (65 ml) and sodium borohydride (5 eq, 0.57 g, 15.8 mmol) was obtained a yellow oil which was adequately purified by filtration through a short silica bed to give the product **28** (0.86 g, 98%), mp 107-9 °C. (Found C, 64.9; H, 7.4; M^+ 294.1290. $C_{16}H_{22}O_3S$ requires C, 65.3; H, 7.5; M^+ 294.1280). ν_{max} (CH_2Cl_2 solution) 3605 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.75(2H, d, J=8Hz), 6.80(2H, d, J=8Hz), 4.01(1H, dd, J=14, 8Hz), 3.67(1H, m), 3.29(1H, bs), 3.25(1H, dd, J=14, 7Hz), 2.51(1H, m), 2.47(1H, m), 1.89(3H, s), 1.75(1H, dt, J=12, 5Hz), 1.52(1H, m), 1.26(1H, m), 1.22(1H, bd, J=11Hz), 0.94-0.80(2H, m), 0.88(3H, d, J=7Hz).

3,3-Dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-ol (29)

3,3-Dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (**23**) (0.12 g, 0.40 mmol) was dissolved in methanol (10 ml) and treated with sodium borohydride (5 eq, 75 mg, 1.98 mmol). The reaction mixture was stirred 2 days at room temperature and then quenched by the dropwise addition of 2N HCl until no more gas was seen to be evolved. Evaporation left a residue which was partitioned between ethyl acetate (10 ml) and water (10 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine (30 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to leave a residue which was seen by NMR to be a mixture of unreacted starting material and product. The residue was dissolved in dry ether (10 ml) and treated with lithium aluminium hydride (2.0 eq, 30 mg, 0.79 mmol). The reaction mixture was stirred under argon for 16 h and then quenched by cautious addition of wet ether, water and 2N HCl. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine (30 ml) and dried over magnesium sulfate. Evaporation left a residue which was purified by flash column chromatography on silica eluting with 45% ethyl acetate/ light petroleum to give the product **29** (0.12 g, 95%) as a clear oil. (Found C, 66.0; H, 7.9; S, 10.35; $(M+H)^+$ 309. $C_{17}H_{24}O_3S$ requires C, 66.2; H, 7.8; S, 10.4; $(M+H)^+$ 309). ν_{max} (CH_2Cl_2 solution) 3608 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55(2H, d, J=8Hz), 7.35(2H, d, J=8Hz), 4.05(1H, dd, J=14, 10Hz), 3.85(1H, dd, J=4, 1.5Hz), 3.28(1H, dd, J=14, 6.5Hz), 2.65(1H, m), 2.60(1H, m), 2.45(3H, s), 2.37(1H, m), 1.76(1H, m), 1.66(1H, ddt, J=10.5, 3, 1.5Hz), 1.60(1H, m), 1.41(1H, ddd, J=13, 5, 3Hz), 1.18(1H, dt, J=10.5, 1.5Hz), 1.02(3H, s), 0.90(3H, s).

5,5-Dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-ol (30)

Following the general procedure (above), from 5,5-dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-one (**24**) (0.13 g, 0.41 mmol), methanol (10 ml) and sodium borohydride (5 eq, 78 mg, 2.06 mmol) was obtained a residue which was purified by flash column chromatography on silica eluting with 40% ethyl acetate / light petroleum to give the product **30** (0.12 g, 94%) as a clear oil which solidified on standing, mp 141-3 °C (ethyl acetate). (Found C, 66.0; H, 7.8; S, 10.5; M^+ 308. $C_{17}H_{24}O_3S$ requires C, 66.2; H, 7.8; S, 10.4; M^+ 308). ν_{max} (CH_2Cl_2 solution) 3608 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.79(2H, d, J=8Hz), 7.36(2H, d, J=8Hz), 4.40(1H, m), 4.08(1H, dd, J=13.5, 12.5Hz), 3.01(1H, m), 2.96(1H, dd, J=13.5, 5Hz), 2.85(1H, m), 2.46(3H, s), 2.10(1H, m), 1.90-1.50(4H, m), 1.31(1H, dt, J=10.5, 1.5Hz), 1.02(3H, s), 0.95(3H, s).

6-*endo*-Methylbicyclo[2.2.1]heptan-2-*endo*-ol (31)

6-*Endo*-methyl(4-methylphenyl)sulfonylbicyclo[2.2.1]heptan-2-ol (**27**) (1.19 g, 4.26 mmol) was dissolved in dry methanol (130 ml) and disodium hydrogen phosphate (4.0 eq, 2.45 g, 17 mmol) was added, followed by an excess of 6% sodium amalgam (6.41 g). The reaction mixture was vigorously stirred at room temperature under argon for 16 h and during this time more sodium amalgam (3 x 2.0 g) was added. The reaction mixture was poured into water (100 ml) and the aqueous layer was extracted with ether (4 x 80 ml). The combined organic layers were washed with brine (150 ml) and dried over magnesium sulfate. Evaporation left a residue which was purified by flash column chromatography on silica eluting with 10% ethyl acetate / light petroleum to give the product **31** (0.41 g, 77%) as a waxy white solid, mp 85-88 °C. (Found C, 76.2; H, 11.3; M^+ 126. $C_8H_{14}O$ requires C, 76.1; H, 11.2; M^+ 126). ν_{max} (CH_2Cl_2 solution) 3610 cm^{-1}. ^1H NMR (400

MHz, C_6D_6) δ 4.06(1H, m), 2.05-1.83(5H, m), 1.41(3H, d, J=7Hz), 1.13-1.10(2H, m), 1.05(1H, bs), 0.95(2H, m).

3-*exo*-6-*endo*-Dimethylbicyclo[2.2.1]heptan-2-*endo*-ol (32)

Following the general procedure (above), from 3-*exo*-methyl-6-*endo*-methyl(4-methylphenyl)sulfonyl-bicyclo[2.2.1]heptan-2-ol (**28**) (0.80 g, 2.7 mmol), dry methanol (30 ml), disodium hydrogen phosphate (4.0 eq, 1.55 g, 10.8 mmol) and sodium amalgam (6%, 1 x 4.1 g and 3 x 2.1 g) over 16 h was obtained a residue which was purified by flash column chromatography on silica eluting with 10% ethyl acetate / light petroleum to give the product **32** (0.30 g, 80%) as a clear liquid at room temperature. (Found C, 77.0; H, 11.8; M^+ 140. $C_8H_{16}O$ requires C, 77.1; H, 11.5; M^+ 140). ν_{max} (CH_2Cl_2 solution) 3610 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.78(1H, m), 2.12(1H, bs), 2.09(1H, m), 2.00(1H, ddd, J=15, 11, 5Hz), 1.81(1H, m), 1.73(1H, m), 1.44(1H, bdd, J=10, 2Hz), 1.27(3H, d, J=7Hz), 1.27(1H, m), 1.20(1H, dq, J=10, 2Hz), 1.02(3H, d, J=7Hz), 0.93(1H, ddd, J=11, 5, 2.5Hz).

3,3,6-*endo*-Trimethylbicyclo[2.2.1]heptan-2-*endo*-ol (33)

Following the general procedure (above), from 3,3-dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonyl-bicyclo[2.2.1]heptan-2-ol (**29**) (0.30 g, 0.96 mmol), dry methanol (10 ml), disodium hydrogen phosphate (4.0 eq, 0.21 g, 3.84 mmol) and sodium amalgam (6%, 2.0 g) over 2 h was obtained a residue which was purified by flash column chromatography on silica eluting with 15% ether / light petroleum to give the product **33** (61 mg, 41%) as a clear oil. (Found M^+ 154.1285. $C_{10}H_{18}O$ requires M^+ 154.1285). ν_{max} (CH_2Cl_2 solution) 3605 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.80(1H, dd, J=4, 1.5Hz), 2.22-1.60(6H, m), 1.56(1H, ddt, J=10.5, 3, 1.5Hz), 1.28(3H, d, J=8Hz), 1.16(1H, dt, J=10.5, 1.5Hz), 1.02(3H, s), 0.96(3H, s).

5,5,6-*endo*-Trimethylbicyclo[2.2.1]heptan-2-*endo*-ol (34)

Following the general procedure (above), from 5,5-dimethyl-6-*endo*-methyl(4-methylphenyl)sulfonyl-bicyclo[2.2.1]heptan-2-ol (**30**) (0.39 g, 1.27 mmol), dry methanol (15 ml), disodium hydrogen phosphate (4.0 eq, 0.27 g, 5.09 mmol) and sodium amalgam (6%, 2.0 g) over 2 h was obtained a residue which was purified by flash column chromatography on silica eluting with 15% ether/ light petroleum to give the product **34** (0.14 g, 71%) as waxy white needles. (Found M^+ 154. $C_{10}H_{18}O$ requires M^+ 154). ν_{max} (CH_2Cl_2 solution) 3607 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 4.31(1H, m), 2.12(1H, m), 1.52-1.40(7H, m), 1.12(3H, d, J=7.5Hz), 0.98(3H, s), 0.97(3H, s).

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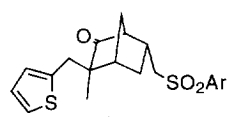
12. In our hands, mixtures of α-1,4- and, predominately, γ-1,4-addition products were usually isolated (see ref. 7). Using shorter reaction times (see ref. 4), we tended to recover significant amounts of unreacted starting material.
13. The vinyl sulfones **13** and **17** were assigned the *trans* configuration on the basis of the coupling constant (11Hz) between H-2 and H-3.
14. During the course of another investigation, the three component coupling of sulfone **18**, 2-methylcyclopentenone, and 2-bromomethylthiophene produced the bicyclic compound **35** in 63% yield.



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