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Lipase catalyzed resolution of α-hydroxymethyl sulfones. Determination of absolute configuration by semiempirical calculation of CD spectra and verification by X-ray structure analysis †

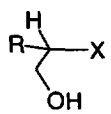
Hans-Joachim Gais*,* Ingo von der Weiden, Jörg Fleischhauer*, Josef Esser and Gerhard Raabe

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule Aachen, Professor-Pirlet-Straße 1, 52056 Aachen, Germany

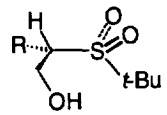
Abstract: The *Candida antarctica* lipase catalyzed esterification of the hydroxymethyl sulfones *rac*-**1a** and *rac*-**1b** led to the isolation of *ent*-**1a** (92% ee) and **1b** (≥99% ee), respectively. The acyloxymethyl sulfone *ent*-**7a** (≥99% ee) was obtained by the *Candida antarctica* lipase catalyzed hydrolysis of *rac*-**7a**. Not only *Candida antarctica* lipase but also *Pseudomonas cepacia* lipase showed the opposite enantiomer differentiation in the esterification of the methyl substituted alcohol *rac*-**1a** and the benzyl substituted alcohol *rac*-**1b**. The absolute configuration of *ent*-**1a** and **1b** was determined by measurement of their circular dichroism and the calculation of the CD spectra of **1a** and **1b** by semiempirical methods. The configurational assignment was verified by X-ray structure analysis of **1b** and *ent*-**7a**. © 1997 Elsevier Science Ltd

Introduction

The enzymatic resolution of alcohols has gained considerable importance in recent years.[1] Currently the resolution of functionalized primary alcohols of type *rac*-**I** using lipases receives much attention.[2] Empirical rules have been proposed for the enantiomeric differentiation of several lipases towards *rac*-**I**.[2a,3] We became interested in the lipase catalyzed resolution of the hydroxymethyl sulfones *rac*-**1**.[4,5] Sulfones **1** are required as educts for our planned enantioselective synthesis of the dianions **2** which are expected to be configurationally stable at low temperatures.[6] In addition to the present objective, the investigation of the lipase catalyzed resolution of *rac*-**1** should yield useful information as to the reliability of the empirical rules which have been proposed for the enantiomer differentiation of lipases towards *rac*-**I**.[2a,3] We now describe in the first part of this paper a study of the resolution of *rac*-**1a–d** by using lipases[7] and in the second part the determination of the absolute configuration of **1a** and **1b** by a semiempirical calculation of their CD spectra and its verification by X-ray structure analysis.



rac-**I**



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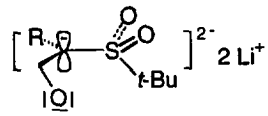

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Results and discussion

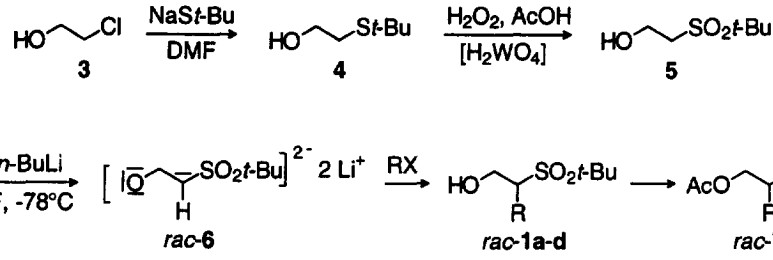
Synthesis of hydroxymethyl sulfones

The α-hydroxymethyl sulfones *rac*-**1a–d** were readily prepared as shown in Scheme 1. Treatment of the chloride **3** with sodium *tert*-butyl thiolate gave the hydroxy sulfide **4** in 90% yield.[8] Oxidation

† Dedicated to Prof. Dr F. Asinger on the occasion of his 90th birthday.

* Corresponding author. Email: Gais@RWTH-Aachen.de

of **4** with hydrogen peroxide in acetic acid/water in the presence of a catalytic amount of tungstic acid afforded the hydroxy sulfone **5** in 75% yield.[9] Deprotonation of **5** with 2.2 equivalents of *n*-butyllithium in tetrahydrofuran at −75°C led to the formation of the dilithium salt *rac*-**6**[10] which upon treatment with methyl iodide, *n*-propyl iodide, allyl iodide and benzyl bromide afforded *rac*-**1a–d** in 70–83% yield. The acetates *rac*-**7a–d** were prepared by esterification of *rac*-**1a–d** in practically quantitative yield.

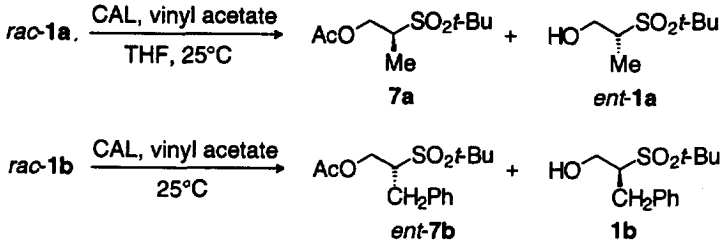


a: R = Me; **b**: R = CH_2Ph; **c**: R = $CH_2CH{=}CH_2$; **d**: R = *n*-Pr

Scheme 1.

Lipase catalyzed resolution

The lipase catalyzed resolution of *rac*-**1a–d** by esterification with vinyl acetate[11] (Scheme 2) was studied under variation of the enzyme and the solvent (Table 1). The best results in the resolution of the methyl substituted alcohol *rac*-**1a** were obtained with immobilized *Candida antarctica* lipase. *E*-Values[12] up to 18 were found for the reaction in methyl *tert*-butyl ether, tetrahydrofuran, diisopropyl ether and neat vinyl acetate, which served as the acyl donor in all cases.



Scheme 2.

All lipases, except *Pseudomonas sp.* lipase, showed a preference for the alcohol **1a** having the (*S*) configuration. The kinetic resolution of the propyl substituted alcohol *rac*-**1d** and the allyl substituted alcohol *rac*-**1c** yielded *E*-values of only up to 6. Selectivities were much higher in the case of the *Candida antarctica* lipase catalyzed esterification of the benzyl substituted alcohol *rac*-**1b**. In this case the *E*-value was strongly dependent on the solvent.

Interestingly, *Candida antarctica* lipase and *Pseudomonas cepacia* lipase showed a reversal of the enantiomer differentiation on going from *rac*-**1a** to *rac*-**1b**. Whereas in the case of the methyl substituted alcohol *rac*-**1a** the (*S*) enantiomer **1a** reacted faster, it was the (*R*) enantiomer *ent*-**1b** in the case of the benzyl substituted alcohol *rac*-**1b** which was transformed preferentially. The empirical rule for *Pseudomonas cepacia* lipase correctly predicts the (*R*) enantiomer *ent*-**1b** to react faster.[2a] It is interesting to note that this rule, which is based on the different size of the substituents that are attached to the stereogenic center, fails in the case of the methyl substituted sulfone *rac*-**1a** where the difference in size is the greatest. The reversal of enantiomer differentiation observed with two different lipases on changing the alkyl substituent from methyl to benzyl suggests that there is another

Table 1. Lipase catalyzed esterification of the alcohols *rac*-**1a–d**[a]

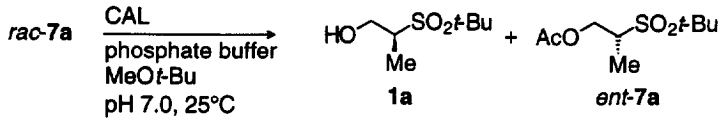
substrate	lipase	solvent	time (h)	conversion (%)	ee (%) alcohol[b]	ee (%) acetate[b]	*E*
rac-**1a**	CAL	THF	5	57	92 (*R*)	73 (*S*)	18
rac-**1a**	CAL	DIPE	2	62	91 (*R*)	60 (*S*)	11
rac-**1a**	CAL	MTBE	2	59	91 (*R*)	66 (*S*)	14
rac-**1a**	CAL	-	3	60	86 (*R*)	66 (*S*)	10
rac-**1a**	CAL	toluene	2	41	44 (*R*)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

[a] CAL, *Candida antartica* lipase; PCL, *Pseudomonas cepacia* lipase; PFL, P*seudomonas fluorescens* lipase; AKL, *Pseudomonas sp.* lipase; PPL, *Porcine pancreas* lipase; THF, tetrahydrofuran; DIPE, diisopropyl ether; MTBE, methyl *tert*-butyl ether. [b]Absolute configuration is given in parenthesis. [c] In neat vinyl acetate.

common factor besides the size of the substituents.[13a] No empirical rule has yet been proposed for the enantiomer differentiation of *Candida antartica* lipase towards primary alcohols.[13b]

The *E*-values found in the case of *Candida antartica* lipase suggested that the synthesis of *ent*-**1a** and **1b** should be feasible on a preparative scale. Thus, the *Candida antartica* lipase catalyzed esterification of *rac*-**1a** in tetrahydrofuran with 5 equiv of vinyl acetate gave the alcohol *ent*-**1a** with an ee-value of 92% in 36% yield and the ester **7a** with an ee-value of 73% in 52% yield (*E*=18). By carrying the esterification further it should be possible to obtain *ent*-**1a** enantiomerically pure. The *Candida antartica* lipase catalyzed esterification of *rac*-**1b** in neat vinyl acetate gave the alcohol **1b** with an ee-value of ≥99% in 40% yield and the ester *ent*-**7b** with an ee-value of 81% in 51% yield (*E*=49).

Resolution by hydrolysis was studied in the case of the esters *rac*-**7a–c**. Much to our surprise, the *Candida antartica* catalyzed hydrolysis of *rac*-**7a** at room temperature in phosphate buffer at pH 7.0 or even in an emulsion of 0.01 M phosphate buffer and methyl *tert*-butyl ether[14] proceeded much slower than the esterification of the corresponding alcohol *rac*-**1a**. However, the *E*-value of 22 suggested that the synthesis of *ent*-**7a** should be possible on a preparative scale (Scheme 3). Thus, the *Candida antartica* lipase catalyzed hydrolysis of *rac*-**7a** in a phosphate buffer/methyl *tert*-butyl ether emulsion gave the ester *ent*-**7a** with an ee-value of ≥99% in 27% yield and the alcohol **1a** with an ee-value of 41% in 61% yield. In the case of *rac*-**7b** (*E*=4) and *rac*-**7c** (*E*=2) the *Candida antartica* lipase catalyzed hydrolysis proceeded only with a low selectivity.



Scheme 3.

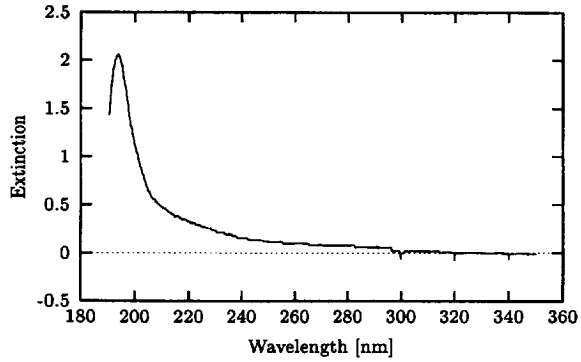


Figure 1. UV spectrum of *ent*-**1a** (c=65.2 mmol/l, d=1 cm) in acetonitrile.

The sulfone *ent*-**1a** of ≥99% ee was prepared without racemization by hydrolysis of *ent*-**7a** with potassium carbonate in methanol/water.

Determination of absolute configuration

Semiempirical calculation of CD spectra

Knowledge of the absolute configuration of the hydroxymethyl sulfones *ent*-**1a** and **1b** is important not only for the planned synthesis of **2** but also for the development of a substrate model for *Candida antartica* lipase whose crystal structure was recently determined.[13b] Since initial attempts to determine the absolute configuration of *ent*-**1a** and **1b** by chemical correlation were only partially successful,[7,15] we decided to measure their circular dichroism and compare it with the calculated CD spectra. The calculation of CD spectra by semiempirical methods has been successfully used for the configurational assignment of biaryl systems[16a,b] and bis(tetrahydropyran-2-yl)methanes.[16c] Because of the high conformational flexibility of the sulfones **1a** and **1b**, it was especially interesting to see whether this method could be applied in these cases too.

The UV spectrum of the sulfone *ent*-**1a** (Figure 1) shows only one sharp band with a maximum at λ=195 nm (ε=32.21·10^3·cm^2·mol^{-1}).

In the UV spectrum of **1b** two absorptions with maxima at λ=259 nm (ε_1=186.72·10^3·cm^2·mol^{-1}) and at λ=210 nm (ε_2=313.73·10^3·cm^2·mol^{-1}), respectively, are observed (Figure 2). The structured band at longer wavelength is easily assigned to the L_b-transition of the phenyl group. The broad absorption around 210 nm is a superposition of the aromatic L_a-band and a $\sigma \rightarrow \sigma^*$-transition, probably occurring at about 190 nm.

For the sulfone *ent*-**1a** the one CD band at λ<180 nm ([θ]>550, $\Delta\varepsilon$>0.167) (Figure 3) is positive. The sulfone **1b** causes two CD bands which are both negative but of significantly different magnitude (Figure 4a,b). The first one is observed at λ=258 nm ([θ]=−90, $\Delta\varepsilon$=−0.027) while the second one occurs at λ<190 nm ([θ]<−43000, $\Delta\varepsilon$<−13). Thus, contrary to the CD band of *ent*-**1a** the CD effects of **1b** are negative.

The CD spectra of **1a** and **1b** were calculated on the basis of MM3-optimized[17] geometries. In both cases the calculations were performed for the (*S*) enantiomer. While in the case of **1a** we found 21 stationary points on the corresponding hypersurface, 40 structures were obtained for **1b**. We then calculated the CD spectra for each of the stationary points by using the semiempirical CNDO/2S

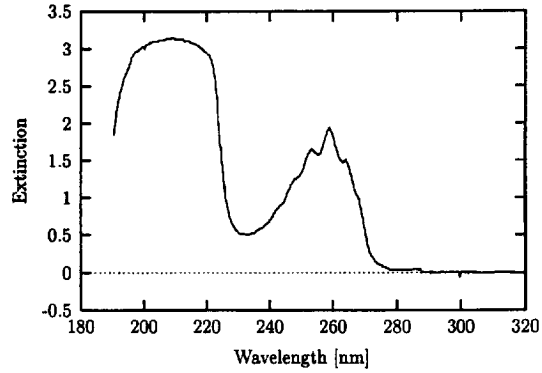


Figure 2. UV spectrum of **1b** (c=10.2 mmol/l, d=1 cm) in acetonitrile.

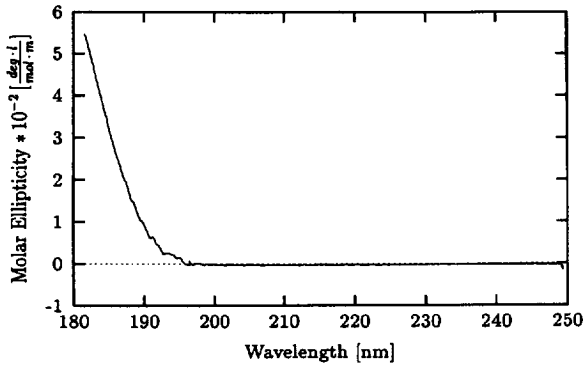


Figure 3. Experimental CD spectrum of *ent*-**1a** (c=0.198 mol/l, d=0.02 cm) in acetonitrile.

method[18] as implemented in the DZDO/MCD3SP[19] package of quantum chemical routines. This method allows calculation of excitation energies and rotational strengths at given molecular geometries. The same calculations, which were performed without d-orbitals, were previously used successfully to calculate the CD spectra of some biaryl systems[16a,b] and bis(tetrahydropyran-2-yl)methanes.[16c] For each molecule 169 singly excited configurations[20] were included in the CI (configuration interaction) calculations. The calculated $\Delta\varepsilon$ curves for each conformer of **1a** and **1b** were represented as sums of Gaussians multiplied with the rotational strength and centered at the wavelengths of the corresponding transitions.[21,22] The final calculated CD spectra were then obtained as Boltzmann-weighted superpositions of the $\Delta\varepsilon$ curves for each conformer[23a] (Figs 5 and 6).

Compared with the experimentally observed CD spectra, the most intensive calculated bands are shifted to the red by about 50 nm. Somewhat smaller red shifts were observed for other compounds,[16a] and in those cases it was shown that this shortcoming does not impair the ability of the method to unambiguously assign the absolute configuration of the molecule. Consequently in the case of the sulfone **1b** the absorption calculated at 243 nm was assigned to the experimentally observed band at 190 nm. According to our calculations the corresponding transition is widely located in the SO_2 segment. The agreement between the observed (Figure 4a) and calculated (Figure 6) sign of the first CD band strongly emphasizes that the absolute configuration of **1b** is indeed (*S*).[23b] Things are different in the case of the sulfone **1a**. Our calculations assuming the (*S*) configuration at C_α result in a *negative* CD band at about 240 nm (Figure 5) which is also due to a transition in the SO_2 group. However, for *ent*-**1a** the experimentally observed CD spectrum shows a *positive* Cotton effect at 190 nm (Figure 3). Thus we conclude that the absolute configuration of *ent*-**1a** is rather (*R*) than (*S*)!

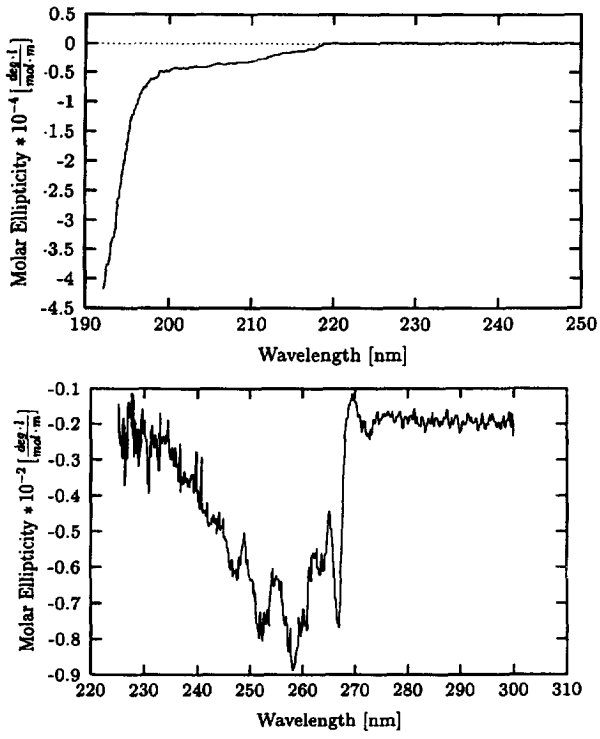


Figure 4. **a.** Experimental CD spectrum of **1b** (c=3.027 mol/l, d=0.01 cm) in acetonitrile. **b.** Experimental CD spectrum of **1b** (c=48.40 mmol/l, d=0.1 cm) in acetonitrile.

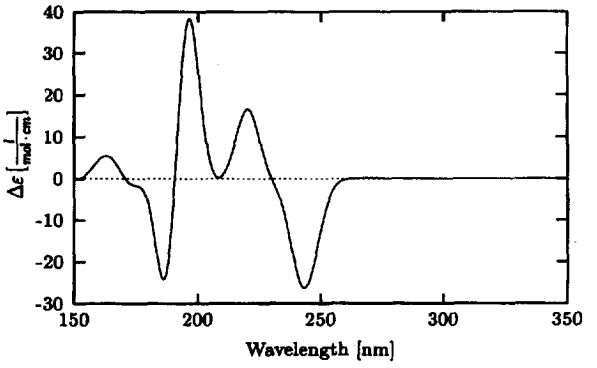


Figure 5. Calculated CD spectrum of **1a**.

X-Ray structure analysis

An independent verification of the above results is not only of high value as far as chemical aspects are concerned but also from the theoretical point of view, since it allows conclusions as to the reliability of the computational approach especially in the case of conformationally highly flexible molecules such as the sulfones **1**. We therefore decided to subject both compounds to X-ray structure analysis.[24] While single crystals of suitable quality were easily obtained in case of **1b**, all attempts to prepare such crystals of compound *ent*-**1a** met with failure. However, the corresponding acetate *ent*-**7a**, in which the absolute configuration at C_α is retained, gave crystals suitable for this purpose. The absolute configuration of both compounds as given in Figs 7 and 8 was determined by refining Flack's absolute

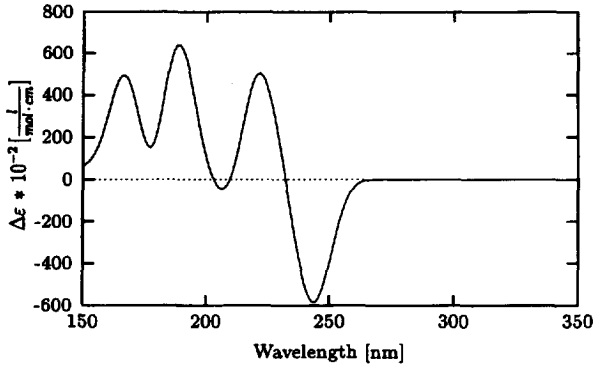


Figure 6. Calculated CD spectrum of **1b**.

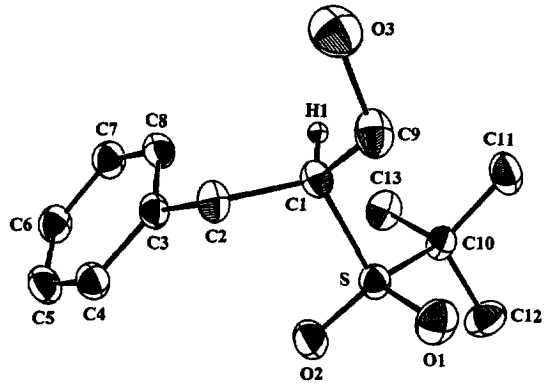


Figure 7. ORTEP drawing of **1b**. The ellipsoids are plotted at the 30% probability level.

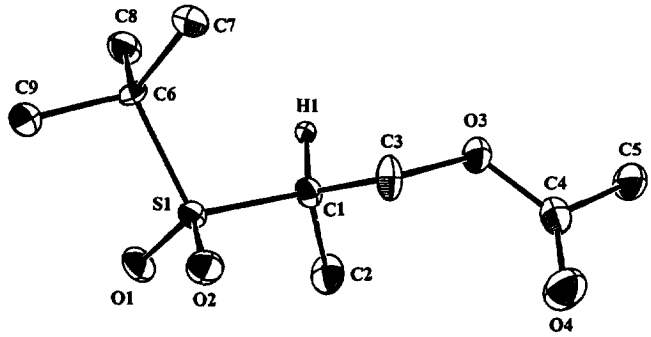


Figure 8. ORTEP drawing of *ent*-**7a**. The ellipsoids are plotted at the 30% probability level.

structure parameter.[25a] It is immediately seen that the results of the X-ray structure determinations confirm our theoretical results. The computational procedure described above can therefore provide a tool to determine the absolute configuration in such cases where X-ray structure determination is not possible.

Experimental

Materials and methods

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise noted. THF was distilled from sodium/benzophenone under nitrogen. DMF was distilled from CaH_2. *n*-BuLi was standardized by titration with diphenylacetic acid. PFL (31 U/mg) was obtained from Fluka, PPL (2000–100000 U/mg) from Sigma, AKL and PCL (30 U/mg) from Amano and immobilized CAL (150 U/mg) (Novozym 435) from Novo Nordisk. TLC was carried out with Merck silica gel coated aluminum foils. Chromatography was performed with Merck silica gel 60 (0.063–0.100 mm). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian VXR 300 or a Varian Unity 500 spectrometer. Peaks in the ^{13}C NMR spectra are denoted as 'u' for carbons with zero or two attached protons or as 'd' for carbons with one or three attached protons, as determined by APT experiments. Mass spectra were obtained with a Varian MAT 212 spectrometer. IR spectra were recorded on a Perkin Elmer PE 1760 spectrometer. Elemental analyses were carried out at the Institut für Organische Chemie microanalytical laboratory. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 22°C. UV-Spectra were recorded on a VARIAN CARY 1-E spectrometer. CD spectra were measured with an AVIV 62 DS spectrometer. The ee-values of **1a–d**, **7a**, **7c** and **7d** were determined by GC with a CP-Chirasil-DEX-CB column (Chrompack, 25 m×0.25 mm). The ee-value of **7b** was determined by HPLC with a chiracel OD-H column (Baker) (*n*-hexane/*i*-PrOH, 95:5, 0.5 mL/min, RI detector).

tert-*Butyl-(2-hydroxyethyl)sulfide* ***4***

t-BuSH (45 g, 0.5 mol) was added dropwise at 5°C under stirring to a suspension of NaH (18 g, 0.6 mol) in DMF (400 mL). After stirring the suspension for 30 min at room temperature, the chloride **3** (44.3 g, 0.55 mol) was added dropwise at 5°C. After stirring the mixture for 12 h at room temperature, it was heated to 80°C for 3 h. The solution was cooled to room temperature, diluted with water (400 mL) and acidified with conc. HCl until a pH of 6.0 was reached. The mixture was extracted with ether and the organic phase washed with saturated aqueous $NaHCO_3$, water and brine. The organic phase was dried ($MgSO_4$) and concentrated under vacuum. Distillation of the residue gave **4** (58.6 g, 87%) as a colorless liquid: bp 80°C (30 Torr); R_f=0.59 (EtOAc/*n*-hexane, 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.55 (s, 1H), 2.77 (t, 2H, *J*=6.1 Hz), 3.72 (q, 2H, *J*=6.1 Hz); ^{13}C NMR (175.64 MHz, $CDCl_3$) δ 31.15 (d), 31.77 (u), 42.36 (u), 61.51 (u); MS (EI, 70 eV): m/z (%) 134 (M^+, 10), 57 (100); IR (kap) ν 3362 (br, s), 2960 (s), 2898 (s), 1667 (w), 1459 (s), 1364 (s), 1288 (m), 1162 (s), 1046 (s), 1008 (s) cm^{-1}. Anal. Calcd for $C_6H_{14}OS$: C, 53.68; H, 10.51. Found: C, 53.41; H, 10.65.

*2-(*tert-*Butylsulfonyl)-ethan-1-ol* ***5***

To a solution of **4** (26.8 g, 0.2 mol) in AcOH (150 mL), which contained a catalytic amount of H_2WO_4, was added at 5°C dropwise 30% aqueous H_2O_2 (91 mL, 0.8 mol). After stirring the mixture for 12 h at room temperature, it was heated to 70°C for 1 h, cooled to 5°C and aqueous NaOH added until a pH of 7.0 was reached. The mixture was extracted with CH_2Cl_2 and the organic phase washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated under vacuum. Distillation of the residue gave **5** (25 g, 74%) as a colorless oil: bp 90°C (0.1 Torr); R_f=0.18 (EtOAc/*n*-hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.90 (s, 1H), 3.20 (t, 2H), 4.20 (dt, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.16 (d), 48.20 (u), 55.68 (u), 59.46 (u); MS (EI, 70 eV): m/z (%) 166 (M^+, 35), 111 (50), 57 (100); IR (kap) ν 3489 (br, s), 2983 (m), 2942 (m), 2360 (w), 1466 (w), 1278 (s), 1113 (s), 1051 (m) cm^{-1}. Anal. Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.48. Found: C, 43.22; H, 8.60.

*(±)-2-(*tert-*Butylsulfonyl)propan-1-ol* rac-***1a***

To a solution of **5** (10.0 g, 0.06 mol) in THF (200 mL) was added dropwise at −78°C *n*-BuLi (1.5 M in *n*-hexane, 88 mL, 0.132 mol). The clear yellow solution was stirred for 30 min, treated dropwise with methyl iodide (7.5 mL, 0.12 mol) and subsequently warmed to 0°C. After the addition of saturated

aqueous NH_4Cl to the mixture, it was extracted with EtOAc. The organic phase was washed with saturated aqueous $Na_2S_2O_3$ and brine, and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by chromatography (EtOAc) afforded *rac*-**1a** (10.7 g, 99%) as a colorless viscous oil: R_f=0.41 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, 3H, *J*=7.39 Hz), 1.44 (s, 9H), 3.16 (dd, 1H, *J*=5.04 Hz), 3.53 (m, 1H), 3.77 (m, 1H, *J*=12.76 Hz), 4.05 (m, 1H, *J*=12.76 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.40 (d), 23.54 (d), 54.71 (d), 60.91 (d), 62.96 (d); MS (EI, 70 EV): m/z (%) 180 (M^+, 20), 125 (55), 57 (100); IR (kap) ν 3476 (br, s), 2983 (s), 2941 (s), 1729 (w), 1643 (w), 1479 (m), 1399 (m), 1278 (s), 1202 (m), 1108 (s),1047 (m), 699 (m) cm^{-1}. Anal. Calcd for $C_7H_{16}O_3S$: C, 46.64; H, 8.95. Found: C, 46.65; H, 9.03.

*(±)-2-(*tert-*Butylsulfonyl)-3-phenyl-propan-1-ol* rac-***1b***

Following the above procedure **5** (15.0 g, 0.09 mol) gave *rac*-**1b** (19.6 g, 86%) as colorless crystals: mp 79°C (EtOAc/*n*-hexane); R_f=0.35 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.00 (dd, 1H, *J*=14.43, 11.08 Hz), 3.01 (s, 1H), 3.26 (dd, 1H, *J*=14.44, 3.69 Hz), 3.54 (m, 1H), 3.89 (t, 2H), 7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.57 (d), 32.46 (d), 59.77 (d), 60.57 (d), 61.37 (u), 127.14 (d), 128.92 (d), 129.10)d), 137.13 (u); MS (EI, 70 eV): m/z (%) 257 (M^++1, 9), 223 (8), 201 (73), 183 (80), 117 (100), 105 (10), 57 (63); IR (KBr) ν 3402 (br, s), 3036 (m), 2975 (m), 2940 (m), 1604 (m), 1500 (s), 1476 (s), 1456 (s), 1400 (s), 1266 (s), 1103 (s), 1049 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_3S$: C, 60.91; H, 7.86. Found: C, 60.64; H, 7.87.

*(±)-2-*tert-*Butylsulfonyl)-pent-4-en-1-ol* rac-***1c***

Following the above procedure **5** (5.00 g, 0.03 mol) gave *rac*-**1c** (4.95 g, 80%) as colorless crystals: mp 36°C; R_f=0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.44 (m, 1H), 2.64 (m, 1H), 3.04 (dd, 1H, *J*=6.05 Hz), 3.38 (m, 1H), 3.97 (m, 2H, *J*=6.05 Hz), 5.19 (m, 2H), 5.80 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 23.48 (d), 31.35 (u), 58.51 (d), 60.27 (u), 61.06 (u), 118.90 (u), 133.21 (d); MS (EI, 70 eV): m/z (%) 207 (M^++1, 2), 151 (70), 133 (7), 67 (30), 57 (100); IR (kap) ν 3494 (br, s), 2980 (m), 2940 (m), 1743 (s), 1641 (w), 1479 (m), 1399 (m), 1368 (m), 1280 (s), 1113 (s), 1045 (m), 925 (m), 664 (m) cm^{-1}. Anal. Calcd for $C_9H_{18}O_3S$: C, 52.40; H, 8.79. Found: C, 52.71; H, 8.97.

*(±)-2-(*tert-*Butylsulfonyl)-pentan-1-ol* rac-***1d***

Following the above procedure **5** (5.24 g, 0.031 mol) gave *rac*-**1d** (4.8 g, 75%) as a viscous, colorless oil; R_f=0.44 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J*=7.38 Hz), 1.43 (s, 9H), 1.38–1.90 (m, 4H), 3.11 (dd, 1H, *J*=6.05 Hz), 3.31 (m, 1H), 3.97 (m, 2H, *J*=6.05 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.94 (d), 20.41 (u), 23.52 (d), 28.73 (u), 59.23 (d), 60.55 (u), 60.99 (u); MS (EI, 70 eV): m/z (%) 209 (M^++1, 2), 153 (20), 135 (6), 105 (5), 69 (11), 57 (100); IR (kap) ν 3496 (br, s), 2964 (s), 2875 (m), 1641 (w), 1466 (m), 1399 (m), 1367 (m), 1278 (s), 1193 (m), 1108 (s), 1051 (m), 802 (w), 657 (m) cm^{-1}. Anal. Calcd for $C_9H_{20}O_3S$: C, 51.89; H, 9.68. Found: C, 52.22, H, 9.74.

*(±)-2-(*tert-*Butylsulfonyl)-propyl acetate* rac-***7a***

To a solution of *rac*-**1a** (15.7 g, 0.087 mol) in toluene (150 mL) were added Ac_2O (8.87 g, 0.087 mmol) and 4-dimethylamino pyridine (DMAP) (10 mg). After stirring the mixture for 12 h at ambient temperatures, it was filtered through a pad of silica gel (EtOAc). The filtrate was washed with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Concentration of the solution gave *rac*-**7a** (18.9 g, 98%) as colorless crystals: mp 35°C; R_f=0.47 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.50 (d, 3H, *J*=7.1 Hz), 2.10 (s, 3H), 3.61 (m, 1H, *J*=7.39, 4.70 Hz), 4.13 (dd, 1H, *J*=7.39, 11.75 Hz), 4.61 (dd, CH_2, *J*=4.7, 11.58 Hz);^{13}C NMR (75 MHz, $CDCl_3$) δ 12.84 (d), 20.77 (d), 23.65 (d), 51.28 (d), 61.14 (u), 63.61 (u), 170.62 (u); MS: m/z (%) 102 (9), 61 (59), 57 (100); IR (KBr) ν 2982 (m), 2943 (m), 1744 (s), 1468 (m), 1394 (m), 1289 (s), 1114 (s), 1039 (m), 802 (w), 722 (m), 663 (m) cm^{-1}. Anal. Calcd for $C_9H_{18}O_4S$: C, 48.63; H, 8.16. Found: C, 48.33; H, 8.29.

*(±)-2-(*tert*-Butylsulfonyl)-3-phenylpropyl acetate* rac-**7b**

Following the above procedure *rac*-**1b** (3.0 g, 0.012 mol) gave *rac*-**7b** (3.4 g, 95%) as colorless crystals: mp 68°C; R_f=0.51 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.99 (s, 3H), 3.06 (dd, 1H, *J*=9.74, 14.44 Hz), 3.41 (dd, 1H, *J*=4.70, 14.44 Hz), 3.70 (m, 1H), 4.30 (dd, 1H, *J*=5.04, 12.09 Hz), 4.41 (dd, 1H, *J*=5.04, 12.09 Hz), 7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.64 (d), 23.59 (d), 32.94 (u), 57.21 (d), 61.48 (u), 127.09 (d), 128.84 (d), 129.11 (d), 137.29, 170.45; MS (EI, 70 eV): m/z (%) 238 (6), 133 (6), 118 (100), 105 (3), 91 (16), 77 (2), 57 (59); IR (KBr) ν 3090 (w), 3068 (m), 3033 (m), 1741 (s), 1605 (w), 1497 (m), 1457 (s), 1383 (m), 1364 (m), 1289 (s), 1236 (s), 1116 (s), 804 (m), 698 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_4S$: C, 60.38; H, 7.43. Found: C, 60.41; H, 7.62.

*(±)-2-(*tert*-Butylsulfonyl)-pent-4-enyl acetate* rac-**7c**

Following the above procedure *rac*-**1c** (3.0 g, 0.015 mol) gave *rac*-**7c** (3.53 g, 98%) as colorless crystals: mp 49°C; R_f=0.40 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.09 (s, 3H), 2.66 (m, 2H), 3.50 (m, 1H, *J*=5.37 Hz), 4.30 (dd, 1H, *J*=5.71, 12.09 Hz), 4.53 (dd, 1H, *J*=5.37, 12.08 Hz), 5.20 (m, 2H), 5.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.79 (d), 23.52 (d), 31.39 (u), 55.07 (d), 61.29 (u), 61.40 (u), 119.34 (u), 133.17 (d), 170.54 (u); MS (EI, 70 eV): m/z (%) 249 (M^++1, 1), 193 (1), 96 (9), 68 (93), 57 (100); IR (KBr) ν 3079 (w), 2981 (m), 2939 (m), 1736 (s), 1643 (m), 1475 (m), 1458 (m), 1392 (m), 1277 (s), 1242 (s), 1114 (s), 1092 (m), 919 (m), 720 (w), 676 (w) cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.29; H, 8.12.

*(±)-2-(*tert*-Butylsulfonyl)-pentyl acetate* rac-**7d**

Following the above procedure *rac*-**1d** (3.0 g, 0.014 mol) gave *rac*-**7d** (3.33 g, 95%) as a viscous, colorless oil: R_f=0.47 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J*=7.39 Hz), 1.44 (s, 9H), 1.40–2.04 (m, 4H), 2.09 (s, 3H), 3.42 (m, 1H, *J*=5.37, 5.71 Hz), 4.27 (dd, 1H, *J*=5.71, 12.08 Hz), 4.56 (dd, 1H, *J*=5.37, 12.08 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.92 (d), 20.25 (u), 20.81 (d), 23.59 (d), 28.91 (u), 55.55 (d), 61.16 (u), 61.88 (u), 170.64 (u); MS (EI, 70 eV): m/z (%) 70 (54), 57 (100); IR (kap) ν 2965 (s), 2937 (m), 2875 (m), 1745 (s), 1479 (m), 1466 (m), 1385 (m), 1367 (m), 1283 (s), 1111 (s), 1047 (m), 802 (w), 704 (m) cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_4S$: C, 52.77; H, 8.86. Found: C, 53.11; H, 9.14.

Enzymatic esterification

In a typical experiment the crude lipase (50 mg) and vinyl acetate (5 equiv) were added to a solution of the hydroxy sulfone (100 mg) in the solvent given (7 mL) in a 10 mL vial. Prior to this it was shown that no uncatalyzed conversion took place by running each experiment for 12 h without the enzyme. Periodically aliquots were taken from the stirred reaction mixture and assayed by GC and HPLC as described above.

*(R)-2-(*tert*-Butylsulfonyl)propan-1-ol* ent-**1a**

To a solution of *rac*-**1a** (2.5 g, 14 mmol) in THF (50 mL) and vinyl acetate (6.45 mL, 5 equiv) was added CAL (700 mg) and the suspension stirred at ambient temperature. After GC analysis indicated a 57% conversion (5 h), the enzyme was filtered off and the solvent evaporated. Chromatography of the residue (EtOAc) gave *ent*-**1a** (908 mg, 36%): 92% ee; $[\alpha]_D$ −28.6 (*c* 1.07, $CHCl_3$) and **7a** (1.61 g, 52%): 73% ee; $[\alpha]_D$ −9.62 (*c* 1.06, $CHCl_3$).

*(S)-2-(*tert*-Butylsulfonyl)-3-phenyl-propan-1-ol* **1b**

To a solution of *rac*-**1b** (10 g, 39 mmol) in vinyl acetate (80 mL) was added CAL (10 g) and the suspension stirred at ambient temperature. After GC analysis indicated a 55% conversion (48 h), the enzyme was filtered off and the solvent evaporated. Chromatography of the residue (EtOAc/*n*-hexane, 1:3) gave **1b** (4.00 g, 40%): ≥99% ee (GC); $[\alpha]_D$ −28.4 (*c* 1.10, $CHCl_3$) and *ent*-**7b** (5.88 g, 51%): 81% ee; $[\alpha]_D$ +7.0 (*c* 1.03, $CHCl_3$).

(R)-2-(tert-Butylsulfonyl)-propyl acetate ent-7a

To a solution of *rac*-**7a** (1.0 g, 4.5 mmol) in 0.01 M phosphate buffer, pH 7.0 (100 mL) and MTBE (2 mL) was added CAL (600 mg). The suspension was stirred in such a way that an emulsion formed. The pH of the mixture was maintained at 7.0 by a pH-stat. After GC analysis indicated a 61% conversion (114 h), the enzyme was filtered off and the filtrate was extracted with EtOAc. The organic phase was washed with brine and dried ($MgSO_4$). Concentration of the solution under vacuum and purification of the residue by chromatography (EtOAc) gave **1a** (440 mg, 54%): 61% ee; $[\alpha]_D$ +21.7 (*c* 1.57, $CHCl_3$) and *ent*-**7a** (373 mg, 37%): ≥99% ee; $[\alpha]_D$ +12.2 (*c* 1.40, $CHCl_3$). The hydrolysis has been carried out on an 83 mmol scale with the same results.

Synthesis of ent-***1a*** *from* ent-***7a***

To a solution of *ent*-**7a** (100 mg, 0.45 mmol) in MeOH/H_2O, 10:1 (22 mL) was added K_2CO_3 (62 mg, 0.45 mmol). After stirring the mixture for 3 h at ambient temperatures, it was diluted with H_2O and extracted with EtOAc. The organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave *ent*-**1a** (70 mg, 86%): ≥99% ee, $[\alpha]_D^{23}$ −32.4 (*c* 1.00, $CHCl_3$). The hydrolysis has been carried out on an 18 mmol scale with the same results.

X-Ray structure determination of ***1b*** *and* ent-***7a***

A crystal of **1b** was transferred to a glass capillary and mounted on the goniometer head of a diffractometer. Graphite-monochromated Cu–Kα radiation (λ=1.54179 Å) was used to collect data in the range $\pm h,k,\pm l$ at room temperature. A crystal of *ent*-**7a** was mounted directly on top of a glass capillary tipped with highly viscous joint grease in a stream of cooled nitrogen. In this case graphite-monochromated Mo-Kα radiation (λ=0.71069 Å) was used to collect data in the range *h,k,l* at −70°C. The data sets of both compounds were collected using an ENRAF NONIUS CAD4 four circle diffractometer. Data were corrected for Lorentz and polarization effects but not for absorption effects. The structure of *ent*-**7a** was easily solved by direct methods as implemented in the XTAL3.2 crystallographic program package,[25b] employing GENSIN[25c] to generate structure invariant relationships and GENTAN[25d] for the general tangent phasing procedure. In the case of compound **1b** the space group $P\,2_1$ was indicated by the systematically absent intensities. However, no solution was obtained assuming this symmetry. Therefore, the structure was solved in the triclinic space group $P1$ resulting in two symmetrically independent molecules in the asymmetric unit. The refined coordinates of one of them were then fitted to the $P\,2_1$ cell, and they turned out to be a suitable starting point for final full-matrix least-squares refinement in this space group. Most hydrogen atoms were calculated in idealized positions, and their positional parameters were kept constant in the refinement process. Their U_{is} were fixed at 1.5 times the equivalent isotropic displacement parameter of the relevant heavy atoms prior to the final full-matrix least-squares refinement. Friedel pairs were collected for both compounds and the Friedel-equivalent data were not merged in the final refinement process.

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22. The Gaussians were generated using a half bandwith of 10 nm.
23. (a)

$$\Delta\varepsilon = \sum_{i=1}^{N} w_i \cdot \Delta\varepsilon_i, \qquad w_i = [\exp(-E_i/R \cdot T)]/[\sum_j \exp(-E_j/R \cdot T)]$$

N is the number of located stationary points, $\Delta\varepsilon_i$ is the superposition of Gaussians, w_i and E_i are the Boltzmann factor and the energy of the i-th local minimum, respectively. (b) The experimentally observed CD band occuring with very low intensity at λ=258 nm does not appear in our calculated CD spectrum. Perhaps more local minima have to be taken into account to reproduce this part of the spectrum.
24. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [Fax: +44 (1223) 336033; Email: deposit@chemcrys.cam.ac.uk].
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