A Facile Chemoenzymatic Route to Enantiomerically Pure Oxiranes: Building Blocks for Biologically Active Compounds

Ulrich Goergens and Manfred P. Schneider*

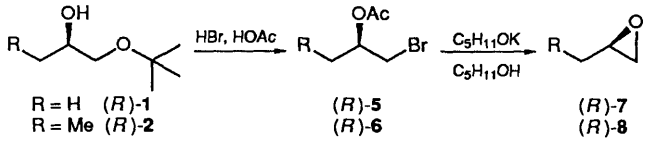
FB 9-Bergische Universität, GH-Wuppertal, D-5600 Wuppertal 1, Germany

The enantiomerically pure building blocks (*R*)- and (*S*)-**1–4** were prepared both by enantioselective, enzymatic hydrolysis and by acyl transfer, and subsequently converted into the corresponding enantiomerically pure oxiranes (*R*)- and (*S*)- **7** and **8**.

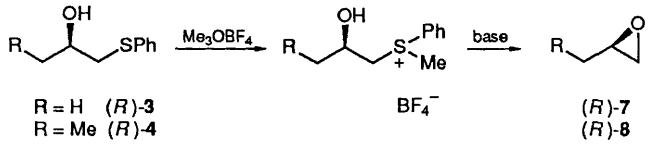
Enantiomerically pure oxiranes are versatile building blocks for the preparation of optically pure natural products, pharmaceuticals and polymers.[1] In spite of the availability of numerous methods for the synthesis of these compounds a short and facile route leading with high chemical yield to enantiomerically pure oxiranes would be very useful. In view of our previous work in this area we felt that an ester hydrolase-catalysed resolution of suitable precursors may provide an attractive alternative route to these target molecules. Suitable precursors should carry a temporary, sterically demanding substituent in order to achieve the required high degree of enantiomer differentiation which could finally be transformed into a good leaving group. The use of tosylates[2] for this purpose proved to be unsatisfactory in our hands. We found that monotosylates of diols are difficult to manipulate and to prepare in chemically pure form.

We found that a highly efficient process can be based on alkan-2-ols carrying *tert*-butyl-[(±)-**1**,**2**] or phenylthio-[(±)-**3**, **4**] protecting groups. These substrates are either available commercially [(±)-**1**][3] or can be prepared easily from readily available starting materials [(±)-**2**–**4**].†

Ester hydrolases are well known for their capability to differentiate between enantiomeric esters or alcohols by hydrolysis [eqns. (1), (2)] or acyltransfer [eqns. (3), (4)]



Scheme 1



Scheme 2

† (±)-**2** is easily obtained by reaction of butane-1,2-diol with isobutene under acid catalysis; (±)-**3**,**4** were prepared by nucleophilic ring opening of the oxirane with sodium benzenethiolate.

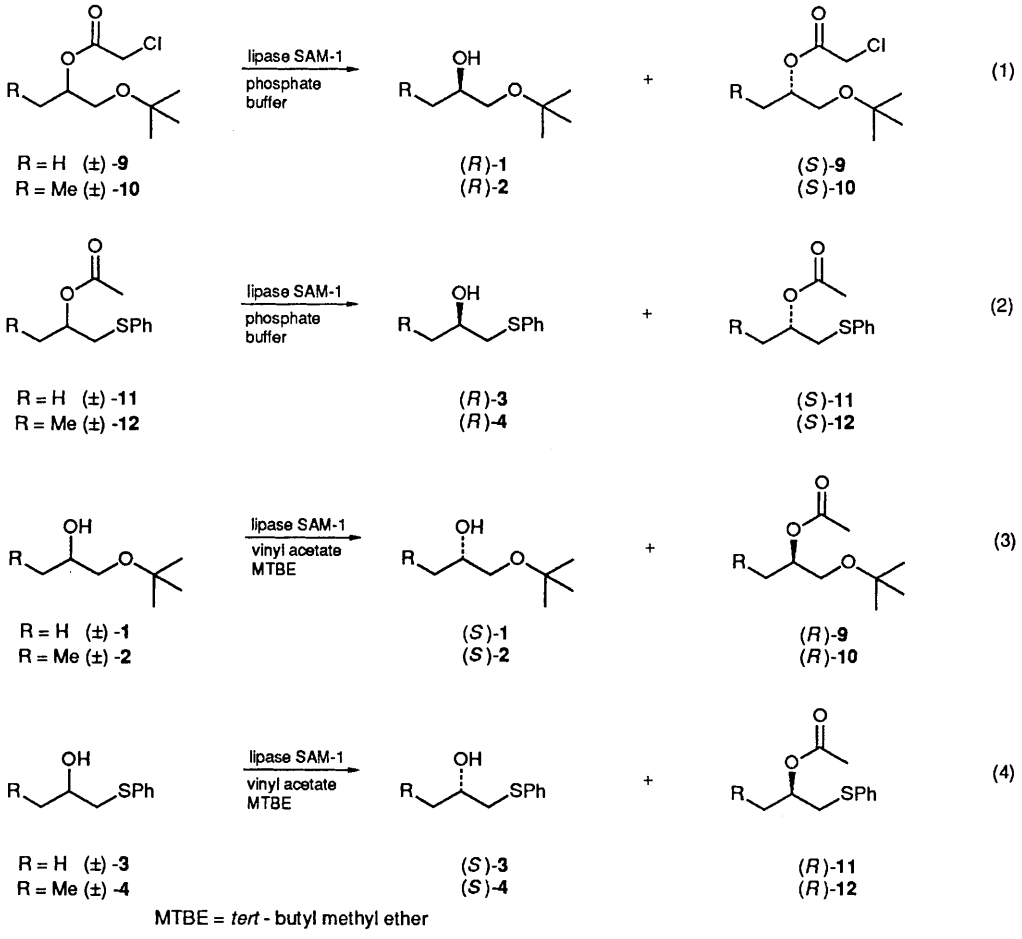


Table 1 Enzymatic hydrolysis of **9**, **10** and **11**, **12** in the presence of a lipase from *Pseudomonas fluorescens* (SAM-1)[4]

	Conversion (%)	Product	E.e. (%)	$[\alpha]_D^{20}$[d]	*c*	*Ef*
(±)-**9**	50	(*R*)-**1**	>98[a]	−24.2°	1.1	>100
		(*S*)-**9**	>98[a]	−15.6°	5.1	
(±)-**10**	50	(*R*)-**2**	>98[a]	−13.2°	5.1	>100
		(*S*)-**10**	>98[a]	−34.4°	5.1	
(±)-**11**	51	(*R*)-**3**	88[b]	−8.4°	1.1[e]	50
		(*S*)-**11**	90[c]	+9.9°	1.1[e]	
(±)-**12**	48	(*R*)-**4**	>98[c]	−63.9°	1.0	>100
		(*S*)-**12**	91[c]	−4.7°	1.0	

[a] Enantiomeric excess determined by GC on a Cyclodex β-*I*/P column supplied by CS-Chromatographie Service, D-5163 Langerwehe, Germany. [b] Determined by HPLC on a Chiracel OD column (supplied by Daicel Chemical Industries, Ltd.) after acylation to the acetate (*R*)-**11**. [c] Determined by HPLC on a Chiracel OD column (Daicel). [d] In $CHCl_3$ stabilised with 1% EtOH. [e] In MeOH. [f] For definition see ref. 12.

respectively. A lipase derived from *Pseudomonas fluorescens*[4] proved to be extremely useful in the past for the resolution of numerous secondary alcohols[5] and seemed to be the reagent of choice also for the resolution of (±)-**1**–**4**. The enzymatic hydrolysis of the chloroacetates (±)-**9**,**10** carried out under pH-state conditions in phosphate buffer at pH 7 indeed proceeded with very high enantioselectivities ($E > 100$, Table 1) leading to both enantiomeric series of products in optically pure form. The corresponding experiments with the acetates (±)-**11**,**12** surprisingly led to products with somewhat lower enantiomeric purities. Interestingly, the complementary enzymatic esterification of (±)-**1**–**4**, carried out in Bu^{t}OMe as solvent under the conditions of irreversible acyl transfer [eqns. (3), (4)], yielded very high enantiomeric purities for all products (Table 2). In both reaction modes, products could easily be separated by distillation (chloroacetates, alcohols) or silica gel chromatography (acetates, alcohols).

The enantiomeric purities of all products were determined by direct analysis using chiral GC or HPLC columns (see footnotes, Table 1). The absolute configurations of **3** and **4** are known from the literature[7]‡ and were secured for **1** and **2** by chemical correlation with the known bromohydrin derivatives

‡ Optical rotations for **3** are reported in MeOH[6a,b] and $CHCl_3$;[6c,7] the literature shows that data reported by different authors do not coincide.

Table 2 Enzymatic esterification of **1–4** with vinyl acetate in presence of a lipase from *Pseudomonas fluorescens* (SAM-1)[4] as biocatalyst

	Conversion (%)	Product	E.e.[a] (%)	$[\alpha]_D^{20}$[b]	*c*	*E*[c]
(±)-**1**	50	(*S*)-**1**	>98	+23.9°	1.5	>100
		(*R*)-**9**	>98	+22.7°	5.6	
(±)-**2**	50	(**S**)-**2**	>98	+13.2°	5.1	>100
		(*R*)-**10**	>98	+40.7°	5.1	
(±)-**3**	50	(*S*)-**3**	96	+60.6°	0.9	>100
		(*R*)-**11**	95	+0.5°	1.0	
(±)-**4**	51	(*S*)-**4**	>98	+64.3°	1.0	>100
		(*R*)-**12**	96	+5.0°	1.0	

[a] For the determination of optical purities see footnotes, Table 1. [b] In $CHCl_3$ stabilised with 1% EtOH. [c] For definition see ref. 12.

5,6.§ All esters were converted (K_2CO_3, MeOH) into the corresponding alcohols.

As outlined in Scheme 1 for one enantiomeric series, compounds (*R*)-**1,2** were then first converted with high yields (80–85%) into the corresponding bromohydrin acetates (*R*)-**5,6** by reaction with 30% HBr in glacial acetic acid.[8,9] Treatment of (*R*)-**5**, **6** with base following a literature procedure[8] led to the enantiomerically pure methyl- and ethyl-oxiranes (*R*)-**7,8** in very good (70–80%) yield.[10] Using again a known procedure[11] (*R*)-**3,4** can be converted in a one-pot reaction into (*R*)-**7,8** as outlined in Scheme 2. Alkylation at sulphur with Meerwein salt converted the sulphide moiety into the required excellent leaving group which can then be eliminated upon treatment with base leading to the enantiomerically pure oxiranes (*R*)-**7,8** in excellent yield (80%).

Received, 28th November 1990;¶ Com. 0/05382A

§ Obtained by the reaction of HBr–HOAc with enantiomerically pure 1,2-diols as a mixture with 6–10% of 1-acetoxy-2-bromoalkane: (*R*)-**5**: $[\alpha]_D^{20}$ + 14.2°, *c* 6.0 ($CHCl_3$), lit.,[8] $[\alpha]_D^{20}$ + 14.1°, *c* 5.8 ($CHCl_3$), (*R*)-**6**: $[\alpha]_D^{20}$ + 20.9°, *c* 2.8 (Et_2O), lit.,[9] $[\alpha]_D^{21}$ + 17.8°, *c* 2.7 (Et_2O).

¶ Received in revised form, 2nd May 1991.

References

1 Review: A. S. Rao, S. K. Pakinikar and J. G. Kirtane, *Tetrahedron*, 1983, **39**, 2323, and cited literature.
2 S. Hamaguchi, T. Ohashi and K. Watanabe, *Agric. Biol. Chem.*, 1986, **50**, 1632; C.-S. Chen and Y.-C. Liu, *Tetrahedron Lett.*, 1989, **30**, 7165.
3 Fluka Chemie AG.
4 Lipase from *Pseudomonas fluorescens* (SAM-1) from Amano Pharmaceutical Co.; (±)-**9** was also successfully resolved by cholesterol esterase derived from *Pseudomonas fluorescens* and supplied by Boehringer Mannheim GmbH.
5 K. Laumen, D. Breitgoff and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1988, 1459.
6 (*a*) H. Ohta, Y. Kato and G.-I. Tsuchihashi, *J. Org. Chem.*, 1987, **52**, 2735; (*b*) S. Iruchijima and N. Kojima, *Agric. Biol. Chem.*, 1978, **42**, 451; (*c*) R. L. Crumbie, B. S. Deol, J. E. Nemorin and D. D. Ridley, *Aust. J. Chem.*, 1978, **31**, 1965.
7 T. Fujisawa, T. Itoh, M. Nakai and T. Sato, *Tetrahedron Lett.*, 1985, **26**, 771.
8 M. E. Ellis and B. T. Golding, *Org. Synth.*, 1985, **63**, 1985.
9 H. K. Chenault, M.-J. Kim, A. Akijama, T. Mijazawa, E. S. Simon and G. M. Whitesides, *J. Org. Chem.*, 1987, **52**, 2608.
10 The enantiomeric purities of the oxiranes were determined by ^1H NMR spectroscopy in the presence of chiral shift reagents: E. S. Simon and G. M. Whitesides, *J. Org. Chem.*, 1987, **52**, 4042.
11 C. R. Johnson, C. W. Schroeck and J. Shanklin, *J. Am. Chem. Soc.*, 1973, **95**, 7424.
12 C. S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294.