A Facile Chemoenzymatic Route to Optically Pure Building Blocks for Cyclopentanoid Natural Products

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Compound (1*R*,4*S*)-(**4a**), a central chiral building block for cyclopentanoid natural products, was prepared in high yield and optically pure by enantioselective hydrolysis of (**5a**) in the presence of several lipases, and was further transformed into (*R*)-(**1a**), (1*R*,5*S*)- and (1*S*,5*R*)-(**2**), (**7**), and (**8**), important synthons for this class of compounds.

Cyclopentanoid natural products (*e.g.* prostaglandins, prostacyclins, thromboxanes) display a great variety of biological activities and have been major synthetic targets over many years.[1] Recent developments of physiologically highly potent prostaglandin analogues with interesting (antithrombotic, antineoplastic, antihypertensive, and especially antiulcer) activities have prompted a great current interest in facile and economic routes to these molecules in enantiomerically pure form.

Compounds (**1**)—(**3**) are among the most important chiral building blocks for these compounds (Scheme 1).[1—4] They can be correlated retrosynthetically to (1*R*,4*S*)-(**4a**), from which they are all accessible by simple chemical transformations. Obviously, a simple and economical route to large quantities of (1*R*,4*S*)-(**4a**) would greatly facilitate the synthesis of biologically active cyclopentanoids also on a pharmaceutically interesting scale.

We found that (1*R*,4*S*)-(**4a**) can be prepared easily, optically pure {$[\alpha]_D^{20}$ 65.6° (*c* 2.3, $CHCl_3$ + 1% EtOH)} and with excellent chemical yields by enantioselective enzymatic hydrolysis of the prochiral 1,4-diacetoxycyclopent-2-ene (**5a**) in the presence of lipases from different origins (equation 1, Table 1). The *initial* enantiomeric purities (prior to work-up) were obtained by g.c. analysis of the diastereoisomeric 'Mosher' esters.[5] In *isolated* samples of (1*R*,4*S*)-(**4a**) no trace of the other enantiomer is detectable. In contrast to porcine liver esterase[6,7] all lipases selectively hydrolyse the (*S*)-ester group.† The high chemical yields indicate that only very little (1*R*,4*S*)-(**4a**) is transformed into the diol (equation 1). Compound (**5a**) is preferred over (**5b**) as substrate, (1*R*,4*S*)-(**4a**) being crystalline, whereas (1*R*,4*S*)-(**4b**) is an oil.

Crude enzyme preparations were used throughout.‡ Luckily the very inexpensive porcine pancreatic lipase (PPL, E.C.

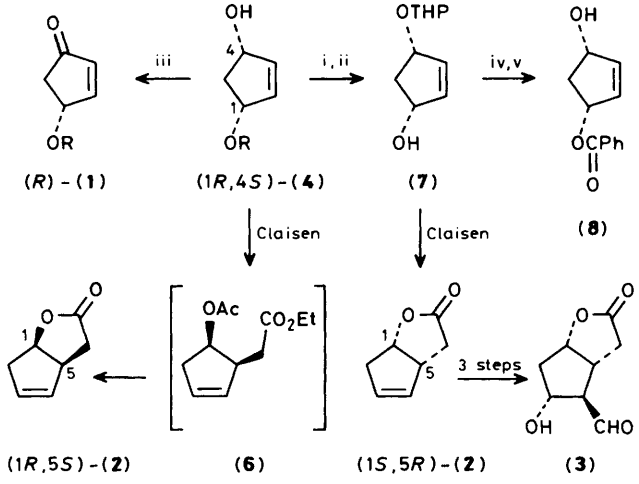
† We[6] and others[7] had shown earlier, that the other enantiomer, (1*S*,4*R*)-(**4a**), can be obtained by enzymatic hydrolysis in the presence of porcine liver esterase (E.C. 3.1.1.1.). The method has, however, disadvantages on a preparative scale: (a) initial enantiomeric purities are max. 67% e.e., requiring yield reducing recrystallisations; (b) a relatively expensive mammalian enzyme was used.

‡ PPL is commercially available (Fluka 62300); preparations from the micro-organisms which we found most suitable in our screening are under development as enzymatic 'reagents' and will become commercially available shortly.

Table 1. Enzymatic hydrolysis of (**5**) in the presence of different lipases.

Substrate[a] (mmol)		Buffer[b]	Lipase[c]	% Conversion[f]	Product	% Yield	% E.e. (recryst.)[e]
(**5a**)	5	20	Porcine pancreas (PPL)	52	(1*R*,4*S*)-(**4a**)	87	92
(**5b**)	10	30	,,	50	(1*R*,4*S*)-(**4b**)	86	95 (oil)
(**5a**)	10	20	*Pseudomonas* sp.	47	(1*R*,4*S*)-(**4a**)	84	92 (>99)
(**5a**)	10	30	,,	50	(1*R*,4*S*)-(**4a**)	80	94
(**5a**)	10	30	*Mucor miehei*	50	(1*R*,4*S*)-(**4a**)	85	95 (>99)
(**5a**)	20	20	,,	50	(1*R*,4*S*)-(**4a**)	90	96 (>99)
(**5a**)[d]	20	25	,,	48	(1*R*,4*S*)-(**4a**)	90	97 (>99)
(**5a**)	65	40	,,	51	(1*R*,4*S*)-(**4a**)	89	97
(**5b**)	10	25	,,	49	(1*R*,4*S*)-(**4b**)	80	93 (oil)
(**5a**)	5	20	*Chromobacterium viscosum*	50	(1*R*,4*S*)-(**4a**)	76	91
(**5a**)	20	15	,,	50	(1*R*,4*S*)-(**4a**)	80	93

[a] **a**; acetate, **b**; butyrate. [b] 0.1 M Phosphate buffer pH 7. [c] Crude enzyme preparations were used throughout. [d] T = 40 °C. [e] Et_2O : light petroleum 1 : 1.4, 0 °C. [f] Refers to the hydrolysis of both ester groups.

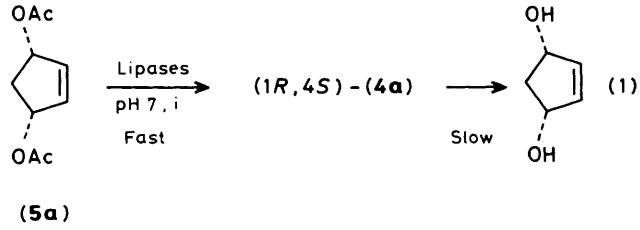


a; R = Ac
b; R = $COPr^n$

THP = tetrahydropyran-2-yl

Scheme 1. i, DHP, *p*-$MeC_6H_4SO_3H$; ii, K_2CO_3, MeOH; iii, PDC, 85%; iv, PhCOCl, pyridine; v, *p*-$MeC_6H_4SO_3H$, MeOH.

3.1.1.3) was extremely well suited for this transformation, reducing the cost for the biocatalyst to negligible amounts. Two-phase reactions using only very small quantities of buffer were employed. In scale-up experiments 200 g of (**5a**) can thus be converted in a 1 l flask. Oxidation of (1*R*,4*S*)-(**4a**) [93% enantiomeric excess (e.e.), prior to recryst.] with pyridinium dichromate (PDC)[8] (CH_2Cl_2, room temp., 85%) produced crystalline (*R*)-(**1a**) {m.p. 15 °C, $[\alpha]_D^{20}$ 94° (*c* 1.17, MeOH), 93% e.e.; 101°, 100% e.e.}.[9] Claisen rearrangement,[10,11] [$MeC(OEt)_3$, hydroquinone, 140 °C, 80%] of (1*R*,4*S*)-(**4a**) {$[\alpha]_D^{20}$ 63.2° (*c* 2.3, $CHCl_3$), 97% e.g.} yields [*via* (**6**)] (1*R*,5*S*)-(**2**) {$[\alpha]_D^{20}$ 102.8° (*c* 1.3, MeOH), 97% e.e.; 106°, 100% e.e.}.[3] Reaction of the same material with dihydropyrane (DHP) (*p*-$MeC_6H_4SO_3H$, room temp.; 10 min, quant.) followed by removal of the acetate group (K_2CO_3, MeOH) produced (**7**) {$[\alpha]_D^{20}$ − 25.7 ° (*c* 2.35, $CHCl_3$), mixture of diastereoisomers}, which was transformed into the monobenzoate (**8**) {m.p. 64.5—65 °C; $[\alpha]_D^{20}$ 128.2° (*c* 2.3, $CHCl_3$) 97% e.e.; 133°, 100% e.e.}.[11] Both (**7**) and (**8**) had been



Reagent: i, continuous addition of 2 M NaOH.

transformed previously[6,11] into (1*S*,5*R*)-(**2**) and (1*R*,5*S*)-(**2**) which was converted into the 'Corey lactone' (**3**).[4] The above results should help to facilitate the enantioselective synthesis of biologically active cyclopentanoids also on a pharmaceutically interesting scale.

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