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ENZYMATIC ENANTIOSELECTIVE HYDROLYSIS OF 2,2-DIMETHYL-1,3-DIOXOLANE-4-CARBOXYLIC ESTERS

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Abstract : *2,2-Dimethyl-1,3-dioxolane-4-carboxylic acid derived chiral building blocks were prepared from substituted α,β-unsaturated acids with high enantiomeric purities by enzymatic hydrolysis of their n.butyl esters.*

Optically active α,β-dihydroxy-carboxylic acids and their derivatives are interesting chiral building blocks for the total synthesis of biologically active compounds such as tocopherol[1], bicyclomycin[2], citreoviral[3], the aminosugar L-daunosamine[4] and the chemotactic substance leukotriene B_4[5]. The lower homologue, α,β-dihydroxypropionic acid (glyceric acid, R or S isomer) is related to optically active glycerol derivatives such as **1**, which are of invaluable importance as chiral educts[6] for the total synthesis of e.g. platelet activating factor (PAF)[7], β-blockers[8] and GABOB[9]. Although both enantiomers of solketal (**1**) are accessible from chiral pool compounds[6,10], intensive attention has been paid to the enzymatic resolution of (±)-**1**. However, as reported independently by Whitesides et al.[11] and Fuganti et al.[12], the hydrolysis of racemic esters **2a** and **2b** with pig pancreatic lipase (PPL) and penicillin acylase respectively, occurs with disappointingly low enantiomeric excess. Also the action of hydrolases on other glycerol derivatives, such as the prochiral 1,3-diesters of 2-O-benzyl-glycerol, has been investigated successfully.[13,14] With regard to the results obtained for **1**, we decided to investigate the enzymatic hydrolysis of the corresponding ester (±)-**3** and the higher homologues (±)-**4** and (±)-**5**, for which we expected a higher enantioselectivity. Indeed, in contrast with **2**, esters **3**, **4** and **5** possess a stereogenic center adjacent to the carbonyl carbon attacked by the enzyme.

The synthesis of the racemic substrates is given in scheme 1. n.Butyl ester (±)-**3** is readily available from racemic solketal (**1**) via catalytic oxidation and esterification. The higher homologues, the methyl-substituted n.butyl 2,2-dimethyl-1,3-dioxolane-4-carboxylates (±)-**4** (**a** - **d**) and (±)-**5** (**a**,**b**), were prepared from the appropriate α,β-unsaturated acids **6**, involving (i) a syn-dihydroxylation[15] for (±)-**4** (**a** - **d**), and (ii) an epoxidation and subsequent hydrolysis[16] for (±)-**5** (**a**,**b**).

The results of the enzymatic resolution are shown in scheme 2 and in the table. The hydrolysis was carried out using two lipases (EC 3.1.1.3) : pig pancreatic lipase (PPL) and Candida cylindracea lipase. In a typical experiment, an emulsion of racemic **3** (1 mmole) and a lipase (50 mg) in a 0.1 M phosphate buffer (pH 7, 10 ml) are stirred at 35°C, while the pH is kept constant by continuous addition of 1 M NaOH via an autoburette. The hydrolysis is terminated, after the desired degree of conversion has been reached (as indicated by the amount of base added), by extraction of unreacted ester (S)-**3** with ether, followed by careful acidification (pH 3) and extraction of the acid

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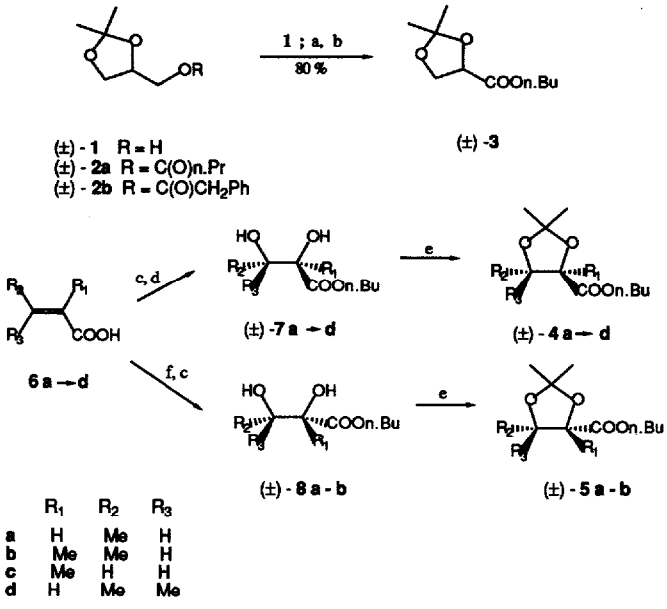
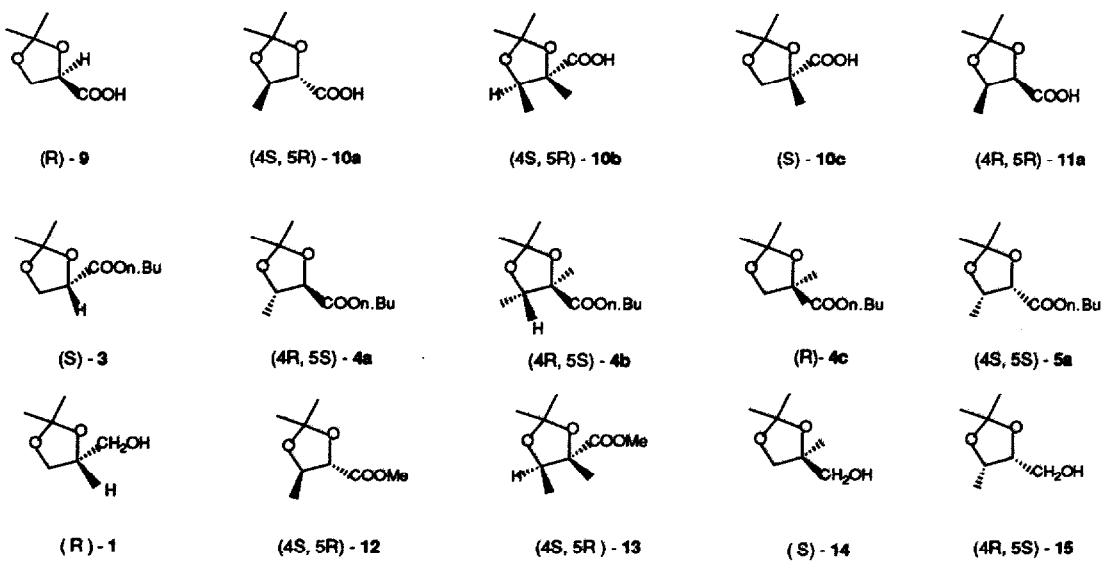
(R)–9 with methylene chloride. Although Candida cyl. lipase proved to be superior for all other substrates, PPL gave the best results in the case of 3 (entries 1-3). Remarkably, immobilization of PPL by acetone precipitation on celite enhances the enantioselectivity (entry 3).



a : 10 % Pt/C, air, H_20, pH 9, 50°C; b : n.BuCl, KI, DMF, 100°C, 4 days; c : n.BuOH, pTSA, PhH, reflux; d : OsO_4, TBHP, Et_4NOAc, acetone, rt; e : acetone, pTSA, $CuSO_{4anh.}$, rt; f : (i) H_2O_2, HOAc, H_20, reflux; (ii) NaOH, reflux

Scheme 1



Scheme 2

TABLE : Results of the enzymatic hydrolysis

Entry	Substrate	Enzyme[a]	Time (h)	mmole	% conv[b]	Product	chem.yield	% ee	$[\alpha]_D^{20}$ [c]	
1	(±)-**3**	Cand.cyl.	1.5	2	67	(R)-**9**	25	19[d]	+2.2	(c = 1.1)
						(S)-**3**	24	61[e]	-7.2	(c = 1.0)
2	(±)-**3**	PPL	6	1	61	(R)-**9**	56	50[d]	+5.4	(c = 0.8)
						(S)-**3**	38	77[e]	-9.2	(c = 1.1)
3	(±)-**3**	PPL/celite[f]	8	1	57	(R)-**9**	53	71[d]	+7.5	(c = 1)
						(S)-**3**	40	>95[e]	-12.8	(c = 1.1)
4	(±)-**4a**	Cand.cyl.	15	5	69	(4S,5R)-**10a**	38	42[d]	-7.8[g]	(c = 4.6)
						(4R,5S)-**4a**	19	95[e]	+11.2	(c = 2.1)
5	(±)-**4a**	PPL	65	1.5	53	(4R,5S)-**10a**	36	78[d]	+15.0[g]	(c = 0.95)
						(4S,5R)-**4a**	35	88[e]	-10.8	(c = 1.5)
6	(±)-**4b**	Cand.cyl.	153	2.5	45	(4S,5R)-**10b**	41	95[d]	-11.5[g]	(c = 3.3)
						(4R,5S)-**4b**	35	77[e]	+12.7	(c = 1)
7	(±)-**4b**	PPL			no hydrolysis					
8	(±)-**4c**	Cand.cyl.	144	2	50	(S)-**10c**	40	33[d]	+2.1[g]	(c = 1.2)
						(R)-**4c**	45	32[e]	-1.8	(c = 1)
9	(±)-**4c**	PPL			no hydrolysis					
10	(±)-**4d**	Cand.cyl., PPL			no hydrolysis					
11	(±)-**5a**	Cand.cyl.	91	4	50	(4R,5R)-**11a**	35	93[d]	-23.8[g]	(c = 2.9)
						(4S,5S)-**5a**	47	94[e]	+21.7	(c = 2.3)
12	(±)-**5a**	PPL			no hydrolysis					
13	(±)-**5b**	Cand.cyl., PPL			no hydrolysis					

[a] Pig pancreatic lipase (PPL; Sigma, type II); Candida cylindracea lipase (Sigma, type VII);

[b] calculated from the % ee values of acid and remaining ester;

[c] all optical rotations were measured in $CHCl_3$ at 20°C;

[d] determined as under e) on the corresponding methyl ester, obtained by treatment of the acid with CH_2N_2;

[e] determined by ^1H NMR (360 MHz, $CDCl_3$) in the presence of Eu(hfc)$_3$;

[f] prepared by precipitation with acetone;

[g] optical rotation of the corresponding methyl ester.

Comparison of the methyl-substituted homologues **4** and **5** reveals some remarkable substitution effects. Both **4a** and **5a** are hydrolyzed by Candida cyl. lipase with high enantioselectivity, although the cis-isomer (**5a**; entry 11) reacts considerably slower than the trans-isomer (**4a**; entry 4). When an additional 4-methyl group is present, only the trans-isomer **4b** is a substrate (compare entries 6 and 13), hydrolysis also occurring with high enantioselectivity. Remarkably, with regard to C_4, the enantioselectivity for the resolution of **4a** and **4b** is opposite to that observed for **5a** and seems to be determined by the stereogenic center C_5. In the case of **4c** (entry 8), without 5-methyl substituents, the enantioselectivity drops to the range observed for **3** (entry 1). When a 5,5-disubstitution is present, as in **4d** (entry 10), the ester is no longer accepted as a substrate.

PPL seems to be much more sensitive to steric influences, as from all the methyl-substituted homologues tested, only **4a** is a substrate (entry 5). The enantioselectivity in this case is contrary to that observed for Candida cyl. (entry 4).

The absolute configurations of (S)–**3**, (R)–**9**, (R)-**4c**, (S)-**10c**, (4S,5S)–**5a** and (4R,5R)–**11a** were determined by reduction ($LiAlH_4$, THF, 0°C) to the corresponding known alcohols (R)–**1**, (S)–**1**, (S)-**14**, (R)-**14**[2], (4R,5S)–**15** and (4S,5R)–**15**[17] respectively, while (4S,5R)–**10a** and (4S,5R)-**10b** were transformed to their methyl esters (4S,5R)–**12**[18] and (4S,5R)-**13**[19] respectively, with known absolute configuration.

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