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STEREOSELECTIVE SYNTHESES OF γ-HYDROXY-α,β-UNSATURATED ESTERS: AN ASYMMETRIC VERSION OF THE "SPAC" REACTION

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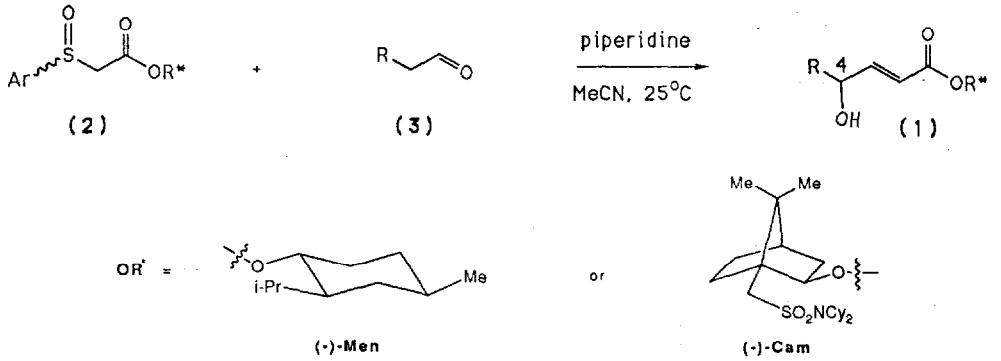
Abstract: Double diastereoselection in the **S**ulfoxide **P**iperidine **A**nd **C**arbonyl (**SPAC**) reactions of sulfinyl acetate esters **(2)** with α-unsubstituted aldehydes **(3)** has been investigated to facilitate asymmetric syntheses of γ-hydroxy-α,β-unsaturated esters **(1)**.

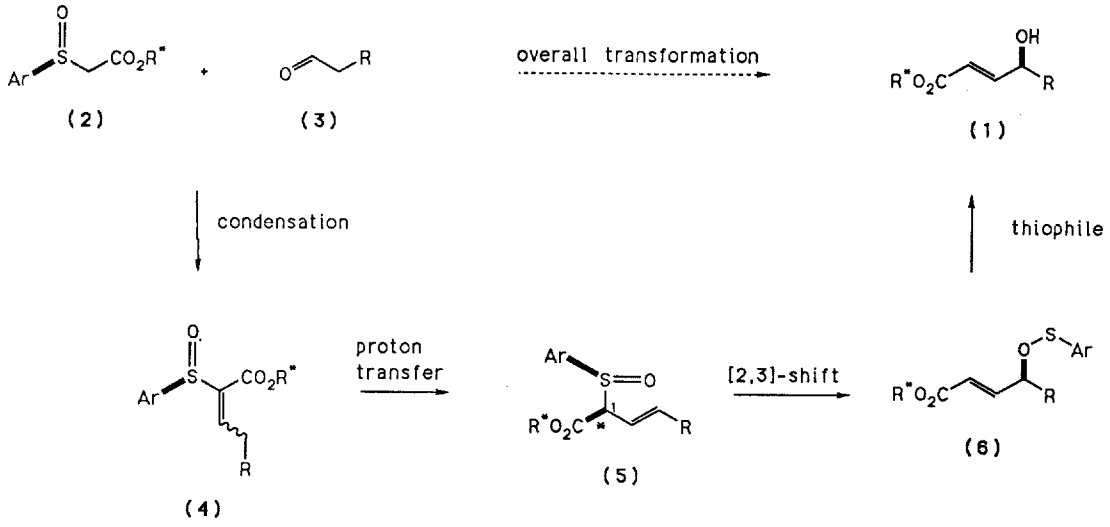
Reactions of sulfinyl acetate esters **(2)** with α-unsubstituted aldehydes **(3)** can be used to effect C=C bond formation with concomitant functional group interconversion of methylene into hydroxymethine groups.[1] The products, γ-hydroxy-α,β-unsaturated esters **(1)**, have functionality suitable for a wide range of chemical manipulations hence this reaction has considerable potential in organic syntheses. Furthermore, the "SPAC" reaction is easy to perform; the aldehyde **(3)** is simply added to an acetonitrile (or benzene) solution of the sulfoxide reagent **(2)** and piperidine.[1] The *only major restriction on this methodology* is lack of effective variants that will furnish the products **(1)** in homochiral form. Recently we initiated research to establish routes to homochiral esters **(1)** starting with a systematic study of double diastereoselection in the reactions of sulfinyl acetate esters **(2)** with α-unsubstituted aldehydes **(3)**; our preliminary results are described here.



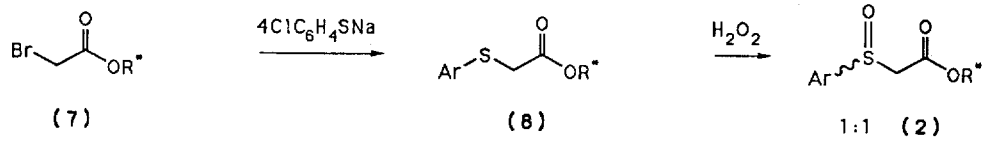
The notion that esters **(2)** of *homochiral* alcohols could produce significant induction in the SPAC reaction was based on mechanistic considerations (Scheme 1). Studies of the [2,3]-sigmatropic shifts of allylic sulfoxides indicate *the*

configurations of alcohols formed in this process are determined exclusively by the asymmetric carbon C^1. The sulfoxide chirality of intermediate **(5)** does not directly effect the stereochemical sense of the [2,3]-sigmatropic shift **{(5) to (6)}**. Asymmetry at sulfur is only significant in the formation of chirality at C^1 in the preceding proton transfer **{(4) to (5)}**; the induction in this step is then expressed in the rearrangement.[2,3] Others have reported that homochiral sulfoxide reagents **(2)** (where R^* is an achiral group) give products of moderate optical activity (less than 72 % e.e. in all cases and usually in the range 15 - 65 % e.e.)[2,4] but the effect of including a chiral auxiliary in the ester group R^* had not been investigated previously. We reasoned the camphor-based auxiliary **(-)-Cam**, widely employed for diastereocontrol of other enolate/electrophile reactions, could be a useful stereochemical template for the key proton transfer step so we prepared sulfinyl acetates functionalized with this auxiliary and examined their behavior in the rearrangement process. Similar reagents were also prepared from (-)-menthol **[(-)-Men]**; this cheap and readily available auxiliary was selected to provide a comparison to gauge the effect of the camphor based system.

Scheme 1



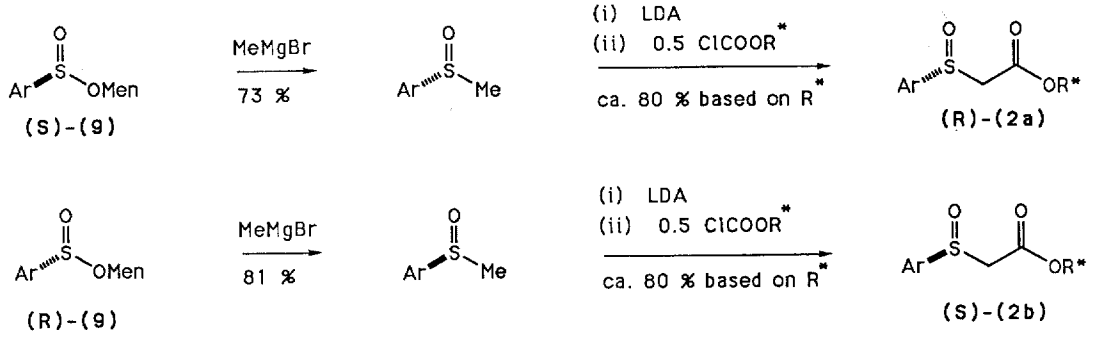
The sulfoxides required for this work were prepared as shown below. Oxidation of the sulfide **(8)** with hydrogen peroxide gave a 1:1 mixture of stereoisomers **(2)** epimeric at sulfur (these were not separable via flash chromatography).



Stereochemically pure reagents **(2a)** and **(2b)** were prepared via an Anderson synthesis using the resolved menthyl sulfinate **(9)** and its enantiomer (Scheme 2).[5] Both optical antipodes of menthol and of the auxiliary **Cam** are commercially available[6] consequently this route is flexible with respect to the preparation of any stereoisomer. For the

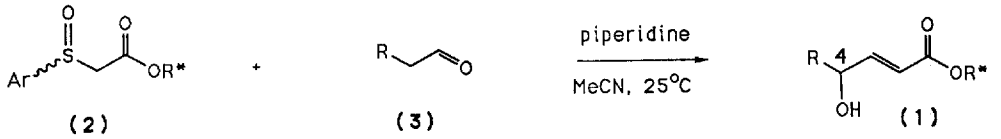
purposes of this study we used one antipode of the auxiliary **[(-)-Cam]** throughout and varied the stereochemistry at sulfur.

Scheme 2



Representative results for the reactions of these reagents are shown below and a typical experimental procedure is given in note 7.

Table Diastereoselective Syntheses of γ-Hydroxy-α,β-unsaturated Esters **(1)**



	OR*	R	configuration at sulfoxide (2)	yield (1) %[a]	ratio of diastereomers R:S (at C^4)[b]
1	(-)-Men	Me	1:1 mixture	69	54:46
2	(-)-Cam	Me	1:1 mixture	78	64:36
3	(-)-Cam	Me	S	83	25:75
4	(-)-Cam	Me	R	69	88:12
5	(-)-Cam	Et	R	89	87:13
6	(-)-Cam	n-Pr	R	93	91:09
7	(-)-Cam	phalCH_2	R	59[c]	88:12
8	(-)-Cam	^{i}Pr	R	98	82:18
9	(-)-Cam	$CyCH_2$	R	86	82:18
10	(-)-Cam	Thex$Me_2SiO(CH_2)_2$	R	98	78:22

[a] Isolated yields after flash chromatography. [b] Determined from ^{1}H NMR of (MPTA) Mosher's ester derivatives.[8] [c] Unoptimized yield, 39 % of the sulfoxide reagent was recovered.

Entries 1 and 2, corresponding to use of reagents **(2)** which are epimeric mixtures of different sulfur configurations, indicate menthyl groups have little influence on the stereochemical outcome of this reaction but the camphor-based

system **Cam** exerts an appreciable effect. The remainder of the results presented in this table illustrate destructive and constructive stereochemical pairing between the sulfoxide functionality and the chiral auxiliary **(-)-Cam**. This camphor system is mismatched[9] with (S)-sulfoxide asymmetry (entry 3) and matched[9] with (R)-chirality (entry 4). Entries 4 - 10 show that the stereochemically-matched reagent reacts highly stereoselectively with different aldehydes. The products of these reactions are crystalline and their stereochemical purity can be improved by recrystallization; for instance, a single recrystallization (absolute ethanol) of the ethyl-substituted compound (from entry 5) gave a sample consisting of more than 95 % of the major diastereomer.

These results show that the sulfoxide asymmetry dominates the diastereoselectivity of these reactions but the auxiliary **Cam** also has a significant effect. We anticipate the stereochemically matched reagent **(2a)** will be most useful for reactions with valuable aldehydes **(3)**, for instance, in ones formed in advanced stages of total syntheses. This approach may also be useful when the rearrangement step is to be followed by Michael additions or Diels Alder cyclizations; such reactions of α,β-unsaturated esters containing the auxiliary **Cam** are likely to be highly stereoselective.[10] Other aspects of asymmetric induction in the SPAC reaction will be reported soon.

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References and Notes

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5 Our procedure was based on Solladie's method for resolving menthyl sulfinates (G. Solladie, J. Hutt, and A. Girardin, Synthesis, 1987, 173) formed from 4-chlorobenzenesulfonic acid (M. Kulka, J. Am. Chem. Soc., 1950, **72**, 1215).
Preparation of the "matched" reagent (2a): A solution of 1.75 g (10.0 mmol) of (R)-(-)-(4-chlorophenyl)methyl sulfoxide in 12 mL of THF was added to 11.00 mmol of LDA in 31 mL of THF and 6 mL of hexane at -78 °C. The resulting deep yellow solution was stirred at -78 °C for 30 minutes. A solution of the chloroformate of the camphor-based auxiliary **(X)** in 22 mL of THF was added dropwise to the solution of the deprotonated sulfoxide at -78 °C; an orange solution formed. (The chloroformate of the camphor auxiliary **(-)-(X)** was formed by reaction of 1.99g, 5.00 mmol, of the alcohol with excess phosgene in the presence of 0.710g, 5.50 mmol, of quinoline in 40 mL of toluene at 0 °C for 52 h; this solution was then filtered and the solvent removed on a vacuum line with *careful disposal of the solvents/excess phosgene removed.)* This was stirred at -78 °C for 45 min.then stored at -23 °C for 45 h. The reaction was quenched by cautious addition of 20 mL of sat. $NH_4Cl_{aq.}$. The organic layer was separated and the aqueous fraction was extracted with 3 X 100 mL of CH_2Cl_2. The combined organic fractions were dried over magnesium sulfate. Removal of solvent gave a residue which was purified by flash chromatography (20 % ethyl acetate in hexane) to give 2.46 g (82 %) of a colorless crystalline substance which was recrystallized from ethyl acetate/hexane. M.p. 111 -112 °C. $[\alpha]_D$ = + 45 ° (c = 0.0098 M in $CHCl_3$). ^1H NMR (δ, p.p.m. at 300 MHz): 7.61 (d, 8.1 Hz, 2H); 7.48 (d, 8.1 Hz, 2H); 5.02 (m, 1H), 3.72 (d, 14.5 Hz, 1H); 3.61 (d, 14.5 Hz, 1H); 3.21 (m, 2H); 3.20 (d, 13.3 Hz, 1H); 2.61 (d, 13.3 Hz; 1H); 2.01 - 0.84 (m, 27 H); 0.97 (s, 3H); 0.84 (s, 3H). ^{13}C NMR (δ, p.p.m. at 300 MHz): 163.9, 142.2, 137.8, 129.8, 125.5, 80.5, 62.5, 57.6, 54.0, 49.8, 49.2, 44.5, 39.4, 32.8, 32.7, 30.5, 27.0, 26.5, 25.2, 20.4, 20.1.
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7 **Reaction of reagent (2a) with pentanal:** A solution of 0.035 g (0.40 mmol) of pentanal in 0.5 mL of acetonitrile was added over 1 h to a stirred solution of 0.034 g (0.40 mmol) of piperidine and 0.048 g (0.0809 mmol) of **(2a)** in 0.20 mL of acetonitrile. The resulting solution was stirred at 20 °C for 56 h. Removal of the volatiles and flash chromatography (20 % ethyl acetate in hexane) gave 0.0395 g (93 %) of the product. This mixture of epimers (87:13, R:S at C^4) is a colorless crystalline material; recrystallization from ethyl acetate/ hexane enhances the purity of the major epimer.
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