An Efficient Procedure for Preparing γ-Hydroxy α,β-Unsaturated Sulfones

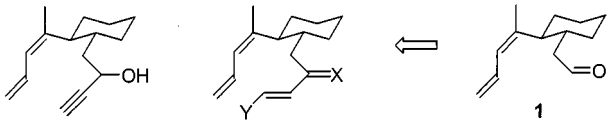
Thomas Zoller,[a] and Daniel Uguen*[a]

Keywords: Takai–Hiyama–Nozaki–Kishi coupling / Sulfones / β-Ionone

Chromium(II)-mediated Barbier condensation of β-iodovinyl *p*-tolylsulfone with aldehydes and β-ionone afforded the title hydroxysulfones in good to excellent yields.

Introduction

In the course of an ongoing project concerned with the generation of the A-B-C ring system of 6-keto steroids by intramolecular Diels−Alder reaction,[1] we were faced with the problem of converting the aldehyde **1** into the keto sulfone **2a**. A conceivable strategy for executing this transformation was, as summarised in Scheme 1, to convert this aldehyde into the hydroxysulfone **2b**, oxidation of which would have then furnished **2a**.



3 **1**

2a, X = O; Y = Tosyl
2b, X = H, OH; Y = Tosyl
2c, X= H, OH; Y = *p*Tolylthio

Scheme 1

A variety of efficient methods have been devised for the preparation of related 3-hydroxy-1,2-alkenylsulfones,[2−9] as a result of their utility in organic synthesis.[10] However, none of these procedures seemed appropriate for a straightforward **1** → **2b** conversion. A possibility might have been a condensation of **1** with acetylene, followed by treatment of the resulting propargylic alcohol **3** with *p*-thiocresol, and finally oxidation of the vinylic sulfide **2c**.[11] Unfortunately, nucleophilic additions of thiols to parent propargylic alcohols are known to proceed with a *trans* selectivity, thereby furnishing (*Z*) adducts; in order to obtain addition products of (*E*) configuration free radical conditions are necessary,[11b−c] which are difficult to apply in the present case owing to the presence of a 1,3-diene moiety in **3**.

These considerations prompted us to explore the coupling of aldehydes with the readily available iodosulfone **4a**[12] under the conditions of the Takai−Hiyama−Nozaki−Kishi (THNK) reaction (Scheme 2).[13] Related β-halovinylsulfones are known to react with various metallic species with displacement of the halogen atom.[14] For instance, treatment of a β-iodovinyl phenylsulfone with Zn powder was shown to afford the corresponding 2-iodozinc sulfone, which decomposed only very slowly at room temperature, with formation of a zinc sulfinate.[14b] Additionally, 2-tributylstannylvinyl phenylsulfone has been prepared from the corresponding chlorosulfone **4b** by a Pd^0-catalysed exchange process.[14a] Thus, it might be envisaged that the sulfone **4a** would undergo the iodine−nickel−chromium exchange that occurs theoretically in any THNK reaction, and that the resulting organometallic species would have a sufficiently long lifetime to facilitate an efficient condensation with an aldehyde.

Results and Discussion

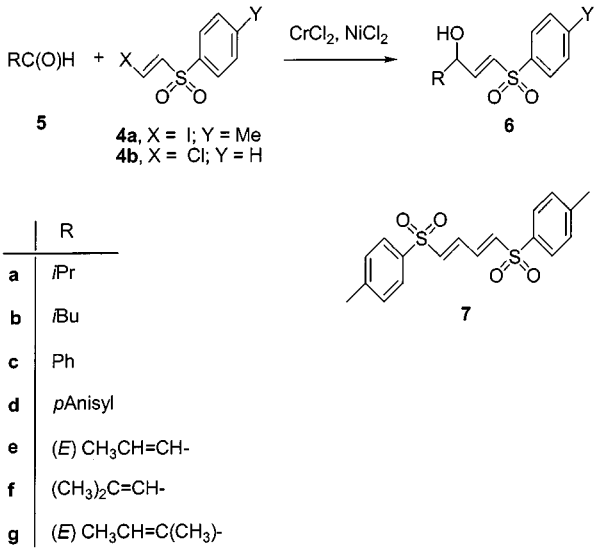
Using isobutyraldehyde **5a** as a model substrate, the planned THNK coupling was first attempted under conditions (Table 1, entry 1) that have previously proved efficient in a related context,[15] the aldehyde and the iodosulfone **4a** being used in stoichiometric amounts (one molequiv. each). Disappointingly, no trace of the expected hydroxysulfone **6aa** could be detected under these conditions. Since the iodosulfone **4a** was completely consumed, this failure was most probably attributable to a possible (vide supra) decomposition of a transient β-sulfonylvinylnickel (or -chromium) species. In any event, the use of either an excess of the aldehyde or a less polar solvent should favour the desired condensation, which was indeed found to be the case.

When the aldehyde **5a** was used in six-fold excess (entry 2), the target hydroxysulfone **6aa** was formed in an encouraging 24% yield. The starting iodosulfone **4a** was fully consumed, however. A change of solvent from DMSO to DMF did not significantly modify this result (entry 3), although the reaction proceeded somewhat more rapidly in the latter solvent medium.

Next, the use of less polar solvents was examined. With the aldehyde **5a** being still used in large excess, a modest yield (10%) of the sulfone **6aa** was attained after 24 h in diethyl ether (entry 4), but, promisingly, no side-decomposition of the starting material occurred, the non-reacted iodosulfone **4a** being largely recovered (80%) upon chromatography of the crude reaction product. The **4a**−**5a** condensation also proceeded slowly in monoglyme (DME), but, at higher temperatures (ca. 60°C), an enticing 70% yield of hydroxysulfone **6aa** was obtained after 17 hours.

[a] Laboratoire de Synthèse Organique, E.C.P.M.,
25, rue Becquerel, F-67087 Strasbourg, France
E-mail: uguen@chimie.u-strasbg.fr

  1434−193X/99/0707−1545 $ 17.50+.50/0



Scheme 2

Table 1. Conditions for the **4a**−**5a** condensation

Entry	**5a** (mol. equiv.)	$CrCl_2$ (mol. equiv.)	$NiCl_2$ (mol. equiv.)	Solvent	Time[a] (hours)	**6aa** yield (%)
1	1	10	0.1	DMSO	24	–
2	6	6	0.01	DMSO	24	24
3	6	6	0.01	DMF	4	27
4	6	6	0.01	Et_2O	24	10
5	6	6	0.01	DME	17[b]	70
6	6	6	0.05	THF	2	93
7	4	6	0.05	THF	4	88[c]
8	1	6	0.05	THF	4	87[c]
9	1	6	0.01	THF	3	93[c]
10	4	4	0.01	THF	3	93

[a]Room temp. – [b]At 60°C. – [c]Disulfone **7** formed.

A more dramatic change resulted from the use of THF. As can be seen in Table 1 (entries 6−10), the **4a**−**5a** coupling proceeded within a few hours in this solvent, leading to high yields of compound **6aa** irrespective of the **5a**/**4a** ratio. Moreover, the yields did not change significantly by decreasing the excess of aldehyde (entries 6−8). When the **4a**/**5a** ratio was fixed to unity (entry 8), side formation of the dienylsulfone **7**, assumed to result from homocoupling of the iodo sulfone **4a**, was noticed, a self-coupling reaction that could be suppressed in some extent by reducing the Ni^{II}/Cr^{II} ratio (compare entries 7 and 10).

Thus, provided the required aldehyde is, as in the case of **5a**, both cheaper than chromous chloride and more accessible than the sulfone **4a**, the most appropriate, practical, conditions are those corresponding to entry 10 of the Table 1. Clearly, however, should the aldehyde (e.g. **1**) be more elaborate than **4a**, the conditions of entry 9, although requiring the use of larger excess of the costly chromous chloride, will be preferred. Hence, reaction of the aldehyde **1** with a slight excess (ca. 1.3 equiv.) of the iodosulfone **4a** under these conditions gave, after separation of the bis(sulfone) **7** (27%) by chromatography, the target hydroxysulfone **2b** in a 89% yield as a 1:1 (NMR) mixture of diastereomers.

Next, oxidation of **2b** into the keto sulfone **2a** was examined, the preliminary optimisation of the reaction conditions was carried out by using first the simpler hydroxysulfone **6aa**. Whereas a fairly good yield (77%) was obtained with PCC deposited onto silica gel, as recommended in related cases,[10b−10c] the use of either Swern conditions[16a] or nickel peroxide[16b] proved to be less effective, the ketone **8** being formed under these conditions in yields no higher than 34%. The best result was obtained with the Dess−Martin reagent,[16c−16d] use of which led to isolation of the keto sulfone **8** in high yield (81%). Treatment of the hydroxysulfone **2b** with this reagent afforded the desired ketone **2a** almost quantitatively (96%), within a few minutes.

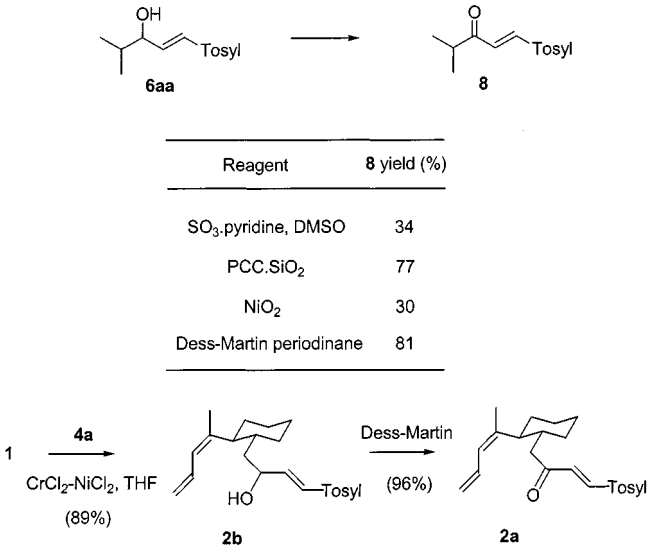


Figure 1

In order to assess the scope of this emerging synthetic process, THNK condensations of the iodosulfone **4a** with various aldehydes were attempted under the conditions of entry 10 of Table 1. In each case (Table 2), the expected coupling product was isolated in high yield, the reaction being particularly fast with α,β-unsaturated aldehydes, going then to completion in less than 5 min., virtually as a titration.

Table 2. Condensation of the sulfones **4** with various aldehydes[a]

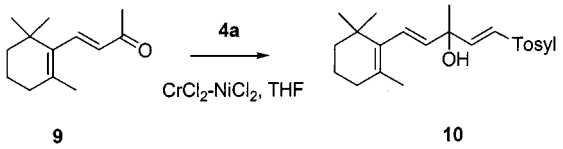
Sulfone	Aldehyde	Time	Product, Yield (%)
4a	**5b**	7 h	**6ba**, 94
4a	**5c**	1 d	**6ca**, 96
4a	**5d**	1 d	**6da**, 80
4a	**5e**	5 min	**6ea**, 89
4b	**5e**	18 h	**6eb**, 41
4a	**5f**	5 min	**6fa**, 91
4b	**5f**	18 h	**6fb**, 17
4a	**5g**	5 min	**6ga**, 88

[a]Under conditions of the entry 10, Table 1.

Attempts to use the chlorosulfone **4b** in place of the iodosulfone **4a** proved not to be so rewarding. The mobility of

the chlorine atom in **4b** toward nucleophilic species has been mentioned previously and it might reasonably have been hoped that this chlorosulfone would behave similarly to **4a** under the above conditions. Though THNK products could indeed be obtained with a few unsaturated aldehydes (i.e. **5e−f**), the yields were invariably lower than those achieved with **4a**. Moreover, longer reaction times were required and hence the use of this sulfone was not pursued.

The reluctance of common (i.e. dialkyl) ketones to undergo THNK condensation with alkenyl iodides is manifest[13a] and, not too surprisingly, no hydroxysulfone was formed upon attempted reaction of **4a** with acetone under the aforementioned conditions. However, the exceptional rate at which the THNK condensation of **4a** with unsaturated aldehydes took place prompted us to examine enones in this context, β-ionone **9** (Scheme 3) being selected as a candidate since its reaction would have generated a potentially useful sesquiterpenic synthon.



Scheme 3

Attempted condensation of the sulfone **4a** with ketone **9** (four-fold excess) under the same conditions as above was unsuccessful, the only observed product being the bis(sulfone) **7**, which was isolated in a 56% yield. Since the ratio of the rates of the desired and of the unwanted (affording **7**) coupling processes is directly related to the aldehyde concentration, but is inversely proportional to that of the sulfone **4a**, it could be surmised that the former process, leading to **10**, would be favoured by maintaining the **[4a]/[9]** ratio as low as possible during the overall process. Indeed, very slow addition, over a period of five days,[17] of a solution of the sulfone **4a** in THF to a mixture of ionone **9** and the reducing species in the same solvent resulted in the formation of the sensitive hydroxysulfone **10** (67%), which was easily separated from the sulfone **7** (27%) by chromatography.

Conclusion

Aldehydes have been shown to react efficiently with the iodosulfone **4a** under the conditions of the Takai−Hiyama−Nozaki−Kishi reaction, a coupling process which, interestingly, could be extended to β-ionone **9**. The high yield achieved in most cases coupled with the ready availability of the sulfone **4a** and the simplicity of the experimental conditions contribute to make this new procedure for preparing γ-hydroxy-β-vinylsulfones a valuable alternative to existing methods.[18]

Experimental Section

General: Anhydrous $CrCl_2$ and $NiCl_2$ (both from Fluka) were used as received. All solvents used were freshly distilled from an appropriate reagent and under an argon atmosphere (diethyl ether, DME, THF: from sodium/benzophenone; DMSO, DMF: from CaH_2; CH_2Cl_2: from P_4O_{10}). The aldehyde **1**[1] and the sulfone **4a**[12] were prepared as described previously. Aldehydes **5a−g** and β-ionone **9** (Fluka) were freshly distilled under a reduced pressure of argon prior to use. All experiments were performed in flame-dried glassware, under an argon atmosphere, with magnetic stirring. − TLC analyses were performed on silica gel, with spot visualisation by exposure of the plates to UV light (254 nm) or by treatment with the H_2SO_4/vanillin reagent. Unless it is otherwise stated, eluent: hexane/AcOEt, 70:30. − Melting points (uncorrected): Büchi apparatus. − NMR: Bruker W200 (^1H and ^{13}C at 200 and 50 MHz, respectively); for ^1H- and ^{13}C-NMR spectra, $CDCl_3$ as solvent, $CHCl_3$ (δH = 7.25) and $CDCl_3$ (δC = 77.6) as internal standard. − Elemental analyses were performed at the C.N.R.S. microanalysis laboratory (Strasbourg).

General Protocol for THNK Condensations: Chromous and nickel chlorides were weighted into a two-necked flask fitted with a septum and connected to an argon line via a stopcock. The appropriate solvent (1 mL per 1 mmol of $CrCl_2$) was added with a syringe and the resulting mixture was thoroughly degassed by performing the freeze-pump-thaw procedure (three cycles). In a similar manner, a solution of the iodosulfone **4a** (ca. 1 M) and the required aldehyde was prepared in another, identical, flask, and then introduced, via a cannula, into the stirred suspension of the reducing species. When the reaction was complete, as judged by TLC, the reaction mixture was diluted with ethyl acetate and water, and the aqueous layer was thoroughly extracted with further ethyl acetate. The pooled organic extracts were washed successively with saturated (aqueous) $NaHCO_3$, 10% aqueous $NaHSO_3$, and brine, and then dried ($MgSO_4$). The residue left after evaporation of the solvents was then chromatographed on Gudoran® (Merck; hexane/AcOEt mixtures as eluent).

***trans*-2-[(*E*)-3-Hydroxy-4-tosyl-3-buten-1-yl]-1-[(*E*)-1-methyl-1,3-butadien-1-yl]-cyclohexane (2b):** A solution of the aldehyde **1** (305 mg; 1.59 mmol) and the sulfone **4a** (635 mg; 2.06 mmol) in THF (4 mL) was added to a stirred mixture of $CrCl_2$ (1.23 g; 9.51 mmol) and $NiCl_2$ (2 mg; 0.02 mmol) in THF (5 mL). After 3 hours, the brown reaction mixture was worked-up in the standard manner and the crude product was chromatographed to afford successively the hydroxysulfone **2b** (526 mg; 1.41 mmol; 89%) and the bis(sulfone) **7** (101 mg; 0.278 mmol; 27%). − **2b**: White crystals; m.p. 115−117°C. − *R*f (TLC) = 0.33. − ^1H NMR (two diastereomers): δ = 0.96−1.99 (m, 12 H), 2.31−2.45 [m, 1 H, CH=C(CH$_3$)C*H*], 2.43 (s, 3 H, C*H*$_3$), 4.42 [m, 1 H, C*H*(OH)], 4.98 (d, *J* = 10 Hz, C=CH*H*), 5.09 (d, *J* = 16.5 Hz, 1 H, C=C*H*H), 5.87 [(d, *J* = 11 Hz, 1 H, *H*C=C(CH$_3$)], 6.54 (dd, *J* = 15, 1.5 Hz, 1 H, C*H*SO$_2$), 6.60 (ddd, *J* = 16.5, 11, 10 Hz, 1 H, CH$_2$C=C*H*), 6.91 (ddd, *J* = 15, 7.5, 4 Hz, 1 H, C*H*=CHSO$_2$), 7.31−7.34 (m, 2 H, aromatic H), 7.73−7.77 (m, 2 H, aromatic H). $C_{22}H_{30}O_3S$ (374.54). − **7**: White crystals; m.p. 195−196°C (CH_2Cl_2/diisopropyl ether). − R_f (TLC) = 0.17. − ^1H NMR: δ = 2.44 (s, 6 H, C*H*$_3$), 6.7−6.81 (m, 2 H), 7.10−7.21 (m, 2 H), 7.34−7.42 (m, 2 H, aromatic H), 7.73−7.79 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 21.7 (*C*H$_3$), 128.1 (aromatic C), 130.2 (aromatic C), 135.1 (*C*SO$_2$), 136.1 (aromatic C), 139.1 (*C*=CHSO$_2$), 145.3 (aromatic C). − MS (EI): *m*/*z* (%) = 362.1 (6) [M^+], 298 (1.3), 223 (1.5), 207 (2.9), 155 (1.6), 139 (100) [*p*-tolylSO]. − $C_{18}H_{18}O_4S_2$ (362.45): calcd. C 59.65, H 5.01; found C 59.87, H 5.00.

THNK Condensation of Sulfone 4 with Aldehydes (see Table 2): A solution of the aldehyde (6.5 mmol) and **4a** (or **4b**) (1.63 mmol) in THF (5 mL) was added to a mixture of $CrCl_2$ (6.5 mmol) and $NiCl_2$ (0.016 mmol) in THF (5 mL).

(*E*)-4-Methyl-1-tosyl-1-penten-3-ol (6aa): White crystals; m.p. 114−115°C. − R_f (TLC) = 0.43. − ^{1}H NMR: δ = 0.91 [d, *J* = 7 Hz, 3 H, C*H*$_3$CH(CH$_3$)], 0.94 [d, *J* = 7 Hz, 3 H, CH$_3$CH(C*H*$_3$)], 1.81 (m, 1 H, O*H*), 1.84 [heptd, *J* = 7, 2 Hz, 1 H, *H*C(CH$_3$)$_2$)], 2.43 (s, 3 H, C*H*$_3$), 4.17−4.2 [m, 1 H, C*H*(OH)], 6.59 [dd, *J* = 15, 2 Hz, 1 H, HC=C*H*(SO$_2$)], 6.97 [dd, *J* = 15, 4 Hz, 1 H, *H*C=CH(SO$_2$)], 7.31−7.35 (m, 2 H, aromatic H), 7.74−7.78 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 17.2 (C-5), 18.3 (*C*H$_3$), 21.6 (*C*H$_3$), 33.7 (C-4), 75 (C-3), 127.7 (aromatic C), 129.9 (aromatic C), 130.9 (C-1), 137.4 (aromatic C), 144.4 (aromatic C), 146.3 (C-2). − $C_{13}H_{18}O_3S$ (254.3): calcd. C 61.39, H 7.13; found C 61.25, H 7.14.

(*E*)-5-Methyl-1-tosyl-1-hexen-3-ol (6ba): White crystals; m.p. 94−95°C. − R_f (TLC) = 0.21. − ^{1}H NMR: δ = 0.9 [d, *J* = 7 Hz, 3 H, C*H*$_3$CH(CH$_3$)], 0.94 [d, *J* = 7 Hz, 3 H, CH$_3$CH(C*H*$_3$)], 1.37−1.48 (m, 2 H, C*H*$_2$), 1.69−1.86 [m, 2 H, *H*C(CH$_3$)$_2$ plus O*H*], 2.43 (s, 3 H, C*H*$_3$), 4.36−4.48 [m, 1 H, C*H*(OH)], 6.58 [dd, *J* = 15, 2 Hz, 1 H, HC=C*H*(SO$_2$)], 6.96 [dd, *J* = 15, 4 Hz, 1 H *H*C=CH(SO$_2$)], 7.31−7.35 (m, 2 H, aromatic H), 7.73−7.77 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 21.6 (*C*H$_3$), 21.9 (C-6), 23.2 (*C*H$_3$), 24.5 (C-5), 45.4 (C-4), 68.7 (C-3), 127.7 (aromatic C), 129.7 (C-1), 129.9 (aromatic C), 137.3 (aromatic C), 144.4 (aromatic C), 148 (C-2). − $C_{14}H_{20}O_3S$ (268.37): calcd. C 62.66, H 7.51; found C 62.76, H 7.57.

(*E*)-3-Phenyl-1-tosyl-1-propen-3-ol (6ca): White crystals; m.p. 136−138°C. − R_f (TLC) = 0.15. − ^{1}H NMR: δ = 2.36 (d, *J* = 3.5 Hz, 1 H, O*H*), 2.44 (s, 3 H, C*H*$_3$), 5.34 [m, 1 H, *H*C(OH)], 6.73 [dd, *J* = 15, 2 Hz, 1 H, HC=C*H*(SO$_2$)], 7.03 [dd, *J* = 15, 4 Hz, 1 H, *H*C=CH(SO$_2$)], 7.21−7.37 (m, 7 H, aromatic H), 7.71−7.76 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 21.6 (*C*H$_3$), 72.8 (C-3), 126.7 (aromatic C), 127.8 (aromatic C), 128.8 (C-1), 129.0 (aromatic C), 129.9 (aromatic C), 137.2 (aromatic C), 139.8 (aromatic C), 144.5 (aromatic C), 145.8 (C-2). − $C_{16}H_{16}O_3S$ (288.4): calcd. C 66.58, H 5.55; found C 66.42, H 5.27.

(*E*)-3-(4-Methoxyphenyl)-1-tosyl-1-propen-3-ol (6da): White needles; m.p. 126−127°C. − R_f (TLC) = 0.12. − ^{1}H NMR: δ = 2.12 (d, *J* = 3.5 Hz, 1 H, O*H*), 2.44 (s, 3 H, C*H*$_3$), 3.81 (s, 3 H, OC*H*$_3$), 5.32−5.37 [m, 1 H, *H*C(OH)], 6.72 [dd, *J* = 15, 2 Hz, 1 H, HC=C*H*(SO$_2$)], 6.84−6.92 (m, 2 H, aromatic H), 7.02 [dd, *J* = 15, 3.5 Hz, 1 H, *H*C=CH(SO$_2$)], 7.17−7.24 (m, 2 H, aromatic H), 7.31 −7.35 (m, 2 H, aromatic H), 7.74−7.86 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 21.6 (*C*H$_3$), 55.5 (O*C*H$_3$), 72.4 (C-3), 114.4 (aromatic C), 127.8 (aromatic C), 128.2 (aromatic C), 129.8 (C-1), 129.9 (aromatic C), 131.9 (aromatic C), 137.3 (aromatic C), 144.4 (aromatic C), 145.9 (C-2), 160 (aromatic C). − $C_{17}H_{18}O_4S$ (318.4): calcd. C 64.13, H 5.70; found C 64.25, H 5.78.

(*E,E*)-1-Tosyl-1,4-hexadien-3-ol (6ea): Colourless oil. − R_f (TLC) = 0.13. − ^{1}H NMR: δ = 1.69 [ddd, *J* = 6.5, 1.5, 0.5 Hz, 3 H, CH(C*H*$_3$)], 2.34 (m, 1 H, O*H*), 2.42 (s, 3 H, C*H*$_3$), 4.76 [m, 1 H, C*H*(OH)], 5.41 [ddq, *J* = 15, 5, 1.5 Hz, 1 H, *H*C=CH(CH$_3$)], 5.74 [dqd, *J* = 15, 6.5, 1 Hz, 1 H, HC=C*H*(CH$_3$)], 6.57 [dd, *J* = 15, 2 Hz, 1 H, HC=C*H*(SO$_2$)], 6.89 [dd, *J* = 15, 4 Hz, 1 H, *H*C=CH(SO$_2$)], 7.29−7.33 (m, 2 H, aromatic H), 7.71−7.77 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 17.8 (*C*H$_3$), 21.7 (*C*H$_3$), 71.2 (C-3), 127.8 (aromatic C), 129.6 (C-1, C-4), 130 (C-5, aromatic C), 137.2 (aromatic C), 144.6 (aromatic C), 146.5 (C-2). − $C_{13}H_{16}O_3S$ (252.3): calcd. C 61.82, H 6.34; found C 61.80, H 6.29.

(*E*)-5-Methyl-1-tosyl-1,4-hexadien-3-ol (6fa): White crystals; m.p. 116−117°C. − R_f (TLC) = 0.13. − ^{1}H NMR: δ = 1.7 (s, 3 H, C*H*$_3$), 1.73 (s, 3 H, C-6), 1.98 (m, 1 H, O*H*), 2.42 (s, 3 H, C*H*$_3$), 5.06 [m, 2 H, C=C*H*−C*H*(OH)], 6.56 [dd, *J* = 15, 1 Hz, 1 H, HC=C*H*(SO$_2$)], 6.86 [dd, *J* = 15, 1.5 Hz, 1 H, *H*C=CH(SO$_2$)], 7.3−7.4 (m, 2 H, aromatic H), 7.73−7.77 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 18.4 (*C*H$_3$), 21.6 (*C*H$_3$), 25.7 (C-6), 67.3 (C-3), 123.2 (C-4), 127.7 (aromatic C), 129.4 (C-1), 129.9 (aromatic C), 137.4 (aromatic C), 138.3 (C-5), 144.3 (aromatic C), 146.2 (C-2). − $C_{14}H_{18}O_3S$ (266.35): calcd. C 63.07, H 6.76; found C 63.01, H 6.92.

(*E*)-4-Methyl-1-tosyl-1,4-hexadien-3-ol (6ga): White crystals; m.p. 201−202°C. − R_f (TLC) = 0.19. − ^{1}H NMR: δ = 1.54 (t, *J* = 1 Hz, 3 H, C*H*$_3$), 1.62 (d, *J* = 6.5 Hz, 3 H, C-6), 1.79 (m, 1 H, O*H*), 2.43 (s, 3 H, C*H*$_3$), 4.74 [m, 1 H, C*H*(OH)], 5.59 [qd, *J* = 6.5, 1 Hz, 1 H, C*H*(CH$_3$)], 6.62 [dd, *J* = 15, 2 Hz, 1 H, HC=C*H*(SO$_2$)], 6.88 [dd, *J* = 15, 3.5 Hz, 1 H, *H*C=CH(SO$_2$)], 7.29−7.37 (m, 2 H, aromatic H), 7.73−7.79 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 11.3 (*C*H$_3$), 13.2 (C-6), 21.5 (CH$_3$), 75.8 (C-3), 123.8 (C-5), 127.5 (aromatic C), 129.8 (aromatic C), 130.1 (C-1), 134.4 (C-4), 137.3 (aromatic C), 144.3 (aromatic C), 146.1 (C-2). − $C_{14}H_{18}O_3S$ (266.35): calcd. C 63.07, H 6.76; found C 63.14, H 6.83.

(*E,E*)-1-Phenylsulfonyl-1,4-hexadien-3-ol (6eb): White needles; m.p. 87−89°C. − R_f (TLC) = 0.16. − ^{1}H NMR: δ = 1.69 [d, *J* = 6 Hz, 3 H, CH(C*H*$_3$)], 2.26 (m, 1 H, O*H*), 4.74−4.82 [m, 1 H, C*H*(OH)], 5.41 [ddq, *J* = 15, 7, 1.5 Hz, 1 H, *H*C=CH(CH$_3$)], 5.74 [dqd, *J* = 15, 6.5, 1 Hz, 1 H, HC=C*H*(CH$_3$)], 6.59 [dd, *J* = 15, 2 Hz, 1 H, HC=C*H*(SO$_2$)], 6.93 [dd, *J* = 15, 3.5 Hz, 1 H, *H*C=CH(SO$_2$)], 7.48−7.66 (m, 3 H, aromatic H), 7.84−7.90 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 17.7 (*C*H$_3$), 71.2 (C-3), 127.6 (aromatic C), 129.3 (aromatic C), 129.4 (C-1, C-5), 130.3 (C-4), 133.4 (aromatic C), 140.2 (aromatic C), 146.6 (C-2). − $C_{12}H_{14}O_3S$ (238.30): calcd. C 60.43, H 5.87; found C 60.14, H 5.59.

(*E*)-5-Methyl-1-phenylsulfonyl-1,4-hexadien-3-ol (6fb): Colourless oil. − R_f (TLC) = 0.12. − ^{1}H NMR: δ = 1.71 (s, 3 H, C*H*$_3$), 1.73 (s, 3 H, C-6), 2.03 (m, 1 H, O*H*), 5.06 [m, 2 H, C=C*H*−C*H*(OH)], 6.59 [dd, *J* = 15, 1 Hz, 1 H, HC=C*H*(SO$_2$)], 6.90 [dd, *J* = 15, 3.5 Hz, 1 H, *H*C=CH(SO$_2$)], 7.48−7.65 (m, 3 H, aromatic H), 7.85−7.90 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 18.4 (*C*H$_3$), 25.70 (C-6), 67.5 (C-3), 123.1 (C-4), 127.60 (aromatic C), 129.00 (C-1), 129.3 (aromatic C), 133.40 (aromatic C), 138.40 (C-5), 140.30 (aromatic C), 146.80 (C-2). − $C_{13}H_{16}O_3S$ (252.3): calcd. C 61.83, H 6.34; found C 62.14, H 6.23.

(*E,E*)-3-Methyl-1-tosyl-5-[2,6,6-trimethyl-1-cyclohexen-1-yl]-1,4-pentadien-3-ol (10): A solution of sulfone **4a** (500 mg; 1.62 mmol) in THF (5 mL) was periodically added dropwise to a mixture of $CrCl_2$ (1.26 g, 9.74 mmol), $NiCl_2$ (2 mg; 0.02 mmol), and β-ionone **9** (1.25 g, 6.49 mmol) in THF (5 mL) over a period of 5 days. The mixture was stirred for a further 2 days and then worked-up as above, the organic extract being filtered through Celite (AcOEt) prior drying. Chromatography of the residue left upon evaporation of the solvents afforded successively the hydroxysulfone **10** and the bis(sulfone) **7** (83 mg). Recrystallisation of **10** from cold diethyl ether/hexane afforded white crystals (405 mg; 1.08 mmol; 67%); m.p. 89−90°C. − R_f (TLC) = 0.29 (hexane/AcOEt, 80:20). − ^{1}H NMR: δ = 0.92 [s, 6 H, 6′-C(C*H*$_3$)$_2$], 1.4−1.62 (m, 4 H, 4′-C*H*$_2$, 5′-C*H*$_2$), 1.48 (s, 3 H, 2′-CC*H*$_3$), 1.59 (splitted s, 3 H, 3-CC*H*$_3$), 1.74 (s, 1 H, O*H*), 1.96 (t, *J* = 6 Hz, 2 H, 3′-C*H*$_2$), 2.43 (s, 3 H, C*H*$_3$), 5.47 (d, *J* = 16 Hz, 1 H, 5-C*H*), 6.07 (dd, *J* = 16, 0.5 Hz, 1 H, 4-C*H*), 6.60 [d, *J* = 15 Hz, 1 H, CH=C*H*(SO$_2$)], 6.99 [d, *J* = 15 Hz, 1 H, C*H*=CH(SO$_2$)], 7.29−7.33 (m, 2 H, aromatic H), 7.73−7.77 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 19.1 (*C*-4′), 21.3 (*C*H$_3$), 21.6 (*C*H$_3$-C-2′), 27.9 (*C*H$_3$-C-3), 28.7 [(*C*H$_3$)$_2$C-6′], 32.7 (C-3′), 34.00 (C-6′), 39.13 (C-5′), 73.2 (C-3), 127.7 (aromatic C), 128.2 (C-5), 128.6 (C-1), 129.5 (C-1′, C-2′), 129.9 (aromatic C), 136.3 (C-6), 137.5 (aromatic C), 144.4 (aromatic C), 149.8 (C-2). − $C_{22}H_{30}O_3S$ (374.53).

(*E*)-4-Methyl-1-tosyl-1-penten-3-one (8). − Oxidation of 6aa with the Dess−Martin Reagent: A solution of the hydroxysulfone **6aa**

(50 mg; 0.2 mmol) in CH_2Cl_2 (2 mL) was prepared in a three-necked flask fitted with a septum and a tube containing the Dess−Martin periodinane (DMP), and connected to an argon line. The DMP reagent was gradually added to the solution at room temp., with gentle stirring. The solid slowly dissolved and the resulting clear solution was subsequently stirred for a further 20 min. A mixture of diethyl ether (2 mL) and of a solution of $NaHSO_3$ (146 mg; 0.59 mmol) and $NaHCO_3$ (38 mg; 0.45 mmol) in water (0.5 mL) was then added with a syringe, and the resulting mixture was vigorously stirred until two well-defined layers were obtained. The aqueous phase was thoroughly extracted with diethyl ether (3× 20 mL), and the pooled organic extracts were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$), and the solvents were evaporated. Filtration of the resulting residue on silica gel (AcOEt) afforded, after evaporation of the solvents, the pure keto sulfone **8** (41 mg; 0.162 mmol; 81%) as a white solid; m.p. 98−99°C. − R_f (TLC): = 0.58 (hexane/AcOEt, 50:50). − ^{1}H NMR: δ = 1.08 [d, J = 7 Hz, 6 H, CH(CH_3)$_2$], 2.39 (s, 3 H, CH_3), 2.77 [hept, J = 1 H, CH(CH$_3$)$_2$], 7.13 [s, 2 H, HC=CH(SO$_2$)], 7.30−7.34 (m, 2 H, aromatic H), 7.72−7.76 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 17.4 [(CH_3)$_2$C], 21.5 (CH_3), 40.6 (C-4), 128.1 (aromatic C), 130.1 (aromatic C), 133.8 (C-2), 135.5 (aromatic C), 140.6 (C-1), 145.4 (aromatic C), 201.0 (C-3). − $C_{13}H_{16}O_3S$ (252.32): calcd. C 61.83, H 6.34; found C 61.94, H 6.59.

***trans*-1-[(*E*)-1-Methyl-1,3-butadien-1-yl]-2-[(*E*)-3-oxo-4-tosyl-3-buten-1-yl]cyclohexane (2a):** Using the protocol described above for the **6aa** → **8** conversion, the alcohol **2b** (480 mg; 1.28 mmol) was likewise treated with the Dess−Martin periodinane (924 mg; 2.18 mmol) to give the keto sulfone **2a** (458 mg; 1.22 mmol; 96%) as a white solid; m.p. 55°C (dec.). − R_f (TLC) = 0.47. − ^{1}H NMR: δ = 0.96−2.06 (m, 12 H), 2.19 [dd (A part of an ABX system), JAB = 16.5 Hz, JAX = 8 Hz, 1 H, 1″-CH], 2.37 (td, J = 10.5, 4 Hz, 1 H, 2′-CH), 2.45 (s, 3 H), 2.55 [dd (B part of an ABX system), JAB = 16.5 Hz, JBX = 4 Hz, 1 H, 1″-CH], 5.00 (dd, J = 10.0, 2 Hz, 1 H, HHC=C), 5.07 (dd, J = 16.5, 2 Hz, 1 H, HHC=C), 5.82 [d, J = 11 Hz, 1 H, HC=C(CH$_3$)], 6.60 (ddd, J = 16.5, 11, 10 Hz, 1 H, HC=CH$_2$), 6.91 (d, J = 15 Hz, 1 H, 3′′-CH), 7.05 (d, J = 15 Hz, 1 H, 4′′-CH), 7.34−7.39 (m, 2 H, aromatic H), 7.75−7.79 (m, 2 H, aromatic H). − ^{13}C NMR: δ = 19.4 [(CH_3)C-1′], 21.7 (C-4, C-5), 30.7 (C-6), 33 (C-3), 35.8 (C-2), 44.9 (C-1), 47.5 (C-1″), 116 (C-4′), 128.3 (aromatic C), 128.6 (C-2′), 130.2 (aromatic C), 132.00 (C-3′), 135.6 (aromatic C), 135.7 (C-3″), 140.1 (C-4″), 141.6 (C-1′), 145.5 (aromatic C), 197.4 (C-6″). − $C_{22}H_{28}O_3S$ (375.52).

Acknowledgments

Thanks are due to the C.N.R.S. and the Conseil Régional d′Alsace for a grant (to T. Z.), and to Miss Sylviane Abdi for assistance in performing some of the coupling experiments.

[1] T. Zoller, D. Uguen, A. De Cian, J. Fischer, *Tetrahedron Lett.* **1997**, *38*, 3409−3412.

[2] From sulfinylmethyl arylsulfones: [2a] E. Dominguez, J. C. Carretero, *Tetrahedron Lett*. **1990**, *31*, 2487−2490. − [2b] B. M. Trost, T. A. Grese, *J. Org. Chem*. **1991**, *56*, 3189−3192. − [2c] R. F. W. Jackson, S. P. Standen, W. Clegg, *J. Chem. Soc., Perkin Trans. 1I* **1995**, 149−156, and quoted references therein.

[3] From allylic sulfones: [3a] G. S. Ananda, P. J. Crenins, R. J. Stoodley, *J. Chem. Soc., Chem. Commun*. **1987**, 882 and quoted references therein. − [3b] K. Ogura, N. Shibuya, H. Iida, *Tetrahedron Lett*. **1981**, *22*, 1519−1522. − [3c] K. Ogura, N. Shibuya, K. Takahashi, H. Iida, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1092−1096.

[4] From β,γ-epoxysulfones: [4a] A. D. Westwell, M. Thornton-Pett, C. M. Rayner, *J. Chem. Soc., Perkin Trans. 11* **1995**, 847−859. − [4b] D. K. Hutchinson, P. L. Fuchs, *J. Am. Chem. Soc*. **1985**, *107*, 6137−6138. − [4c] J. C. Sadler, R. E. Hutchinson, P. L. Fuchs, *J. Am. Chem. Soc*. **1981**, *103*, 2110−2112. − [4d] J. C. Sadler, P. L. Fuchs, *J. Am. Chem. Soc*. **1981**, *103*, 2112−2114. − [4e] J. E. Bäckvall, S. K. Juntunen, *J. Org. Chem.* **1988**, *53*, 2398−2400. − [4f] T. Sakakibara, I. Takai, A. Yamamoto, H. Iizuka, K. Hirasawa, Y. Ishido, *Tetrahedron Lett*. **1990**, *31*, 3749−3752. − [4g] Y. Pan, S. A. Hardinger, P. L. Fuchs, *Synth. Commun*. **1989**, *19*, 403−416. − [4h] S. A. Hardinger, P. L. Fuchs, *J. Org. Chem*. **1987**, *52*, 2739−2749. − [4i] O. Arjona, R. F. de la Pradilla, A. Mallo, J. Plumet, A. Viso, *Tetrahedron Lett.* **1990**, *31*, 1475−1478. − [4j] J. Adrio, J. C. Carretero, R. G. Arrayàs, *Synlett* **1996**, 640−642. − [4k] A. K. Maiti, P. Bhattacharyya, *Tetrahedron* **1994**, *50*, 10483−10490. − [4l] P. Bhattacharyya, G. K. Biswas, *Synth. Commun.* **1991**, *21*, 569−573. − [4m] J. K. Crandall, C. Pradat, *J. Org. Chem.* **1985**, *50*, 1327−1329. − [4n] C. C. J. Culvenor, W. Davies, W. E. Savige, *J. Chem. Soc*. **1949**, 1419−1423. − [4o] A. M. Bernard, M. T. Cocco, C. Congiu, G. L. Franzone, P. P. Piras, *Synthesis* **1996**, 361−366. − [4p] B. M. Trost, M. G. Organ, G. A. O′Doherty, *J. Am. Chem. Soc*. **1995**, *117*, 9662−9670. − [4q] S. W. Lee, P. L. Fuchs, *Tetrahedron Lett*. **1991**, *32*, 2861−2864.

[5] From 1-arylsulfonyl propargylic alcohols: I. Ryu, N. Kusumoto, A. Ogawa, N. Kambe, N. Sonoda, *Organometallics* **1989**, *8*, 2279−2281.

[6] From 2-hetero-substituted 3-hydroxyalkylsulfones and *O*-derivatives: [6a] S.-K. Kang, *J. Chem. Soc., Perkin Trans. 1I* **1992**, 405−406. − [6b] D. Quiu, R. R. Schmidt, *Synthesis* **1990**, 875−877. − [6c] N. J. Barnes, A. H. Davidson, L. R. Hughes, G. Procter, *J. Chem. Soc., Chem. Commun.* **1985**, 1292−1294. − [6d] S. G. Pyne, D. C. Spellmeyer, S. Chen, P. L. Fuchs, *J. Am. Chem. Soc.* **1982**, *104*, 5728−5740. − [6e] J. F. Cassidy, J. M. Williams, *Tetrahedron Lett*. **1986**, *27*, 4355−4538. − [6f] D. K. Hutchinson, S. A. Hardinger, P. L. Fuchs, *Tetrahedron Lett*. **1986**, *27*, 1429−1432. − [6g] D. K. Hutchinson, P. L. Fuchs, *Tetrahedron Lett*. **1986**, *27*, 1425−1428. − [6h] C. Nàjera, A. Pérez-Pinar, J. M. Sansano, *Tetrahedron* **1991**, *47*, 6337−6352. − [6i] C. Nàjera, B. Baldò, M. Yus, *J. Chem. Soc., Perkin Trans. 1I* **1988**, 1029−1032. − [6j] S. Sengupta, D. Sen Sarma, S. Mondal, *Tetrahedron: Asymmetry* **1998**, 2311−2316.

[7] From allylic bis(sulfones): T. Cuvigny, K. Du Penhoat, M. Julia, *Rec. Trav. Chim. Pays-Bas* **1986**, *105*, 409−421.

[8] From vinyl arylsulfones: [8a] D. H. R. Barton, S. D. Gero, B. Quiclet-Sire, M. Samadi, *Tetrahedron:Asymmetry* **1994**, *5*, 2123−2136. − [8b] D. H. R. Barton, A. Gateau-Olesker, S. D. Gero, B. Lacher, C. Tachdjian, S. Z. Zard, *Tetrahedron* **1993**, *49*, 4589−4602.

[9] From α-oxygenated aldehydes: S. F. Wnuk, N. K. Dalley, M. Robins, *Can. J. Chem.* **1991**, *69*, 2104−2111.

[10] [10a] E. Dominguez, J. C. Carretero, *Tetrahedron* **1994**, *50*, 7557−7566. − [10b] J. C. Carretero, E. Dominguez, *J. Org. Chem*. **1993**, *58*, 1596−1600. − [10c] F. M. Leon, J. C. Carretero, *Tetrahedron Lett*. **1991**, *32*, 5405−5408. − [10d] M. Isobe, Y. Ichikawa, Y. Funabashi, S. Mio, T. Goto, *Tetrahedron* **1986**, *42*, 2863−2872. − [10e] M. Kitamura, M. Isobe, Y. Ichikawa, T. Goto, *J. Am. Chem. Soc*. **1984**, *106*, 3252−3257. − [10f] M. Isobe, Y. Ichikawa, H. Masaki, T. Goto, *Tetrahedron Lett*. **1984**. *25*, 3607−3610. − [10g] P. L. Fuchs, T. F. Braish, *Chem. Rev.* **1986**, *86*, 903−917. − [10h] J. Adrio, J. C. Carretero, R. G. Arrayàs, *Synlett* **1996**, 640−642. − [10i] R. Noyori, M. Suzuki, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847−876, and references cited therein. − [10j] B. M. Trost, P. Seoane, S. Mignani, M. Acemoglu, *J. Am. Chem. Soc*. **1989**, *111*, 7487−7500. − [10k] I. Alonso, J. L. Garrido, V. Magro, C. Pedregal, *J. Org. Chem*. **1997**, *62*, 5682−5683. − [10l] J. C. Carretero, E. Dominguez, *J. Org. Chem*. **1992**, *57*, 3867−3873. − [10m] K. Ogura, K.-I. Ogu, T. Ayabe, J.-I. Sonehara, M. Akazome, *Tetrahedron Lett*. **1997**, *38*, 5173−5176.

[11] [11a] C. Mercier, Doctorate dissertation, Paris VI, **1984**. − [11b] M. Julia, C. Lefebvre, *Tetrahedron Lett*. **1984**, *25*, 189−192. − [11c] C. Mercier, M. Julia, D. Uguen, unpublished results. For instance, (*Z*)-3-methyl-1-(*p*-tolylthio)-1-buten-3-ol, which is formed exclusively upon treatment of 3-methyl-1-butyne-3-ol with *p*-thiocresol in basic, protic media and under strictly anaerobic conditions, was shown to give, besides a small amount of its regioisomer [i.e. 3-methyl-2-(*p*-tolylthio)-1-buten-3-ol], the

stereomeric (*E*)-hydroxysulfide upon treatment with traces of *p*-thiocresol and either AIBN or oxygen, in dichloromethane.
[12] T. Zoller, D. Uguen, *Tetrahedron Lett*. **1998**, *39*, 8089−8092.
[13] [13a] K. Takai, K. Kimura, T. Kuroda, T. Hiyama, H. Nozaki, *Tetrahedron Lett*. **1983**, 24, 5281−5284. − [13b] K. Kishi, *Pure Appl. Chem*. **1992**, *64*, 343−350, and references therein. − [13c] For a review, see: P. Cintas, *Synthesis* **1992**, 248−257; L. A. Luger, A. Wessjohann, G. Scheid *Synthesis*, **1999**, 1−36.
[14] [14a] V. Farina, S. I. Hauck, *J. Org. Chem.* **1991**, *56*, 4317−4319. − [14b] C. J. Rao, P. Knochel, *J. Org. Chem*. **1991**, *56*, 4593−4596. − [14c] M. Ochiai, T. Ukita, E. Fujita, *Tetrahedron Lett.* **1983**, *24*, 4025−4028. − [14d] J. S. Xiang, A. Mahadevan, P. L. Fuchs, *J. Am. Chem. Soc*. **1996**, *118*, 4284−4290. − [14e] W. E. Truce, A. W. Borel, P. J. Marek, *J. Org. Chem*. **1976**, *41*, 401−402.
[15] G. Oddon, D. Uguen, *Tetrahedron Lett.* **1998**, *39,* 1157−1160.
[16] [16a] J. R. Parikh, W. von E. Doering, *J. Am. Chem. Soc*. **1967**, *89*, 5505−5507. − [16b] K. Nakagawa, R. Konaka, T. Nakata, *J. Org. Chem.* **1962**, *27*, 1597−1601. − [16c] D. B. Dess, J. C. Martin, *J. Org. Chem*. **1983**, *48*, 4155−4156. − [16d] S. M. Rubistein, R. M. Williams, *J. Org. Chem*. **1995**, *60*, 7215−7223.
[17] Due to the sensitivity of the aldehyde **1**, which decomposes within a few days on standing at room temperature, execution of the **1**−**4a** condensation by us did not proceed satisfactorily under these conditions.
[18] The results presented herein are taken in part from the Doctorate dissertation of Thomas Zoller and have been presented in brief at the symposium on the "Impact of Organic Synthesis on Drug Discovery", University of Heidelberg, September 6−8th, **1998**.

Received November 18, 1998
[O98521]