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Lipase Catalyzed Resolution of 1-*t*-Butylthio-2-alkanols: Enzyme Mediated Routes to Enantiomerically Pure 1,2-Epoxyalkanes and 2-Alkanols

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Abstract: *A series of 1 - t-butylthio-2-alkanols (R)- and (S)-* ***1 - 5*** *were prepared via lipase catalyzed resolution of the corresponding chloroacetates (±)-* ***1a - 5a*** *and further converted into the optically pure alkyloxiranes (R)-* ***6 - 8*** *and 2-alkanols (R)-* ***14 - 15***

Enantiomerically pure alkyloxiranes (1,2-epoxyalkanes) like (*R*)- and (*S*)- **6 - 10** are versatile precursors for numerous optically pure natural products, pharmaceuticals and polymers [1]. Of similar importance for numerous applications are enantiomerically pure 2-alkanols (*R*)- and (*S*)- **11 - 15** [2], which are of considerable interest also as building blocks for liquid crystalline materials having ferroelectric properties [3]. While compounds of this kind, carrying short aliphatic substituents (with up to four carbon atoms) can frequently be prepared from molecules of the chiral pool, substances with longer alkyl residues are not accessible this way. Consequently, general routes to these molecules in enantiomerically pure form are of considerable synthetic interest.
We now wish to report such facile routes to these classes of compounds *via* the (*R*) - and (*S*) - 1- *t*-butylthio-2-alkanols (*R*)- and (*S*)- **1 - 5**, which are conveniently accessible by esterhydrolase catalyzed resolution of the corresponding chloroacetates (*R,S*)- **1a - 5a** [4] (Scheme).

(*R,S*)- **1 - 5** are easily prepared in high isolated yields (92 - 98 %) *via* nucleophilic ring opening of the corresponding *racemic* oxiranes with sodium *t*-butylthiolate and can be conveniently transformed into the racemic chloroacetates (*R,S*) - **1a - 5a** by acylation with ($ClCH_2CO)_2O$ / pyridine. Enzymatic hydrolysis of (*R,S*)- **1a - 5a** in presence of the esterhydrolase (lipase) from *Pseudomonas cepacia* (SAM -I) [5a] proceeded with very high enantioselectivity. Thus 10 to 500 mmol of the substrate were emulsified in 20 to 500 ml phosphate buffer of pH 7.0 by stirring. The enzymatic hydrolysis was initiated by addition of 50 to 500 mg of the lipase while the pH of the reaction mixture was maintained at pH 7.0 by continous addition of 1 molar NaOH
(pH-stat. conditions). All reactions came to a complete standstill after 50 % conversion in 0.5 to 8 hours leading to (*R*)- **1 - 5** and (*S*)- **1a - 5a** in enantiomerically pure form (Table 1) as determined by ^{1}H-NMR spectroscopy of the corresponding "Mosher esters" [6].

Scheme

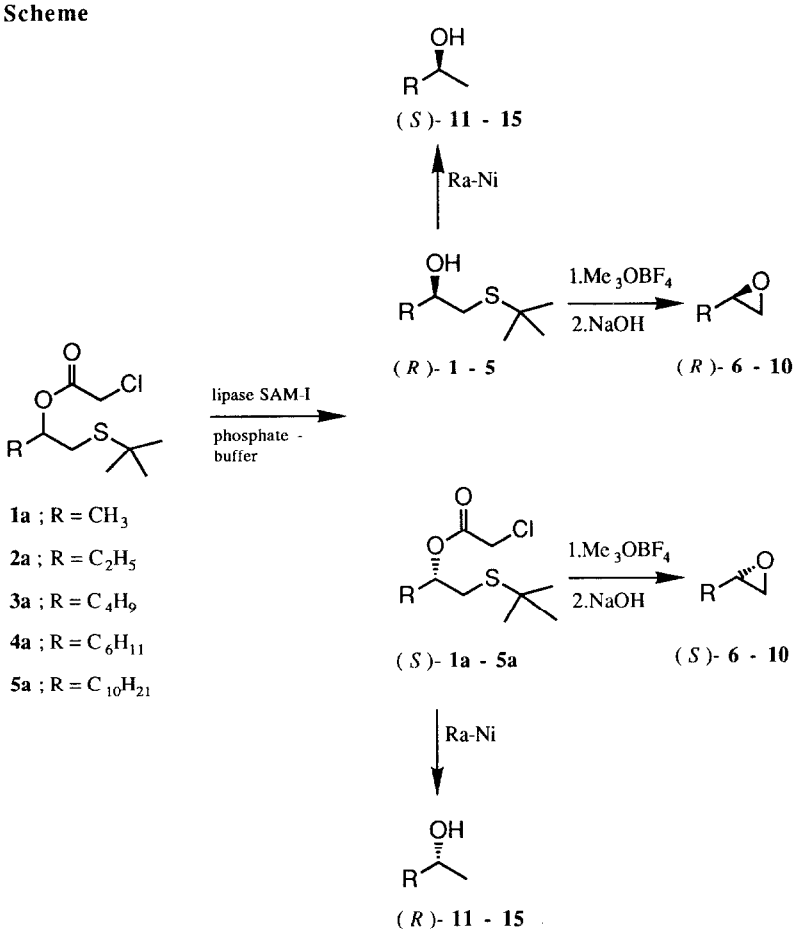

Table 1

Substate	R =	Conversion (%)	Product	% ee [a]	E[b]
(±)- **1a**	CH_3	50	(*R*)- **1**	>96	>100
			(*S*)- **1a**	>96	
(±)- **2a**	C_2H_5	50	(*R*)- **2**	>96	>100
			(*S*)- **2a**	>96	
(±)- **3a**	C_4H_9	50	(*R*)- **3**	>96	>100
			(*S*)- **3a**	>96	
(±)- **4a**	C_6H_{11}	50	(*R*)- **4**	>96	>100
			(*S*)- **4a**	>96	
(±)- **5a**	$C_{10}H_{21}$	50	(*R*)- **5**	>96	>100
			(*S*)- **5a**	>96	

a) Determined by ^{1}H-NMR of the corresponding Mosher - Ester; b) for definition of E see ref. 11

The use of chloroacetates not only led to much more rapid enzymatic hydrolysies as compared to non activated esters [7], but due to the substantial differences in boiling points also allowed an extremely facile separation of the resulting products by simple vacuum distillation. The obtained chloroacetates (*S*)- **1a - 5a** can be conveniently converted into the corresponding alcohols (*S*)- **1 - 5** by hydrolysis using K_2CO_3 / MeOH.

The convenient accessibility of the starting materials, the high enantioselectivity of the resolution step and the facile separation of the reaction products allow a facile preparation of (*R*)- and (*S*)- **1 - 5** in the laboratory on a 50 g scale, quantities which are sufficient for further synthetic transformations as demonstrated below.

Thus S-alkylation of (*R*)- **2 - 4** with Meerwein salt, followed by base treatment [8] led in a one pot reaction to the enantiomerically pure oxiranes (*R*)- **7 - 9** (Scheme, Table 2).

Table 2

substrate	R =	Product	Yield[a] (%)	[a]$^{D;20}$ = (c= , solvent)	ee [b] (%)
(*R*)- **2**	C_2H_5	(*R*)- **7**	63	+13.5 [c] (1.03, ether)	>95
(*R*)- **3**	C_4H_9	(*R*)- **8**	65	+9.6 (0.76, EtOH)	>95
(*R*)- **4**	C_6H_{13}	(*R*)- **9**	76	+14.2 [d] (2.48, EtOH)	>95

a) isolated; b)determined by ^{1}H-NMR in presence of chiral shift reagent ; c) Lit. 12: [α]$^{D;21}$ = +13.6 (1.135,ether); d) Lit 14.: [α]$^{D;21}$ = +14.5 (3.62,EtOH)

These compounds in turn can serve as excellent starting materials for numerous other molecules, e.g. enantiomerically pure δ- lactones of importance as flavour compounds and pheromones [9].

Attempts to prepare chiral 2- alkanols from the β- hydroxythioethers **1 - 5** by reductive desulfuration with commercially available Raney - Nickel failed. Even with a very large exess of Raney - Nickel the desulfuration was too sluggish to be of preparative use. Further investigations showed that best results were achieved by the use of freshly prepared platinated Raney - Nickel T4 [10] in methanol. Thus reductive desulfuration of (*S*)- **4, 5** using this Raney - Nickel led to the enantiomerically pure 2-alkanols (*R*)- **14, 15** in high yields (Scheme , Table 3).

Table 3

substate	R =	Product	Yield[a] (%)	[a]$^{D;20}$ = (c= , solvent)	ee [b] (%)
(*S*)- **4**	C_6H_{13}	(*R*)- **14**	83	-8.0 [c] ($0.88,CHCl_3$)	>96
(*S*)- **5**	$C_{10}H_{21}$	(*R*)- **15**	91	-5.0 [d] (0.55, EtOH)	>96

a) isolated; b) determined by ^{1}H-NMR of the Mosher - Ester; c) Lit.14: for (*S*)- **14** [α]$^{D;20}$ = +8.1 (2.815, $CHCl_3$); Lit.15 : [α]$^{D;20}$ = -4.8, (c = 5, EtOH)

In summary, the convenient accessibility of the title compounds provides excellent starting materials for numerous synthetic applications including the preparation of enantiomerically pure β- hydroxysulfoxides and sulfones, the chemistry which is currently under intensive investigation in our laboratory.

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REFERENCES

1. Review: A.S. Rao, S.K. Pakinikar and J.G. Kirtane, *Tetrahedron* 1983, **39**, 2323 and cited literature.
2. *Aldrichimica Acta* 1980, **13**, 13
3. K. Terashima, M. Ichihashi, M. Kikuchi, K. Furukawa and T. Inukai, *Mol. Cryst. Liq. Cryst.* 1986, **141**,237; K. Seto, H. Shimojitosho, H. Imazaki, H. Matsubara and S. Takahashi, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1020
4. Although in some instances good results were obtained with the previously investigated 1-phenylthio-2-alkanols [5], the achieved enantiomeric purities were often unsatisfactory, especially with derivatives carrying long chain alkyl residues
5. U. Goergens and M.P. Schneider, *J.Chem.Soc.,Chem.Commun.* **1991**, 1064

5a. Lipase from *Pseudomonas cepacia* (SAM-I) from Amano Pharmaceutical Co., supplied by Fluka AG, CH - 9470 Buchs and Mitsubishi International GmbH, D - 4000 Düsseldorf 1, Germany (±)- **4a** is also resolved by a Cholesterolesterase from *Pseudomonas sp.*supplied by Boehringer Mannheim GmbH.

6. J.A. Dale and H.S. Mosher, *J. Am. Chem. Soc.*1973, **95**, 512
7. Typically rate increases of up to 20 fold are observed in comparison to the corresponding acetates; compare: K. Laumen and M.P. Schneider, *J.Chem.Soc.,Chem.Commun.* **1988**, 598
8. C.R. Johnson, C.W. Schroeck and J. Shanklin, *J.Am.Chem.Soc.* 1973, **95**, 7424
9. U. Goergens and M.P. Schneider, *Tetrahedron Asymmetry* 1992, **3**, 831
10. F.Zymalkowski in Houben-Weyl, Methoden Org. Chem. Vol. 4 / 1c, p. 23, Georg Thieme Verlag Stuttgart, New York 1980
11. C.S. Chen, Y. Fujimoto, G. Girdaukas and C.J. Sih, *J.Am.Chem.Soc.* 1982, **104**, 7294
12. K.Mori, M.Sasaki, S.Tamada, T.Suguru, S.Masuda, *Tetrahedron* 1979, **35**, 1601
13. R.K.Hill, *J.Am.Chem.Soc.* 1957, **80**, 1611
14. E.Keinan, E.K.Hafeli, K.K.Seth, R.Lamed, *J. Am. Chem. Soc.*, 1986, **107**, 162
15. G.Kirchner, M.P.Scollar, A.M.Klibanov, *J.Am. Chem. Soc.*, 1985, **107**, 7072