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Preparation of Enantiomerically Pure α-Hydroxymethyl S-*tert*-Butyl Sulfones by *Candida Antarctica* Lipase Catalyzed Resolution

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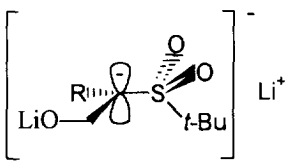
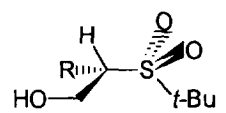
Abstract: *Candida antarctica* lipase (CAL; Novozym 435) catalyzed acylation of racemic methyl and benzyl substituted hydroxy sulfones *rac*-**3a** and *rac*-**3d**, respectively, with vinyl acetate either neat or in ether solvents proceeded with *E*-values of 18 and 49. For the CAL catalyzed hydrolysis of methyl substituted acetoxy sulfone *rac*-**4a** in an emulsion of phosphate buffer and methyl *tert*-butyl ether at pH 7.0 an *E*-value of 22 was found. Acetate (+)-*ent*-**4a** as well as alcohols (-)-**3a** and (-)-(*S*)-**3d** were obtained with ee-values of 99% on a gram scale. Copyright © 1996 Elsevier Science Ltd

Recently we have found that by deprotonation of enantiomerically pure S-*tert*-butyl sulfones, highly enantiomerically enriched α-sulfonyl carbanions can be obtained which are configurationally stable at low temperatures on the time scale of synthesis.[1] This allowed a study of the asymmetric induction exerted by the sulfonyl group in reactions of α-sulfonyl carbanions with electrophiles.[1] We are now interested in non-racemic alkoxide substituted carbanions of type **A**. The introduction of the potentially chelating alkoxide group at the C_α-atom could lead to a significant alteration of the configurational stability and the structure of the α-sulfonyl carbanion. The chemistry of racemic dilithium salts of type **A** has already been successfully explored.[2-6]



A

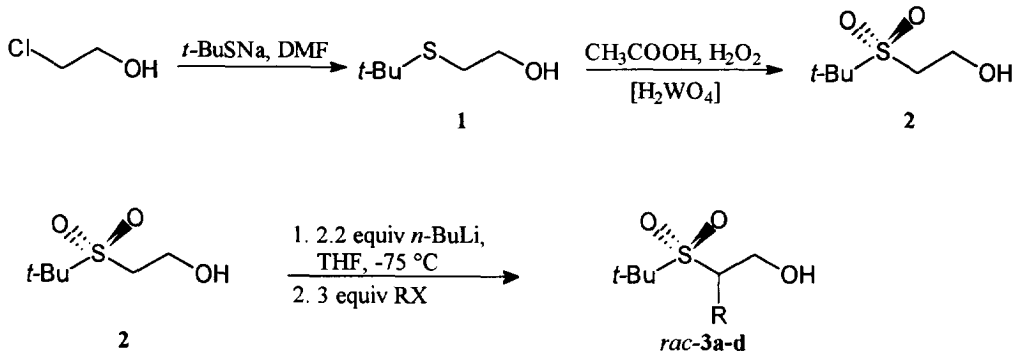


B

Enantiomerically pure hydroxymethyl sulfones of type **B** required for the synthesis of **A** were, however, not available. From our previous work on the lipase catalyzed enantioselective acylation (hydrolysis) of prochiral diols (diacetates)[7] a lipase catalyzed kinetic resolution[8] seemed to be an attractive means to obtain sulfones **B** enantiomerically pure on a gram scale. Hydroxy phenyl sulfones with the stereogenic center other than in the α-position have already been subjected successfully to lipase catalyzed kinetic resolutions.[9-12] We now describe the preparation of enantiomerically pure sulfones of type **B** by a *Candida antarctica* lipase catalyzed resolution.

Synthesis of hydroxy sulfones *rac*-**3a-d** on a gram scale was done as shown in Scheme 1. β-Hydroxyethyl *tert*-butyl sulfide **1** [13] was obtained by treatment of sodium *tert*-butyl thiolate with 2-chloroethanol in 90% yield. Oxidation of **1** with hydrogen peroxide (30%) in glacial acetic acid in the presence of a catalytic amount of tungstic acid gave the hydroxy sulfone **2**[14] in 75% yield. Treatment of sulfone **2** with 2.2 equiv of *n*-butyllithium in tetrahydrofuran (THF) at -75 °C under generation of the corresponding racemic dilithium salt and its reaction with methyl iodide, propyl iodide, allyl iodide and benzyl bromide led to the racemic hydroxy sulfones *rac*-**3a-d** in 70-83% yield.[2-6]

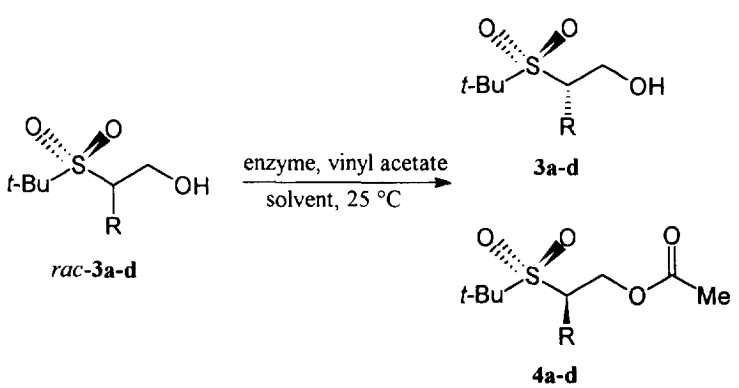
Scheme 1



a: R = Me (82%), **b**: R = *n*-Pr (70%), **c**: R = CH_2-CH=CH_2 (80%), **d**: R = CH_2Ph (83%)

The lipase catalyzed resolution of hydroxy sulfones *rac*-**3a-d** through acylation (Scheme 2) was studied under variation of the enzyme and the solvent with vinyl acetate as acyl donor (Table 1). All reactions were carried out at room temperature. The extend of conversion of the hydroxy sulfone and formation of the acetoxy sulfone were determined by GC. Determination of the ee-values was done by GC on a permethyl β-cyclodextrin fused silica column in the case of **3a-d** and **4a-c**, and by HPLC on a Chiralcel-OD column in the case of **4d**. *E*-values, which characterize the efficiency of the resolution, were calculated according to the literature.[15] The absolute configuration of the hydroxy sulfone (-)-(*S*)-**3d** and thus of the acetoxy sulfone (+)-(*R*)-**4d** was assigned by chemical correlation with (-)-(*R*)-2-(*tert*-butylsulfonyl)-1-phenylpropane[16] via conversion of (-)-(*S*)-**3d** to the corresponding tosylate and its reduction with sodium borohydride.[17]

Scheme 2



From the lipases tested the best results for the resolution of methyl substituted hydroxy sulfone *rac*-**3a** were obtained with immobilized *Candida antarctica* lipase (CAL)[18,19] with *E*-values up to 18 in methyl *tert*-butyl ether (MTBE), THF, diisopropyl ether (DIPE) and neat vinyl acetate with the latter as acyldonor in all cases (Table 1). Lipase AK and lipase PS showed the opposite enantiomer selectivity in the acylation of *rac*-**3a** and *rac*-**3c**, respectively, as compared to CAL. In the kinetic resolution of propyl substituted hydroxy sulfone *rac*-**3b** and allyl substituted hydroxy sulfone *rac*-**3c** under these conditions *E*-values of only up to 6 were found. Selectivities were much higher in the case of the lipase catalyzed acylation of benzyl substituted hydroxy sulfone *rac*-**3d**. However, with the two solvents methyl *tert*-butyl ether and vinyl acetate significantly differing *E*-values were found. From

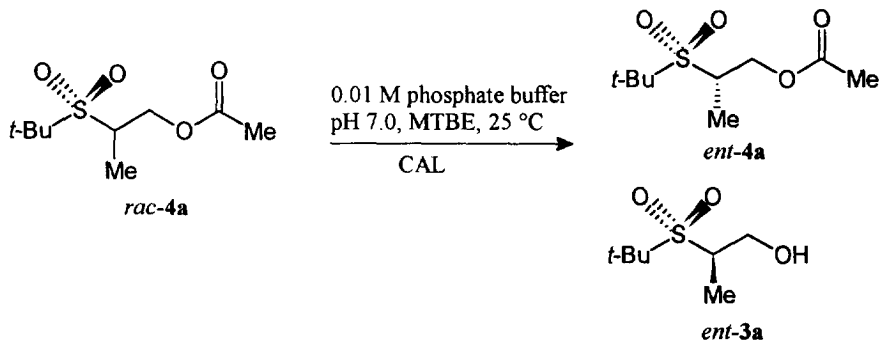
the *E*-values follows that the CAL catalyzed resolution of methyl substituted hydroxy sulfone *rac*-**3a** and benzyl substituted hydroxy sulfone *rac*-**3d** is feasible on a gram scale.[20]

Table 1. Lipase-catalyzed acylation of racemic hydroxy sulfones *rac*-**3a-d**[a,b]

substrate	lipase	solvent	time (h)	conversion (%)	ee (%) alcohol	ee (%) acetate	*E*
rac-**3a**	PCL	toluene	1	69	82	43	5
rac-**3a**	PFL[c]	$CHCl_3$	289	11	5	51	3
rac-**3a**	AKL	toluene	5	44	40	60	5
rac-**3a**	PPL	toluene	191	66	14	9	1
rac-**3a**	CAL	toluene	2	41	44	72	7
rac-**3a**[d]	CAL	THF	5	57	92	73	18
rac-**3a**	CAL	DIPE	2	62	91	60	11
rac-**3a**	CAL	MTBE	2	59	91	66	14
rac-**3a**	PCL	MTBE	3	56	55	49	4
rac-**3a**[e]	CAL	MTBE	2	77	99	-[f]	8
rac-**3a**	CAL	-	3	60	86	-[f]	10
rac-**3b**	CAL	MTBE	68	61	68	43	5
rac-**3b**	CAL	-	167	57	64	47	5
rac-**3c**	CAL	MTBE	49	64	70	42	5
rac-**3c**	CAL	THF	434	51	53	47	5
rac-**3c**	CAL	-	118	65	81	43	6
rac-**3c**	PCL	-	122	63	60	37	4
rac-**3d**[d]	CAL	-	48	55	99	81	49
rac-**3d**	CAL	MTBE	49	54	81	68	13
rac-**3d**	CAL	THF	70	19	18	-[f]	9
rac-**3d**	PCL	-	269	41	38	54	5

[a] In a typical experiment to a solution of the hydroxy sulfone (0.4 to 0.6 mmol) in the given solvent (7 mL) was added the enzyme (50 mg) and vinyl acetate (5 equiv). The suspension was stirred at room temperature for the time given. [b] Lipases used are as follows: *Pseudomonas cepacia* lipase (PCL; lipase PS, Amano), *Pseudomonas sp.* Lipase (AKL; lipase AK, Amano), *Pseudomonas fluorescens* lipase (PFL, Fluka), *Porcine pancreas* lipase (PPL, Sigma), immobilized *Candida antarctica* lipase (CAL; Novozym 435, Novo Nordisk). [c] Only 6 mg enzyme was used. [d] Values taken from the preparative scale experiments. [e] With butyric acid anhydride. [f] Value not determined.

Scheme 3



Resolution by hydrolysis was studied in the case of methyl substituted acetoxy sulfone *rac*-**4a** (Scheme 3). CAL catalyzed hydrolysis of *rac*-**4a** at room temperature in an emulsion of 0.01 M phosphate buffer and MTBE at pH 7.0 proceeded much slower than the acylation of the corresponding

alcohol *rac*-**3a** but with a sufficiently high selectivity as expressed by an *E*-value of 22 (Table 2). The experiment was carried out on a 4.5 mmol as well as on a 83.0 mmol scale.

Table 2. CAL catalyzed hydrolysis of racemic hydroxy sulfone *rac*-**4a**[a]

substrate	conversion (%)	ee (%) *ent*-**3a**	ee (%) *ent*-**4a**	*E*
rac-**4a**	61	61 (54%)[b]	99 (37%)[c]	22

[a] Yields are given in parenthesis. [b] $[\alpha]_D^{23}$ +21.7 (*c* 1.57, $CHCl_3$).
[c] $[\alpha]_D^{23}$ +12.2 (*c* 1.40, $CHCl_3$).

Enantiomerically pure *ent*-**4a** was obtained by carrying the enzymatic hydrolysis of *rac*-**4a** to 61% conversion. The hydroxy sulfone (-)-**3a** (99% ee, $[\alpha]_D^{23}$ -32.4 (*c* 1.0, $CHCl_3$)) was prepared without concomitant racemization by saponification of *ent*-**4a** with K_2CO_3 in MeOH.

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17. Based on this result the absolute configuration of **3a-c** and **4a-c** was tentatively assigned as depicted in Scheme 2.
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20. (a) Alcohol *rac*-**3a** (2.50 g, 14 mmol), CAL (700 mg), vinyl acetate (6.45 ml) and THF (50 mL) were stirred at room temperature. After 57% conversion the enzyme was filtered off and the solvent evaporated. Chromatography of the residue (silica gel, ethyl acetate) gave (-)-**3a** (908 mg, 36%; 92% ee, $[\alpha]_D^{23}$ -28.6 (*c* 1.07, $CHCl_3$)) and (-)-**4a** (1.61 g, 52%; 73% ee, ($[\alpha]_D^{23}$ -9.62 (*c* 1.06, $CHCl_3$)). Saponification of (-)-**4a** with K_2CO_3 in MeOH gave (+)-**3a** (85%; 72% ee). (b) Alcohol *rac*-**3d** (10.00 g, 39 mmol), CAL (10 g) and vinyl acetate (80 mL) were stirred at room temperature. After 55% conversion the enzyme was filtered off and the solvent evaporated. Chromatography of the residue (silica gel, *n*-hexane/ethyl acetate, 3:1) gave (-)-(*S*)-**3d** (4.00 g, 40%; 99% ee, $[\alpha]_D^{23}$ -28.4 (*c* 1.10, $CHCl_3$)) and (+)-**4d** (5.88 g, 51%; 81% ee, $[\alpha]_D^{23}$ +7.0 (*c* 1.03, $CHCl_3$)).

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