The Stereocontrolled Claisen Rearrangement of Tertiary Allylic Sulphone Esters: Stereoselective Formation of Trisubstituted Double Bonds

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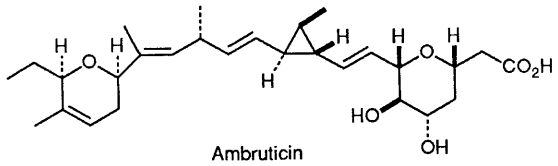
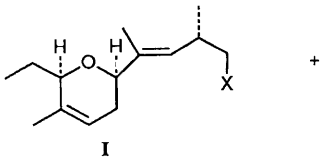
The stereoselective Claisen rearrangement of a series of tertiary allylic sulphone esters is reported.

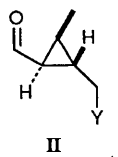
The Claisen rearrangement of secondary allylic alcohols is an extremely valuable method for the formation of γ,δ-unsaturated carboxylic acid derivatrives since it forms *E*-double bonds with a high degree of stereocontrol.[1] However, in the case of tertiary allylic alcohols the ratio of double bond isomers obtained is low and consequently this reaction has found limited use in organic synthesis. Previously[2] we demonstrated that such control could be achieved in the Meerwein–Eschenmoser Claisen rearrangement of tertiary allylic alcohols which possessed an adjacent chiral centre bearing an oxygen atom. In this communication we describe the Ireland–ester Claisen rearrangement of the corresponding tertiary sulphone esters and show how this can be used to prepare trisubstituted γ,δ-unsaturated sulphones in a highly stereocontrolled manner.



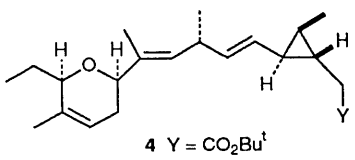
Ambruticin



I
1 X = $CONMe_2$
2 X = CO_2H
5 X = SO_2Ph

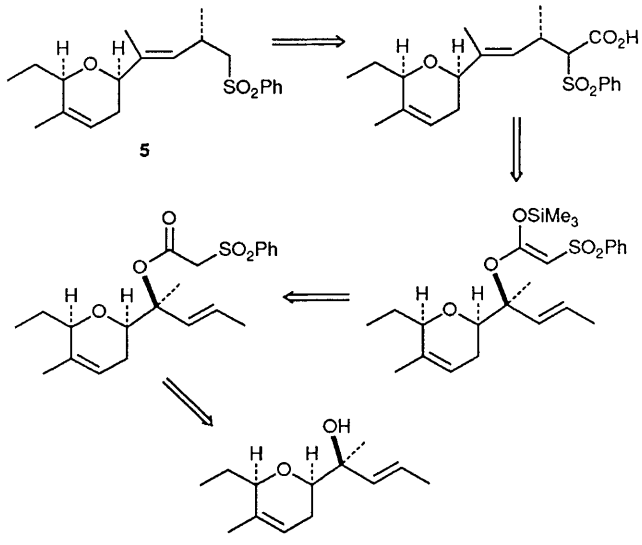


II
3 Y = CO_2Bu^t



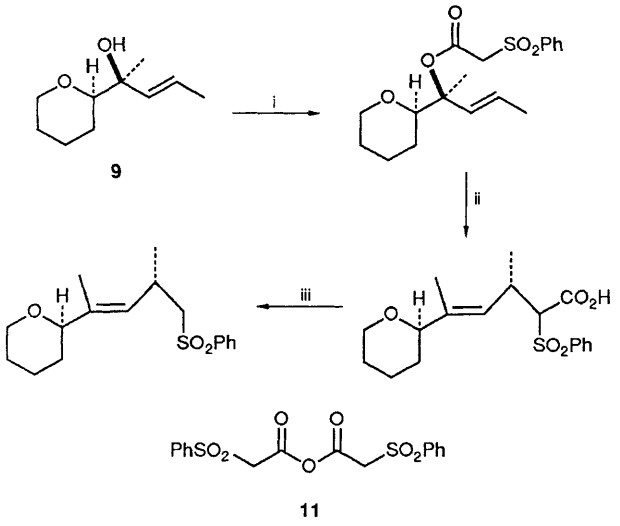
4 Y = CO_2Bu^t

For our work on the antifungal agent ambruticin,[3] we required a fragment (**I**) which was suitably substituted such that it could be coupled to aldehyde (**II**). Although, using our previous route,[2] we were able to obtain amide **1** with a reasonable degree of stereocontrol, we found that the reaction of the amide **1** or the carboxylic acid **2** with aldehyde **3** to form **4** unsatisfactory. As model studies had demonstrated that the best method to form this double bond was *via* a Julia coupling[4] we decided to develop a route to sulphone† **5** which would take advantage of the stereocontrol achieved in our previous work.[2]



Scheme 1

† *Note added in proof*: the total synthesis of ambruticin using a sulphone analogous to **5** has recently been reported: A. S. Kende, Y. Fujii and J. S. Mendoza, *J. Am. Chem. Soc.*, 1990, **112**, 9645.



Scheme 2 *Reagents and conditions*: i, Pyridine, $CHCl_3$, **11**, 20 °C, 80%; ii, lithium diisopropylamide (LDA), Me_3SiCl, −78 °C then 10 h at 20 °C, 75% (90% based on recovered starting material); iii, $NaHCO_3$, dimethylformamide, 10 h at 100 °C, 95%

In order to study the feasibility of this approach (Scheme 1) and the stereocontrol that could be achieved, we investigated the Claisen rearrangement of a series of tertiary sulphone esters prepared by reaction of the corresponding alcohols[2] **6**, **7**, **8**, **9** and **10** with the anhydride **11** (a representative pathway for alcohol **9** is outlined in Scheme 2). The esters proved to be surprisingly stable and could be purified by column chromatography. This was in contrast to the acetates **12**, prepared in order to study the Ireland–ester Claisen rearrangement,[5] which could only be obtained in low yields and could not be satisfactorily purified.

The Claisen rearrangements were carried out by formation of the enolate at −78 °C, trapping with Me_3SiCl and stirring the silyl-ketene acetals at room temperature for 12 hours. This yielded the sulphone carboxylic acids in high yield as mixtures

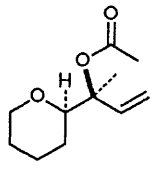


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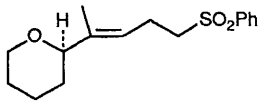
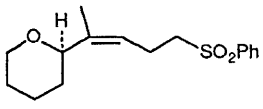
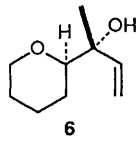
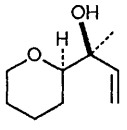
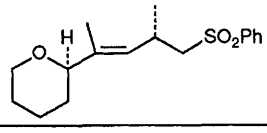
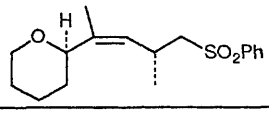
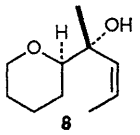
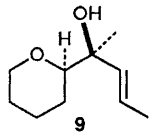
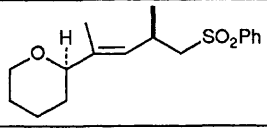
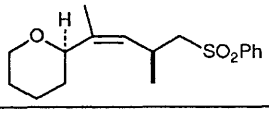
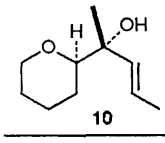
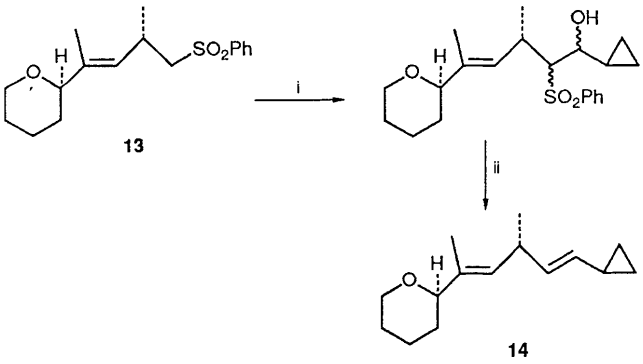
Table 1 Ratios of Claisen rearrangement products obtained after decarboxylation of the intermediate sulphone-carboxylic acids

				Yield (%) [a]
 **6**	2.5	:	1	55
 **7**	15	:	1	60
				
 **8**	3.8	:	1	55
 **9**	15	:	1	60
				
 **10**	3.5	:	1	50

[a] Refers to yield over three steps starting from the tertiary alcohol.



Scheme 3 *Reagents and conditions*: i, LDA, tetrahydrofuran, RCHO, −78 °C, 80%; ii, Na–Hg amalgam, Na_2HPO_4, MeOH 20 °C, 60% (+10% of the *Z* disubstituted double bond isomer)

of stereoisomers.‡ In order to make the analysis of the stereochemical outcome of the reaction more straightforward these were decarboxylated to the corresponding sulphones in high yield (Scheme 2). In our previous studies[2] we had shown that the degree of stereocontrol was determined by the relative stereochemistry of the two adjacent chiral centres. The *RR*(*SS*) diastereoisomers gave a poor selectivity of ~2.5:1 *E*:*Z* but the *RS*(*SR*) diastereoisomers gave a ratio of 7:1 *E*:*Z*. Here again the *RR*(*SS*) isomers **6**, **8** and **10** gave poor ratios but the *RS*(*SR*) isomers **7** and **9** now gave an enhanced selectivity of 15:1. This ratio was again largely unaffected by substitution on the double bond, or double bond geometry, and appears to depend solely on the relative stereochemistry of the chiral centres in the starting alcohol (see Table 1). Having developed a highly stereocontrolled route to the desired γ,δ-unsaturated sulphones we have shown that **13** can be coupled to cyclopropane carboxaldehyde to give the 1,4-diene **14** in high yield (Scheme 3).

In conclusion we have shown that tertiary sulphone esters will undergo a Claisen rearrangement to give trisubstituted γ,δ-unsaturated sulphones with a high degree of stereocontrol. Furthermore, we have shown that this methodology can be used to prepare 1,4-dienes in which not only the stereochemistry of the di- and tri-substituted double bonds is carefully controlled, but also that of the intervening sp^3 carbon atom.

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‡ All new compounds gave satisfactory microanalysis.

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