Enantiomerically Pure Cyclohexanols and Cyclohexane-1,2-Diol Derivatives; Chiral Auxiliaries and Substitutes for (−)-8-Phenylmenthol. A Facile Enzymatic Route

Kurt Laumen, Detlef Breitgoff, Robert Seemayer, and Manfred P. Schneider*

Fb 9 — Bergische Universität, D-5600 Wuppertal 1, Germany

A number of optically active cyclohexanol and cyclohexane-1,2-diol derivatives, chiral auxiliaries and substitutes for (−)- and (+)-8-phenylmenthol, have been prepared by enzymatic hydrolysis of their racemic acetates and chloroacetates in the presence of a highly selective ester hydrolase from *Pseudomonas sp.* (SAM-II).

Enantiomerically pure compounds with cyclohexanol substructures like (−)- and (+)-menthol [(−)/(+)-(**1**)] or (−)-8-phenylmenthol (−)-(**2**) are among the most widely used, classical chiral reagents in organic chemistry, both for analytical and synthetic applications.[1] Although (−)-(**2**) and (+)-(**2**) are among the most powerful auxiliaries in asymmetric synthesis,[2] synthetic routes starting from (+)-pulegone[3] or (−)-pulegone,[4] respectively, are less than satisfactory, often impractical on a synthetic scale. This is also reflected in the high price of these reagents, and so more readily accessible substitutes for (−)- and (+)-(**2**) are highly desirable. Closely related structures are phenyl- and benzyl-cyclohexanols (*R*,*S*)- and (*S*,*R*)-(**3**),(**4**), it was shown recently that (*R*,*S*)-(**3**) is as powerful as (−)-(**2**) for efficient absolute stereocontrol.[5] Also structurally similiar to (−)-(**2**) are the corresponding cyclohexanediol derivatives (*R*,*R*)- and (*S*,*S*)-(**5**),(**6**), while (*R*,*R*)- and (*S*,*S*)-(**7**),(**8**) could be of considerable interest as chiral building blocks or ligands (*e.g.* for the synthesis of chiral crown ethers),[6] respectively.

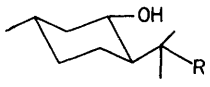
In view of the well documented excellent ability of many ester hydrolases for enantiomer differentiation, the enantioselective, enzymatic hydrolysis of racemic esters derived from (±)-(**3**)—(**8**) [*e.g.* the acetates (±)-(**3a**)—(**7a**),(**8c**)] seemed to be an obvious and facile approach to this whole class of molecules. Although porcine liver esterase (PLE) can be used for the resolution of (±)-(**3a**)[7] and (±)-(**8c**),[8] these reactions proved to be less than satisfactory on a large, preparative scale.† We report here successful experiments using a highly

† In our hands, PLE catalysed hydrolysis of (±)-(**3a**)[7] was extremely sluggish, incomplete, and suffered from severe product inhibition. The earlier described hydrolysis of (±)-(**8c**) was difficult to control and, disappointingly, always produced large quantities of racemic monoacetate (±)-(**8a**).[8]

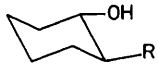
Table 1. Enzymatic hydrolysis of acetates and chloroacetates derived from (±)-(**3**)—(**8**).

Entry	Substrate	% Conversion	*t*/h	Product	% Yield	% E.e.[a,b]	*E*[c]
1	(±)-(**3a**)	27	164	(*R*,*S*)-(**3**)	20	98[b]	140
				(*S*,*R*)-(**3a**)	64	36	
2	(±)-(**3b**)	50	9 (!)	(*R*,*S*)-(**3**)	44	95[b]	180
				(*S*,*R*)-(**3b**)	43	97	
3	(±)-(**4a**)	46	53	(*R*,*S*)-(**4**)	40	98[b]	260
				(*S*,*R*)-(**4a**)	46	83	
4	(±)-(**4b**)	50.8	18	(*R*,*S*)-(**4**)	46	>95[a]	>145
				(*S*,*R*)-(**4b**)	43	>95	
5	(±)-(**5a**)	48	40	(*R*,*R*)-(**5**)	42	>99[b]	>790
				(*S*,*S*)-(**5a**)	45	96	
6	(±)-(**6a**)	51	29	(*R*,*R*)-(**6**)	47	>95[a]	>145
				(*S*,*S*)-(**6a**)	45	>95	
7	(±)-(**6b**)	50	8	(*R*,*R*)-(**6**)	41	88[b]	40
				(*S*,*S*)-(**6b**)	43	86	
8	(±)-(**7a**)	49	44	(*R*,*R*)-(**7**)	45	98[b]	400
				(*S*,*S*)-(**7a**)	49	96	
9	(±)-(**8c**)	25.2	17	(*S*,*S*)-(**8c**)	53	79	120
				(*R*,*R*)-(**8a**)	36	96[b]	
10	(±)-(**8c**)	27.8	22	(*S*,*S*)-(**8c**)	48	84	—
				(*R*,*R*)-(**8a**)	41	94[b]	
				(*R*,*R*)-(**8**)	10	97	
11	(*S*,*S*)-(**8c**) from entry 10	9.3	19	(*S*,*S*)-(**8c**)	81	97	—
				(*R*,*R*)-(**8a**)	17	82[b]	

[a] Determined by 400 MHz ^{1}H n.m.r. using Eu(tfc)$_3$ [tfc = 3-(trifluoromethylhydroxymethylene)-(+)-camphorato] as chiral shift reagent. [b] By g.c. of the isopropylurethanes using a chiral column (ref. 11). [c] See text and ref. 10; $E = k_R/k_s$, calculated ratio of hydrolysis rates for the two enantiomers.



(-)-(**1**) R = H
(-)-(**2**) R = Ph



(**3**) R = Ph
(**4**) R = Bn
(**5**) R = OPh
(**6**) R = OBn
(**7**) R = OMe
(**8**) R = OH

a; acetate derivative
b; chloroacetate derivative
c; diacetate derivative, (**8c**) only

selective lipase from *Pseudomonas sp*,‡ from which this whole class of molecules has become accessible, with excellent chemical and optical yields.

In a series of experiments 50 mmol of the racemic acetates (±)-(**3a**)—(**7a**) were hydrolysed in the previously described way[9] using 40 g of 0.1 M phosphate buffer (pH 7, 20 °C) and 500 mg (16 000 units, standard: tributyrin) of the lipase. Practically all the reactions came to a near standstill after *ca.* 50% conversion (*i.e.* hydrolysis of one enantiomer); this is to be expected for a highly selective enantiomer differentiation with values of $E > 100$[10] and further documented by the high enantiomeric purities of all the products obtained (Table 1).

For (±)-(**3a**) a highly selective, but rather slow transformation was observed; this somewhat limits its synthetic usefulness. Clearly, for synthetic applications on a practically useful scale higher rates of hydrolysis had to be achieved. This problem, encountered previously for other substrates,[9] was successfully solved by the use of activated esters. As can be seen from Table 1 (compare *e.g.* entries 1 and 2, 3 and 4, 6 and 7) considerably higher rates of conversion were found for the corresponding chloroacetates (±)-(**3b**), (**4b**), (**6b**). While in the case of (±)-(**3b**), (**4b**) the enantiomeric purities obtained remained unchanged in comparison with the corresponding acetates (±)-(**3a**), (**4a**), a considerable decrease was observed going from (±)-(**6a**) to (±)-(**6b**) (compare Table 1, entries 6 and 7), (±)-(**6a**) in this case clearly being the preferred substrate.

The enantioselective hydrolysis of the diacetate (±)-(**8c**) [derived from (±)-(**8**)] [200 mmol, 40 g 0.1 M phosphate buffer, pH 7, T 20 °C, 600 mg (19 800 units; standard: tributyrin) lipase SAM-II] was terminated after *ca.* 25% conversion (corresponding to the hydrolysis of one of the four esterfunctions in the racemate) leading to two major [(*R*,*R*)-(**8c**), (*S*,*S*)-(**8a**)] and one minor product (*R*,*R*)-(**8**) with the somewhat conversion-dependent enantiomeric purities listed in Table 1. While (*R*,*R*)-(**8**) both directly, and *via* the chemical hydrolysis (K_2CO_3, MeOH) of (*R*,*R*)-(**8c**), can be obtained nearly enantiomerically pure, changes in the conversion did not yield the monoacetate (*S*,*S*)-(**8a**) with high optical purity. It was finally obtained with 97% enantiomeric excess (e.e.) by enzymatic (low conversion) hydrolysis of enantiomerically enriched (*S*,*S*)-(**8c**) (Table 1, entry 11).

All products were isolated by the extraction of the crude reaction mixtures with Et_2O, followed by column chromatography on silica gel (petrol, ether). Acetates and chloroacetates were converted into the corresponding alcohols (K_2CO_3, MeOH), the enantiomeric purities were determined either by (i) g.c. separation of the isopropyl urethanes on a chiral g.c. column[11] or (ii) 400 MHz ^{1}H n.m.r. studies using Eu(tfc)$_3$ as

‡ Lipase SAM-II from Amano Pharmaceutical Co., supplied by Fluka AG, CH-9470 Buchs, Switzerland (Cat. No. 62312) and Mitsubishi Int. GmbH, D-4000 Düsseldorf, Germany.

chiral shift reagent, observing the signal of the methyl group in the acetate functions (see Table 1).

Absolute configurations were either known [(*R*,*S*)-, (*S*,*R*)-(**3**)][5] or correlated by (i) oxidation of (1*R*,2*S*)-(**4**) to the known (*S*)-2-benzylcyclohexanone,§ (ii) chemical degradation (ether cleavage) of (*R*,*R*-, (*S*,*S*)-(**5**)—(**7**) to the known (*R*,*R*)- and (*S*,*S*)-(**8**) whose absolute configurations were confirmed earlier.[8]

We feel that the results in this paper further demonstrate the synthetic usefulness of ester hydrolases, allowing the preparation of a whole class of compounds with high enantiomeric purity and in synthetically useful quantities.

We are grateful to Prof. Dr. W. A. König (Hamburg) for the determination of the enantiomeric purities and to Prof. J. Buddrus (Dortmund) for his assistance in the use of n.m.r. techniques. Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Eastman Kodak Co, Rochester, U.S.A., is gratefully acknowledged.

Received, 19th July 1988; Com. 8/02908C

§ Oxidation of (1*R*,2*S*)-(**4**) (pyridinium dichromate, CH_2Cl_2, room temp., 77%) produced the known[12] (*S*)-2-benzylcyclohexanone with the highest optical rotation recorded {$[\alpha]_D^{25}$ −47°, *c* 3.8 MeOH; lit.,[12] $[\alpha]_D^{25}$ −41.4°, *c* 4.9 MeOH}.

References

1 H. Kipphardt and D. Enders, *Kontakte* (*Merck*), 1985 (2), 37; J. Sauer and J. Kredel, *Angew. Chem.*, 1965, **77**, 1037; *Tetrahedron Lett.*, 1966, 6359; W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt, and F. Moffat, *Helv. Chim. Acta*, 1981, **64**, 2802; G. Quinkert and H. Stark, *Angew. Chem.*, 1983, **95**, 651.
2 J. K. Whitesell, D. James, and J. F. Carpenter, *J. Chem. Soc., Chem. Commun.*, 1985, 1449 and other papers in that series.
3 J. K. Whitesell, C. L. Liu, C. B. Buchanan, H. H. Chen, and M. A. Minton, *J. Org. Chem.*, 1986, **51**, 551.
4 E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, 1975, **97**, 6908; E. J. Corey, H. E. Ensley, and J. W. Suggs, *J. Org. Chem.*, 1976, **41**, 380; H. E. Ensley, C. A. Parnell, and E. J. Corey, *ibid.*, 1978, **43**, 1610.
5 J. K. Whitesell, H. H. Chen, and R. M. Lawrence, *J. Org. Chem.*, 1985, **50**, 4663.
6 R. C. Hayward, C. H. Overton, and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2413.
7 J. K. Whitesell and R. M. Lawrence, *Chimia*, 1986, **40**, 318.
8 D. H. G. Crout, V. S. B. Gaudet, K. Laumen, and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1986, 808.
9 K. Laumen and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1988, 598.
10 C. S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294.
11 XE-60-L-Valine-(*S*)-α-phenylethylamide, commercially available from: Chrompack International, Middelburg, The Netherlands; W. A. König, W. Franke, and J. Benecke, *J. Chromatogr.*, 1982, **239**, 227.
12 A. I. Meyers, D. R. Williams, and M. Druelinger, *J. Am Chem. Soc.*, 1976, **98**, 3032.