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A FACILE ROUTE TO HOMOCHIRAL SULFOXIDES

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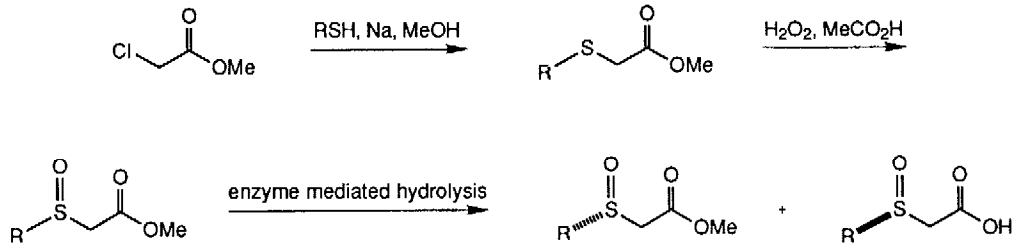
Abstract: Biocatalytic resolutions of methyl sulfinylacetates afford sulfoxides (R)-**(1)** - **(6)** in very high optical yields; the products have been used in a systematic study of the "SPAC" reaction, an asymmetric synthesis of γ-hydroxy-α,β-unsaturated esters.

Applications of enantiomerically pure sulfoxides in organic synthesis[1] have been impeded by lack of convenient methods for their preparation.[2] Generally, the best route to these compounds is still via Andersen's resolution,[3] an approach which requires several steps and is suitable only for the preparation of aryl sulfoxides. Contemporary methods, like those based on diastereoselective[4-6] and enantioselective[7-10] oxidations, give poor induction, are of limited generality, and /or are experimentally tedious. This paper describes a simple, flexible route to homochiral sulfoxides which requires no expensive reagents or special expertise.

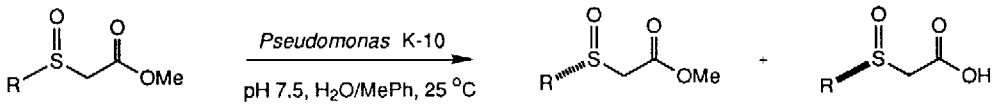


R = 4-$NO_2C_6H_4$, 4-ClC_6H_4, Ph, 4-$MeOC_6H_4$, n-Bu, Cy, t-Bu; compounds **(1)** - **(7)** respectively.

Racemic methyl sulfinylacetates **(1)** - **(7)** are conveniently accessible from reactions of thiolates with methyl chloroacetate followed by hydrogen peroxide oxidation,[11] as shown above. We planned kinetic resolution of these substrates via enzyme mediated hydrolysis. In five screening experiments the 4-chlorophenyl derivative **(2)** was stirred

In pH 7.5 phosphate buffer with different crude enzyme preparations. From the experiments with *Pseudomonas* sp. K-10 (Amano), porcine pancreatic lipase (EC 3.1.1.3, Sigma), and *Pseudomonas* sp. AK (Amano) we recovered optically pure (R)-methyl sulfinylacetate **(2)**. Experiments using *Candida Cylindracea* (EC 3.1.1.3, Sigma) gave optically enriched material (but contaminated with other products) and racemic material was recovered from the experiment with *Mucor Meihei*. *Pseudomonas sp.* K-10 was selected for further studies and the results are shown in Table 1.

Table 1. Biocatalytic Kinetic Resolution of Methyl Sulfinylacetates (1) - (6)



(1) - (7)

compound	R	time (h)[a]	ester		acid[c]	
			% yield	% e.e.[b]	% yield	% e.e.[c]
(1)	4-$NO_2C_6H_4$[d]	96	33	>98	22	97
(2)	4-ClC_6H_4	25	48	>98	38	91
(3)	Ph	55	48	>98	17	92
(4)	4-$MeOC_6H_4$	96	48	>98	34	88
(5)	n-Bu	96	33	>98	-[e]	
(6)	Cy	96	49	>98	18	>98

[a] In general 5 mL of a 1M toluene solution of the racemic sulfoxide was stirred with 40 mL of 0.05 M phosphate buffer (pH 7.5) with 1.0 g of the crude enzyme preparation. After the time indicated the unreacted ester was extracted with diethyl ether, the aqueous phase was then acidified and the acid was extracted with chloroform. The configurations are as shown above. [b] From chiral shift experiments with $Eu(hfc)_3$, monitoring the CO_2CH_3 signal. [c] The crude acid was esterified with diazomethane and the optical purity of the ester produced was determined by chiral shift experiments. [d] This substrate is not very soluble in toluene; however, it did react as a suspension under the conditions outlined in note a but with five times the amount of toluene. [e] The butyl sulfoxides are appreciably less stable than others in this series; the acid was not isolated in this particular experiment. In another run we isolated 40 % of the unreacted ester (90 % e.e.) and 19 % of the acid (54 % e.e.); some racemization of the acid apparently occurred in the work-up procedure.

Pseudomonas K-10 facilitates hydrolyses of functionalized aromatic and aliphatic sulfoxides with high enantioselectivity and at a convenient rate. It is remarkably insensitive to substrate structure, the only case we have observed where this hydrolysis is not successful is for the t-butyl sulfoxide **(7)**. Hydrolysis proceeds at a convenient rate when equal masses of the enzyme and substrate are used, consequently this process is very economical.

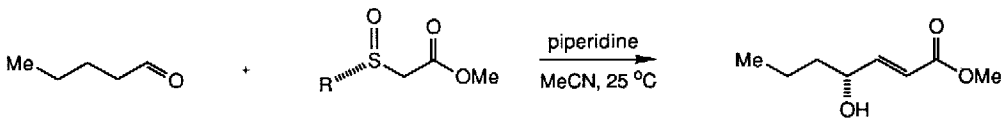
These biocatalytic resolutions can be performed on a large scale as illustrated by the following procedure. A solution of 23.25 g (0.10 mole) of the racemic ester **(2)** in 100 mL of toluene was mixed with 800 mL of pH 7.5, 0.05 M phosphate buffer and 4.65 g of *Pseudomonas* sp K-10 (Amano). This heterogeneous mixture was stirred at 25 °C for 4 days. The mixture was filtered to remove the enzyme and extracted three times with 250 mL of dichloromethane. The aqueous layer was retained and treated as described below. The combined organic fractions were dried ($MgSO_4$); removal of solvent gave 13.16 g of the (R)-ester **(2)**[11,13] of greater than 98 % optical purity ($Eu(hfc)_3$ shift experiment).

Recrystallization of this material from ethanol/hexane gave 8.58 g of sulfoxide **(2)** (mp 63 - 65 °C, $[\alpha]_D$ +201°, 0.0138 M in absolute ethanol). Addition of 200 mL of glacial acetic acid to the aqueous solution and four extractions with 250 mL of chloroform gave an organic fraction that, after drying ($MgSO_4$) and removal of the solvent, gave 3.74 g of (S)-4-chlorophenylsulfinylacetic acid[12] of 96 % e.e.. On recrystallization from ethyl acetate/hexane material of >98 % e.e. was isolated, mp 125 - 127 °C, $[\alpha]_D$ -184° (0.0227 M in absolute ethanol).

We believe this methodology is the most convenient route to homochiral sulfoxides yet reported.[13]

As an initial application of this work we used homochiral (R)-sulfoxides **(1)** - **(6)** to study the effect of sulfoxide substituents on the stereochemical outcome of the "SPAC Reaction", a transformation of particular importance to our research effort.[14] Some of the homochiral sulfoxides required for a systematic study of this kind were hitherto inaccessible. Our results are shown in Table 2.

Table 2. The Effect of Sulfoxide Substituent on the SPAC Reaction



(1) - (6) **(8)**

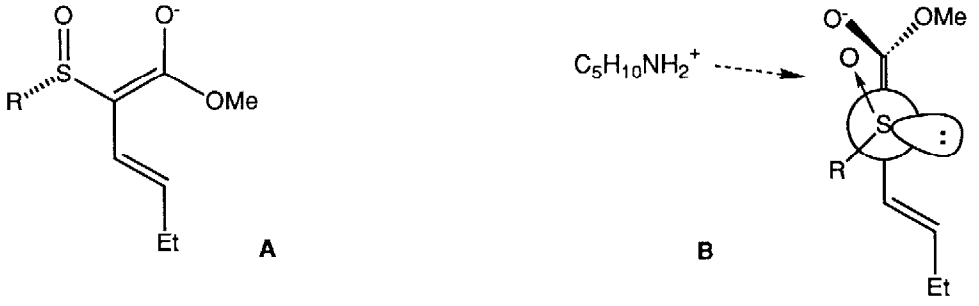
Compound	R	Yield %	Reaction time (h)	% e.e.[b]
(1)	4-$NO_2C_6H_4$	42[a]	8	79
(2)	4-ClC_6H_4	65	3	72
(3)	Ph	68	4	61
(4)	4-$MeOC_6H_4$	52	23	60
(5)	n-Bu	69	20	46
(6)	Cy	74	20	16

[a] Not optimized. [b] Determined by ^1H NMR analysis via the effect of $Eu(hfc)_3$ on the $CO_2C\underline{H}_3$ resonance.

These data indicate large aliphatic substituents (as for compound **(6)**) give poor optical yields of the corresponding (R)-allylic alcohol **(8)**; butylsulfinylacetate **(5)** gives a better induction and the aromatic sulfoxides **(1)** - **(4)** are more effective still. The experiments with the aromatic compounds **(1)** - **(4)** indicate the optical purity of the product is directly related to the electron-withdrawing capacity of the aromatic ring. Stereoselection in this process is determined by diastereofacial selection in protonation of the extended enolate **A** (Figure).[14] Emphatic statements regarding the origin of this induction are premature but, as a working hypothesis, we favor the model **B** shown. This assumes electronic effects are dominant and the reactive conformation of the enolate is therefore that with the sulfur lone pair (the best σ-donor S-substituent) *anti* to the approaching piperidinium ion. Secondary steric effects place the oxygen in the inside

(crowded) position. Diminished stereoselection in the case of the cyclohexyl sulfoxide (**6**), for example, can then be explained in terms of competition of this group for the *anti* position due to its (enhanced) σ-donor properties and large size (we assume the sulfoxide oxygen will occupy the inside crowded position in this case due to a favorable interaction with the approaching electrophile). We are testing this model with respect to other sulfoxides designed to give higher levels of asymmetric induction in the SPAC process.

Figure. A Model Rationalizing Stereoselectivity in the SPAC Reaction



Further papers from our laboratory will focus on other chemistry of homochiral sulfinylacetates.

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