Enzymatic Differentiation of the Enantiotopic Hydroxymethyl Groups of Glycerol; Synthesis of Chiral Building Blocks

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The prochiral (**3b**), derived from glycerol, was transformed by enantioselective, enzymatic hydrolysis into the central chiral building block (*R*)-(**4**) of high enantiomeric purity, which was further elaborated into a variety of chiral building blocks with the glycerol skeleton.

Chiral glycerol derivatives [*e.g.* (*S*)- and (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol (**1**) or the corresponding aldehydes (*R*)- and (*S*)-(**2**)] have been used widely in the past as building blocks for the preparation of enantiomerically pure, biologically active molecules such as phospholipids,[1] PAF (platelet aggregation factor),[2] β-blockers,[3] GABOB,[4]† prostaglandins,[5] brefeldin A,[6] and many others.[7] They are usually prepared from D-mannitol [(*S*)-(**1**) and (*R*)-(**2**)][8] and L-serine[8,9] or ascorbic acid[4] [(*R*)-(**1**) and (*S*)-(**2**)].

Surprisingly, glycerol itself has never been seriously considered as an alternative source of chiral building blocks with the glycerol skeleton. Differentiation of the two enantiotopic groups in prochiral glycerol derivatives [*e.g.* (**3**)] would in fact lead to chiral molecules [*e.g.* (*R*)-(**4**)] which could be transformed in *both* enantiomeric series by selective functional group manipulation (Scheme 1).

Hydrolytic enzymes are well known for their capability of enantiotopic group differentiation in prochiral diesters. On the basis of our previous experience[10] they were the obvious choice for transformations such as (**3**) → (*R*)-(**4**). Triglycerides, the cheapest and most logical substrates for these enzymatic transformations, proved to be unsuitable owing to the occurrence of rapid acyl migrations in the products. Clearly, the 2-position in glycerol had to be protected and compounds (**3**) were chosen as substrates in order to produce versatile chiral molecules like (*R*)-(**4**) with three chemically very different functional groups which could be manipulated selectively. In order to provide as much 'chirality' as possible per mole, the diacetate (**3b**) was preferred over derivatives with longer-chain fatty acids.

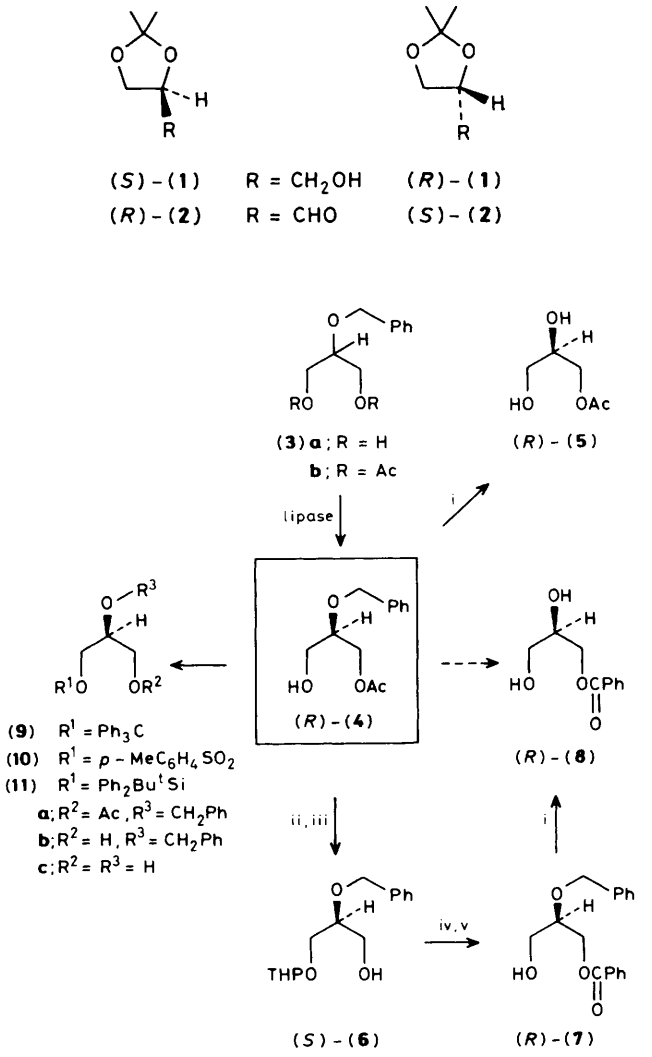
Glycerol can in fact be transformed easily *via* a known route[11] into 2-*O*-benzylglycerol (**3a**) which is simply acetylated to produce (**3b**) conveniently in several hundred gram quantities.

The enzymatic saponifications of (**3b**) [reaction (1)] were studied in the presence of several hydrolases using experimental conditions described previously.[10] The results are summarized in Table 1. In addition to the desired monoacetates (*R*)- and (*S*)-(**4**) variable amounts of (**3a**) are formed which can, however, be easily removed by 'filtration' of the reaction mixture over silica gel.

$$\text{(3b)} \xrightarrow[\text{pH 7, 0.1 M phosphate buffer}]{\text{Hydrolase}} \text{(R)-/(S)-(4)} + \text{(3a)} \qquad (1)$$

Ideally, in a highly enantioselective transformation only one acetate group should be removed in order to obtain high optical and chemical yields. The best results in this respect were obtained with porcine pancreatic lipase (E.C.3.1.1.3) and a lipoprotein lipase (E.C.3.1.1.34), the latter producing (*R*)-(**4**) in very good chemical yield (75%) and remarkably high optical purity (91% enantiomeric excess, e.e.) as determined by ^{1}H n.m.r. spectroscopy of the diastereoisomeric 'Mosher' esters.[12]

The acetate (*R*)-(**4**) {$[\alpha]_D^{20}$ −13.2° (*c* 3, EtOH)} was transformed (H_2/Pd–C) into the known[13] monoacetate (*R*)-(**5**) {$[\alpha]_D^{22}$ −9.2° (*c* 1.7, pyridine)} thereby confirming both the optical purity and the absolute configuration. Reaction with dihydropyran (*p*-$MeC_6H_4SO_3H$, room temp., 95%), followed by removal of the acetate group (K_2CO_3, MeOH, 95%) produced (*S*)-(**6**) {$[\alpha]_D^{20}$ −8.7° (*c* 2, $CHCl_3$ +1% EtOH),



Scheme 1. *Reagents:* i, H_2, Pd/C; ii, dihydropyran, *p*-$MeC_6H_4SO_3H$; iii, K_2CO_3, MeOH; iv, PhCOCl, pyridine; v, *p*-$MeC_6H_4SO_3H$, MeOH. THP = tetrahydropyran-2-yl.

† GABOB = (*R*)-4-amino-3-hydroxybutyric acid, an antiepileptic and hypotensive drug. See ref. 4.

Table 1. Enzymatic hydrolysis of (**3b**).

Enzyme[a]	% Conversion[b]	% Yield[c]	Abs. conf.	% E.e.[d]
Candida cylindracea	51	38	—	0
PLE (E.C.3.1.1.1)	51	43	*S*	29
Mucor sp.	45	42	*R*	35
Chromobacterium viscosum	52	52	R	29
Pancreatin	52	50	R	65
PPL (E.C.3.1.1.3)	50	40	R	60
PPL (E.C.3.1.1.3)[e]	50	40	R	80
Lipase (E.C.3.1.1.34)	53	75	R	91

[a] Crude enzyme preparations were used. PLE = porcine liver esterase; PPL = porcine pancreatic lipase. [b] 50% conversion corresponds to the hydrolysis of *one* acetate group; [c] Isolated. [d] Enantiomeric excess, determined from ^{1}H n.m.r. spectra of the 'Mosher' esters,[12] ±3%. [e] +15% tetrahydrofuran cosolvent.

mixture of diastereoisomers}, an entry into the other enantiomeric series. (*S*)-(**6**) in turn was transformed *via* (*R*)-(**7**) into the known[14] monobenzoate (*R*)-(**8**) {$[\alpha]_D^{20}$ −13.3° (c 1.3, pyridine)}. The great utility of (*R*)-(**4**) and its synthetic versatility was further demonstrated by its transformation into the trityl, tosyl, and silyl derivatives (**9**)—(**11**) (Scheme 1). While most of these are oils, (**10b**) {$[\alpha]_D^{20}$ −32° (*c* 1, $CHCl_3$ + 1% EtOH} and (**10c**) {$[\alpha]_D^{20}$ 9.3° (*c* 5, MeOH)} could be obtained with >97% e.e. by simple recrystallization.[15]

Obviously, starting from (*R*)-(**4**), a wide variety of useful chiral glycerol derivatives of both enantiomeric series can be made available by this method. To the best of our knowledge the experiments described constitute the first successful attempts to use glycerol itself for this purpose in a chemoenzymatic approach. In view of the ready availability of large quantities of lipids (fats and oils) these preliminary results could allow their use for the preparation of chiral building blocks for organic syntheses.

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