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

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Compound (1R,4S)-(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), (1R,5S)- and (1S,5R)-(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 (1R,4S)-(4a), from which they are all accessible by simple chemical transformations. Obviously, a simple and economical route to large quantities of (1R,4S)-(4a) would greatly facilitate the synthesis of biologically active cyclopentanoids also on a pharmaceutically interesting scale.

We found that (1R,4S)-(4a) can be prepared easily, optically pure $\{[\alpha]_D^{20} 65.6^\circ (c \ 2.3, CHCl_3 + 1\% EtOH)\}$ 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 (1R,4S)-(**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 (1R,4S)-(**4a**) is transformed into the diol (equation 1). Compound (**5a**) is preferred over (**5b**) as substrate, (1R,4S)-(**4a**) being crystalline, whereas (1R,4S)-(**4b**) is an oil.

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

[†] We⁶ and others⁷ had shown earlier, that the other enantiomer, (15,4R)-(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 th	ne presence of	different lipases
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Substrate	^a (mmol)	Buffer ^b	Lipasec	% Conversion ^f	Product	% Yield	% E.e. (recryst.) ^e
(5a)	5	20	Porcine pancreas (PPL)	52	(1R, 4S)-(4a)	87	92
(5 b)	10	30	,, ,, ,, ,, ,, ,, ,, ,, ,, ,, ,, ,, ,,	50	(1R, 4S) - (4b)	86	95 (oil)
(5a)	10	20	Pseudomonas sp.	47	(1R, 4S) - (4a)	84	92 (>99)
(5a)	10	30	,,	50	(1R, 4S) - (4a)	80	94
(5a)	10	30	Mucor miehei	50	(1R, 4S) - (4a)	85	95 (>99)
(5a)	20	20		50	(1R, 4S)-(4a)	90	96 (>99)
(5a)d	20	25		48	(1R, 4S)-(4a)	90	97 (>99)
(5a)	65	40		51	(1R, 4S) - (4a)	89	97
(5b)	10	25		49	(1R, 4S) - (4b)	80	93 (oil)
(5a)	5	20	Chromobacterium viscosum	50	(1R, 4S) - (4a)	76	91
(5a)	20	15	,,	50	(1R, 4S) - (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 Et₂O: light petroleum 1:1.4, 0 °C. ^f Refers to the hydrolysis of both ester groups.



THP = tetrahydropyran-2-yl

Scheme 1. i, DHP, p-MeC₆H₄SO₃H; ii, K₂CO₃, MeOH; iii, PDC, 85%; iv, PhCOCl, pyridine; v, p-MeC₆H₄SO₃H, 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 (1R,4S)-(4a) [93% enantiomeric excess (e.e.), prior to recryst.] with pyridinium dichromate (PDC)⁸ (CH₂Cl₂, 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 (1R,4S)-(4a) $\{[\alpha]_{D^{20}} 63.2^{\circ} (c 2.3, CHCl_3), 97\% e.g.\}$ yields [via (6)] (1R,5S)-(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-MeC₆H₄SO₃H, room temp.; 10 min, quant.) followed by removal of the acetate group (K_2CO_3 , MeOH) produced (7) { $[\alpha]_D^{20} - 25.7 \circ (c \ 2.35, \text{CHCl}_3)$, mixture of diastereoisomers}, which was transformed into the monobenzoate (8) {m.p. $64.5-65 \,^{\circ}C$; $[\alpha]_{D}^{20} 128.2^{\circ} (c \, 2.3, CHCl_3) 97\%$ 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 (1S,5R)-(2) and (1R,5S)-(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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